

**Regulatory convergence or
harmonisation? Exploring regional
approaches for streamlining chemistry
manufacturing and control variations
and its application in Latin America
compared to initiatives in Southeast
Asia**

Ivy Ifeatu Essiam

A thesis submitted in accordance with the
conditions governing candidates for the degree of
Philosophiae Doctor in Cardiff university

January 2024

Cardiff School of Pharmacy and Pharmaceutical
Sciences

Cardiff University

ACKNOWLEDGEMENT

“TETELESTAI”

ALL GLORY TO JESUS!

My utmost thanks goes to the Almighty God for giving me strength, grace, wisdom and understanding to complete this piece of work. It's been a long journey but it has only been by His grace!

I would like to thank Prof Sam Salek and Susan Renee Forda for helping me at the start of this journey. To my direct supervisors, Prof Routledge (retired) and Prof. James Coulson, thanks for agreeing to supervise me and for all your support. To Fraser Stodart, my external supervisor, you agreed to supervise me and found time out of your busy schedule to help and support me with your wealth of knowledge. Thank you.

To Prof. Emma Kidd and Dr Louise Hughes, your commitment to help me see this research through is amazing, even though not my direct supervisors, you have held my hand and helped me cross the finish line! Thank you so much!

I would like to thank my 'gentle giant', Rev. Samuel Essiam, for his unflinching support and encouragement. To Ruth, Josiah and Jedidiah, thanks for the light banter and for spurring mummy on to complete this PhD.

To Apostle Dr. Lord Elorm Donkor, Apostle Dr. Ben Debrah, Apostle Prof. Kobby Koduah, Apostle Newton Ofosuhene, Rev. Dr. Caleb Nyanni my sincere gratitude to you all for your constant encouragement and for always checking up on the 'status' of the research.

To the COPUK fraternity, especially the young men and women who have cheered me on - thank you! This research has been through five transfers, as well as NYC13, NYC15, NYC17 and Breakout19! It has been interesting juggling it all!

To my gatekeepers and all the individuals who took part in this research, thank you so much for being a part of this research and giving your time and sharing your expertise and knowledge. It has been a wonderful experience to learn from you.

ABSTRACT

Post-approval chemistry, manufacturing and control changes (PACs) are essential in the lifecycle of a medicinal product in improving quality and maintaining supply. In recent years, the focus of harmonisation or convergence initiatives are beginning to shift to PACs due to the divergent regulations between different National Regulatory Authorities (NRAs) and the resulting complexity it brings to maintaining quality and supply. The benefits of streamlining PAC requirements and regulations across regions, for industry, NRAs and ultimately patients is widely accepted.

The aims of this research were threefold. The first was to explore and assess the effectiveness of harmonisation of PACs among three ASEAN markets, namely Malaysia, Singapore and Thailand. Secondly, the research aimed to assess whether streamlining of PACs was a priority in six Latin America markets (LATAM), namely Argentina, Brazil, Chile, Colombia, Cuba and Mexico; and to ascertain whether streamlining was occurring through 'harmonisation within the region' or 'convergence to international guidelines'. Lastly, the research compared the ASEAN harmonisation initiative with the LATAM experience to determine any areas of strength from ASEAN which could be applied to LATAM.

A qualitative case study approach including a systematic review, online questionnaires, group and individual interviews was adopted to achieve the research objectives. The perspectives of the Regulatory Affairs Professionals stakeholder group and harmonisation network was obtained by individual interviews. In parallel, perspectives of one LATAM industry association was obtained via group interview. An online questionnaire was complete by personnel with LATAM NRA working experience and followed up with either an online or email interview.

The ASEAN interviews showed that the main motivations for harmonised requirements were trade, security and a unified mindset. However, despite their harmonisation initiatives, challenges remained for effective implementation which led some participants to believe that convergence was a better process to associate with the streamlining initiatives in ASEAN.

The LATAM interviews and questionnaires exposed the low priority the region had for streamlining chemistry, manufacturing and control (CMC) requirements. The results also confirmed that convergence through reliance was the best model to describe streamlining efforts across the region, in spite of various challenges. Harmonisation could possibly occur across the region as each market converges to international guidelines, however, this may take a long time due to challenges such as political rivalry and lack of a unified mindset.

The comparison between ASEAN and LATAM showed similar challenges across the two regions which could be an indication of regions which have markets with varying degrees of disparity in regulatory capacity and expertise. The LATAM region, however, has much to learn from ASEAN's united goal of leverage across markets to support becoming an economic bloc plus the desire for patients to have access to quality and innovative medicines.

Table of Contents

LIST OF ABBREVIATIONS.....	viii
GLOSSARY OF TERMS.....	x
LIST OF FIGURES.....	xiii
LIST OF TABLES.....	xiv
1 INTRODUCTION.....	1
1.1 Regulatory Requirements and initiatives to streamline.....	1
1.2 Benefits of ICH	2
1.3 Life-cycle management of a medicinal product.....	7
1.3.1 Submission in multiple markets - with diverse requirements	8
1.3.2 Variations – categorisation: differences across markets.....	8
1.3.3 Selected Post-Approval Variations	10
1.4 Latin America, PAHO and PANDRH	14
1.5 Objectives and scope of a Regional Reference NRA (NRAr)	19
1.6 Summary and Research Question.....	20
2 STUDY RATIONALE, RESEARCH PHILOSOPHY AND METHODOLOGY.....	21
2.1 Study Rationale.....	21
2.2 Research Paradigm	22
2.2.1 Post-positivist paradigm	23
2.2.2 Methodological Approaches	25
2.3 Methodological Framework.....	25
2.3.1 Systematic review - Study 1	25
2.3.2 Search Strategy	29
2.3.3 Inclusion / Exclusion Criteria.....	30
2.3.4 Data extraction and analysis	30
2.4 Qualitative Case Studies – Studies 2 and 3.....	32
2.4.1 Research Methods - qualitative case-study methods.....	32
2.4.2 Case Study Design.....	33
2.4.3 Choice of Research Methods used	37
2.5 Reflexivity	45
2.6 Research Design.....	47
2.6.1 Overview of research design	47
2.7 Recruitment Strategy (population recruitment, sampling).....	49
2.7.1 Sample Size	50
2.7.2 Recruitment of Regulatory Affairs professionals	51
2.7.3 Recruitment of NRA personnel.....	52
2.7.4 Recruitment of others.....	53
2.8 Data collection and analysis	54
2.8.1 Data collection from RAs: Individual Interviews	54
2.8.2 Data collection and analysis from FIFARMA (Group interviews) & Other Experts (PAHO, MERCUSOR/EFPIA).....	60
2.8.3 Data collection from NRAs: Online Questionnaires	61
2.8.4 Data collection from NRAs: Individual Interviews.....	63

2.8.5	Using Interpreters (recruitment and ethical considerations	65
2.8.6	Secondary Data collection and Analysis	71
2.9	Ethical Considerations.....	72
2.10	Triangulation	73
2.11	COVID impact statement.....	73
2.12	Summary.....	74
3	SYSTEMATIC REVIEW OF THE LITERATURE.....	75
3.1	Introduction	75
3.2	Method.....	78
3.2.1	Literature Search	78
3.2.2	Inclusion and exclusion criteria	79
3.2.3	Data Extraction/abstraction.....	80
3.2.4	Organisational website search	80
3.3	Results	82
3.4	Review of published literature	88
3.5	Review of Organizational websites	91
3.5.1	EFPIA	91
3.5.2	PANDRH.....	92
3.5.3	FIFARMA	94
3.5.4	ICH.....	94
3.5.5	ASEAN CMC INITIATIVES.....	95
3.6	Discussion	103
3.7	Limitations	107
4	RESULTS FROM ASEAN INTERVIEWS.....	108
4.1	Introduction	108
4.2	Method.....	109
4.2.1	Interviewee characteristics.....	109
4.2.2	Semi-Structured Interviews.....	112
4.2.3	NRA Questionnaires/Interviews	114
4.2.4	Secondary Data	114
4.2.5	Thematic Analysis	115
4.3	Results	118
4.3.1	How ASEAN achieved harmonization: the process and history of harmonising CMC requirements.....	119
4.3.2	Motivation and Incentives for Harmonisation	121
4.3.3	Real-world effectiveness of harmonization: realisation and implementation	123
4.3.4	Challenges to effective harmonisation (effective/actual/full)	128
4.3.5	Ways to improve harmonization within ASEAN or to ensure better alignment	136
4.4	Discussion	137
4.5	Strengths and Limitations	142
4.6	Implications for future research.....	143
4.7	Implications for policy.....	144
4.8	Conclusion.....	145

5	RESULTS FROM LATAM INTERVIEWS & QUESTIONNAIRES	147
5.1	Introduction	147
5.2	Method.....	148
5.2.1	Interviewee characteristics.....	149
5.2.2	NRA Questionnaires followed by Interviews	151
5.2.3	Secondary data/reports	152
5.2.4	Semi-Structured Interviews.....	160
5.2.5	Thematic Analysis	160
5.3	Results	161
5.3.1	CMC Variation landscape and NRA characteristics	162
5.3.2	Attitudes towards streamlining	192
5.3.3	Perceived benefits of streamlining CMC requirements	198
5.3.4	Perceived Challenges to streamlining CMC requirements	201
5.3.5	Industry Associations & Networks and their influence or impact in the region on streamlining initiatives	208
5.3.6	Global Engagement	218
5.3.7	What process is being used to streamline CMC requirements?.....	221
5.4	Discussion	232
5.5	Limitations	237
5.6	Future studies	238
5.7	Conclusion.....	239
6	COMPARISON BETWEEN ASEAN AND LATAM RESULTS.....	240
6.1	Introduction	240
6.2	Results and Discussion	241
6.2.1	Comparing ASEAN and LATAM	241
6.2.2	Framing the benefits	242
6.2.3	Mobilising an organising body	246
6.2.4	Consensus on guidelines	249
6.2.5	Legal backbone.....	251
6.2.6	Government buy-in.....	252
6.2.7	The priority in streamlining CMC requirements	253
6.2.8	General challenges to streamlining	255
6.3	Discussion	263
6.4	Limitations	264
6.5	Future Research.....	264
6.6	Conclusion.....	264
7	GENERAL DISCUSSION AND CONCLUSIONS.....	266
7.1	Introduction	266
7.2	General discussion.....	268
7.3	Limitations	273
7.4	Future Work.....	274
7.5	Conclusions.....	274
	REFERENCES.....	276

APPENDICES305

LIST OF ABBREVIATIONS

ACCSQ-PPWG ASEAN Consultative Committee for Standards and Quality
Pharmaceutical Product Working Group

ACTD ASEAN Common Technical Document

ACTR ASEAN Common Technical Requirements

AEC ASEAN Economic Community

AFIDRO Asociación de Laboratorios Farmacéuticos de Investigación y Desarrollo
(Association of Pharmaceutical laboratories for Research and Development)

AHC Asia Pacific Economic Cooperation (APEC) Harmonization Centre

ALIFAR: Asociación Latinoamericana de Industrias Farmacéuticas (Latin American
Association of Pharmaceutical Industries)

AMLAC (Agencia Reguladora de Medicamentos y Dispositivos Médicos de
Latinoamérica y el Caribe).

ANMAT Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

ANVISA Agência Nacional de Vigilância Sanitária. Ministério da Saúde

APEC Asia Pacific Economic Cooperation

APEC RHSC Asia Pacific Economic Cooperation Regional Harmonisation Steering
Committee

API Active Pharmaceutical Ingredients

ASEAN Association of Southeastern Nations

ATPR Authorised Third Party Reviewers (ATPR)

CARICOM Caribbean Community and Common Market

CAEME Cámara Argentina de Especialidades Medicinales (Argentine Chamber of
Medical Specialists)

CELAC Comunidad de Estados Latinoamericanos y Caribeños (The Community of
Latin American and Caribbean States)

CECMED Centro para el Control Estatal de la Calidad de los Medicamentos

CIF Camara de la Innovation Farmaceutica Chamber of Pharmaceutical Innovation

CBER Center for Biologics Evaluation and Research

CIRS Centre for Innovation in Regulatory Science

CMC Chemistry, manufacturing and control(s)

COFEPRIS Comisión Federal para la Protección contra Riesgos Sanitarios

CRS Caribbean Regulatory System

CTD Common Technical Document

EAC East African Community

e-CTD Electronic Common Technical Document

EFPIA European Federation of Pharmaceutical Industries and Associations

EMA European Medicines Agency

EC European Community

EU European Union

FIFARMA The Federacion Latinoamericana de la Industria Farmaceutica (Latin
American Federation of the Pharmaceutical Industry)

GCC Gulf Cooperation Council

GHC GCC Health Council
GCC-DR Gulf Central Committee for Drug Registration
GCG Global Co-operation Group
GDP Gross Domestic Product
GDPR General Data Protection Regulation
GMP Good Manufacturing Practice
HSA Health Singapore Agency
ICH International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human
ICDRA: International Conference of Regulatory Drug Authorities
IFPMA International Federation of Pharmaceutical Manufacturers & Associations
INTERFARMA Asociación Latinoamericana de Industrias Farmacéuticas (Association of the Research Pharmaceutical Industry)
INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
ISP Instituto de Salud Pública de Chile (Public Health Institute of Chile)
IWG Implementation Working Group
LATAM Latin America
MDSAP Medical Device Single Audit Program
MERCOSUR Mercado Común del Sur (Southern Common Market)
MRA Mutual Recognition Agreements
NRA National Regulatory Authority
NRAr National Regulatory Authority of Regional Reference/ Regional Reference NRA
NGO: Nongovernmental organizations
PAC Post-approval CMC changes
PAHO Pan American Health Organization
PANDRH Pan American Network for Drug Regulatory Harmonization
PATE Parecer de Análise Técnica de Empresa
PICs Pharmaceutical Inspection Co-operation Schemes
PPWG Pharmaceutical Product Working Group
PRAIS Regional Platform on Access and Innovation for Health Technologies
RDC Resolution of the Collegiate Board (in Portuguese) Name given to ANVISA guidelines
RHIs Regional Harmonisation Initiatives
SADC The Southern African Development Community
SC: Steering Committee
SINDUSFARMA Sindicato da Indústria de Produtos Farmacêuticos no Estado de São Paulo (Industry Syndicate of pharmaceutical products)
TF Task Force
WHO World Health Organization

GLOSSARY OF TERMS

Regulatory convergence, “represents a voluntary process whereby regulatory requirements across economies become more uniform, or “aligned,” over time, as a result of the gradual adoption of internationally recognized technical guidance documents, standards, and scientific principles (harmonization), and common or similar practices and procedures. It does not represent the harmonization of laws and regulations, which is not necessary to allow for the alignment of technical requirements and for greater regulatory cooperation.” It involves instances where regulatory authorities work towards adopting processes and standards that align under the same scientific principles to yield similar outcomes but use context-specific processes that are not harmonized across systems. Convergence is generally gradual and focuses less on the adoption of identical pathways but more on achieving the same outcomes using similar—and not identical—regulatory requirements (PAHO, 2019)

Reliance is, “the act whereby the NRA in one jurisdiction may consider and give significant weight to—i.e. totally or partially rely upon—evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken even when it relies on the decisions and information of others.” Reliance implies “that the work done is shared by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities (PAHO, 2019)

Harmonization “represents the development and adoption of the same standards or requirements. Harmonization may also be applied to procedures and practices, so they are the same across economies. Harmonization represents an important means for achieving regulatory convergence over time, as does the adoption of common procedures and practices.” It has also been defined as “the process by which

technical guidelines are developed to be uniform across participating authorities.” (PANDRH/WHO). In the ICH case, “harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side- by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines (PAHO, 2019)

Cooperation: A practice among regulatory authorities for efficient and effective regulation of medical products. May be practised by an agency, an institution or a government. The formal mechanisms include creation of joint institutions, treaties and conventions such as mutual recognition agreements, while less formal mechanisms include sharing information, scientific collaboration, common risk assessment, joint reviews and inspections and joint development of standards. May also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to improvement of international regulatory governance practices (PAHO, 2019).

Recognition: WHO defines recognition as “the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or multilateral and may be subject of a mutual recognition agreement.” (WHO)

Large pharmaceutical company: Usually refers to the very largest employers, those with tens of thousands of workers and billions of dollars in revenue

Small pharmaceutical company: On average has about 500 employees with a revenue of less than \$1B

Generic companies: Manufacture medicines where the patent protection has expired from the innovator company

Medium-sized pharmaceutical company: On average does between \$1B-\$4BN in annual sales. They are often concentrated in a smaller number of therapeutic areas than their larger peers, and while they’re typically multinational, they often have a specific geographic as well.

Consultancy: Pharmaceutical consultants advise companies on the development and sales of drugs and pharmaceuticals. They have expert knowledge on industry

regulations so that they can aid and better enable companies to effectively deliver medical treatments to those in need

PATE: The Parecer de Análise Técnica de Empresa, translating as Opinion of Technical Analysis of the Company or Company Technical Evaluation Opinion is a document similar to the "AF" in Japan and the PACMP described in ICH Q12. It needs to be filled in each post-approval change application and the company has to describe the product characteristics according to the last approval by the Agency (similar to the EC) and the change itself evaluating how the change impacts the controls, quality and efficacy of the drug product, very similar to the PACMP process described in ICHQ12 (Rodrigues, 2018)

LIST OF FIGURES

Figure 1.1 Harmonisation Milestones of the ASEAN group	5
Figure 2.1 Diagram showing the components of the intended Case Study	35
Figure 2.2 The rationale, methodology and methods chosen for the study	37
Figure 2.3 Diagram showing the difference between Group Interviews and Focus Groups	40
Figure 2.4 Steps in the overall research design	48
Figure 3.1 Flow diagram for the selection of studies according to PRISM.....	83
Figure 4.1 Characteristics required for harmonisation from the ASEAN perspective	145

LIST OF TABLES

Table 1.1 A table showing the designated Regulatory competency Level assigned to each market under study by PAHO/WHO, after assessment	19
Table 2.1 Keywords used for systematic review search	29
Table 3.1 Organisational websites searched as part of in systematic review	81
Table 3.2 Characteristics of included studies including a summary of their relevance	87
Table 3.3 Comparison between three CMC variation classifications based on Singapore, Malaysia and ASEAN Variation guidelines	97
Table 3.4 ASEAN, Singapore and Malaysia requirements compared for the “change in DP manufacturing site” variation.	101
Table 4.1 Characteristics of ASEAN participants.....	111
Table 4.2 Themes generated from ASEAN qualitative interviews and secondary data.....	119
Table 5.1 Characteristics of the LATAM participants	159
Table 5.2 Themes generated from LATAM qualitative interviews and questionnaires	162
Table 5.3 Staff numbers of CMC reviewers in the NRAs.....	166
Table 5.4 NRA published review timelines versus actual review timelines for the CMC variations under review	167
Table 5.5 NRA classification of CMC variations under review.....	167
Table 5.6 NRA responses about preference of harmonisation occurring in the region	222
Table 5.7 NRA responses concerning convergence as a preference in the region.....	226
Table 5.8 Regulatory processes being used by NRAs to support convergence in their market	229
Table 6.1 Comparing key drivers of harmonisation	242
Table 6.2 Comparing ASEAN and LATAM Themes: Benefits for streamlining requirements	244
Table 6.3 Comparing Themes: Mobilising an organising body.....	248
Table 6.4 Comparing Themes: Consensus	250
Table 6.5 Comparing Themes: Legal backbone	251
Table 6.6 Comparing Themes: Government buy-in	253
Table 6.7 Comparing Themes: Priority in streamlining CMC requirements	254
Table 6.8 Comparing Themes: Shared Challenges to streamlining CMC requirements	257
Table 6.9 Themes: Challenges experienced in LATAM for convergence.....	261

1 INTRODUCTION

1.1 Regulatory Requirements and initiatives to streamline

Between the 1960s-1970s, there were increased legislation and guidelines for testing the safety, efficacy and quality of new medicinal products before being available to the general public. These guidelines however varied from market to market and the Pharmaceutical Industry was frequently required to duplicate expensive and time-consuming clinical trials and test procedures in order to bring their medicines to market. An urgent need to streamline regulations was further fueled by the rising cost of research and development and an expectation for quick access to safe medicines by healthcare providers and the public. This streamlining initiative was to be achieved by having a common scientific content, thus avoiding the need for duplication of expensive studies. Another area to be looked at was a common format of the presentation of data, which drive consistent data expectations and aid consistent assessment (Juillet, 2003; ICH website, no date a)

In the European Union (EU), this streamlining process termed “harmonisation” coincided with the development of submission routes or procedures which would drive the review of the data packages – creating the mutual registration and centralised registration procedures (Juillet, 2003).

Harmonisation of pharmaceutical development requirements was first explored and established by the European Community (EC), now the European Union in the 1980s. There were parallel discussions on harmonisation between the EC, United States of America (USA) and Japan and aided by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the International Conference on Harmonisation (ICH) was established in April 1990 (ICH website, 2020). ICH defined harmonisation as the agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or regions. It may also influence the review process and assessment and can be adopted as legislation (Juillet, 2003; APEC RHSC, 2011).

The remit of ICH was originally limited to new chemical entities and biologics, however the scope has widened over time and other fields of biomedical science are now subject to ICH oversight and review including, generics, biosimilars and active pharmaceutical

ingredients (APIs) or pharmaceutical starting materials (WHO, 2002). ICH was unique in that it provided a common platform for scientific and regulatory experts to discuss and agree on common solutions.

The ICH was to therefore act as a vehicle through which harmonisation of requirements would be achieved and this by:

- constructive dialogue between regulatory authorities and the pharmaceutical industry,
- Monitoring and updating of harmonized technical requirements,
- Facilitating the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety;
- To facilitate the dissemination and communication of information on harmonized guidelines and their use such as to encourage the implementation and integration of common standards” (WHO, 2002).

Within the ICH, scientific and regulatory experts continuously work together to develop harmonised efficacy, safety and quality guidelines to inform pharmaceutical development and ensure consistent output. Through these guidelines, an agreed common dossier content, presenting one set of scientific data in one language has resulted. Also, since 2003, the Common Technical Document (CTD), an agreed common dossier format, has also been achieved (Juillet, 2003). The CTD has removed the need for industry to reformat the submissions dossier to meet the specific needs of each National Regulatory Authority (NRA) (Juillet, 2003; Molzon *et al.*, 2011).

The CTD was a paper-based dossier consisting of thousands of pages, very bulky and weighty, the ICH worked on producing harmonised guidance for the electronic-CTD (e-CTD). This is essentially an electronic form of the CTD which is submitted to the NRAs electronically through web-based systems for the European Medicines Agency (EMA) or on compact disc (CD) for individual European markets (Juillet, 2003).

1.2 Benefits of ICH

Harmonisation initiatives of the ICH have helped build similar review practices, reduce clinical trial duplication, harmonise global manufacturing standards and made exchange of information easier. The e-CTD has enabled the reviewer to access and review different sections of the dossier in a much easier and faster way than the old paper CTD dossier (Molzon *et al.*, 2011). After 10 years of ICH, 37 guidelines had successfully developed

across quality, safety and efficacy topics and there are now over 80 guidelines to date (Tellner, 2020). This number has increased greatly since 2000 meaning more deliberations and guidance for industry in providing the right scientific content expected by National Regulatory Agencies (NRAs). Implementation of guidelines on Good Clinical Practice have for instance significantly reduced the number of duplicative clinical trials undertaken in Japan as they have gradually recognized global development a lot more compared to their high emphasis on local clinical trials in the past, even though local trials have not been totally ruled out (Wileman and Mishra, 2010).

Most of these guidelines have been automatically transposed into use in the EU/US/Japan with some becoming legislation, especially in the EU. The ICH initiatives are claimed to indirectly increase the public's trust in approved medicines (Molzon *et al.*, 2011). Due to the reduced resource required in generating duplicative regional data and compiling the common technical dossier content, Pharmaceutical companies can re-allocate resources (time, money, staff) to continuing work on development to discover new and more efficacious treatments for the patient. The ICH has introduced simplified review processes which coupled with the CTD enables innovative new drugs to be submitted and launched within similar time periods across the ICH regions. Above all the ICH initiative is claimed to have brought medicines to patients at a much quicker rate and reduced cost through reduced development and review of timelines, more so in Japan (Molzon *et al.*, 2011). These reduced costs then benefit governments and patients. Due to its success, the ICH has become the "mother" of harmonisation initiatives, impacting non-ICH or the "Emerging Markets" as in recent times, the ICH guidelines have been recognised as standards and have been referenced or served as educational resources for these non-ICH markets, especially where WHO guidelines were not available (WHO, 2002).

Within the Pharmaceutical industry, the term "Emerging Markets" (EMs) refers to all markets outside of the "developed markets" which are recognised as the US, EU (Western Europe), Japan, Australia, Switzerland New Zealand and Canada. These "developed" markets are also known for their adherence to the ICH guidelines (Juillet, 2003). Simply put, the EMs can be said to be those countries within Africa, Middle East, Asia, Eastern Europe or Intercontinental Regions and Latin America. Due to economic development, demographics and the change in disease profile to one more akin to developed markets, the 100 + EMs are becoming the focus of every company. The patient population overall is greater than the combined population of the Western developed markets, hence companies stand to gain a competitive advantage in revenue if they are able to

successfully register and commercialize their products in these markets. Expansion into the EMs also enables millions of patients' access to new and innovative medicines (IMS Institute for Healthcare Informatics, 2012).

The EMs generally reference the approval of the “developed markets” and rely on certain documentation issued by them, such as a Certificate of Pharmaceutical Product (CPP) (Morrison and Singh, 2012). Key markets are the BRICK-MT namely, Brazil, Russia, India, China, South Korea, Mexico, Turkey because of their fast-expanding economies. One of the major challenges to Pharma in seeking approval of medicines in the EMs is the myriad of regulatory requirements that need to be fulfilled and the varied review processes. These requirements and processes even within a small geographical area can be so diverse and labile, that companies always have to keep up with these changes at a great financial and resource cost to them. Sometimes because of long review/approval timelines and constant parallel change in requirements, companies are faced with the challenge of ensuring their dossier packages are current in order to avoid rejection during the review. However, in the EU and US, the harmonization of requirements and legislation, has led to a single dossier content with similar/same data expectations and formalized review processes making it easy for companies to provide "right first time data packages" (Juillet, 2003) as discussed previously.

Harmonization of requirements is a possible way of reducing these regulatory obstacles to patient access to medicines. This has been proven through the initiatives of the ICH which has had great influence not only on requirements but also on the review process, postulated by some to reduce the drug lag and leading to swifter approvals in US and EU (Wileman and Mishra, 2010).

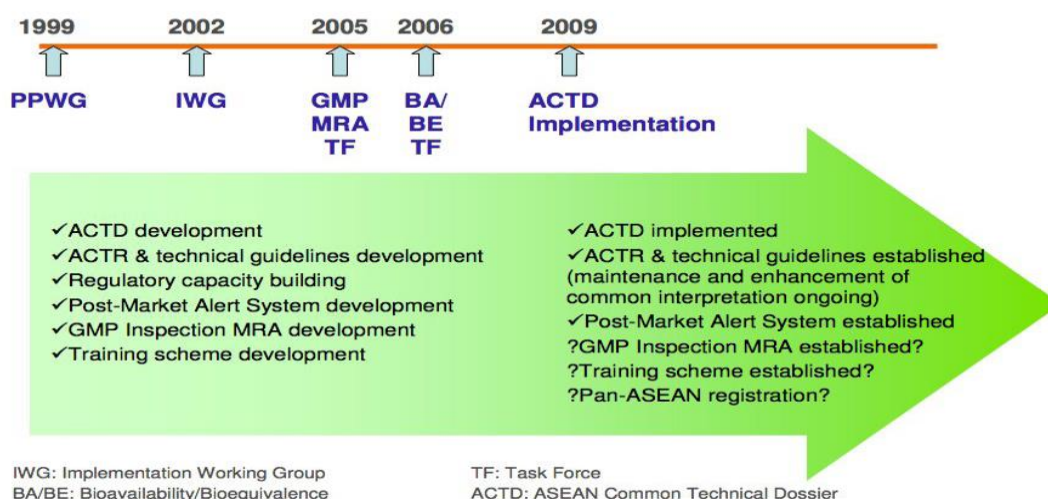
Within the EMs, attempts have been made to harmonize quality, safety and efficacy, legislative and guidance requirements and to streamline review processes in the bid to decrease review timelines and speed up the approval of medicines, with varying degrees of success. Examples of these are the Gulf Health Council (GHC) for Middle East and the Association of South Eastern Nations (ASEAN) committee (ICH website, 2020; 'ASEAN website (ACTD)', 2022).

The GCC-DR (Gulf Central Committee for Drug Registration) in the Gulf Region was approved and established in May 1999. Its objective is to provide safe and effective medication at an affordable price. Harmonisation efforts are focused on technical

guidelines and regulatory processes (Hashan *et al.*, 2022). A harmonised regulatory review process is now in place across the 7 GCC markets, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen. This was achieved through collaborative efforts in strengthening the individual capabilities of the NRAs in these markets (Hashan *et al.*, 2022).

In South East Asia, the ASEAN group was established in August 1967 mainly as an alliance to foster peace and economic growth (Mason School of Business, 2010). It later turned its focus on other areas such as healthcare which saw the development of the ASEAN CTD (or ACTD as it is commonly known), in 1999 with its implementation in 2009 (Mason School of Business, 2010). The ACTD is the common dossier format used in the ASEAN markets with an agreed content; the group developed the dossier with the help of ICH guidelines (Mason School of Business, 2010). Through the ASEAN Consultative Committee for Standards and Quality Pharmaceutical Product Working Group (ACCSQ-PPWG), the ASEAN countries agreed to harmonise standards and regulations of pharmaceutical products. With this harmonization initiative, it was the aim that drug companies could follow one set of regulatory requirements for all ASEAN countries (Mason School of Business, 2010). The group consists currently of 10 markets including Singapore, Malaysia, Vietnam and Thailand.

Harmonisation Milestones



PPWG Pharmaceutical Product Working Group; GMP Good Manufacturing Practice; MRA: Mutual Recognition Agreements

Figure 1.1 Harmonisation Milestones of the ASEAN group

(Mason School of Business, 2010)

In Southern Africa, the Southern African Development Community (SADC) was established in 1992 following a previous regional conference established in 1980. Its main aims are to enhance peace and security in the region, alleviate poverty and include enhancing the standard and quality of life of its members. It adopted the objective of “Health for all” by the year 2020 (SADC website, 2020) which has progressed on to Vision 2050 aiming for all citizens to enjoy sustainable economic well-being, justice, and freedom by 2050 (SADC website, 2022).

In light of that, the SADC Pharmaceutical Programme was set up in 2004 to help standardise legislation for pharmaceutical use and help provide safe and affordable medicines to patients. The group has also set up a Registrations Harmonisation project in 2011 to aid with harmonisation across the region. SADC consists of 15 member states including South Africa, Botswana, Namibia and Zimbabwe (SADC website, 2020). To help contribute to these already established initiatives in the Emerging Markets, the ICH set up the Global Co-operation Group (GCG) in 1999 (ICH website, 2020). Fueled by globalization and an increasing interest in the ICH guidelines by these non-ICH markets, the GCG was established to facilitate the understanding, acceptance and implementation of ICH guidelines in these markets. Their mission statement being “to promote a mutual understanding of regional harmonization initiatives in order to facilitate harmonization processes related to ICH guidelines regionally and globally, and to strengthen the capacity of drug regulatory authorities and industry to implement them” (WHO, 2002; Ward, 2005). The GCG was seen as a mechanism for communication and engagement with non-ICH markets (Ward, 2005). In order to support this exchange of information, partnerships were formed with the existing Regional Harmonisation Initiatives (RHIs). From 2004, these partners were allowed to listen in on technical discussions throughout all sections of the ICH group (Ward, 2005). Currently, there are six such RHI present in the GCG; these are Asia Pacific Economic Cooperation (APEC), ASEAN; GHC; SADC, East African Community (EAC) and the Pan American Network for Drug Regulatory Harmonisation (PANDRH). In order to aid further collaborations among the GCG, in 2007, the ICH created the Regulators Forum as an extended and complimentary group of the GCG, which had representatives from the individual NRAs. This mix of RHIs, NRA and ICH representatives has fostered trust and open dialogue on the ICH guidelines, impacting the implementation of the ICH guidelines in the non-ICH regions (Molzon *et al.*, 2011).

Other non-profit organizations such as the Centre for Innovation in Regulatory Science (CIRS) play an active role in the evolution and harmonization of regulatory requirements; trying to bridge the gap between Pharma and Regulatory bodies (CIRS, 2023b).

From the above discussions, it is clear that harmonisation initiatives are considered to have global benefits both to the industry and to the patient. The ICH and other groups discussed above initially focused their efforts on harmonisation of requirements for initial application of new chemical entities and biologics. More recently, focus has shifted to management of post-approval chemistry, manufacturing and control (CMC) changes, otherwise called PACs, highlighting the importance of streamlining these types of changes (WHO, 2015).

This project/thesis will concentrate on post-approval/life-cycle maintenance activities in Latin America and aims to contribute positively to the current efforts on global harmonisation of regulatory requirements, enabling patients to have quicker access to their medicines.

1.3 Life-cycle management of a medicinal product

Changes in a medicinal product's life cycle after the initial regulatory approval are common and there are many reasons for these. Lifecycle maintenance or management is the term used to describe the continuous update of regulatory safety, quality or efficacy data due to changes to the drug product or processes related to the manufacture of the medicine (EFPIA, 2017). These changes can be driven by technical (upgrade to state-of-the-art methods and processes) and scientific improvement, to allow cost reduction, or to fulfil regulatory agency requirements, as a reaction to supply demands (EFPIA, 2017); with the goal to remain commercially attractive & competitive. The majority of these changes are related to the chemistry, manufacturing and control (CMC) of the drug product, commonly referred to in industry as "CMC" (O'Keefe, 2015; EFPIA, 2017).

These changes to the registered dossier of a medicine are referred to as variations, amendments or post-approval changes (EFPIA, 2017). Lifecycle maintenance or management is essential to maintain compliance of the supplied product with the registered dossier, as there are strict guidelines from regulatory agencies for companies to report changes to a medicinal product. This is because such changes have the potential to

impact the quality, safety or efficacy, and in extreme cases may impact the benefit risk profile of the product, with potential to directly impact the end-user (the patient) (EFPIA, 2020). Any errors or omissions in updating the license could result in product recalls, or supply shortages meaning the patient's access to the drug would be hindered and the Pharmaceutical Company could lose reputation and or revenue (EFPIA, 2017).

Companies therefore dedicate considerable resource and expense to maintaining the license of each registered product they hold. Diverse regulatory requirements, differences in categorisation, differences in implementation rules and timelines and often long review times in each market present challenges to the review, approval and implementation of these variations (EFPIA, IFPMA and Vaccines Europe, 2021). As medicinal product licenses are normally available in multiple markets, this complexity then becomes magnified. This presents an opportunity for simplification and harmonisation or convergence to reduce the risks of non-compliance across markets and prevent shortage of supply to the patient, access being the end goal (O'Keefe, 2015; IFPMA, 2018).

1.3.1 Submission in multiple markets - with diverse requirements

A further challenge presented with lifecycle maintenance is that from the preparation of the initial registration dossier across the different regions, differences already exist due to the varying degree of data required in the dossiers (IFPMA, 2018). During the review of the initial application, questions received from Drug Regulatory Authorities cause further diversity to the dossiers. The result is different data being registered for the same product in different markets (Hoath, Chang and Ramalingam, 2016). This poses a challenge to the drug developer to maintain a record of what information was filed where, remain abreast of any changes in national regulatory guidelines and assess how this potentially impacts the data registered in each market (EFPIA, IFPMA and Vaccines Europe, 2021).

1.3.2 Variations – categorisation: differences across markets

A change in one market may be categorised differently in another market. This affects the review time for the change, the data required to be submitted and the complexity of review, making it difficult for sponsor companies to accurately predict what resource should be assigned to the global support of each variation and the implementation timelines (Hoath, Chang and Ramalingam, 2016).

For example, a drug developer elects to change one of the manufacturing sites in its global supply chain for a product. Country X may deem it as a minor change and will require minimal documentation with a review time of 2 months. Country Y deems it as a major variation, requiring a more detailed dossier package than Country X and a longer review time, 18 months. The requirements could include a minimal stability data requirement, which could take a minimum of 6-12 months for the site to generate before compiling. This means whilst the change could be submitted and approved in Country X within 2-3 months, Country Y would take a minimum of 12-18 months before the change was even submitted. Extend this change to a further 50 or more markets and the last market to submit the change might possibly approve it 5-6 years after approval in the first. Logistically, the drug developer would need to carefully manage supply of the product to all the markets whilst going through this change.

The ICH, recognising these challenges and because of concerns about patient access and potential shortages in supply, introduced the Q10 quality guideline so that by its "Implementation throughout the product life cycle, it would facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities (EMA, 2015)." It was aimed at having a robust quality system to manage change and continual improvement. It was envisaged that by implementing this earlier on in the product lifecycle it would reduce the requirement for post-approval filings (Kirk, 2008). Since Q10 was implemented in 2008, the ICH have progressed onto Q12, a guideline to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product's lifecycle (ICH website, no date c).

Whilst much emphasis in the last few decades has been on harmonisation of requirements for new Marketing Authorisations, the focus is now shifting to post-approval changes due to the global landscape, the complex global supply chains required by Industry to support supply and demand and the need for advanced planning of changes (EFPIA, 2017). For instance, the ICH guidelines and discussions are moving towards harmonisation of CMC post-approval activities and efficient life cycle maintenance (ICH, 2019). The Pharmaceutical Industry and in particular Asian organisations such as the Asia Pacific Economic Cooperation (APEC) Harmonization Centre (AHC) and the ASEAN network also recognise the need to have a harmonised approach or at least work towards convergence of post-approval CMC requirements and timelines (AHC, 2014). In fact, the APEC gave a definition for convergence as follows, "a voluntary process whereby the regulatory requirements across economies become more similar or "aligned" over time as a result of the gradual adoption of

internationally recognized technical guidance documents, standards and scientific principles (harmonization) and common or similar practices and procedures (APEC RHSC, 2011)." Other regions of the world have not progressed as much and are still deliberating on harmonisation of Marketing Authorisation requirements, Latin America being an example (Lezotre, 2014a).

This thesis will consider some of the common and supply critical changes that affect a medicinal product's lifecycle. In terms of this thesis, all these changes are in reference to the Drug Product (DP) and not to Active Pharmaceutical Ingredients (API) or Drug Substance (DS) [as referred to in regulatory dossiers for example the electronic common technical document (eCTD) used by EU, US and Japan], nor excipients. They are also discussed in the context of new chemical entities and not biologics, vaccines, biosimilars, generics or medical devices.

1.3.3 Selected Post-Approval Variations

Described below is a list and short description of the variations to be explored:

➤ Addition of manufacturing site

To facilitate global supply, mitigate supply chain risks and to enhance flexibility in the supply chain and sourcing of critical raw materials, companies can or would want to include multiple sites in a medicinal product license (Dellepiane *et al.*, 2020). Sometimes during the product's lifecycle certain circumstances mean that extra sites need to be included in the supply chain, for example an acquisition of a product from another company where the new company has to exit the former company's manufacturing sites.

➤ Change in formulation

A Medicines developer may develop an intravenous presentation in addition to an existing oral presentation (tablet) to improve drug substance availability and/or delivery, to improve patient compliance, or to meet the needs of different patient groups (Murteira *et al.*, 2013); changing a tablet to an oral liquid for children or the elderly is an example of the latter (Abelson, 2010).

➤ Change in storage condition

Medicinal products can undergo physical and chemical changes at different temperatures, so it is important that they are kept at the specified storage conditions. Sometimes pharmaceutical developers have to change the registered storage condition of a product if ongoing stability testing reveals that the product's stability profile does not support the shelf life registered. Changes in storage could also be affected by new packaging (Du *et al.*, 2011). This change in storage condition would need to be reported to Regulatory Authorities to satisfy them that the change does not affect the safety, quality and efficacy of the product (Biolife Solutions, 2019).

➤ Change in Shelf Life

The shelf life refers to the expiry period of the product. After the shelf life (expiry date), the product is no longer safe for the patient's use or the potency drops (Capen *et al.*, 2012). Sometimes at the initial application stages a company may not have sufficient stability data to support an extended shelf life (a long life is of benefit to the patient and to the manufacturer) (Du *et al.*, 2011).

At a later stage, when data becomes available, the company may elect to increase a product's shelf life and would have to provide information to the Regulatory Agency proving that the quality, safety and efficacy of the product is not affected by increasing this shelf life.

➤ Changes in manufacturing method

This is primarily driven by ongoing enhancements to the manufacturing process aimed at optimising and refining the product's production with the aim of driving down manufacturing cost whilst ensuring or improving product quality (Tudor, 2019). Again Regulatory Agencies require proof that the safety, quality and efficacy of the product is either enhanced or maintained (Kruse, 2015) .

It is the Regulatory Agency's responsibility to reassess the benefit/risk ratio of the product based on the new data submitted to support changes or variations, before granting approval and permitting release of the modified product to the patient.

Association of Southeast Asian Nations (ASEAN) and Harmonisation of Regulatory Requirements

The ASEAN network was formed in 1967 with the aims of accelerating the economic growth, social progress and cultural development in the region and; promoting regional peace and stability ('ASEAN website (ACTD)', 2022).

It has a population of about 700 million people, a combined GDP of US\$3.2 trillion as of 2019 (Lee and Adam, 2022) and offers an attractiveness for the pharmaceutical industry in its attempt to have Free Trade by 2015 (Tongia, 2018). The establishment of an ASEAN Economic Community (AEC) by 2020 was discussed and agreed by the ASEAN member states in 2003 (IMS Institute for Healthcare Informatics, 2012) and was actually delivered in 2015 (Ishikawa, 2021). This AEC would be a Single Market and Single Production Base for the free flow of goods, services, Skilled Labour, investments and capital. The ultimate aim was to remove technical barriers to trade in various sectors, one of them being the pharmaceutical sector to allow free flow of medicinal products through the harmonisation of registration guidelines across the region (IMS Institute for Healthcare Informatics, 2012). They are thus working towards defining the regulatory landscape for the region.

The ASEAN markets have been successful in establishing a core dossier for new marketing applications called the ASEAN Common Technical Document (ACTD). Alongside the ACTD is the ASEAN Core Technical Requirements (ACTR) which guides member states on preparing fit-for-purpose ACTDs. The ACTR is applicable to new marketing applications and for post-approval CMC variations but not necessarily for safety labelling or new indication variations (Morrison and Singh, 2012). Malaysia, Singapore and Thailand were part of the initial drivers in creating the ASEAN network, part of the ASEAN 6, the others being the Philippines, Indonesia and Brunei. The 3 afore-mentioned markets were involved in coordinating the key guidelines and ACTD sections (IMS Institute for Healthcare Informatics, 2012). They have also implemented the ACTD.

Singapore

Their national health authority or regulatory body is the Health Singapore Agency (HSA). This agency was established in April 2001 and its competencies have been recognised by international bodies such as the World Health Organisation (Health Sciences Authority, 2022). Singapore, as of May 2023, has a population of approximately 6 million (World Population Review, 2023). Healthcare projected expenditure in Singapore was \$12.59 billion for 2023 (International Trade Administration, 2023b). Total healthcare spending is expected to sky-rocket to almost \$49.4 billion by 2029 (International Trade Administration, 2020).

Thailand

In 2023, Thailand had a population of 73 million, a 0.15% increase from 2022 (Macrotrends, 2024). In 2019, Thailand had a healthcare market of \$25.3 billion (International Trade Administration, 2023a). The pharmaceutical market in Thailand had a 2021 value of \$6.4 billion (Global Data, 2022). Already the second largest market in Southeast Asia, the Thai drug market's value is projected at 6.9 billion by 2024 (Pharmexcil, 2020). The Thai FDA is the regulatory body for registration of medicinal products (Pharmexcil, 2020).

Malaysia

Malaysia, as at 2023, has a population of 34 million (Macrotrends, 2023). The total healthcare market in Malaysia was valued at \$17.4 billion in 2021 (Netherlands Enterprise Agency, 2022). This market is approximately the same size as the healthcare markets in Vietnam and the Philippines – which have populations three times as large as Malaysia (CFR.org editors, 2023) (Research and Markets, 2023).

The National Pharmaceutical Regulatory Agency (NPRA) of Malaysia, formerly the National Pharmaceutical Control Bureau (NPCB), a section of The Drug Control Authority (DCA), was established in 1978 for the regulation of drug products (Research and Markets, 2023). In view of the technical expertise and training capabilities of NPCB, it received recognition as a "WHO Collaborating Centre in the Regulatory Control of Pharmaceuticals" in 1996 (NPRA website, 2023)

Among the Southeast Asian nations, as of 2020, Singapore, Thailand and Malaysia had among the highest expenditure of health care per capita (combined public and private (theglobaleconomy.com, 2023)). This same trend can be seen for pharmaceutical

expenditure. In both cases, Singapore leads the three markets (OECD and Organization, 2014).

In light of the pharmaceutical industry's interest in Singapore, Thailand and Malaysia, coupled with the fact that these three markets are heavily involved in at least two major harmonisation activities, this thesis will seek to examine further harmonisation or convergence initiatives of post-approval variation requirements in these markets, notably their implementation phases, challenges faced and how they are overcoming these challenges.

1.4 Latin America, PAHO and PANDRH

Latin America, herein referred to as LATAM has been chosen mainly because of its commercial attractiveness to the Pharmaceutical Industry (Tanner Pharma Group, 2022), the growing eagerness to harmonise requirements (Deloitte, 2015) and processes within their regions (CIRS, 2015), and the fact that regulations within this region are currently not harmonised (Prat, 2013; Wojcicka-Swidorska, 2021). After the Asia Pacific Region, the LATAM region is seen as the next most commercially attractive for the Pharmaceutical Industry (González Peña, López Zavala and Cabral Ruelas, 2021). Some of the smaller markets may reference approvals in Brazil or Mexico, however, almost all of the LATAM markets reference EU or US approvals even in their labelling text (Prat, 2013). The majority of the markets have developed their own local requirements and have review processes in place through their Regulatory Authority, however the smaller Caribbean markets do not have very rigorous regulatory requirements (Preston, Freitas and Peña, 2020).

As at 2022,, the population of Latin America was 662 million with rapidly growing economies (ECLAC, 2022). The top five Latin American pharmaceutical markets accounted for more than 90% of the total population in 2020: Brazil (20.8 billion), Mexico (7.4 billion), Colombia (4.8 billion), Argentina (4.8 billion) and Chile (1.6 billion). Latin American pharmaceutical sales in 2020 were valued at \$43 billion (Precisionadvisors, 2023). This is particularly significant when considered within the context of estimated global sales of \$1.48 trillion in 2022 (Statista, 2023). Health care spending is projected to increase by around 3.2% annually over 2018-2050; several governments are trying to improve public health care systems amid general budget constraints (Rao *et al.*, 2022). Due to positive projections for future pharmaceutical sales,

government policies and public health spending, the region is becoming more attractive to Industry (Tanner Pharma Group, 2022).

The Pan American Health Organisation (PAHO) founded in 1902, has been providing technical cooperation and mobilizing partnerships to improve health and quality of life in the region. It is the regional office for the Americas on behalf of the World Health Organization (WHO) and is the oldest international public health organisation (PAHO website, 2023). The Pan American Network for Drug Regulatory Harmonization (PANDRH) was established in 1999 during the second Pan American Conference for Drug Regulatory Harmonisation in the region (PAHO website, 2020a). It was established in response to the need for initiatives that promote regulatory harmonisation across the region; harmonisation as defined in section 1.1 (PAHO website, 2020a).

Harmonisation initiatives in Latin America were initiated for new marketing authorisation applications (MAAs) prior to 2015 (PAHO, 2013). Guidelines were written, but historically had no legislative support, providing only recommendations for countries to consider implementation. These harmonisation initiatives have not been successful and have not brought the region closer to any form of harmonised dossier content or review system for new marketing authorisations (Wellcome, 2022); there is still considerable work to be done to align markets within the region (Alvarez *et al.*, 2023). Thirteen cross-national working groups (WGs) were initially established since the creation of PANDRH and were responsible for developing harmonized proposals on subjects of priority and interest in the area of pharmaceutical regulation. These Working Groups were (PAHO website, 2020b):

- Bioequivalence
- Biotechnological Products
- Counterfeit medicines
- Good Clinical Practices
- Good Laboratory Practices
- Good Manufacturing Practices
- Medical Plants
- Medicines Classification
- Medicines Promotion
- Medicines Registration

- Pharmacopoeia
- Pharmacovigilance
- Vaccines

Technical guidance was produced to cover ten of the above topics including pharmacovigilance, vaccines and registration of medicines. In 2011, during one of the Network's conferences, the National Regulatory Authorities (NRA) requested that PAHO coordinate the preparation of a strategic development plan to tackle new challenges the region will face in the future (PANDRH Secretariat, 2014). The plan would be developed by a group made up of NRA representatives and observer members. It would cover areas like regulatory challenges and degree of implementation of technical documents by NRAs. It was also proposed that the plan should review PANDRH's impact on the NRAs in the Region, set the Network's priorities for 2014–2020, review the Network's current bylaws, propose more efficient communication and decision-making mechanisms for the Network, and suggest a sustainable mechanism to strengthen regulatory training in the region (PANDRH Secretariat, 2014). The PANDRH 2014–2020 Strategic Development Plan (SDP) was produced as a result of this request (PANDRH Secretariat, 2014). The aim of PANDRH through this SDP was to: To strengthen the capacity of National Regulatory Authorities (NRAs) in the Americas, so that they can fulfil their regulatory mandate efficiently, effectively, and transparently through greater cooperation efforts that should lead towards regulatory convergence and harmonization.

Its objectives were to (PANDRH Secretariat, 2014):

1. promote the efficient governance of PANDRH and the active participation and cooperation of the NRAs towards regulatory convergence and harmonization.
2. periodically define strategies and mechanisms for regulatory convergence and harmonization, and support their dissemination, adoption, and implementation by the regional NRAs.
3. promote the strengthening of skills in Good Regulatory Practices and Regulatory Sciences.
4. promote the exchange of experiences and regulatory knowledge between NRAs within the Network and with NRAs outside PANDRH.

This SDP was to act as a tool to help steer the region through their harmonization or convergence journey. PANDRH has now adopted the PAHO strategic plan 2020-2025 as a follow on to SDP 2014-2020 (PAHO, 2022a).

Other Harmonisation Initiatives in Latin America

Apart from PANDRH, other harmonisation initiatives exist amongst individual countries in the Region. Examples of these are:

- The U.S.-Mexico-Canada Agreement (USMCA), also known as 'NAFTA 2.0' entered into force on July 1, 2020, replacing the North America Free Trade Agreement (NAFTA) which was established in 1994. NAFTA was set up to discuss the development of harmonisation within their current regulatory requirements, as well as to create free trade between the countries.(Labonté *et al.*, 2019; Int Trade Assoc, 2020)
- The Mercado Común del Sur (MERCOSUR) established in 1991 by Argentina, Brazil, Uruguay and Paraguay to agree on harmonised regulations for pharmaceuticals as part of creating a common market for the involved parties (CFR.org editors, 2021).
- The Andean Group established in 1969 includes Bolivia, Colombia, Ecuador, Peru. Venezuela joined but withdrew in 2006. Drug policy, drug regulation and common registration have been topics openly and widely discussed (Brewer, 2022).

Cooperation agreements within the region

Across the region, there are also transnational agreements at different stages between individual countries. These are at the Memoranda of Understanding (MoU) stage and largely exist to exchange, share information and eventually to mutually recognise marketing authorisations. Among the LATAM countries, MoUs exist between (Rodriguez, De Lucia and Liberti, 2022):

- Chile and Mexico
- Chile & Colombia
- Argentina & Colombia
- Colombia and Peru
- Colombia and Ecuador
- Colombia and El Salvador
- Brazil and Argentina (Argentina.gob.ar, 2023)
- Argentina and Brazil, Colombia, Cuba, Mexico (Argentina.gob.ar, 2023)

PAHO assessment of NRAs

PAHO, having assessed the National Regulatory Authorities in LATAM, designated the following Levels to the markets (PAHO, 2022b) being studied in this research:

Level 4: National regulatory authority that is competent and efficient in performance of the health regulation functions recommended by PAHO/WHO in order to guarantee the safety, efficacy, and quality of medicines. Also designated as a National Regional Reference Authority (NRAr) (PAHO, 2022b).

Level 3: National regulatory authority that is competent and efficient, which shall improve performance of certain health regulation functions recommended by PAHO/WHO in order to guarantee the safety, efficacy, and quality of medicines (PAHO, 2022b).

Table 1.1 below gives an overview of the designated levels given to each LATAM market in this study.

Market	NRA	PAHO Designated Level
Argentina	ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica	Level 4 status, December 2009
Brazil	ANVISA, Agencia Nacional de Vigilancia Sanitaria. Ministério da Saúde	Level 4 status, May 2010
Chile	ISP de Chile, Instituto de Salud Pública (Chilean Public Health Institute)	Level 4 status, August 2016 (was Level 3 in 2009) (<u>Rodriguez and De Lucia, 2021</u>)
Cuba	CECMED, Centro para el Control Estatal de la Calidad de los	Level 4 status, July 2010

	Medicamentos. Ministerio de Salud Pública	
Colombia	INVIMA, Instituto Nacional de Vigilancia de Medicamentos y Alimentos	Level 4 status, July 2010
Mexico	COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios	Level 4, June 2012

Table 1.1 A table showing the designated Regulatory competency Level assigned to each market under study by PAHO/WHO, after assessment

1.5 Objectives and scope of a Regional Reference NRA (NRAr)

The following are the objectives and scope of each NRAr (PAHO, 2023)

- a) Participate in the quality assurance, safety, and efficacy processes for the products purchased by PAHO on behalf of the countries.
- b) Collaborate as referents in the implementation and follow-up of recommendations approved by the PARF network.
- c) Support PAHO in the strengthening activities for other national regulatory authorities in the Region, so that they can be designated as regional reference regulatory authorities.
- d) Exchange public information through its Web sites and in the framework of the current national legislation on the products approved by the regional reference regulatory authorities. This will enable authorities with more limited capacities to have elements available for decision-making about their own products, considering that the products registered and sold in the countries with regional reference regulatory authorities will fulfil the quality standards recommended by WHO.
- e) Establish mechanisms in agreement with PAHO that can favour the mutual recognition processes for the functions of the pharmaceutical regulatory bodies.

1.6 Summary and Research Question

Chemistry, manufacturing and control variations are necessary in order to improve product quality and enhanced medicines for patients. However, the myriad of different requirements across the Emerging markets poses significant challenges to Industry and NRAs leading, sometimes, to a delay in patients receiving the product and/or continuity of supply one product approved. Whilst other regions are ahead in their discussions regarding streamlining requirements for CMC variations, Latin America seems to be lagging behind. There is no published literature discussing the streamlining of CMC requirements in Latin America in relation to small molecules. This research seeks to address this gap found for Latin America. Secondly, the research seeks to highlight lessons that can be learnt from the three leading ASEAN markets who have a degree of success in the area of streamlining requirements for CMC post approval variations. Based on the information reviewed so far, it is proposed the research will address the following aims:

Aim 1: To assess appropriate models for streamlining CMC requirements in LATAM: harmonisation or convergence?

Aim 2: To examine or review streamlining processes in ASEAN markets (Singapore, Malaysia, Thailand) and lessons that can be learnt and applied in LATAM

The aims will be fulfilled through the following objectives:

- I. To identify any streamlining efforts in LATAM and the process for ASEAN markets through a Systematic literature review. (Chapter 3)
- II. To explore the factors that have aided implementation of streamlining initiatives in Singapore, Malaysia, Thailand (Chapter 4)
- III. To review challenges in LATAM until present date; assess priority & feasibility in order to determine whether the region is moving towards harmonization or convergence (Chapter 5)
- IV. To assess if any lessons can be learnt from ASEAN markets and applied to LATAM markets (Chapter 6)

2 STUDY RATIONALE, RESEARCH PHILOSOPHY AND METHODOLOGY

2.1 Study Rationale

Chemistry, manufacturing and control (CMC) variations or changes are necessary in order to improve product quality and enhanced medicines for patients. However, the myriad of different requirements across the markets poses significant challenges to Industry and NRAs, leading sometimes to a delay in patients receiving the product (WHO Drug Information, 2018). The known benefits of streamlining requirements include reducing costly duplication for industry and regulators; optimizing use of limited resources; sharing of experience and knowledge amongst regulators (Weisfeld and Lustig, 2013).

Whilst the Latin America (LATAM) region seems to be seeking global harmonisation, there remains an expectation for country-specific requirements for the CMC section of the dossiers, which follows through to the post-approval variation space (Chapman, 2020).

An initial literature search shows much interest and discussion surrounding streamlining of requirements in the new marketing authorisation space in Latin America (Wileman and Mishra, 2010; Prat, 2013; Padua *et al.*, 2020; Durán *et al.*, 2021). In relation to streamlining of CMC requirements for small molecules in Latin America however, there is limited published literature.

This research seeks to address this gap by comparing efforts in Latin America to the three leading ASEAN markets who have a degree of success in the area of streamlined CMC variation requirements (Latzel, 2007).

The key research questions are listed below:

- Will streamlining of CMC post-approval changes be feasible across these LATAM markets and is it a priority?
- If so, which will work better in the LATAM region; convergence or harmonisation?
- What are the critical factors that have aided the implementation of harmonisation initiatives in Singapore, Thailand and Malaysia through the ASEAN network? What were the challenges?
- Are there any lessons that LATAM can learn and apply from these ASEAN markets?

These research questions, will be addressed through four main studies as follows:

1. A Systematic Review of the literature to identify existing information about convergence or harmonisation of CMC variations initiatives in chosen/specified LATAM/ASEAN markets and identify any gaps.
2. A study exploring stakeholder perspectives which include Regulatory Affairs Professionals, other industry stakeholders and National Regulatory Authorities on lessons that can be learnt from ASEAN's CMC streamlining process that can be applied to LATAM markets.
3. A study exploring stakeholder perspectives which include Regulatory Affairs Professionals, other industry stakeholders and National Regulatory Authorities, on appropriate models for streamlining CMC requirements in LATAM.
4. Comparison of lessons learnt for ASEAN and their applicability to LATAM

The chapter discusses the methodology, methods and research design chosen for each of these studies. In addition, the population, samples, sources of data, data collection, data analysis and ethical considerations are explained. The researcher concludes by summarising the key points raised in the chapter.

First, the researcher describes the rationale for using qualitative methods to address the study's research questions. Then the methodology for the systematic review is presented, with a specific focus on alternative methods adopted to incorporate extensive grey literature from regulatory affairs. In the subsequent sections, the researcher covers the various qualitative methods used in collecting data from the ASEAN and Latin American countries, including structure, recruitment and methodology analysis, as well as reflexivity.

2.2 Research Paradigm

Before turning to the study designs, the chosen research paradigm is explained in light of the research aims and objectives. A paradigm is an approach or conceptual framework about how research is thought about and executed. It implies a pattern, structure or system of scientific and academic ideas, values and assumptions (Abdul Rehman and Alharthi, 2016)

For this research project, the aim is to gain different perspectives through qualitative methods and obtain a holistic view of the desire to streamline and the process and direction of travel of this process in the selected Latin America markets.

Due to the exploratory nature of the study, the study did not start from an *a priori* hypothesis but focused on generating hypotheses (Casula, Rangarajan and Shields, 2021). These hypotheses could then potentially draw insights from how streamlining occurred in the ASEAN markets that could be applicable to these processes in Latin America markets.

2.2.1 Post-positivist paradigm

To this end, the study approach will follow a post-positivist paradigm. Before articulating the post-positivist approach, it is distinguished from alternative approaches and its selection for this research is justified below.

The post-positivist paradigm assumes that an objective, observable reality exists but acknowledges that it can never be perfectly apprehended, as attempts to understand it are influenced by human understanding (Hall, Griffiths and McKenna, 2013). Possible influence from the researcher's own beliefs and values is also not ruled out. (Abdul et al 2016) This paradigm can apply to both qualitative and quantitative studies, offering the use of multiple methods and techniques in research so the subject is studied from various angles and aspects (Panhwar, Ansari and Shah, 2017). This fits particularly well with the research approach for several reasons. First, there is no *a priori* hypothesis to be tested (Casula, Rangarajan and Shields, 2021). Second, interviewees have differing realities and perspectives on regulatory development, which the researcher seeks to explore in order to understand an overall process of harmonisation or convergence. Third, the researcher pursues a mode of knowing mainly through induction, induction being theory generating, not starting from any hypothesis and being exploratory in nature. With induction, the researcher seeks to find the best plausible explanation (Abdul Rehman and Alharthi, 2016). An element of deduction will also be employed where information generated from one set of data will be sought for in another set of data (theory testing) (Abdul Rehman and Alharthi, 2016). Thus the researcher draws on a set of empirical observations and patterns in an attempt to develop a forward-looking hypothesis or theory (Abdul et al, 2016). Abduction is ruled out because it usually starts with an existing theory (Abdul Rehman and Alharthi, 2016). Abduction is defined as the creative process of generating new theories based on "surprising research evidence," (Timmermans and

Tavory, 2012) which ultimately leads a researcher away from old ideas to new insights coded into theory (Collins and Stockton, 2018).

Before choosing to pursue the post-positivist paradigm, several alternatives were evaluated. One is the positivist paradigm which assumes 'that there is an orderly reality that can be objectively studied' and that knowledge can be independent of the research (Polit and Beck, 2017). Positivists have a tendency to align more with quantitative research (Abdul Rehman and Alharthi, 2016), testing *a priori* hypotheses through quantifiable variables and deductive reasoning (Rashid *et al.*, 2019). Since this research does not test a specific hypothesis, this approach was ruled out.

The constructivist paradigm was also considered as an alternative. This paradigm assumes that reality cannot be objectively discovered, but instead 'people, including researchers, construct the realities in which they participate (Rieger, 2019). Constructivism is more interested in investigating qualitative differences in the meaning people give to experiences (Haigh *et al.*, 2019). It believes there are multiple socially constructed realities, ungoverned by natural laws, causal or otherwise (Haigh *et al.*, 2019). This paradigm tends towards qualitative methods and inductive reasoning (Morgan, 2007). This paradigm could have been suitable for this research but the emphasis of this study is to capture participants' experiences in the most objective manner by minimising the effect of the researcher, and not to co-construct knowledge as per this paradigm, hence the constructivist paradigm was rejected for this study.

Another paradigm rejected for this study was the pragmatic paradigm. In pragmatism, the researcher starts off with the research question to determine their research framework. The emphasis is on what works best to address the research problem at hand and hence it embraces plurality of methods. Hence pragmatists favour working with both quantitative and qualitative data, as it enables them to better understand the reality being studied, so choosing whichever method is best suited to the research question (Wahyuni, 2012). Although this does cohere with the study approach, pragmatism tends to view the world from multiple realities. This study, however, sought to ascertain an objective reality as to whether harmonisation was occurring or not and so did not fit with pragmatism as a research paradigm.

Critical realism, like pragmatism, also tends to view the world from the perspective of multiple realities like pragmatism. However, researchers with a critical perspective focus on critiquing the current power structures with the ultimate goal of changing and

transforming or influencing those structures. This study does not aim to change the underlining structures that produce the real or observable effects but mainly to explore and understand the observable effects (Haigh *et al.*, 2019). If the research had sought to affect the power structures like the organisational structure in the NRA, then this paradigm would have been a better fit for the study.

2.2.2 Methodological Approaches

Following the post-positivist paradigm, the researcher sought to understand the phenomenon from multiple viewpoints, seeking out participants who have a thorough understanding of the phenomenon from various angles, thus getting as close to objective reality as possible.

In order to be as objective as possible, the researcher acknowledges their own personal experiences and biases and how it may affect what is being observed (Abdul Rehman and Alharthi, 2016), The researcher employs the use of reflexivity to overcome this potential bias as explained later in Section 2.5.

2.3 Methodological Framework

2.3.1 Systematic review - Study 1

Systematic review of streamlining processes of CMC variation requirements in ASEAN or LATAM

In the first research chapter, a systematic review is presented, to identify whether pharmaceutical CMC variation requirements are being streamlined in LATAM via convergence or harmonisation; and secondly how the process developed for ASEAN markets.

Systematic reviews are widely recommended as the most robust way to synthesise in a reproducible and replicable way, evidence on a given health-related topic or specific research question (Munn, Peters, *et al.*, 2018; Turney, 2022). It also evaluates the quality of the evidence and through the review, the researcher generally aims to produce statements to guide decision-making (Turney, 2022). This approach differs from literature reviews which tend not to be replicable and are more widely used to scope or map existing information about a topic. Systematic reviews can avoid the critiques of 'cherry-picking' of

literature reviews (Rousseau, Manning and Denyer, 2008) and critical appraisal is performed to assess risk of bias (Munn, Peters, *et al.*, 2018). As such they can provide valuable information on a phenomenon from which the researcher can identify and verify gaps on their chosen topic. Narrative reviews do not focus on a clearly defined research question or standardized methodology like systematic reviews. They are more descriptive, providing the researcher's subjective perspective. Hence narrative reviews were ruled out (EDANZ, 2023). Scoping reviews were also ruled out even though they follow a standardized methodology, they tend to give an overview of a large and diverse body of literature or to explore a topic, not to answer a specific question (Turney, 2022). They are sometimes used to inform a systematic review (Munn, Peters, *et al.*, 2018; EDANZ, 2023). Since the aim was to collate empirical evidence from a relatively smaller number of studies on a focused question (EDANZ, 2023), the option of systematic reviews was best suited to this research.

To standardize systematic reviews and improve quality, a set of so-called PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines have been developed (Selcuk, 2019). At each stage in the systematic review, these guidelines were followed to ensure adherence with best-practices in the field. By following the guidelines, relevant literature is identified, screened, and their eligibility assessed by applying inclusion and exclusion criteria (Selcuk, 2019). The guideline also includes a 27-item checklist covering areas like as title, abstract, introduction, methods, results, discussion and financing of the systematic review (Liberati and Altman, 2009; Selcuk, 2019; PRISMA website, 2023). The systematic review consists mainly of three phases: planning, conducting and reporting (Tranfield, Denyer and Smart, 2003). In planning the review, a panel, consisting of experts in the field is normally formed to discuss the research question, formulate clear inclusion and exclusion criteria and develop a review protocol. In the second stage, search terms are formulated in discussion with the panel. Also synonyms, abbreviations and spelling variants are considered when searching in electronic databases (Lange, 2014). A search strategy is developed to enable the researcher to detect the literature relevant to the research question, this ensures validity of findings and replicability (Kable, Pich and Maslin-Prothero, 2012; Lange, 2014). To assess the suitability of the retrieved literature after the search, an initial check of titles and abstracts comparing against the inclusion and exclusion criteria can be conducted in order to cut down on the number of articles to be read thoroughly as the next assessment stage (Lange, 2014).

The next stage is to perform a quality appraisal to ensure the reliability of the findings in the relevant literature (Lange, 2014). The final stage is the synthesis or reporting of findings; this can be narrative or meta-analysis (Tranfield, Denyer and Smart, 2003).

The narrative synthesis summarises the main topics captured by the literature whereas meta-analysis is used to pool data of research findings, for statistical purposes (Lange, 2014). In this research, the narrative synthesis is more suited. From an initial literature review, it was observed that the search would probably return more grey literature (eg. Industry reports, NRA guidelines) capturing industry narratives, rather than peer-reviewed journals with statistical data. Industry narratives are preferred over statistical data for this research, due to the nature of the topic. Due to its exploratory nature, the research seeks to gather detailed and descriptive information. Statistical analysis may not be feasible with such literature, where the body of knowledge is not authoritative or does not cover reliable and rigorous techniques developed and tested over time (Popay, Roberts and Sowden, 2006). The literature may also be too diverse clinically or methodologically to combine in a meta-analysis (CRD, 2009). The narrative synthesis uses text to 'tell a story' (Popay, Roberts and Sowden, 2006) and to analyse the relationships within and between studies and gives an overall assessment of the robustness of the evidence (CRD, 2009). It includes investigation of the similarities and the differences between the findings of different studies, as well as exploration of patterns in the data (Ryan, 2013; Munn, Peters, *et al.*, 2018). Traditionally, systematic reviews have been predominantly conducted to assess the effectiveness of health interventions by critically examining and summarizing the results of randomized controlled trials (RCTs) (Eriksen and Frandsen, 2018; Munn, Stern, *et al.*, 2018) (Miller, 2001). For those studies which are usually quantitative studies, the PICO framework (population, intervention, comparator and outcome) has been used to formulate a robust research question where the terms to be searched are clearly designed (Eriksen and Frandsen, 2018; Munn, Peters, *et al.*, 2018). The PCC (population, concept and context) framework is another framework used primarily for scoping studies where clarification around a concept or theory is required (Munn, Stern, *et al.*, 2018). As this is not a scoping review, the PCC framework was not applicable.

For other studies where the effectiveness of a therapy or intervention is not in question, and especially for qualitative studies, the PICo framework can be applied depending on the research question (Munn, Stern, *et al.*, 2018). PICo covers the population, the phenomenon of Interest and the context (Munn, Stern, *et al.*, 2018). The PICo framework was applied to this research as the best fit.

This systematic review aims to identify existing information about convergence or harmonisation or streamlining of post-approval CMC variations in the LATAM/ASEAN markets in scope and identify any gaps.

The question for the systematic review was, “Is there evidence of harmonisation, convergence or streamlining of post-approval CMC variations in LATAM or ASEAN?”

Therefore PICO applied to the research question, is as follows, highlighting the key concepts (Bramer *et al.*, 2018):

Is there evidence of harmonisation (I), convergence (I) or streamlining (I) of post-approval CMC variations (Co) in LATAM or ASEAN (P)

After applying PICO to the question, the search terms were identified from the research aims and key concepts of the research question (Bramer *et al.*, 2018). The search terms covered: markets under study, terms related to streamlining requirements and terms related to chemistry, manufacturing and control(s).

The following keywords were used as search terms:

Population	Brazil, Argentina, Colombia, Cuba, Mexico, Chile, LATAM, Latin America, Singapore, Thailand, Malaysia, APEC, ASEAN
Phenomenon of Interest	Harmonisation, convergence, streamlining
Context	Chemistry, manufacturing and control(s) CMC, post-approval variations, post-

	approval changes (PACs)
--	----------------------------

Table 2.1 Keywords used for systematic review search

Where applicable, variant forms of the same word (US and UK English), synonyms or alternative spellings were used as well as matching search terms to those included in the database's thesaurus eg. MeSH terms for PUBmed (King's College London, 2017; Bramer *et al.*, 2018)

For the population, the various NRA names and pharma associated networks for the concerned markets were also included to widen the search parameters and ensure retrieval of relevant literature eg APEC, ASEAN, HSA (See Appendix 1 for full list search terms/key words).

2.3.2 Search Strategy

Following the approach of systematic reviews in pharmaceutical research (Johnson and Hennessy, 2019), the following electronic bibliographic databases were searched: Web of Science (all years), Scopus (all years), Medline (Ovid) Pubmed, Embase, SciFinder and ScienceDirect. These databases cover the peer-reviewed literature in this field (Bramer *et al.*, 2018). However, given that many important documents on this subject are not published in peer-reviewed journals, the search was supplemented with a detailed search of Google Scholar and Google (Gehanno, 2013).

Google and Google scholar are considered important sources of grey literature and are widely used in reviews even to retrieve peer-reviewed journals too (Gehanno, Rollin and Darmoni, 2013; Herman, 2015; Bramer, Giustini and Kramer, 2016; Piasecki, Waligora and Dranseika, 2018). Grey literature includes conference papers, industry papers, white papers, online articles, relevant website contents and unpublished theses (Hartling *et al.*, 2017). Even though there are cited downsides of grey literature use in systematic reviews like reduced reproducibility (Paez, 2017), they have been noted to also give a balanced overview of available evidence and reduce publication bias (Paez, 2017; Johnson and Hennessy, 2019) as pertains to this research. Since the initial literature search showed minimal peer-reviewed journals, the grey literature was used to highlight any other information on the phenomenon (Hartling *et al.*, 2017).

This was complemented by a manual search of the following organizational websites: ASEAN and PAHO official websites, including the PANDRH section of the PAHO website

specifically, the EFPIA, FIFARMA, APEC, MERCUSOR and CIRS websites (Stansfield, Dickson and Bangpan, 2016). These organisations interact with the pharmaceutical sector in the regions under study and either liaise with or help shape ongoing discussions on requirements and streamlining of requirements/processes.

A manual search of the bibliographies of retrieved articles was also performed (Vassar 2016, Lange, 2014). The search strings are provided in Appendix 1.

2.3.3 Inclusion / Exclusion Criteria

Inclusion Criteria

The systematic review included drug product CMC variations made on New Chemical Entities of pharmaceutical drugs. No restrictions were applied on the dates to ensure historical and current data were captured; neither were there restrictions on the type of articles, to ensure no information was missed out. All articles, regardless of methodology and language were included. Spanish and Portuguese articles were expected as these are native languages of the LATAM markets.

Exclusion Criteria

It excluded variations on drug substance, generics, biologics, biosimilars, vaccines or medical devices as these were out of scope of the research question.

2.3.4 Data extraction and analysis

To ensure a high rigour of searching Google Scholar, Publish or Perish (Jacsó, 2009) was used to extract peer-reviewed journals, theses and grey literature from Google Scholar, as Google scholar is not capable of exporting results in bulk (Harzing, 2016; Tay, 2022) Publish or Perish is a software program that retrieves and analyses academic citations, presenting metrics such as number of papers on the topic, total citations and the h-index (Harzing, 2016). It also facilitates for identification and removal of duplicates and allows a variety of export options and formats like the comma separated value (CSV) file format which can then be transferred to a software like Microsoft Excel for further sorting (Jacsó,

2009). The researcher is able to select which sections of the articles to be exported, in this case, the title, abstract, author and year of publication (Harzing, 2016). The Software is not without limitations, for instance, articles may be duplicated multiple times and the search results can only display 1000 references (Harzing, 2016). The quality of the search results are only as good as Google Scholar itself. Despite these limitations, the tool is useful in extracting and filtering search results. A known tip used by researchers to overcome the 1000 references limit, is to split the search into batches by publication year. This is a great workaround to the 1000 articles limit (Tay, 2022).

Articles from bibliographic databases were exported into MS Excel with the title, published date, and abstract as the main headings. A comments section was also created for the researcher's remarks. Appendix 2 shows the template used in organising the literature.

The suitability of the retrieved articles was reviewed by the researcher and a supervisor, Fraser Stodart (FS) to verify whether they were applicable or fit the inclusion criteria. The titles and abstracts were assessed first. This first assessment phase excluded any articles that did not fit the inclusion criteria. The remaining articles were read in full to again confirm suitability against the inclusion criteria, quality was also assessed.

Google Translate was used to translate any titles/abstracts in Portuguese and Spanish before determining whether they fit the inclusion criteria or not.

If they fit the inclusion criteria, Google Translate was used to do an initial translation of the introduction, results and conclusion sections to further determine a fit against the inclusion criteria. If further translation proved the article fits the inclusion criteria, the article was translated through a translation agency for a more accurate translation before final suitability was assessed.

Google translate is a free, quick and user-friendly web-based translation engine that is widely used to translate between a variety of languages (Groves and Mundt, 2015; Habeeb, 2020) A downside of the translation engine is its inability to evaluate the context of a stretch of text, hence syntactical errors result (Groves and Mundt, 2015). The goal of the translation engine is not high-quality translation but rather usable translation (Groves and Mundt, 2015) This initial translation suits the purposes of the research since a more accurate translation will be obtained if need be.

A thematic analysis approach was used to identify 'key concepts' (Thomas and Harden, 2008) or themes in addition to the narrative analysis as described earlier (Ryan, 2013). Relevant information about the history and recent status of streamlining activities of CMC variations in the regions was extracted from the articles and used to inform the qualitative case study in Chapters 4 and 5. In addition, the systematic review also generated documents which, where appropriate, were used as secondary data in the research (Chapters 4 and 5). The systematic review report is captured in Chapter 3.

2.4 Qualitative Case Studies – Studies 2 and 3

2.4.1 Research Methods - qualitative case-study methods

Based on the adopted post-positivist approach where an objective stance of the phenomenon is sought through probing stakeholder perceptions to obtain 'thick' insights from a small number of individuals about streamlining of post-approval variation requirements in Latin America and ASEAN; a qualitative method was deemed appropriate.

Qualitative methods are especially appropriate for the research questions because the research area is not well-developed (Sofaer, 1999). In general, qualitative methods are well-suited when broad, open-ended questions are required to generate new theories and hypotheses, whereas quantitative studies are better suited for 'closed-ended' and highly specific theory testing (Haradhan, 2018)

Another advantage of the qualitative method is that it can provide a rich description of complex phenomena and contexts (Sofaer, 1999). This is especially important to understanding differences in regulatory patterns within and across ASEAN and Latin America regions. This approach contrasts with the conventional deductive model; ideas and concepts 'emerge' from the data and can help generate hypotheses and ideas for future inquiry. Thus, qualitative research can help identify patterns in the data for later quantitative testing. Qualitative research has also been used in health services, as well as the social sciences (Murphy *et al.*, 1998).

As with all research, it is important to follow best practices and maintain scientific rigour. Too often qualitative methods are viewed as inherently biased because the results may not seem to be replicable and instead depend on the researcher's skill and own experience (discussed further in the reflexivity section 2.5). However, there are multiple important methods to ensure rigor, objectivity, and replicability in performing qualitative data collection and data analyses ((Roberts, Dowell and Nie, 2019).

First, in all qualitative research, it is important to differentiate participant subjective views from the actual reality. This is done by the researcher through the practice of reflexivity where the researcher notes their experiences and explains how that may influence data collection ensuring objectivity (Olmos-Vega *et al.*, 2023).

Second, detailed recruitment methods and data generation processes must be reported to ensure replicability (Roberts, Dowell and Nie, 2019).

Third, it is important to record, transcribe, and report qualitative data, so that all scientists can observe and question the assumptions and interpretations made ensuring rigor (Roberts, Dowell and Nie, 2019).

The research has multiple stakeholders who all bring their own views to the phenomenon. Each view is essential to understanding or exploring the process, which is unravelling, the phenomenon being a moving target, changing over time in Latin America. Likewise for the ASEAN countries, the researcher is interested in why they did what they did; how they did it and how the outcome is affecting them positively or negatively. Hence the researcher uses individual interviews, questionnaires, group interviews and secondary data to achieve their objectives, all these methods being widely used in qualitative research.

2.4.2 Case Study Design

A qualitative multiple case study best captures the study's design. Qualitative studies are generally inductive in nature (Haradhan, 2018), this study employs an inductive process to generate or discover a theory out of the data, grounded in the view of the participants. The theory developed might help explain practice or provide a framework for further research (Creswell, 2013). This approach is consistent with Glaser and Strauss' version of grounded theory, emphasising a qualitative approach with objectivity (Levers, 2013; Ralph, Birks and Chapman, 2015). Grounded theory is known to be a strong inductive research method for developing new theories; the data collected guides the analysis and theory creation (Delve and Limpaecher, 2021). Grounded theory is used when there is no existing theory that offers an explanation for the phenomenon under study. It can also be used when there is an existing but incomplete theory as the data used to derive that theory was collected from participants other than the ones being studied (Delve and Limpaecher, 2021). Inductive research approaches data collection and data analysis processes from a discovery-oriented standpoint, as opposed to beginning research with the goal of proving

or disproving a particular hypothesis or set of hypotheses (Cooper, Chenail and Fleming, 2012). The latter is the case in deductive research, that is using existing theories to generate hypotheses, and then test them empirically to prove or disprove that hypothesis (Cullen and Brennan, 2021).

Case studies utilising grounded theory where theories are generated within the case study, is not a new approach (Fernandez and Lehmann, 2011). The case study approach concerns an understanding of *how* and *why* something may have happened or why it might be the case. Case studies understand the phenomenon's true meaning within its contemporary real-life context (Yin, 2018). The assumption in a case study is that with a great deal of intricate study, looking at the subject from many and varied angles one can get closer to the why and the how. Researchers using case studies need to look at their subjects from many and varied angles. In looking from several directions, a more rounded, richer, more balanced picture of the subject is developed (Thomas, 2019). A three-dimensional view is observed and appreciated. It's a means of getting "close to reality" as described by (Flyvbjerg, 2001). Case studies therefore help to corroborate findings with multiple sources of evidence. This is what this study aims to do, taking a view of the phenomenon from as many angles as practically possible to gain an overall picture. The research therefore uses different stakeholder groups and different methods for collecting data (interviews, questionnaires and secondary data).

Case Studies need to have a defined boundary clearly identified from its context as stated by Yin (Yin, 2018). The case in this study is the 'process' by which or through which the streamlining of CMC variations will occur or have occurred in LATAM and ASEAN respectively. This will be observed through interviews, questionnaires, and the use of secondary data (discussed in section 2.4.3.3). The boundary is the selected markets within the region, the chosen LATAM markets being National Regional markets of reference (NRAR) as defined by PANDRH, i.e. seen to be the more mature regulatory markets in the region. The three ASEAN markets are also acknowledged to be the more mature regulatory markets in their region. The study employs a multiple case approach (based on differences) where there are two cases, the Latin America process and the ASEAN process. The two cases will be compared to find similarities and/or differences which could be applied to other settings.

Multiple case studies are preferred over single case studies as they help minimize observer biases, enhances validity and increases confidence in findings (Yin, 2018). The goal of a multiple case study is to predict similarities or contrasting differences in order to

replicate findings across cases, which is one of the aims of this study (Yin, 2018; Saunders, Lewis and Thornhill, 2019).

From the ASEAN perspective, the case will look at the process by which they arrived at their common set of CMC requirements. How did they do it? How did they agree? What was their basis? The researcher would like to understand better how ASEAN arrived at their decision and how they went about it. Hence it will involve exploring all avenues of the process from different stakeholder perspectives.

In terms of differences, the ASEAN is in a different region with different cultural and political contexts when compared to Latin America. The ASEAN process has a documented level of success in harmonised requirements using the ACTR guidance as a basis across the ASEAN region. In Latin America however, it is not clear whether the streamlining process is a priority, and if it is whether harmonisation or convergence is the process, hence this study. By studying the ASEAN process the researcher seeks to uncover characteristics or theories that can possibly be applied to Latin America or that can act as learnings for the Latin America region.

Figure 2.1 shows an overview of the case study with the various components.

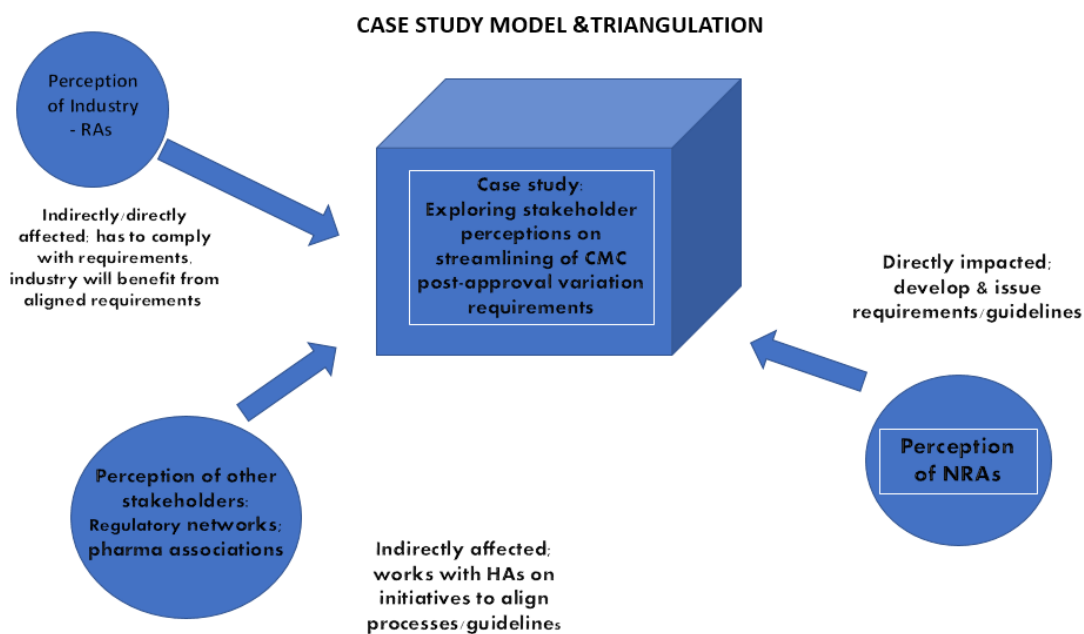


Figure 2.1 Diagram showing the components of the intended Case Study

The weakness or limitation of a case study design is the inability to generalise statistically from one or a small number of cases (Choy, 2014). This is not an issue for this research as

the research does not seek to generalise since the LATAM markets under investigation are all NRAs with mature Health Agencies compared to the rest of the LATAM region. In other words, generalisability of case studies could have been increased by the strategic selection of cases (Seawright and Gerring, 2008). The results however could act as a basis for further studies on streamlining of CMC variations within the LATAM region in particular.

Other designs like phenomenology, ethnography, and action research were ruled out for the below reasons:

Phenomenology deals with exploring 'lived experiences' of participants, drawing participants views together to explain a 'shared experience (Kumar, 2014). 'This research is not a phenomenological one as it is not studying a "shared or lived experience" but rather trying to understand participants' understanding of a process which is external to them but one they are observing unfold as they work in that environment. The phenomena being studied is the streamlining of the CMC requirements - participants are giving their views on which direction the process of streamlining could head in, based on their experience working directly or indirectly with the NRAs. The phenomenon being observed is not static but has the tendency to evolve over time, hence experiences may change.

Action research is a means to improve or take action to deal with a problem or issue (Kumar, 2014) and would fit with the critical realism paradigm. The researcher normally initiates an action based on theory, such as a process/technology in response to real problems to cause a desired change. The researcher then observes the results of that action, modifying if necessary; while learning from the action and generating theoretical insights about the target problem and intervention (Bhattacharjee, 2012). This research study is not action research as the researcher is not initiating an action themselves to cause a desired change, however, the researcher seeks to encourage an action by the NRAs in the streamlining of their CMC variations. The NRAs may or may not implement any recommended changes; and the change depends on which direction the streamlining process will head - either convergence or harmonisation.

With Ethnography research, the researcher immerses themselves in a group for an extended period of time, to observe, listen to conversations between others and themselves, ask questions, take copious field notes then writes up a detailed account of what they have observed or experienced (Bryman, 2016). Since the process of streamlining variations cannot be observed through immersing oneself, but mainly

understood through stakeholder perceptions, this paradigm could not fit the research objectives.

Figure 2.2 highlights the overall rationale, methodology and methods chosen for the study.

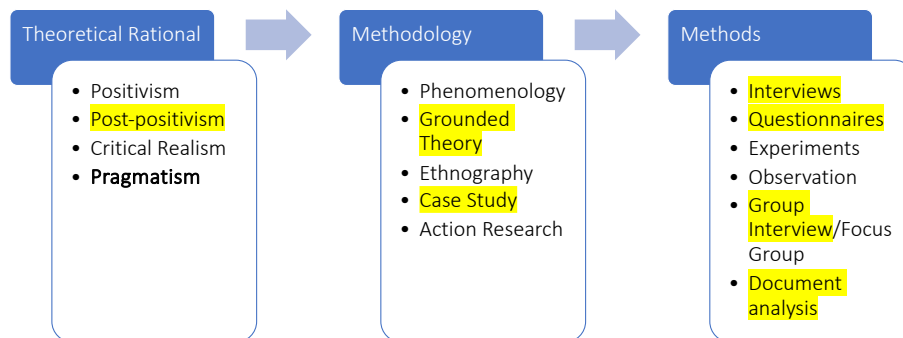


Figure 2.2 The rationale, methodology and methods chosen for the study

Source: adapted from (Crotty, 1998)

2.4.3 Choice of Research Methods used

The types of data collection used for scientific research include primary and secondary data. This research study used both; the secondary data aiming to complement the primary data and strengthen the case study by providing holistic information from multiple angles of the phenomenon. Secondary data can help discover relationships not observed in the primary data. It also gives access to data otherwise impossible for a single researcher to collect in the same scale and scope and time frame of the research (Arzuaga Palomino, 2014).

Secondary data comprises documents available in the public domain or from confidential sources and government guidelines/reports. It is data not collected by the researcher (Arzuaga Palomino, 2014). Primary data collection can occur through interviews, focus groups/group interviews, questionnaires, observations. This research study used semi-structured individual and group interviews, questionnaires and secondary data (document

analysis) for the reasons described below. Also highlighted are the strengths and weaknesses of these methods in relation to the study.

2.4.3.1 Interviews

Qualitative research commonly uses interviews as a method for data collection (Bryman, 2016). Interviews were used in this study for their ability to gather rich and detailed data about stakeholder experiences (Nyanchoka *et al.*, 2019); the ability to probe further and adapt questions as interviews progress (Rubin and Rubin, 2005). Whilst post-positivists do not normally use interviews in isolation, it was appropriate for this research as the topic required participants to be clarified and be probed in more detail than a more quantitative method would allow (Rubin and Rubin, 2005).

Participants had the choice of Face-to-face; online audio-visual or online audio only interviews depending on individual circumstances and location. Participants also had the option of responding to questions by email. The reasons are outlined below.

Individual Interviews

Individual Interviews enabled the researcher to explore each participant's views about the streamlining process, by giving them a voice as well as confirming information shared by other participants (Fox, 2009). With Individual interviews participants have more time to share their views as opposed to group interviews, and also share more openly as no one else is present apart from the researcher (Nyanchoka *et al.*, 2019).

Some potential disadvantages of individual interviews are that personal bias and poor interviewing skills may distort data, they could be expensive or impractical if done face-to-face; data may not be generalisable depending on sample size and it is sometimes difficult to obtain 'experts' or Subject Matter Experts (SMEs) for focused interviews due to its time-consuming nature (Bryman, 2016).

The researcher considered whether to do unstructured, semi-structured or highly structured interviews, ultimately proceeding with a semi-structured approach. First, unstructured interviewing was not a good fit as the necessary data may not have been generated as participants could go 'off topic' as questions are generally formulated as the interview progresses, based on a general topic (Rubin and Rubin, 2005). Highly structured interviews by their design, may not allow participants to truly express their views or give room for expansion or clarification hence valuable data could be missed. Semi-structured interviews allowed for a good mix of open-ended and closed questions. Open-ended

questions provided participants the flexibility to share their experiences. Closed questions restricted participants to choices given in the question and were used mainly to start off and ease into the interview.

Group Interviews

Although individual interviews were the preferred method of data collection, it was recognised that logistically this could be challenging, and the researcher may need to act opportunistically depending on participant availability and preference. For this reason, group interviews would also be used, for example where the participants found it more convenient and could agree on a set time for all of them to be present. In group interviews, the researcher interacts with each individual in the group and occasionally checks the level of consensus in the group (Brown and Edmunds, 2010). This mode of interviewing is necessary for research when the researcher has specific questions that need answering whilst still allowing for some flexibility in the experiences participants shared. The researcher guides the discussions.

Focus groups however are types of group interviews where the emphasis is on participants interacting with each other so the resulting response is a varied view (Brown and Edmunds, 2010). The discussion must develop among the participants, with as little intervention from the moderator as possible - the aim is not necessarily to reach consensus within the group (Brown and Edmunds, 2010). The researcher is more of a facilitator encouraging the discussion amongst participants rather than an interviewer asking questions (NSW, 2021). Focus groups encourage homogenous groups where level of expertise and status are similar; focus groups may or may not be naturally constituted (Leask, Hawe and Chapman, 2001; Onwuegbuzie *et al.*, 2009). For this research, the intended participants in the group are work colleagues in the same organisation and not ad hoc participants therefore making the group homogeneous and naturally constituted. Rapport will be easily established making it easier for the group to share opinions. (Acocella, 2012). Group interviews are a way to gather many opinions from individuals within a group setting but are largely didactic between an interviewer and each individual in the group (Coe and Waring, 2021). Focus groups, however, are interactive, the group opinion is as important as the individual opinion, and the group itself may take on a life of its own not anticipated or initiated by the researcher (Coe and Waring, 2021).

The group interview is therefore more suited than focus groups the research because the researcher aims to guide the discussions by asking specific questions about the streamlining process, producing individual responses and reaching a consensus. The interaction desired is between the moderator and the participants, not amongst the participants which could yield non-specific information in relation to the research question. Figure 2.3 provides a pictorial representation of the group interview versus the focus group.

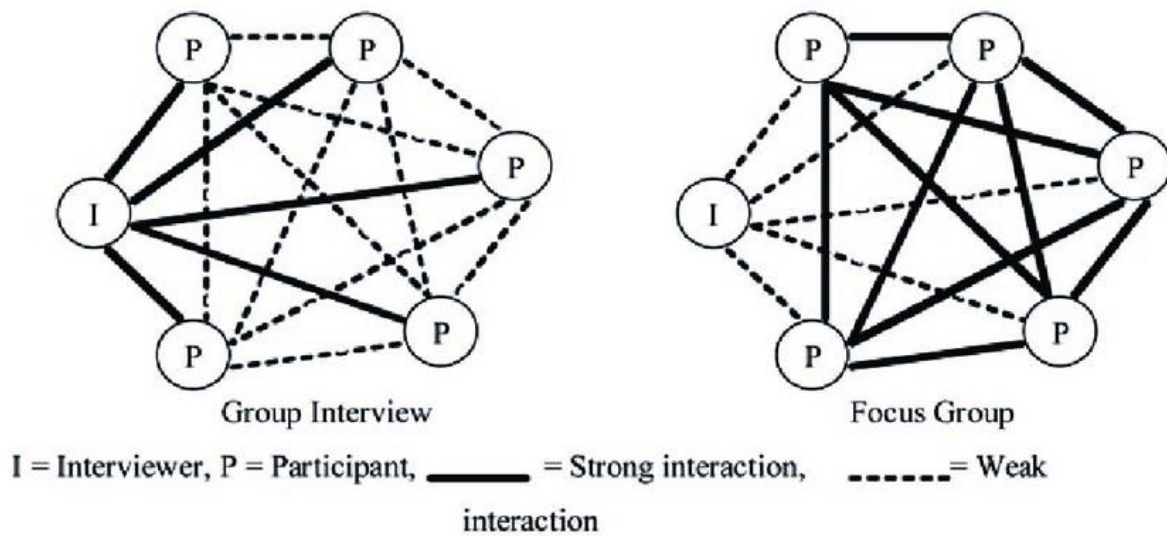


Figure 2.3 Diagram showing the difference between Group Interviews and Focus Groups
Adopted from Brown & Edmunds, 2000

Face-to-face

This is normally the most frequently used format as it allows for easier rapport building and enables attention to non-verbal behaviour (Shapka *et al.*, 2016). It is also preferred when the subject matter is very sensitive. They can however be time-consuming and expensive if researcher has to travel to participants (Saarijärvi and Bratt, 2021a). For this study, face-to-face interviews occurred only where participants were readily and conveniently accessible to the researcher (Fox, 2009). Given the geographical spread of participants due to the global nature of the research topic, in most cases, face-to-face interviews were not possible.

Online

Online interviewing can mean web chatting or instant messaging, (Bowden and Galindo-Gonzalez, 2015) (Shapka *et al.*, 2016) or video conferencing via the use of Voice over Internet Protocol (VoIP)-mediated technology (VoIP) like Zoom, Skype, Microsoft Teams.

The use of VoIP enables researchers to conduct audio-visual calls in order to get as close a feel to a face-to-face interviewing as possible. This method has the ability to engage individual as well as multiple stakeholder groups and communicate with geographically dispersed individuals in contexts with limited resources (Saarijärvi and Bratt, 2021a). It is also convenient, efficient, cost-effective, and flexible (Archibald *et al.*, 2019). Another advantage is the ease of transcription as these VoIPs can sometimes automatically transcribe the interviews, although the transcription quality would need to be reviewed.

The advantages of using Zoom specifically are reliability, effectiveness, convenience and its user-friendliness as observed by other researchers (Sah, Singh and Sah, 2020; Allen, 2023). It allows for participants to share online documents which was required in this study and has the feel of a face-to-face interview, meaning rapport can be as easily established. Microsoft Teams has similar functionalities and advantages as Zoom (Sah, Singh and Sah, 2020). One disadvantage observed with Microsoft Teams was the need to record to the cloud before downloading to a secured folder on a computer. Zoom allows for recording directly to a secured folder even though the option to record to the cloud is also available. Zoom has also been known to provide better video quality than Microsoft Teams (Allen, 2023).

Skype, although having similar functionalities as Zoom and Microsoft Teams has been known to have breaks in connection whilst using it (Archibald 2019). Others have found it less user-friendly as it requires one to login with passwords unlike Zoom and Microsoft Teams (Archibald *et al.*, 2019)

The choice of this method was due to the geographical location of the participants (mainly in Latin America, Asia, or within the UK not local to the researcher as anticipated by the researcher), also real time interaction (Sah, Singh and Sah, 2020).

As some interviews were also conducted during the Covid pandemic, online interviewing was practical, safer and more effective than having to employ face-to-face interviewing.

Some challenges that have been reported with Voice over Internet Protocol (VoIPs) include dropped calls and pauses, poor audio or video quality, and the inability to read nonverbal cues because of inconsistent and delayed connectivity; challenges in connectivity or poor audio/visual feed being down to poor internet connectivity or low bandwidth or lack of internet services completely (Archibald *et al.*, 2019). Other downsides could be non-familiarity with the software; training could alleviate that issue (Archibald *et al.*, 2019).

Despite these disadvantages, the use of online interviewing was still one of the best methods of data collection for this study due to the geographical location of the participants and its practicality, flexibility and convenience especially for participants.

Email interviews

Even though email interviews eliminate the boundaries of time and space, are not expensive and prioritize the participant's comfortability, they have many disadvantages.(Shapka *et al.*, 2016). There could be delays in receiving responses, the responses can be more reflexive and not reveal as much or the real intent of the participant, establishing rapport is not easier than face to face, the person responding may not be the intended participant (Shapka *et al.*, 2016). In this research, use of email interviews was justified only where face to face interviews were not appropriate due to geographical location, or online interviewing was not possible due to connectivity issues or to clarify comments given during an online interview. Email interviewing can be synchronous or asynchronous, it also allows for follow-up questions (Amri, Angelakis and Logan, 2021).

Telephone

Telephone interviewing is known to be costly moreover, the interactivity and personal feel from the lack of visual expressions experienced through the online platform or face to face interactions are lost (Fox, 2009). The length of a telephone interview may also be limited. (Bowden and Galindo-Gonzalez, 2015). Telephone interviewing was not suitable for this research due to the cost involved and its inflexible nature.

So in summary, it was decided the preferred approach was online individual semi-structured interviews using Zoom/MS Teams. However, where participant availability or preference dictated, face-to-face, group interviews or email interviews might also be used.

2.4.3.2 Questionnaires

As mentioned with interviews, sometimes a downside is not being able to use it on Subject Matter Experts (SMEs) due to their time-consuming nature because of the conversational nature of interviews, whether face to face or online (Kuter and Yilmaz, 2001). The qualitative questionnaire however, allows participants to express their ideas, experience or behaviour on their own terms, but, at the same time, within a format that facilitates or guides the process of data analysis (Kuter and Yilmaz, 2001). Questionnaires are generally filled out as a one off event and the researcher does not have the opportunity for follow-up questions if responses are not clear or questions are omitted (unlike email interviews), which can be a disadvantage of this method (Kuter and Yilmaz, 2001)

Traditional postal questionnaires were not suitable for this research because responses can take longer or get lost in the post; responses can get buried in junk mail; response rates may be low as there is no way of guaranteeing that the participant received the questionnaire; it requires follow up to obtain responses (Diem, 2002).

Online questionnaires are known for their ease of facilitation, quick responses are possible; the ability to gather information from participants in remote locations; ease of readability as responses are obtained electronically so handwriting is not a problem (Rowley, 2014). When English is a second language for participants they have more time to reflect on questions and responses. They are also easily accessed geographically and take less time to fill in compared to interviews which was essential for the specific participant group it was used for in the research (Diem, 2002).

A disadvantage of online questionnaires is that participants must have access to the internet. Generally, questionnaires can fail because participants don't understand them, cannot complete them, get bored or offended by them, or dislike how they look (presentation or structure) (Boynton, 2004). However this was unlikely to be an issue for this group of participants because their work involves using such questionnaires from time to time.

The researcher therefore opted for the online qualitative questionnaire tool as they are a useful precursor for follow-on interviews or focus groups as they help identify initial themes or issues to then explore further in the interview (Diem, 2002; Seixas, Smith and Mitton, 2018).

The research utilised mainly online interviewing and online questionnaires; face-to-face and email interviewing where used where appropriate.

2.4.3.3 Secondary data - Existing documents and records

Secondary Data refers to data collected by someone else for other purposes and use (Cheong *et al.*, 2023) They are documents and records available in the public domain (e.g. libraries, the internet, public archives), obtainable without the authors permission. Other times they can be obtained from confidential sources such as government agencies or individuals (e.g. letters and diaries) by requesting and gaining approval to access them (Cheong *et al.*, 2023). They are less costly and less time-consuming (data selection not collection) than other forms of research methods. (Bowen, 2009).

Secondary data gives access to data otherwise impossible for a single researcher to collect in the same scale and scope. It is possible to uncover relationships that were not observed before or observed from the primary data (Arzuaga Palomino, 2014).

Secondary data is known to be used commonly in case studies as a way of data triangulation – ‘the combination of methodologies in the study of the same phenomenon (Bowen, 2009). By examining information collected through different methods (in this research, interviews, secondary data and questionnaires), the researcher seeks to corroborate findings across data sets and thus reduce potential biases that can exist in a single study whilst also increasing the credibility of the information (Bowen, 2009).

Moreover, documents of all types can help the researcher uncover meaning, develop understanding and discover insights relevant to the research (Bowen, 2009). Secondary data can be either printed or electronic material, including but not limited to:

advertisements, agendas, meeting minutes, diaries and journals, books and brochures, organisational or institutional reports and public reports. They can be found in libraries, newspaper archives, historical offices and organisations or institutional files (Bowen, 2009).

They are devoid of the researcher’s influence and thus any researcher bias, however, the validity and credibility of secondary documents cannot always be verified (Bowen, 2009).

For example, the quality of the data could be questioned because of insufficient knowledge on how rigorous the original research design and collection processes were (Intellspot, 2024). It may sometimes be impossible to assess bias (Arzuaga Palomino, 2014). Further disadvantages include that they are not always suited to the exact research questions, they may not have sufficient details or they may not always be retrievable (Bowen, 2009).

Despite these limitations, the documents can still provide a historical background to the streamlining processes to be studied as well as give insight into key decisions behind the processes.

In this research, the secondary documents most likely to be relevant included pharma association reports, white papers, position papers and NRA regulatory requirements of the various CMC variations.

2.5 Reflexivity

For research that carries a social component, the researcher is immersed in the social world of its participants and their views, however, the researcher brings along their own beliefs and assumptions which to an extent can bear on the knowledge that is generated. By practicing reflexivity, the researcher can become aware and alleviate some of the biases though not totally all (Saunders, Lewis and Thornhill, 2019). Reflexivity is the awareness of the researcher's role in the practice of research, enabling the researcher to acknowledge the way they affect both the research process and outcomes (Haynes, 2012). The researcher reflects on how their values, ideologies and various assumptions affect the interpretation of the data collected (Haynes, 2012). The researcher needs to develop the skills of reflexivity which means asking themselves questions about their beliefs and assumptions and treating these with the same scrutiny as they would apply to the beliefs of others (Saunders, Lewis and Thornhill, 2019). Since this study is based on a post-positivist paradigm, reflexivity as mentioned previously can help situate the researcher's bias to help them be as objective as practically possible.

Here, the researcher would like to provide insight into their world which inevitably acts as a lens through which the study is conducted and may impose some bias or affect the data collection and analysis. The researcher is a Regulatory Affairs professional with 15 years' experience. They have worked with CROs, large and small sized pharmaceutical

companies mainly dealing with small molecules but not generics or biological and veterinary medicines or vaccines. They have a few months' experience in medical devices. The researcher has not had direct contact with any NRAs but has always worked through local agents or local operating offices of the pharmaceutical company.

The researcher's main expertise is in emerging or international markets in regulatory strategy, filing of MAAs, renewals and life cycle maintenance (labelling & CMC updates). The researcher does not consider themselves an expert in the CMC section of the dossier and relies heavily on the CMC expertise from participants to interpret requirements and provide input based on their experience. The researcher has worked extensively with Latin America and ASEAN markets over the course of their career and hence is familiar with the general regulatory landscape in those regions. This familiarity with the general landscape is one of the main reasons why the researcher chose this topic. The researcher had been aware of streamlining activities in other regions especially in requirements for new marketing authorisations, however, within Latin America and within the CMC sphere, they had not yet encountered anything, hence the interest arose to explore this topic in further detail.

The researcher may personally know some of the participants, in particular regulatory affairs professionals (RA). The researcher acknowledges that responses from the known participants could be different if they were interviewed by someone unknown to them (Quinney, Dwyer and Chapman, 2016). This awareness caused the researcher to remain constantly reflexive throughout the research (Quinney, Dwyer and Chapman, 2016) as a means to manage this potential bias. However, knowing some of the participants can be seen as positive as there is already a level of trust and rapport built before the interviews, which makes the participant more comfortable (Quinney, Dwyer and Chapman, 2016). Also there is a joint sharing of pre-existing knowledge and a common language which helps with knowledge sharing (Shenton, 2004; Quinney, Dwyer and Chapman, 2016). In order to reduce further bias and curtail any influence on the research, a reflective diary was kept by the researcher to document the researcher's thoughts and feelings after interaction with each participant for the interviews and after going over the video/audio recordings again (Haynes, 2012). This allowed the researcher to 'see' the participant responses for what they were and not be tainted by their own thoughts or feelings. In this way, the reflexive diary was used to enhance the trustworthiness of the data (Nadin and Cassell, 2006). It was also used to identify common themes as the interviews progressed, allowing the researcher to highlight interesting aspects of the data, acting as a source of

notes about interpretations and questions about the data (Strauss and Corbin, 1998; Nadin and Cassell, 2006). Participants were informed about the diary and made aware that the purpose of the diary was for self-reflection and interview skills development (Hubbs and Brand, 2005)

2.6 Research Design

2.6.1 Overview of research design

A case study approach through which the opinions of a number of stakeholder groups were explored through individual/group interviews and questionnaires was used. In addition, secondary data (document analysis) was used to explore the research questions further, as a means of data triangulation. This added rigour to the research process (Anderson, 2010). The overall research design is shown in Figure 2.4.

Overall Study Design

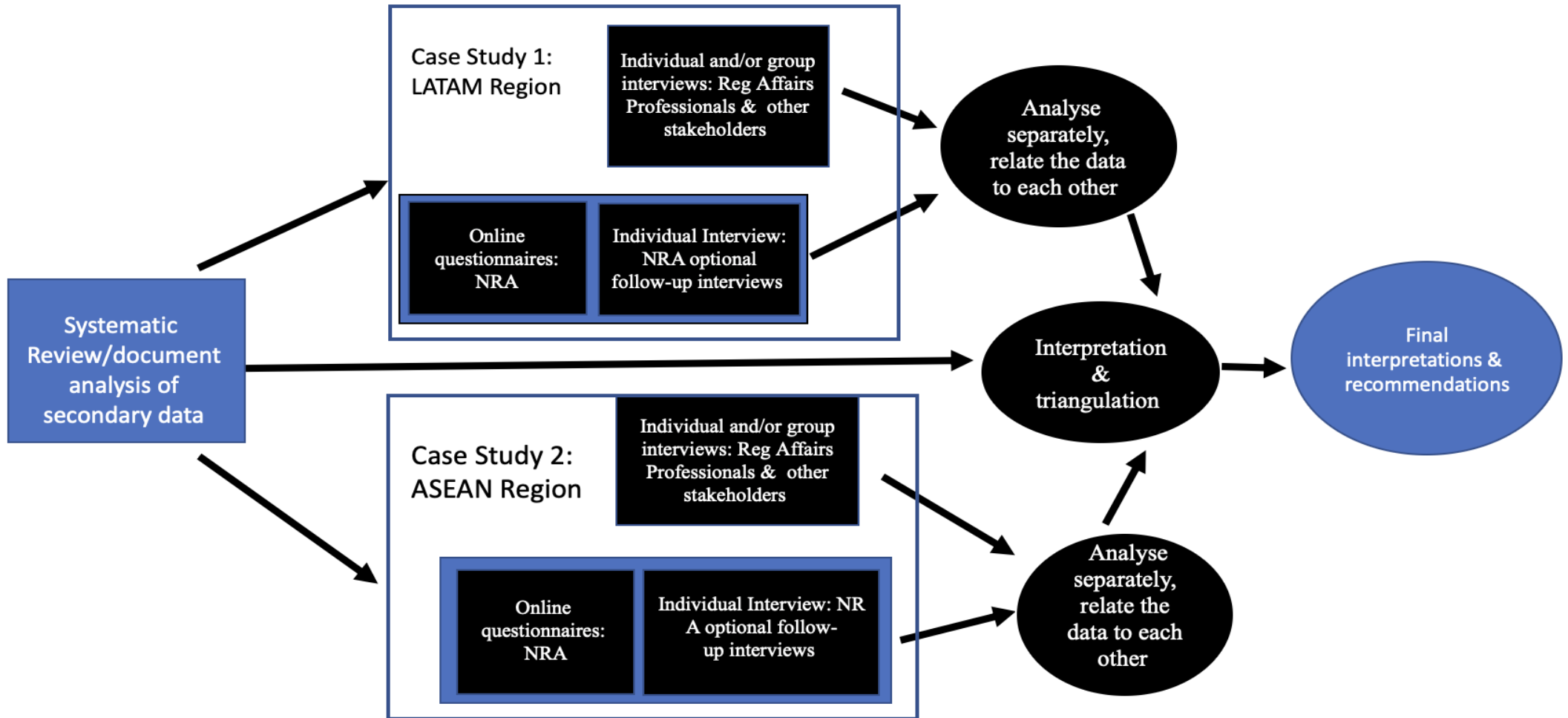


Figure 2.4 Steps in the overall research design

2.7 Recruitment Strategy (population recruitment, sampling)

To develop a comprehensive picture of the perceived streamlining process in LATAM and how harmonisation occurred in ASEAN, the researcher recruited stakeholders who could speak to the multiple facets of the unravelling streamlining process (Shenton, 2004). This included regulatory affairs professionals from pharmaceutical companies, consultancies or independent practitioners (RA); NRA personnel with CMC background and personnel from Harmonisation Networks or Pharmaceutical associations (other).

This was done through purposive sampling, where participants are selected according to predetermined criteria relevant to a particular research objective (Guest, Bunce and Johnson, 2006). Snowballing and opportunistic sampling were also employed.

Snowballing is a recruitment technique where research participants are asked to assist researchers in identifying other potential subjects (Dragan and Isaic-Maniu, 2013). It allows participants to use their networks to suggest potential interviewees and is often used to recruit hard-to-reach populations (Dragan and Isaic-Maniu, 2013; Naderifar, Goli and Ghaljaei, 2017). Opportunistic or emergent sampling occurs when the researcher makes sampling decisions during the process of collecting data (Cohen and Crabtree, 2006). As the researcher gains more knowledge of the phenomenon, they can make sampling decisions that take advantage of events, as they unfold (Cohen and Crabtree, 2006)

Alternative approaches were used to recruit interviewees for each group:

- A. Regulatory Affairs professionals
- B. NRA personnel
- C. Other associations/networks (PAHO/EFPIA/FIFARMA/ASEAN/MERCUSOR)

A consistent set of inclusion and exclusion criteria were applied as follows:

Inclusion criteria

The study required regulatory affairs professionals (RAs) with experience working with the specified markets and/or CMC variations related to the drug product of small molecules or professionals in policy and intelligence. Similarly, regulatory professionals involved with pharmaceutical trade associations or regulatory network/harmonisation bodies were also required.

NRA personnel involved in the review of CMC post-approval variations; involved in harmonisation initiatives or discussions or involved in policy & intelligence.

Exclusion criteria

Data related to API CMC variation requirements or RAs with experience in generics, vaccines, biologics, medical devices, veterinary medicine were excluded from the study.

2.7.1 Sample Size

The sample size for each group differed, as explained below. In general, the researcher sought to achieve thematic saturation whereby additional data did not lead to any new emergent themes or the data produced little or no new information to address the research question (Guest, Namey Emily and Chen, 2020). Data saturation was also observed through the diversity of experience of the RA participants within the same settings; yet the responses could be generalised i.e. they were coming from different experiences but shared the same insight or similar themes emerged (Guest, Namey Emily and Chen, 2020). Hence, for the RAs, the sample size depended on how many participants were needed or could be recruited until no new themes emerged from the data i.e. saturation. The NRA participant and other participant group, are highly skilled professionals with specialist knowledge in their field hence the sample size is drastically reduced as there is a limited number of these knowledgeable experts, especially in the NRAs (von Soest, 2022). These professionals are generally very busy and are hard to access (Littig and Pochhacker, 2014; von Soest, 2022). Due to their speciality and scarcity, having access to more than one participant is not always feasible, as is the case with this research. The aim of these interviews therefore was to collect 'full and rich accounts' (Rubin and Rubin, 2005; McGrath, Palmgren and Liljedahl, 2019; Saunders, Lewis and Thornhill, 2019) and not to achieve data saturation. Rather, the concept of 'information power' can be applied to the NRA participant group (Malterud, Siersma and Guassora, 2016). This concept means that the more information the sample holds relative for the research, the lower number of participants is needed and ultimately explains that a low sample size does not mean inferior information (Malterud, Siersma and Guassora, 2016). The perspectives of these groups may or may not align with the RA perspectives as the RAs are providing their perspectives based on personal experience. The OEs/NRAs may agree or disagree with those perspectives. However, in order to answer the research question, analysis from both points of view is required to obtain a balanced response to the research question.

2.7.2 Recruitment of Regulatory Affairs professionals

To recruit participants in regulatory affairs (RA), the researcher advertised on their personal LinkedIn page and other regulatory affairs associated pages (see Appendix 3); Facebook and through channels like The Organisation of Professionals in Regulatory Affairs (TOPRA) and their personal networks, using the research advertisement (Appendix 4). To maximise participants, the advert was posted at differing time points throughout the day, both morning and evenings, as well as repeated advertisements three to four times during the recruitment stage to promote greater numbers of responses. Potential participants either contacted the researcher directly through direct messages or left a comment on the advertisements indicating interest in participating. The Supervisory team was also used to access participants via their networks (snowballing).

The potential interviewees were screened for inclusion in two stages. First, the researcher emailed all who expressed interest asking if they had experience in CMC or regional/market expertise for LATAM or ASEAN covering the specific markets under study- Malaysia Thailand and Singapore for ASEAN and the 6 markets for LATAM.

Snowballing was used to recruit other regulatory affairs professionals and professionals from other harmonisation networks or pharmaceutical associations. Interviewees at the end of the interviews were asked to recommend other individuals who would wish to participate in the research (snowballing); either by providing email addresses (with permission from the individual) or for individuals to get in contact with the researcher directly (by email) (Salganik and Heckathorn, 2004). Interviewees were encouraged to share the information sheet to these new individuals as a way of introducing the research and enabling individuals to understand their role in the interviews. The information sheet was reshared to the individuals when they agreed to participate and be interviewed as per the research process.

While at the outset the researcher did not have a prespecified number of interviewees as an objective target, they did seek to surpass 12 interviews which was a threshold suggested by Guest and colleagues as the minimum required for data saturation (Guest, Namey Emily and Chen, 2020). Others suggested numbers needed to be ≥ 18 for single case studies (Yin, 2018). In practice, recruitment continued, and interviews conducted till

interviews no longer provided additional relevant information (i.e. saturation) (Negrin *et al.*, 2022).

As part of the recruitment process, it was important to obtain informed written consent. The included participants were emailed the information sheet (Appendix 5) and informed consent form (Appendix 6) plus the Zoom link within 1 week of initial contact. Participants were advised to read the information sheet and email if they had any questions. Informed consent forms were returned (via email) before the scheduled date of the interview. Before interviews started, the researcher went through the information sheet, participants were also informed about confidentiality, who would have access to the data and how data would be used (Brinkmann and Kvale, 2015). Participants were given the opportunity to refuse to participate and also to withdraw at any time without the need for explanation.

Participants were also encouraged to check that the Zoom function worked well, as the software had to be downloaded prior to use. For users of Microsoft Teams, a meeting invite was sent via Microsoft Calendar to participants within 1 week of contact. An email reminder was sent out to each participant before the scheduled date and time.

2.7.3 Recruitment of NRA personnel

Recruitment of NRA personnel took a different approach from the RAs. Since this group involved high level government officials, the chances of recruitment directly via social media was very low. Alternatively, the researcher applied direct contact via the official NRA websites; use of snow balling (via RA participants); direct LinkedIn messaging and use of gatekeepers. This recruitment happened in parallel to the recruitment of the RAs

Use of Gatekeepers

Gatekeepers are people who have administrative positions, or in-depth information about a particular setting and can be helpful, if not crucial, to gain access to a particular community or setting (Rugkåsa and Canvin, 2011). The gatekeepers were from the Centre for Innovation of Regulatory Science (CIRS) organisation, though one gatekeeper had recently retired from the organisation. The CIRS was introduced to the researcher through TOPRA, Cardiff University and external supervisor. The researcher reached out to one gatekeeper (CIRS retired) and the external supervisor reached out to the other

gatekeeper, this was done through a recruitment email (gatekeeper letter), which included information about the research and the roles of the gatekeeper for the research study (Appendix 7). Gatekeepers upon their agreement to participate, were also provided with the following for the recruitment of NRA participants: NRA-specific participant information sheets (Appendix 11); NRA recruitment email (Appendix 8) to send to potential participants and an NRA recruitment follow up email (Appendix 8.1).

The gatekeepers voluntarily reached out to the various NRAs through their organisational and personal networks. One gatekeeper reached out to the LATAM NRAs and the other reached out to the ASEAN NRAs.

The Gatekeepers' NRA recruitment email (Appendix 8), provided by the researcher, also contained a link to an online questionnaire which was region-specific (Appendix 9 and 10). Their main role was to pass on the online questionnaire and information sheet to their contacts within those agencies. They were also asked to send a reminder to their contacts, 2 weeks after initial contact (Appendix 8.1). The researcher was not copied in on correspondence however gatekeepers informed the researcher/external supervisor once the messages had been sent to the NRA contacts. Gatekeepers were reminded of participants' right to confidentiality and anonymity. They were reminded that participation in the study was voluntary (i.e. no coercion should be used) and participants were able to withdraw at any point before or during the research (Dahlke and Stahlke, 2020).

2.7.4 Recruitment of others

A group of individuals representing the Latin American Federation of the Pharmaceutical Industry (FIFARMA) were invited to participate in the research via opportunistic and snowball sampling for a group interview, due to their availability and ease of access (Coe and Waring, 2021). The individual participants had varied levels of expertise and knowledge on the phenomenon in relation to their role with FIFARMA. This was useful as the group could provide rich and varied information about the phenomenon (Kirchherr and Charles, 2018). Snowballing and purposive sampling through RAs and the researcher's external supervisor was employed to reach out to individuals with direct experience of PAHO, MERCOSUR and EFPIA.

2.8 Data collection and analysis

2.8.1 Data collection from RAs: Individual Interviews

Development of Interview Schedule

Interview schedules for LATAM and ASEAN RAs were developed separately based on the research questions. The questions were well planned with the aim of building rapport at the start of the interview hence the guide started with questions about themselves and the participant's experience in the field (Rubin and Rubin, 2005). The questions were organised so they flowed logically, clustered per topics. The schedules included opening and closing questions (Rubin and Rubin, 2005). The questions were reviewed by checking the questions against the intended purpose – did they answer the research question?

The interview schedule (Appendix 12) had a set list of questions and started off with personal questions which were easy to start off with, asking about the participant's career, level and area of expertise. It then moved on to ask of their experience within the region they responded to (LATAM or ASEAN) and the specific markets/NRAs they had experience with. The next section asked for their views on the specific CMC requirements for the chosen variations. The next section focused on their views on harmonisation or convergence within the region or the specific market they had experience in. Open-ended questions allowed participants to describe their unique experiences (Patton, 2014).

The guide was piloted by testing it out on the researcher's external supervisor, (Fraser Stodart), who has experience in the field of regulatory affairs. This was done to test the clarity of questions, whether the questions would illicit the right responses, whether the order of questions flowed logically. Responses to this pilot helped to adapt and refine the initial schedule as well as included with the LATAM results.

The interview schedule also evolved during the interviews to ensure that new areas of questioning not thought of originally were captured and posed to subsequent participants (Braun and Clarke, 2013).

Online Interview Setting

Audio-visual or audio-only interviews were conducted via Zoom or Microsoft Teams within a week or two of participants responding as per their preferred schedules. Online interviews were advantageous due to the geographical location of participants who were mainly based in Latin America or Asia. For convenience, participants based in the UK

were also interviewed online, although where geographically possible, and at the participant's request, there was an option of a face-to-face interview.

It was anticipated that online interviews would not diminish the quality of the interview process. Indeed, during the Covid pandemic, Zoom was reported to be one of the most used online platforms for companies, educational settings, government agencies and in research (Boland *et al.*, 2022). Consumer research also identified ease of access and careful work to keep latency below 150 milliseconds (the maximum time before conversations start to feel unnatural) being cited as potential reasons for the use of Zoom during the pandemic (Mansoor, 2022)

Participants who could not take part in the interviews due to unavailability or poor internet connectivity were provided the Interview questions by email and invited to respond by email. Responses were at their convenience but within a timeframe of 2 weeks to ensure the researcher met their timelines for the research (Bowden and Galindo-Gonzalez, 2015). This meant responses were asynchronous, not given in real time (Saarijärvi and Bratt, 2021b), but the researcher believed that the benefits of not missing those participant views outweighed the difference in approach.

Other participants did not see the questions beforehand (apart from the FIFARMA group, see section 2.9.2) so that responses would be natural and not pre-rehearsed. There is not much literature discussing the option of sending questions out to participants before interviews (Stanlick, 2011). Knox, Taherdoost and Stanlick state that it depends on what is considered appropriate for the research as defined by the researcher and what makes the participants comfortable (Knox and Burkard, 2009; Stanlick, 2011; Taherdoost, 2022). Sending questions beforehand can potentially affect the responses, on the other hand for other research studies, sending the questions out beforehand can be advantageous where the interviewees need to provide technical responses which may require some preparation on their part; other times it may act as a way to build trust (Knox and Burkard, 2009; Stanlick, 2011). Some researchers have sent out a summary of the type of questions to be asked as a way to make interviewees more comfortable and to reduce fear or anxiety before the interviews (Stanlick, 2011). For this research, the interview questions were mostly non-technical and asked for participant opinions hence the researcher wanted unrehearsed and authentic responses and not 'polished' responses. Indeed, it has been said that most times participants do not even read the questions or not thoroughly before

the interview, other times it may affect their participation if they feel that some of the questions are too sensitive and hence, they decline (Knox and Burkard, 2009).

On the day of the interview, the interview recordings were done in a secure room of the researcher's home (McGrath, Palmgren and Liljedahl, 2019). Participants were asked to join the interview from a private and quiet space such as at home or in a secure room at their offices (McGrath, Palmgren and Liljedahl, 2019). All participants had the opportunity to ask questions before the interview and where the participant had not read through the information sheet, the researcher did that before the start of the interview (Neris *et al.*, 2023). Participants were also informed that confidentiality would be maintained. Consent forms were checked for completeness before interviews began (Neris *et al.*, 2023).

Data Storage and Security

Recorded files (audio, visual and transcripts) were stored on a password protected folder on the researcher's laptop and could only be accessed by researcher (Neris *et al.*, 2023). As the researcher was a part time student not located on or near the university campus, saving them on university computers/cabinets was not possible. Zoom recordings were made directly to password protected folders on the researcher's laptop and not to the Zoom cloud to enhance security and avoid potential data breach (Archibald *et al.*, 2019). A handheld encrypted recording device [Philips Voice Tracer DVT5500] was used as a back-up. This device was also locked in a secure cabinet in the researcher's home (Neris *et al.*, 2023). For Microsoft Team users, recording to the University's Microsoft cloud was the only option for recordings. After interviews, the file was downloaded into the password protected folder and immediately deleted from the Cloud for enhanced security (Archibald *et al.*, 2019). Transcripts were also saved to the password protected folder (Neris *et al.*, 2023).

The researcher adhered to the University's policies on data management, storage and security.

Interview Structure

The researcher decided the format and content to be asked of the participant, by starting out with a set list of questions (interview schedule) agreed beforehand. Follow up questions and probes were introduced based on participant responses (Rubin and Rubin, 2005). Based on the research objectives to gain in-depth knowledge of the phenomenon,

the questions evolved or were adapted during the interview or amended for better clarity or focus for subsequent participants (reflexivity). The wording and order as specified in the interview schedule was not applied rigidly, but depended on the conversational flow, however the researcher guided discussions to ensure all questions from the schedule was covered (Rubin and Rubin, 2005). This way, the interviews were more natural and flexible and data could still be compared from one interview to the next. Flexibility was critical to the case study to obtain a variety and diversity of views from participants. The mix of open-ended & closed questions also aided this flexibility and naturalness (Rubin and Rubin 2005).

The questions in the interview schedule flowed in such a way that participants might answer some questions without being asked as they responded to some of the open-ended questions. However, the researcher used the schedule to guide participants back to the topic ensuring that all the relevant questions were answered (Rubin and Rubin 2005). Participants had an opportunity to provide further comments or information at the end of the detailed questions in the schedule.

At the start of each interview, participants were asked if they had read the information sheet, if not the researcher took some time to explain the study. Participants were informed that notes (interview diary) would be taken during the interview (Charmaz, 2003). This also aided in developing rapport with the participants as they had the chance to ask the researcher questions about the study and about their career and their personal reasons for the study. A disclaimer was given before the start of the interview to confirm that the views were the views of the participant and did not reflect the view of the company(ies) or organisations they work for or have worked for in the past. Participants gave consent to be audio/video-recorded and for transcription and analysis. The researcher took notes during the interview as cues to return back to specific points for clarification, to jot down emerging themes, points to be discussed with subsequent participants as they were not on the interview schedule (Brinkmann and Kvale, 2015). The researcher probed or prompted the participant for clarity or additional information during the interview (Rubin and Rubin, 2005).

The semi-structured interviews were designed to last about 1 hour 30 minutes. Even though there was a set list of questions (as described above), the researcher also allowed flexibility for participants to share other experiences related to the phenomenon which were not on the schedule (Rubin and Rubin, 2005). When this happened, the researcher

made a note of those questions to ask subsequent participants hence the interview schedule evolved to the point where no new questions emerged (Rubin and Rubin, 2005). Hence the researcher drove the interview in a particular direction but still allowed for flexibility for participant's experiences the researcher might not have thought of or been aware of to ask (Taherdoost, 2022).

The researcher took notes, seeking to be as inconspicuous as possible (by making bullet points as opposed to lengthy sentences) and maintain conversational flow so participants didn't have uncomfortable silences. The notes reminded the researcher to return to earlier points and suggest how they might frame follow-up questions (Charmaz, 2003). They also acted as a reminder to ask the next participants similar questions as they weren't on the interview schedule but were deemed to be important or good to ask to solicit more information, hence the interview schedule evolved from one interview to the other but not that much (Charmaz, 2003).

To ensure validity, care was taken to ask open-ended questions when soliciting the participants' perceptions, this was to avoid imposing the researcher's preconceived notions onto the participant which would skew the data (Rubin and Rubin, 2005). The open-ended questions served to solicit rich material with the participants' own expressions and definitions. When certain expressions or words were unfamiliar to the researcher, care was taken to ask for clarity, definitions, and contexts to ensure the participant's actual meaning, view and perception came through (Charmaz, 2003).

After the interview, the researcher also spent time to reflect on the whole interview and note any emerging themes and assess the overall interviewing process so they could improve upon for the next participant (Rubin and Rubin, 2005).

An interview diary was also kept to evaluate and assess the questions (Nadin and Cassell, 2006). Did the questions needed modifying for the next interview? Were they producing the right answers to tackle the research problem? The interview diary was also used to capture interesting or striking statements/ideas or explanations given by participant in relation to the research question, statements that gave the researcher a wider perspective to the research problem (Nadin and Cassell, 2006).

Interview transcription and analysis

Transcripts of the audio files were generated via a third-party company, Rev.com, within 1-2 days. All confidentiality, security and GDPR rules were followed by the third party to ensure the integrity of the data. Transcripts were anonymised to remove any personal identifiers and sent back to participants with comments for participants to clarify within 1 week of transcription. It also gave participants a chance to check that their interviews were captured as per their intended meaning (Rowlands, 2021).

The emphasis of the data analysis was on 'what' participants were saying and not 'how' it was being said. The researcher used Braun & Clarke's thematic analysis method to draw out themes from the data. It was an iterative process where the researcher went back and forth within the data to identify initial codes, then themes. The themes were aligned to form theories, which were then tested against additional data (Braun and Clarke, 2006). The stages of thematic analysis (TA) followed are listed below:

Stage 1) Data familiarisation

The researcher initially read through the transcripts whilst listening back to the recording to ensure accuracy. The transcripts were read again in order to be immersed in the data and find repeated patterns of meaning, whilst also referring to any notes made during the interview (Braun and Clarke, 2006). This allowed familiarisation with the data.

Stage 2) Generation of initial codes

Codes were then generated to capture interesting features of the data which were of potential relevance to the research question (Clarke & Braun, 2014); 'generated' because the researcher had to make active interpretive choices in generating the codes. Codes are descriptive labels given to portions of the raw text, transforming the raw data into standardised form for analysis (Babbie, 2013). The Codes captured both semantic (surface) and latent (underlying) meanings from the data (Clarke and Braun, 2014). These codes were generated through the process of induction where no prior knowledge or theories were referenced in the process of coding. The codes came out purely from the data with no external influence. Even though inductive TA is always shaped to some extent by the researcher's standpoint, disciplinary knowledge and epistemology (Nowell *et al.*, 2017); by keeping a reflexive diary, the researcher was able to note ideas that differed from their experience or differed from what they thought they knew, to further alleviate any bias and keep the codes as true to the participant voices as possible (Nowell *et al.*, 2017).

The first few pages of the first transcript were coded by a supervisor, LH, as a way of checking for bias in the coding process as coding by another person without any regulatory affairs experience could yield different results (Anderson, 2010; Nowell *et al.*, 2017). However, the researcher's initial codes aligned with LH's codes which added some validity to the codes generated, in relation to them coming from the data alone and not any preconceived notions or external influence (Nowell *et al.*, 2017). LH has no prior knowledge or experience in Regulatory Affairs. The initial codes were also discussed with a second supervisor with working experience of Regulatory affairs, which also aligned. These allowed the researcher to check their own bias and ascertain whether their application of codes and interpretation was reasonable (Shenton, 2004)

Stages 3-5: Search for themes; review of themes; review and refine themes

Codes with similar context/meanings were highlighted in the same colour within the transcripts. As patterns emerged from the codes, they were then collated in a separate Word document according to their colour highlights. These groups of codes with similar context/meaning, were grouped into themes and given a provisional definition (Frith and Gleeson, 2004). Themes capture broader patterns of meaning from the codes (Clarke and Braun, 2014). The definitions or contexts were used to guide the researcher on which codes should be assigned to which themes.

This process continued until all relevant codes were identified, and no new themes emerged from the data, at which point thematic saturation could be asserted within the data set. During the review, some themes were broken down further into subthemes; merged or removed completely to accurately represent the essence of the data.

2.8.2 Data collection and analysis from FIFARMA (Group interviews) & Other Experts (PAHO, MERCUSOR/EFPIA)

FIFARMA (Group Interview)

The data collection and analysis process for the group interview followed the same approach as the individual RA interviews with a few differences. One difference was the interview schedule which was specific to the group due to the unique insight of the group (Appendix 13). For this set of participants, questions were provided beforehand to enable the participants provide the best technical answers and to represent FIFARMA adequately in order to meet the research objective as explained in section 1.8.1 (online interview setting).

The group interview was conducted on Zoom. Each participant was in a secure and quiet location to minimise distractions and disruptions (Brinkmann and Kvale, 2015)

The interview schedule (Appendix 13) started off with each individual introducing themselves and the role they played within FIFARMA. Further questions covered the structure and role of FIFARMA within the LATAM region. The next set of questions focused on FIFARMA's interactions with other organisations in the region. Lastly, the participants were asked to share their observations on streamlining processes for CMC variations in the region, and whether these aligned to harmonisation or convergence. The group was a mixture of native English speakers, and English as a second language hence like the LATAM NRA group, words in Portuguese/Spanish were clarified and the researcher spoke clearly when asking questions. The rest of the interview followed the RA interview structure.

Other Experts

The data collection and analysis process for the group interview followed the same approach as the individual RA interviews (section 1.8.1). The interview schedule was the same as the RAs (Appendix 12). Section 6 of the schedule already captures specific questions relating to these organisations and their role (if any) in shaping the LATAM CMC streamlining environment. The questions in Section 6 were posed to the RA participant group as well in order to gain their perspective on these organisations as well.

2.8.3 Data collection from NRAs: Online Questionnaires

Development of Questionnaire

The online questionnaire used open-ended questions developed from the research questions and the objectives of the study. The aim was to produce long-form written/typed answers. Questions aimed to reveal opinions, experiences, narratives or accounts this helped where English is not the first language (Seixas, Smith and Mitton, 2018) so participants had time to formulate their responses. As English was not the first language of the participants, the researcher was careful not to use jargons but clear language within the questionnaires (Boynton, 2004).

The aim was to solicit NRA participant perceptions regarding the process of streamlining CMC variations, whether it was a priority for their NRA, whether it was being thought of or executed and in what way. The questionnaire was not developed from an existing questionnaire. The questionnaire was sent to a group of regulatory affairs professionals in

the researcher's personal network to test, as well as 2 supervisors. It was also sent to one of the RA participants who had experience working with NRAs. They tested whether it would gather the required data, whether the arrangement of the questions made sense, whether the questions were clear and could be understood and were necessary and reasonable in relation to the research objectives (Boynton, 2004). Feedback was received by email and was used to update and enhance the questionnaire before sending out to NRAs.

Online Questionnaire setting

Online questionnaires were used as a way to gain initial access to the NRA participant group. The idea was to ask open-ended but targeted questions to solicit information from the NRA's perspective on the research questions. Participants were invited to interview at the end of the questionnaire. The idea of the interview was to help the researcher expand on or clarify any responses so as to prevent the questionnaire from being long and tedious reducing questionnaire fatigue (Lavrakas, 2022). Respondents had the opportunity to save their progress and return to the questionnaire later, though the questionnaire could be answered within approximately 30 minutes. As the questionnaire mainly asked for personal opinions, respondents did not need to consult other documents in order to respond, but just recall past events or construct opinions (Lavrakas, 2022).

The questionnaire was hosted by Alchemer.com (formerly Survey Gizmo). Again, all confidentiality, security and General Data Protection Regulation (GDPR) rules were followed by the third party to ensure the integrity of the online data held. The online questionnaire was set up to alert the researcher by email once a response had been submitted. The researcher was the only one who had access to the responses.

Questionnaire structure

The questionnaires were region specific. Participants gave informed consent which was embedded in the first section of the online questionnaire. The questions were open-ended apart from the LATAM questionnaire which included some Likert scale questions. Gatekeepers were able to confirm the appropriateness of questionnaires being in English since they corresponded with the NRA personnel in English and therefore did not anticipate issues in understanding. This was supported by the fact that other

questionnaires/data collection tools for similar research had been provided in English to these same markets (CIRS, 2023a)

The LATAM questionnaire had the following sections:

- introduction of the study and consent;
- general information about the participant and NRA;
- interaction with regulatory networks;
- about CMC variations;
- transparency between NRA and industry;
- interview request.

The ASEAN questionnaire had the following sections:

- introduction and consent;
- general information about the participant and NRA;
- ASEAN common technical requirements (ACTR);
- interview request.

The researcher took time to reflect on the responses, making note of areas that needed further clarification or expansion in preparation for the interview.

Questionnaire analysis

Thematic analysis was again applied to the open-ended responses. As the sample size for the NRAs was always going to be minimal, only simple comparisons could be made with the Likert scale questions.

2.8.4 Data collection from NRAs: Individual Interviews

Online interview setting

Respondents to the questionnaire were invited to participate in a follow-up interview. The online interview and setting were the same as for the RA participant group. Consent was obtained for the interviews separate from the questionnaire and were NRA specific (Appendix 14).

Interview Structure

The main aim of the NRA interviews was to expand on responses given in the questionnaire, hence no interview schedule or set questions were required beforehand. Questionnaire responses were reviewed, and questions formulated from responses that required further clarification. This allowed participants to expand or further explain concepts raised in the questionnaire. Questions were therefore specific for each NRA participant. The researcher prepared the specific questions ahead of the interview and allowed participants to express and expand on their responses.

The researcher was careful to speak clearly and concisely so questions were not misunderstood. Where the researcher could not understand a response from an NRA participant, clarification was sought. Sometimes words were provided in Spanish or Portuguese which were later explained in English. Participants were asked to spell any Spanish or Portuguese words during the recording in addition to written annotation by the researcher.

From the researcher's professional experience and conference experiences, LATAM NRA personnel use English as a second language; Portuguese or Spanish being the first. To overcome potential challenges with this, the researcher spoke slowly and clearly; using non-technical jargon and known regulatory affairs terminology to ensure questions were understood (Marshall and While, 1994) Sometimes the researcher would replace words without losing the meaning of the question (Marshall and While, 1994). In order to ensure that the participant's meaning had been grasped, probing was used in a subtle and non-threatening way (Marshall and While, 1994) instead of trying to guess or pre-empt what participants are saying, which could be biased or leading (Schembri and Jahić Jašić, 2022). Oftentimes times the researcher would reiterate participant responses to ensure their view had been understood, especially for participants with strong accents. Some words were given in Spanish or Portuguese as they had no English equivalent.

Participants were asked to provide the meaning for these words as best they could, they mostly described regulatory acronyms or regulatory processes which occurred locally.

Another limitation of interviewing participants with English as a second language is that interpretation or meaning could be lost during analysis (Murray, 2001).

Reworded: To overcome that limitation, the researcher emailed transcripts back to participants for clarification on sections that seemed ambiguous or were not captured

properly due to accents. This was especially necessary when time was constrained during interviews.

Though all questionnaire responses were given in English, the participants had the option of requesting for interpreters for the online interviews. An interpreter provides oral translation services during an interaction between two or more people who do not speak the same language (Squires, 2008)

2.8.5 Using Interpreters (recruitment and ethical considerations)

Recruitment

For the interviews, NRA participants were given the option of requesting for interpreters for the online interviews.

Online searches were conducted to identify local regulatory consultancies which were then vetted against the research aims and objectives to confirm their suitability based on the services the consultancy provided. These consultancies were approached via email to offer interpretation services (Egill, 2023).

In order for the use of interpreters to be effective in research, the researcher considered the following:

The role of the interpreter was clearly outlined in the interpreter information sheet (Appendix 15) Interpreter's role involved sitting in on NRA interviews to interpret the participant responses (in a neutral capacity) with the consent of the participant, through the NRA interview participant consent form (Appendix 14). The following documents were also made available to interpreters:

- Interpreter invitation/recruitment letter (Appendix 16)
- Interpreter consent form (to be signed and returned before any training), Appendix 17

Prior training was mandatory for all interpreters who expressed interest in order for them to understand their role and know what to expect in the interview (Egill, 2023).

The training covered the aims and objectives of the research, so interpreters understand the focus of the research. This provided an understanding of the questions being asked of

the participants and helped familiarise them with the research (Egill, 2023). The training also covered the questions from the general interview guide and questions arising from the questionnaire responses, so interpreters were familiar with the line of questioning before the interview. The training highlighted the researcher's desired outcome from the interviews so as to minimise risk/bias in misunderstanding the questions or in the delivery of the questions by the interpreter.

The training also highlighted the role of the interpreter to be a neutral one, i.e. they had to translate the questions/answers exactly as heard without modifying (Murray, 2001). If the translator felt the need to modify for any reason, they were told they must consult with the researcher during the interview so there is consensus. The researcher prepared an interpreter training schedule (Appendix 18) which acted as a guide for the researcher.

Confidentiality

The confidential nature of the interviews was explained as well as GDPR/data protection policies. The interpreters by signing the consent form, agreed to adhere to the University's data protection policies in the recruitment letter. Participant identities were to be kept anonymous; no part of the interview could be shared (Egill, 2023). Interpreters could withdraw their services at any time. The interpreter services were a paid service. The service fee covered training and interpretation times. Time spent in training was estimated at one hour. Interpretation during interviews varied depending on the interview but on average was estimated to be one and half hours maximum. Interpreters were used based on their availability however only trained interpreters could be part of the research. Different dates were suggested for training to maximise attendance and secure more interpreters in the pool.

2.8.5.1 Other Considerations

Potential conflict of interest: The interviewee's responses could be compromised as they may not want to mention certain things in front of the interpreter. This may affect the validity of the data, but this will be discussed in the research limitations in the relevant empirical chapters (Kapborga and Berterö, 2002).

Questions & intrusiveness

The only personal data shared in the interview were: name, job role, Agency working for. No other questions were probing or personal. The questions surround the participant's

understanding of a process; they were not emotive; or sensitive questions or did not go into intimate details of the participant's life. The only "sensitivity" around the questions was the interpreter's awareness of participant opinions on the matter being discussed. The interpreter however signed and agreed not to divulge any information shared in the interview, hence this was mitigated (Egill, 2023). The participants gave express consent for the interpreter to join the interview.

Depending on the proficiency of the interpreter, the researcher guided the interview to ensure the most pertinent responses were followed up or questions asked first; other questions were more for context and background. With the introduction of the interpreter, the time needed for the interview could run over the stipulated time. To mitigate this, the researcher started with the most pertinent questions first and dealt with any background questions later (Kapborga and Berterö, 2002)

Rapport

Rapport is an essential part of interviews which supports participants in feeling comfortable. With the inclusion of an interpreter, rapport could be jeopardised, building rapport could become challenging (Egill, 2023). To mitigate, researchers can have multiple interviews to help develop rapport but for this research it was not possible as participants are high profile personnel with busy schedules. The researcher instead factored in some time before the interview started for the participant and interpreter to get acquainted, thereby building a level of rapport before the interview started (Murray, 2001). There was also a test run of the interview with some informal questions so the participant could get used to the format of the interviewing.

Selective translation

It is possible that not all words are conveyed in the translation however this does not mean that "meaning" is lost. Sometimes, Due to the confines of time interpreters would have to summarise or choose the best way to express the participant's responses (Egill, 2023). It is also possible that the interpreter may be selective because they do not want to convey the meaning- this may be seen more with social science research where the interpreter may feel they need to protect the community/participant from potential or perceived harm due to the response given(Kapborga and Berterö, 2002).

In the first instance, with further probing by the researcher, the intended meaning can be drawn out. Also, since the participant will allow for an audio or video recording, the text which is not in English will be back translated by the selected local Regulatory Consulting service (mentioned earlier) to check the interpreter's response as well (Murray, 2001). In the second instance, this will not apply to this interview as the questions are of a technical nature and do not imply any relationship to personal or communal feelings or perception. There could however be a perception of the NRA developed through the responses; however, it has been established that the responses are the individual's opinions and do not reflect the views of the Agency.

Involvement of interpreter

The degree of involvement of the interpreter needs to be defined before the interview. It is possible that the interpreter may take the lead in steering the interview depending on the set up and this could lead to the interpreter deciding what was relevant information (Egill, 2023). To avoid this, during the training phase, the researcher informed interpreters to follow the researcher's lead in asking the questions and defer to the researcher where the participant is asking for further clarification (Egill, 2023). In this way, the researcher leads the interview and directs it the way they require. However, the interpreter should neither be too active nor too passive e.g. they may provide further context as part of their interpretation to make a point clearer (Egill, 2023). The interpreter should always discuss any modifications to questions or responses together with the reasons, with the researcher during the interview.

Reliability of interpretation

The researcher needs to be confident that the participant's responses are being relayed the way intended. The proficiency of the interpreter's English and participant's language is one indicator of reliability. As the interviews were recorded, the researcher can obtain a second interpretation to verify the first interpreted accounts (Kapborga and Berterö, 2002). The other aspect of reliability is where the participant says something unclear, the interpreter may try to make sense of the response and present it in a more congruent way. During the training, interpreters were briefed on remaining as close to the words and meanings of the participants statements as much as possible, so they do not try to give their own meaning to participant responses. A second translation was employed to check if such cases occurred during the interview (Kapborga and Berterö, 2002).

Impartiality of the interpreter

In the instance of this research, the researcher does not believe there is cause for the interpreter to be impartial in their interpretation (Kapborga and Berterö, 2002)- the culture, values and beliefs of the interpreter had no influence due to the technical nature of the questions being asked. Even though the participant shared their opinions, the questions themselves related primarily to factual information.

Confidentiality

The research seeks to respect the privacy and confidentiality of participants for which ethics approval was sought. Since the participants were drawn from a select number of people, the participants were assured of anonymity and anything that could lead to their identification removed (Murray, 2001). The researcher stressed the importance of the interpreter not sharing any information heard during the interview with anyone else. This was captured in the translator recruitment letter which was signed by all interpreters (Murray, 2001).

Conducting the interview

The interviews were conducted online via zoom. The researcher was aware that the presence of an interpreter added a third person to what was normally a one-to-one interview relationship (Murray, 2001). The researcher allowed for more time in between questions to accommodate the expected back and forth and clarifications that occurred (Egill, 2023).

Documenting & reflexivity

In order to capture the use of an interpreter, it has been suggested by Murray et al, to encourage the interpreters to translate in the third person, making it clear for documentation purposes that the participant's words were subject to translation (Murray, 2001). In order to capture any biases or lenses that the interpreter brought to their translation, the interpreters could be interviewed for their opinions/reflections which helps capture the dynamics of the interaction in the interpreted interview (Murray, 2001) .

Payment of interpreter

In paying for the interpreter's service, the researcher believes that it will support the proper administration of the service as good service was linked to interpreter's professional integrity; this helps ensure the translator is doing what they have been instructed or trained to do (Murray, 2001).

Weighing the considerations versus the potential benefits of using the translator, the researcher believed the advantages to the research outweighs any potential concerns.

The literature the researcher found regarding use of interpreters for qualitative research involved topics which were far more intrusive than this research. Interpreters are used in the disciplines of psychology, work and family research and social research among others, mainly to reach out to marginalised communities; non-English speaking groups (or who do not speak the main language of the researcher and their community) (Edwards, 1998; Squires, 2008).

Ethics and confidentiality:

The use of interpreters in this research was covered in the Ethics approval granted by The Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS) Research Ethics Committee. All interpreters signed the Interpreters Consent form outlining the consent they were giving. Interpreters had the right to withdraw from the research at any time and their identity was anonymised (Kapborga and Berterö, 2002). Personal information of participants to be shared as mentioned above, may already be known by the interpreter as they are local and have knowledge of the pharmaceutical industry/NRAs (Berman and Tyyskä, 2011). All other questions were not of a personal nature, hence this limited further concerns. Interpreters however consented not to divulge any information about participants or participant responses (Berman and Tyyskä, 2011). The interpreters did not have access to the interview recording, the interview was recorded directly to the researcher's computer. GDPR requirements were explained to the interpreters and included in the translator's letter/information sheet.

Interview transcription and analysis

The same procedure was used for the NRA interviews as per the RA participant group.

2.8.6 Secondary Data collection and Analysis

Data Collection

Secondary data in the form of Document Analysis was also used to obtain data. Pharma Industry White papers, conference and meeting reports were provided by the researcher's external supervisor as well as obtained from Pharma company, Pharma association or health organisation websites like FIFARMA, EFPIA, WHO, PANDRH. The CMC Regulatory requirements for the ASEAN NRAs were obtained from the ASEAN website as well as the NRA-specific websites and from the researcher's personal network. For CMC Regulatory Requirements for the LATAM markets, the researcher employed the same Regulatory consultancy used to identify the interpreters in the previous section, to extract these documents from the LATAM NRA websites as all the information was either in Spanish or Portuguese. The regulatory consultancy regularly conducts such tasks as part of its business objectives. For some LATAM NRAs, the Consultancy had to send in a request by email as the requirements were not displayed on the NRA website or not easily accessible (Taneja, Chacko and Kedar, 2018). The requirements are public information however some NRAs display them on their websites and other times local regulatory companies would need to request the information from the NRAs as stated on the NRA website (WHO LMIC, 2018). Other times the information is not easily visible on the NRA website (Argotti *et al.*, 2023). Typically, requirements for post-approval CMC variations are not always displayed on NRA websites (Taneja, Chacko and Kedar, 2018). This practice of local regulatory companies requesting requirements from NRAs is common practice. Multinational pharmaceutical companies have local offices who consult the NRAs to gather necessary information for regulatory filings. There are no ethical implications to these type of requests from local or multinational regulatory companies. The systematic review was also a source of secondary data for the case study as outlined in section 2.4.3.3.

Analysis

Once obtained, document analysis was performed on the secondary documents. Document analysis involves skimming, reading and interpretation. It involves both thematic analysis and content analysis (Bowen, 2009). Content analysis involves

organising information into categories related to the research questions; it is the identification of pertinent information (Bowen, 2009) within the documents. Thematic analysis within document analysis is the recognition of patterns within the data, with emerging themes becoming the categories for analysis. It involves the researcher re-reading and reviewing the data in order to generate codes and develop themes inductively (Bowen, 2009) Document analysis was used to pull out relevant information which related to the research questions and incorporated into the case study.

2.9 Ethical Considerations

Ethical approval was required for the study as it involved human participants. This was obtained from Cardiff University, CSPPS Research Ethics Committee (Ref 1616-36). Ethical considerations are the set of principles which guide research designs and practices; they include participant confidentiality, informed consent, right to withdraw, anonymity, results communication and assessment of potential for harm. All these areas were taken into account in this study and the CSPPS Research Ethics Committee was satisfied that participation in studies would be voluntary, informed, and safe for research participants as per the subsequent ethics approval by the Ethics Committee (Yip, Han and Sng, 2016)

The study and study materials were updated with any comments provided by the ethics committee, these were resubmitted before approval was granted. During the study, the study plan or process of data collection changed to enhance recruitment outcomes, for each change, ethics approval was sought before the study continued. Consent was obtained via email and all forms and data were handled in accordance with data protection and ethics as described above. Where applicable, approval from relevant regulatory authorities is required before research is initiated (Yip, 2016). In this research study, opinions were sought from individuals working within the Regulatory Authorities and did not reflect official Regulatory authority positions, hence ethical approval was not required from the Regulatory authorities (Yip, Han and Sng, 2016).

Confidentiality

“Confidentiality is the respectful handling of information disclosed within relationships of trust, especially as regards further disclosure” [(Lowrance, 2012)] (Maldonado-Castellanos and Barrios, 2023). Through the consent form, participants were informed that their data

would be kept confidential and discussed only within the research team. Identities in Interview transcripts were anonymised and anything that could lead to their identification removed. Audio and transcript data were stored on the researcher's password protected laptop and the recording device stored, safely locked away in a cabinet in the researcher's home as the researcher conducted interviews from home).

2.10 Triangulation

In this research, the researcher aimed to integrate information across interviews with people who perceive regulatory processes from differing vantage points, including: RAs, NRAs, other professionals and through secondary data. These were brought together in a process of 'triangulation', a way of interpreting data from multiple sources which can strengthen validity (the extent to which the study accurately captures the phenomena being investigated) and credibility (referring to how trustworthy and believable the study is) (Heale and Forbes, 2013; Noble and Heale, 2019).

Triangulation helps overcome threats to validity from relying upon single observations or perspectives. It is especially important when one person's or set of actors' perceived reality may differ from an actual situation, as a result of subtle and hidden cognitive beliefs or biases (Heale and Forbes, 2013; Noble and Heale, 2019).

By triangulating data, it is possible to see where viewpoints about regulatory trends converge and diverge. In qualitative research, convergence can help researchers verify that the participants are speaking to an underlying true situation (Heale and Forbes, 2013; Noble and Heale, 2019) ; however, in this research, the researcher's use of triangulation was not in an effort to reveal one underlying fundamental truth, but rather to provide a comprehensive map of the streamlining process.

2.11 COVID impact statement

The researcher would like to mention that between 2020 to 2021 recruitment was disrupted or delayed due to the impact of Covid on the healthcare system in the various markets for example with the ASEAN NRA recruitment. NRAs reported of disruptions to normal working patterns and higher workloads as resources were diverted towards pandemic activities. Also change to working patterns for example, adapting to home-

working whilst infrastructure and systems remain in government offices, slowed down activities of the NRA.

2.12 Summary

This chapter outlines the rationale and description of the methodology used for the case study from generation of the interview schedule and online questionnaire to recruitment of participants, obtaining ethics approval through to the interviews and analysis.

Chapter Three (the first of three empirical chapters) will present the results of a systematic literature review covering the research question.

3 SYSTEMATIC REVIEW OF THE LITERATURE

3.1 Introduction

Much has been explored in the area of “regulatory harmonisation” since the 1980s with the emergence of the European Commission (EC) and International Council for Harmonisation (ICH) in the 1990s (ICH website, 2020). Other regional harmonisation initiatives include the establishment of ASEAN in 1967, and GCC, now GHC in 1981 (Lakkis, 2010). APEC was also established in 1989 among 21 countries of the Pacific Rim and SADC (Lakkis, 2010).

In Latin America, the PAHO together with the NRA in the region established PANDRH in 1999 with the intention of “supporting the processes of pharmaceutical regulatory harmonization in the Americas, within the framework of national and sub-regional health policies and recognizing pre-existing asymmetries (PAHO website, 2023). To encourage further collaboration and understanding of ICH guidelines across these regional harmonization initiatives, the GCG of ICH invited representatives of these groups to attend the GCG meetings (Lakkis, 2010).

There is much data to support the benefits of regulatory harmonisation as observed by ICH and bodies such as EMA and FDA, one of them being timely access to medicines by patients, as alignment in regulatory requirements reduces duplication and complexity (Baber, 1994; Lakkis, 2010; Weisfeld and Lustig, 2013; Lezotre, 2014c).

“*Harmonisation*” is the term used to describe alignment of regulations across countries or regions. The terms “*convergence*” and “*regulatory convergence*” are relatively new within the pharmaceutical field, introduced in the 2010s (Tominaga, 2020); and are sometimes used interchangeably with harmonisation or can be seen as opposite terms to harmonization.

The term convergence is being used more liberally now and can have some ambiguity as different forms of convergence can occur - some authorities may align small parts of their regulations; others may align on review processes, and both could be deemed as “convergence” (Tominaga, 2020). The term was first advocated for by the RHSC of APEC in 2011 and defined by them as “*a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual*

adoption of internationally recognized technical guidance documents, standards and scientific principles (Tominaga, 2020).

The harmonisation of national legal frameworks is not necessarily a prerequisite for allowing the alignment of technical requirements and greater regulatory cooperation, the approach adopted by the EU (APEC, 2011). Harmonisation, however, is the process by which technical guidelines are developed to be uniform across participating authorities as described by the CBER (biologics) (FDA, no date); or as put by ICH, harmonisation can be defined as the agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content across a set of markets or region (EMA, no date). It also covers a defined format for the presentation of the scientific data and may also influence the review process and assessment towards obtaining a Health Authority approval. The guidelines can sometimes be adopted as legislation in the markets concerned such as the EU markets.

These harmonization initiatives have largely been focused on new Marketing Authorizations, collaboration on Good Manufacturing or clinical practice (GMP/GCP). Following license approval, however, continuous update of regulatory approvals due to changes to the drug product or processes related to the manufacture of the medicine are required. These are termed post-approval changes or PACs. These changes can be driven by changes in technical methods, quality and process improvement or scientific improvement, process refinement and optimisation to allow manufacturing cost reduction, or to fulfil regulatory agency requirements. It can also be due to the reaction to demands in supply or to remain commercially attractive & competitive. The majority of these changes are related to the chemistry, manufacturing and control (CMC) of the drug product, commonly referred to in industry as “CMC” (EFPIA, 2017). These changes benefit the patient and the companies, however, agency assessment and approval are required before implementation.

Errors or omissions in updating the license prior to supply could result in product recalls, or supply shortages meaning the patient’s access to the drug would be hindered and the loss of reputation and revenue for the pharmaceutical company concerned. Companies therefore dedicate considerable resources and expense to maintaining the license of each registered product they hold. Diverse regulatory requirements, differences in categorisation, differences in implementation rules and timelines and often long review times in each market present challenges to the review, approval and implementation of these variations. As medicinal product licenses are normally available in multiple markets, this complexity then becomes magnified (EFPIA, IFPMA and Vaccines Europe, 2021).

Moreover, 15% of total R&D expenditure is spent on post-approval CMC activities, hence issues in CMC activities can have a huge negative financial impact or lead to product recall (Clarivate, 2018), ultimately affecting the patient. Another challenging aspect is managing the outcome of unexpected Health Authority delays in review and approval. A delay in one market's implementation can have a knock-on effect across the global supply, hence managing these complexities is vital to ensure patient access is not disrupted.

In white papers by EFPIA and IFPMA, they state that convergence either with requirements or processes, could help address these complex challenges to life cycle management across the globe (IFPMA, 2016; EFPIA, 2017) by bringing consistency and predictability to the global management of PACs as NRAs work together with industry.

It is clear from the above that management and global simplification of PACs are important in ensuring that companies may implement changes globally at the same time. This may be important from a quality / patient safety perspective but is also important from a cost of goods and ultimate cost to the patient perspective. It is also clear that regional / cross regional streamlining and harmonisation of requirements is crucial, as is a unified approach to harmonisation rather than the various approaches to streamlining requirements currently followed. This chapter reviews and analyses the literature published on the topic of streamlining or alignment of Chemistry, Manufacturing & Control (CMC) variations/requirements within the Latin America Region, specifically Brazil, Chile, Colombia, Cuba, Mexico and Argentina drawing a comparison to initiatives in the ASEAN region in particular Singapore, Malaysia, Thailand. The aims are to:

1. Assess the current regulatory landscape concerning CMC variations in LATAM;
2. Determine if the LATAM region has a desire to streamline CMC variations and, if so, whether they intend to use the harmonisation or convergence approach and which process would best suit the region;
3. Assess the ASEAN CMC harmonization initiatives;
4. Identify whether LATAM and ASEAN initiatives for CMC harmonisation have ever been compared;
5. Identify what learnings can be generalized for the two regions, if applicable.
6. Assess the ASEAN CMC landscape and assess the extent to which they are truly harmonized;

The research question under investigation is, therefore:

Convergence or harmonisation? A comparison between implementation initiatives in Brazil, Argentina, Colombia, Cuba, Mexico and Chile versus Singapore, Thailand & Malaysia through ASEAN initiatives and lessons which can be applied to post-approval life cycle maintenance submissions.

3.2 Method

3.2.1 Literature Search

The objective of the systematic review was to find any evidence of harmonisation, convergence or streamlining of post-approval CMC variations in LATAM or ASEAN.

The literature search was conducted between October 2015 and March 2016 then updated again in October 2018 and again in Oct/November 2020 to ensure new and emerging evidence was captured. The following electronic bibliographic databases were used to conduct a comprehensive search: Web of Science (all years), Scopus (all years), SciFinder, ScienceDirect, EMBASE, and Medline (Uman, 2011) The search strategy as outlined in Chapter 2 was adhered to.

Initial searches in the databases only yielded 9 peer-reviewed articles, hence Google Scholar and Google were included in the search for grey literature including conference papers, industry papers, white papers, online articles and relevant website contents (Hartling *et al.*, 2017). For Google Scholar, Publish or Perish was used in order to easily extract the results via Excel (Office 365, Microsoft Corporation, San Diego, C.A, United States (Jacso, 2009). The system produced 982 results out of the maximum 1000 the system could extract from Google Scholar. The Google search yielded 333 results which were organized by relevance. The literature search included all publication types but excluded clinical trials and veterinary citations. It included all years to capture the history and changes occurring over time in the industry (Tawfik *et al.*, 2019). Relevant articles in Spanish or Portuguese were included if found as the Latin America markets under investigation speak Spanish with the exception of Brazil, which uses Portuguese as their national language (Uman, 2011). FS, an expert in the field with a link to other experts and industry associations, was also approached for relevant articles (Uman, 2011).

The search terms were organized through the use of the PICO framework applied to the research aims and objectives and the research question (Tawfik *et al.*, 2019) as detailed in Chapter 2. The framework covered markets involved (population), terms related to streamlining requirements (phenomenon of interest) and terms related to chemistry, manufacturing and control(s) (context). The following search terms were used both as

keywords (how other people might describe the topic) (University of South Australia, 2023) and index terms/subject headings (formal controlled vocabulary) (University of South Australia, 2023) in the article titles, abstracts or main body of the articles:

Phenomenon of Interest (I): Streamlining process:

harmoni*ation, standardi*ation, regionali*ation, globali*ation, regulatory requirement*, pharmaceutical, small molecule, pharmaceutical drug, streamline, medicine, pharmaceutical product, converg*, harmoni*e, globali*e, standardi*e

Population (P) Markets/Harmonisation initiatives

Brazil, Argentina, Cuba, Mexico, PANDRH, PAHO, Chile, Colombia, LATAM, Latin America, CECMED, ANVISA, ANMAT, INVIMA, COFEPRIS, ISPCH, ASEAN, Singapore, Malaysia, Thailand, APEC, MERCOSUR, EFPIA, FIFARMA

Context (Co): Post - approval change/CMC

post-approval*, post approval*, post-approval variation*, post approval variation* post approval change*, post-approval change*, chemistry, manufacturing and control*, lifecycle management, life-cycle management, life cycle management, life-cycle maintenance, lifecycle maintenance, life cycle maintenance, chemical, manufacturing and control*

Where applicable, variants, synonyms or alternative spellings were used as well as matching search terms to those included in the database's thesaurus. Bibliographies of retrieved articles were also searched manually. The full list of search terms/keywords is provided in Appendix 1.

3.2.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied to the search as explained in Chapter 2 and summarised here.

Inclusion criteria

The literature review included articles or grey literature covering CMC variations made on New Chemical Entities of pharmaceutical drugs (small molecules). All articles were allowed regardless of language. All methodological designs were allowed unless they did not meet the inclusion criteria (Thorne 2017). This was to reduce the risk of

excluding studies with relevant data as the search yielded few articles overall (Thorne, 2017).

It excluded literature covering variations on generics, biologics, biosimilars, vaccines or medical devices or streamlining activities covering new marketing authorisations, clinical trials or veterinary citations. Other exclusions included unrelated, duplicated, unavailable full texts or abstract-only papers (Tawfik *et al.*, 2019).

3.2.3 Data Extraction/abstraction

The extraction process was followed as detailed in Chapter 2. All retrieved articles were reviewed by a second reviewer, the researcher's supervisor, FS, to verify whether they were applicable or fitted the inclusion criteria (Tawfik *et al.*, 2019). Where there was doubt about article inclusion, it was discussed with FS and decided based on consensus. Generally, it is encouraged to have 3 reviewers in case there is a dispute in opinion between 2 reviewers, so the third reviewer can provide a further opinion to balance out the discussion and decision (Petticrew and Roberts, 2006; Tawfik *et al.*, 2019). In the case of this systematic review, consensus was easily attained after discussion, where differences arose. Bibliographies of screened articles were also searched for any relevant articles. Publish or Perish was used to extract peer-reviewed journals, theses and grey literature from Google Scholar (Jacsó, 2009) as detailed in Chapter 2.

3.2.4 Organisational website search

The following organizational websites were also searched in the same time frames as mentioned above: ASEAN; PAHO official websites, including the PANDRH section of the PAHO website specifically, EFPIA, FIFARMA, APEC, MERCOSUR and CIRS. 'The term 'websites' is used in a broad sense to refer to online resources that lack the functionality to carry out complex Boolean searches, or export results, or do not readily provide a search history' (Stansfield, Dickson and Bangpan, 2016) The researcher is aware that, when websites are relied upon to identify important literature for a review, it can raise the issue of how transparent, accountable and reproducible the search is (Stansfield, Dickson and Bangpan, 2016). The publications sections of the websites were explored to find documents related to the research question; key words from the

search string were used in the search function of these website sections to identify resources. This provides the required transparency, accountability and ensures reproducibility (Stansfield, Dickson and Bangpan, 2016). Table 3.1 lists the organisational website addresses below:

Organisation	Acronym	URL
Association of Southeast Asian Nations	ASEAN	https://asean.org
Pan American Health Organization	PAHO	https://www.paho.org
The Pan American Network for Drug Regulatory Harmonization	PANDRH	https://www.paho.org/en/pan-american-network-drug-regulatory-harmonization-pandrh
European Federation of Pharmaceutical Industries and Associations	EFPIA	https://www.efpia.eu
Latin American Federation of the Pharmaceutical Industry	FIFARMA	https://fifarma.org/
Asia -Pacific Economic Cooperation	APEC	https://www.apec.org
The Southern Common Market (MERCOSUR for its Spanish initials)	MERCOSUR	https://www.mercosur.int/en/
Centre for Innovation and Regulatory Science	CIRS	https://cirsci.org

Table 3.1 Organisational websites searched as part of in systematic review

3.3 Results

Oct 2015 to March 2016 and 2018

The search yielded one relevant article from Scopus, and none from EMBASE, Web of Science or Medline when searched between Oct 2015 to March 2016.

A Google search was also conducted in November 2018 and the first 50 results explored. This yielded 1 industry white paper by The Regulatory Affairs Consultancy (TRAC).

Oct/Nov 2020 Search

The search in Oct/Nov 2020 yielded 9 articles, with 2 industry white papers which fulfilled the inclusion criteria, as shown in Figure 6. The TRAC white paper from 2018 did not come up in the 2020 search as it was no longer available on the internet. This is due to TRAC being acquired by another company (Pharmalex, 2022). The Researcher, however, had the white paper saved as a portable document format (pdf) copy and has included it in the results. The remaining 5 documents came from organizational website searches.

A meta-analysis could not be performed because study methods varied widely and the quality of the articles was not the same (some peer-reviewed, some gray literature) (Petticrew and Roberts, 2006). Also due to the limited number of papers, which cannot provide an objective view, there were not enough to perform a valid statistical analysis (Ahn and Kang, 2018). In addition, the review did not set out to perform a meta-analysis but a narrative analysis as explained in Chapter 2. The quality of the literature, which was mainly 'grey', was assessed based on the ability of the information to answer the research questions and not on research design as most of the articles gave a narrative of the phenomenon and were not based on research studies (Thomas and Harden, 2008). All identified articles were included in the results regardless of quality. The resultant articles included a concept paper provided by the Researcher's supervisor, (FS) which was not publicly available at the time of search. No relevant articles were identified in Portuguese or Spanish. No studies were excluded on quality grounds (Lorenc, Petticrew and Whitehead, 2014) Figure 3.1 shows the PRISMA flow diagram for the systematic review, whilst Table 3.2 shows the retrieved articles/documents.

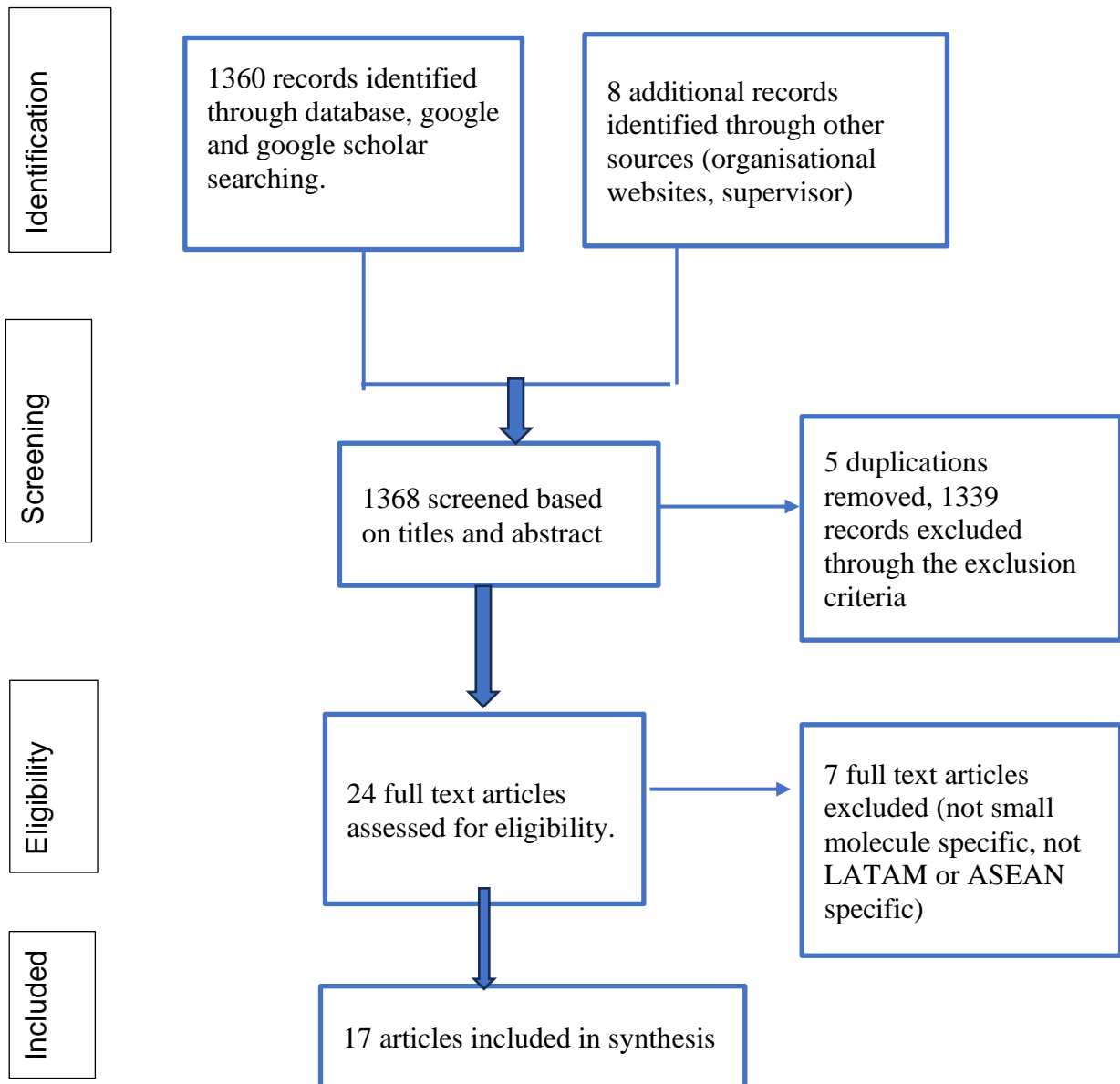


Figure 3.1 Flow diagram for the selection of studies according to PRISM

Article (First author)	Article type (peer-reviewed or gray literature)	Countries covered from LATAM/ASEAN	Relevance	Sampling method
Hoey, 2017	Thesis (unpublished)	Brazil	Study on global regulatory requirements on post-approval change (change in manufacturing site)	Qualitative analysis of Literature based review and secondary documents
Wittner 2019	Peer- reviewed pharmaceutical journal	ASEAN markets, covers markets under study	Study on post approval cycle management	Information from Industry/authors' experience, literature based review
Sukumaran 2020	Peer-reviewed	Malaysia	Study on post approval changes (including manufacturing site change), variation classification	Information from Industry/authors' experience, literature based review
Rajneesh, 2018	Peer-reviewed	ASEAN & LATAM markets including markets under study	Assessment of CMC requirements	Desk research of published NRA requirements; interviews

Institute of Medicine (IOM), 2013	Book publication	APEC and LATAM markets including markets under study	Discussed global regulatory harmonization, also covering post-approval CMC variations.	Workshop summaries, of industry experiences
Lokesh, 2015	Peer-reviewed	Singapore	Study on post approval change (manufacturing site change)	Information extracted from NRA guidelines
The Regulatory Affairs Consultancy (TRAC) Services [merged with and now PharmaLex]	Grey literature	Argentina, Mexico, Colombia	Discussing harmonization of CMC post-approval changes	Industry experience
Chong, 2018	Peer-reviewed	Thailand, Malaysia, Singapore	Discussing regulatory convergence	Information from Industry/authors' experience, literature based review
European Federation of Pharmaceutical industries and	Grey literature, position paper	Global	Discusses harmonization/convergence for managing post-approval variations	Position paper, industry experience

associations (EFPIA), 2017				
EFPIA LATAM, 2016	Grey literature, concept paper	Brazil	Discusses Brazil technical assessment change report (PATE) for post approval changes	Concept paper, industry experience
Centre for Innovation in Regulatory Science (CIRS), 2015	Grey literature	Mexico, Brazil, Argentina, Chile, Colombia	Discussing regulatory environment including CMC post-approval variations	NRA supplied metrics, questionnaires
ASEAN, 2012	Grey literature	ASEAN covering Malaysia, Singapore, Thailand	CMC post-approval guidelines	Regional Network guidelines
Singapore NRA (HSA)	Grey literature; government pharmaceutical CMC requirements/guidelin es	Singapore	CMC post-approval guidelines	No sampling method, Regulatory Authority guidelines
Malaysia NRA (NPRA), 2013	Grey literature; government pharmaceutical CMC	Malaysia	CMC post-approval guidelines	No sampling method, Regulatory Authority guidelines

	requirements/guidelines			
PANDRH, 2016	Grey literature, conference report	LATAM covering markets under study	Discussing regulatory harmonization and convergence in the region	No sampling method, industry experience
Oliveira, 2016 (on behalf of Latin American Federation of the Pharmaceutical Industry) (FIFARMA)	Grey literature, conference presentation	LATAM covering markets under study	Discussing regulatory convergence in the region	Industry experience
International Pharmaceutical Quality, 2010	Grey literature, online article	ASEAN	Discussing efforts on CMC harmonization	Information from NRA websites and updates

Table 3.2 Characteristics of included studies including a summary of their relevance

3.4 Review of published literature

In 2013, a workshop was held by the Institute of Medicine (IOM), to discuss global regulatory harmonization. In the published workshop summary, it was cited that one of the areas of mutual interest and concern for the group was the safety and quality of biomedical products throughout their lifecycle, which would cover CMC changes (Institute of Medicine, 2013a). The workshop reiterated the benefits of harmonized standards which included reduction in costly duplication efforts, encouragement of knowledge & experience sharing amongst regulators and scientists (especially where expertise or regulatory capacity is low) and optimization of limited resources (Institute of Medicine, 2013a). The workshop recognized the current lack of common understanding in the various terms used in relation to “standardization” of requirements, regulations, processes or even structures – this included the terms harmonization and convergence (Institute of Medicine, 2013a). It confirmed that convergence was becoming a widely used term and had a broader outlook as compared to the understanding of harmonization. Harmonisation was more rigid whereas convergence was more flexible in approach and could mean different things to different regions (Institute of Medicine, 2013a). A PAHO delegate noted that even though PANDRH was initially set up to promote regulatory harmonization in the region, the actual process aligns more with convergence where markets look for common ground within the structure of recognized standards (Institute of Medicine, 2013a). It was also cited that certain markets within the LATAM region do not have robust regulatory capacity and may not prioritize regulatory harmonization or standardization. Technical guidelines have been drawn up, however, there is no legal backing for markets to implement consistently (Institute of Medicine, 2013a). The organization is currently supporting the strengthening of regulatory capacity across the region. The summary stipulates that harmonization or convergence is hard to measure as the regulatory environment is constantly changing hence to improve it may just be as challenging (Institute of Medicine, 2013a).

The summary assessed APEC’s initiatives of which the ASEAN-PPWG is a part. It clarified that the Life Sciences Innovation Forum (LSIF) of APEC, which is its regulatory harmonization arm, does not provide harmonized guidance but rather promotes the use of existing international guidelines and best practices which accommodate the differing paces of individual countries (Institute of Medicine, 2013a). APEC aims to use convergence to standardize requirements. The summary also highlighted challenges with CMC reviews under the manufacturing standards and process session. It highlighted the

lack of harmonization of the dossier content in relation to the CMC sections of the dossiers across markets at initial submission, which later produces complexity in managing the post-approval stage (Institute of Medicine, 2013a). Harmonized guidance implemented inconsistently and at varying times, coupled with differences in categorizations of changes, increases the global complexity of life cycle management (Institute of Medicine, 2013a).

This workshop was mainly concerned with harmonization initiatives in general, mostly on the MAA activities, however, the section on CMC highlighted the gap and challenges of a divergent regulatory landscape (Institute of Medicine, 2013a).

According to an industry paper written by The Regulatory Affairs Services (TRAC) in 2015, a regulatory consultancy, their experience showed post-marketing license variation applications to be challenging in Latina markets (TRAC services, 2015). The paper focused on Argentina, Mexico and Colombia and cites that challenges occurred due to diverse regulatory requirements and long lead times for review, sometimes of very minor changes. However, it is anticipated that regulatory requirements will become aligned across the region, and it seems small steps are being made towards a system of co-operation and recognition across the Latina region (TRAC services, 2015).

Lokesh et al, 2015 compared the post-approval submission and approval process between the EU, US, India, Saudi Arabia and Singapore (Lokesh, Gupta and Belagoankar, 2015). It highlighted the different categorizations of CMC changes for Singapore which are MIV1 (MIV = minor variation); MIV2 and MAV1 (MAV = major variation) and MAV2 (Lokesh, Gupta and Belagoankar, 2015). The numbers provide further sub-categorisation of a minor or major variation. Interestingly it points out different review timelines of the same change, when applied to the different dossier types that exist for Singapore, i.e. full, abridged or verification dossiers (Lokesh, Gupta and Belagoankar, 2015).

Regulatory requirements for post approval changes in Japan, Canada and Malaysia were summarised in an article by Sukumaran (Sukumaran and Venkatesh, 2020). The Malaysia categorisation is similar to Singapore as described by Lokesh et al (Lokesh, Gupta and Belagoankar, 2015), however Singapore has a second Major variation category compared to Malaysia. Malaysia's post-approval variations can be categorised as Major (MAV); minor (MiV-N or MiV-PA; notification or prior approval) (Sukumaran and Venkatesh, 2020). An MiV can be rejected with the consequence of the Marketing Authorisation Holder (MAH) having to cease application of the already implemented variation. The Agency reserves the right to re-categorise the application type (Sukumaran and Venkatesh, 2020).

Chong et al re-emphasized APEC's drive towards convergence among APEC economies and expressed key performance indicators in areas of regulatory practice that could be used to measure each market's level of convergence (Chong, Lim and Tominaga, 2018). "Regulatory cooperation" also highlighted by Tominago, is seen to be complimentary to regulatory convergence, where cooperation means information exchange, work sharing, reliance and recognition (Tominaga, 2020).

Brazil's regulation RDC 48/2009 for post-approval changes was replaced by RDC 73 in 2016. This regulation classified post-approval changes and set out the criteria and documentation required to file the various changes. The new classifications have similarity to the US and EU classifications (Hoey, 2017). The information extracted from the ANVISA website was in Portuguese which had to be translated into English. This was highlighted as a potential barrier to harmonisation initiatives. The thesis compared US, EU, China, Brazil, South Africa, Russia to primarily assess the best regulatory strategy to filing a change in manufacturing site (Hoey, 2017). It highlighted differences and similarities in requirements for these six markets.

An article published in the WHO Drug Journal in 2018 (Taneja, Chacko and Kedar, 2018) assessed CMC requirements in Low and Middle Income Countries (LMIC) as per WHO Criteria. Apart from Chile which was classed as a High-Income market, all the other 5 Latin America markets under consideration, were classed as LMIC in a list published by WHO in 2017 (WHO, 2017). A significant portion of the global burden of disease is borne by the LMIC, hence the need for better visibility and interpretation of CMC requirements is vital to ensure patients get access to quality products in good time-, however, this has been challenging for the LMIC (Taneja, Chacko and Kedar, 2018). The article spelt out the implications of this challenge as being higher costs in producing the medicines and delayed patient access (development time & cost essentially). To increase visibility of the different requirements across these LMIC markets, WHO is partnering with Clarivate Analytics to pilot a database that will house all these different requirements with their correct interpretation (Clarivate, 2018). This will enable industry to access the relevant information that will enable them to make informed decisions concerning how and when they submit certain CMC variations to the various markets and minimize the challenge in finding, navigating and planning the submissions (Taneja, Chacko and Kedar, 2018). The article went on to explain that the database could help efforts aimed at harmonising and streamlining local, regional or global regulatory requirements to accelerate development

and delivery of medicines to patients. Therefore, WHO recognizes that requirements are not streamlined but it is advantageous to do so. Secondly, if CMC requirements were streamlined across the region, it would be easier to access the information and possibly easier to interpret. The database is a paid service (Clarivate, 2018).

In an independent report compiled by CIRS, lack of clarity on CMC requirements in the Latin America region, was also raised as a hindrance to expediting the review process during the lifecycle of a medicine (CIRS, 2015).

A paper written by International Pharmaceutical Quality (IPQ) in 2010, after the implementation of the ACTD in 2009, commented on ASEAN's plans to develop a common set of core CMC guidelines for the region (IPQ, 2010). Indonesia was assigned lead country responsible for developing the Quality guidelines. In the draft variation guidelines, definitions of major & minor as well as "do and tell" notifications were outlined (IPQ, 2010). For the draft proposed common regional timelines for review, however, no agreement could be made on these. Upon finalization, each country would be able to propose its own timelines for evaluation. It was observed that some markets had their own specific requirements as well (IPQ, 2010). The Malaysian variation guidelines at the time of the review, indicated that they are adapted from ASEAN variation guidelines of 2012 (ASEAN, 2012), however, they still incorporate market-specific guidance which diverges from the ASEAN guidelines (NPRA, 2013). The ASEAN guidelines also refer readers to market-specific guidelines for further information on some of the variations and for the specific review times which may differ from the ASEAN guidelines. In Singapore, CMC variations fall under the minor variation (MIV) category only (HSA website, 2020) whereas in Malaysia, some CMC variations are categorised as Major (MAV).

3.5 Review of Organizational websites

3.5.1 EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) in a position paper (EFPIA, 2017), confirmed that post-approval CMC changes are critical to continuously improve existing medicines and are as important as bringing new medicines to market. The organisation believes that the requirements to submit and review variations in multiple markets are becoming more complex and that international collaboration and cooperation towards regulatory convergence is the way to address the challenges of

increased workload for the National Regulatory Agencies (NRA). In the opinion paper (EFPIA, 2017), they state that industry believes that convergence will enable companies to prepare dossiers for global submission more efficiently, ensure global implementation of manufacturing, quality and safety-related quality changes more efficiently, and thus ensure patient access to an unbroken supply of high-quality medicines. Challenges currently encountered include: differing classification systems, specific local requirements, unpredictable and variable approval timelines, divergent decisions by regulatory bodies, variable implementation timelines (EFPIA, 2017).

In 2016, Brazil's NRA (ANVISA) issued guidelines in relation to streamlining their CMC requirements (Mittelstand Global, 2016). This new guideline seemed to align the categorisation of CMC variations to international standards, i.e. ICH as noted by Hoey (Hoey, 2017). Amongst the documents introduced was the Company Technical Change Report, abbreviated in Portuguese as PATE (Mittelstand Global, 2016). This document is to enable companies to carry out risk assessments in submitting CMC changes. Again, EFPIA drafted a concept paper (EFPIA, 2016) provided by FS, to be submitted to ANVISA for their consideration due to the complexity of this PATE document and the requirement to submit it for every CMC variation that a company files to ANVISA. This document is unique to Brazil within the Latin America region. EFPIA acknowledged ANVISA's awareness of the importance of regulatory convergence in reducing regulatory burden for handling CMC changes and facilitating mutual collaboration among agencies worldwide (EFPIA, 2016). However, some recommendations to ANVISA were for the assessment to be part of the change dossier and not a separate document and possibly for it to apply to moderate and major changes only instead of to every CMC change (EFPIA, 2016). It is uncertain whether this concept paper will be publicly available in future or whether some sections will be included in a later EFPIA document.

3.5.2 PANDRH

Within the Latin America Region, the Pan-American Network for Drug Regulatory Harmonisation (PANDRH) under the Pan American Health Organisation (PAHO) has been the main organisation leading harmonization initiatives within the Region through establishing technical guidelines for harmonization of processes and standards to improve drug quality; and programs for the strengthening of national regulatory agencies via technical training programs. PANDRH, however, cannot enforce a common set of rules across the Region, like the European Medicines Agency. The markets can decide what

guidelines to implement and when to implement it (PAHO website, 2020a). The VIII PANDRH meeting held in 2016, approved 3 projects out of the 5 presented (PAHO website, 2020a). One of them to be implemented in 2017 being:

“Network for sharing information on the Americas on global regulatory convergence initiatives”, suggested by Brazil (PAHO website, 2020a). The fact that this project was chosen out of 5 others presented, shows that there is a growing interest in streamlining efforts within the region. How regulatory convergence will be managed and what it will look like is, as yet, unclear. The outcomes of the project which was intended to last throughout 2017 have yet to be published, the results would be a good indicator of the direction the region is moving. As of October 2020, the PANDRH Secretariat confirmed that the report is not yet published. This was confirmed via an email request to the Secretariat for the report when it was not found on the website. This project came out of the backdrop of the VII Conference of PANDRH in 2013 (PANDRH, 2013) where the Region adopted the Strategic Development Plan 2014-2020 (PANDRH Secretariat, 2014). A presentation given by a representative of FIFARMA highlighted the importance of convergence to international standards; multilateral agreements between countries in the region and agreements with other harmonization initiatives e.g. bringing benefits to patients, regulators, industry, regional integration (Oliveira, 2016).

So far, PANDRH has issued 11 technical documents consisting of guidelines, frameworks, requirements and recommendations for the region. These documents cover the following subjects: (PAHO website, 2020b)

- harmonized requirements for the licensing of vaccines;
- good practices for control laboratories and a self-evaluation guide;
- good pharmacovigilance practices;
- good laboratory practice;
- evaluation of similar biotherapeutic products;
- equivalence requirements; new medicines registration;
- medicine promotion and advertising.

None of these technical documents relate to the streamlining of post-approval CMC variations.

In 2018, PANDRH had their IX conference celebrating 20 years of PARF network (Panamericana para la armonizacion de la reglamentacion farmaceutica) existence. In an online article, it stated that “Although in the last 20 years, progress has been made in the Americas region in harmonizing national regulatory systems to guarantee access to safe,

effective and of quality medicines, much more remains to be done to have health systems that function well and that seek to achieve universal health” (PAHO, 2018). There was, however, no specific mention of harmonizing post-approval CMC variations.

As at the time of the systematic review, there were no projects dealing with or discussing CMC variations and efforts to streamline within the region.

An online article on pharmtech.com has stated that the Latin American region was most likely to consider convergence over harmonisation due to each market having its own regulatory system, strong political background and policy approach to healthcare and pharmaceuticals (Sackman, 2013). Convergence is a voluntary process in which markets agree to work toward regulatory requirements that are similar but not fully harmonised. Harmonisation would require changing laws in each country which may prove more difficult to achieve due to the sovereignty of each market (Sackman, 2013). How this convergence will be facilitated or whether the discussion is truly about convergence toward other international standards is yet to be defined.

3.5.3 FIFARMA

No specific documents relating to post-approval variations were identified on the FIFARMA website, however, a training was delivered in 2019 to FIFARMA by APEC RHSC. The training focused on development of Centres of Excellence, facilitated by APEC, on convergence/harmonisation for regions (FIFARMA, 2020b). The aim was to try to pull together the various harmonization initiatives across the regions. This is the closest to comparing initiatives between LATAM and ASEAN. This shows that there is interest in learning from other regions by LATAM markets (FIFARMA, 2020a).

3.5.4 ICH

Brazil became a Regulatory member of the ICH in 2016 (Huynh-Ba and Beumer Sassi, 2018). As at 2018, Cuba, Mexico, Argentina, Colombia and PANDRH are observers (ICH website, 2020). This would suggest these LATAM markets are looking to draw on experience from the ICH and more established agencies like the European Medicines Agency (EMA) and Food & Drugs Administration (FDA), and possibly move towards use of full ICH requirements. This may further suggest that instead of the markets streamlining requirements within the Region, it is possible that they are working towards adopting international standards. As of December 2020, Chile was the only market out of the six

that was not an observer or member of ICH. The ASEAN and APEC are also observers whilst Singapore HSA is a regulatory member (ICH website, 2020). The ICH Q12 guideline focusing on post-approval life cycle management was endorsed in 2014 and is currently being implemented by EMA & FDA. Brazil and Singapore as regulatory members of ICH are yet to initiate implementation of this guideline (ICH, 2020). The Guideline is “proposed to provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle” (ICH, 2019). It builds upon Guidelines Q8-Q11. The ASEAN Quality guidelines were based upon Q11 in addition to WHO guidelines as cited by Latzel (Latzel, 2007).

3.5.5 ASEAN CMC INITIATIVES

In 1997, ASEAN vision 2020 was launched to create an ASEAN community with a common market by 2020. The Pharmaceutical Product Working Group (PPWG) was also established in 1997 to aid and assist the harmonisation of pharmaceutical standards (Latzel, 2007). Through the PPWG, national regulatory agency requirements and good international regulatory principles were discussed and reviewed. ASEAN regulations were compared to other internationally accepted standards, e.g. ICH and WHO guidelines (Latzel, 2007). From these meetings and discussions, harmonisation initiatives were divided into Safety, Quality and Efficacy. Chemistry, Manufacturing and Control variations were discussed under the Quality topics (Latzel, 2007). ASEAN adopted all WHO quality guidelines and 11 ICH quality guidelines. The guidelines mainly cover generics as these are the majority of pharmaceutical products manufactured locally (Latzel, 2007). Some guidelines were also developed regionally where ICH guidelines did not exist. The regionally developed variation guidelines were adopted in 2012 and can be found on the ASEAN website (Latzel, 2007; ASEAN, 2012). The guidelines are based on a mixture of internationally recognized standards plus some locally developed ones. Implementation of these guidelines has been protracted and is still ongoing consequently, although progress has been made, differences remain. Depending on regulatory capacity, variation guidelines differ from market to market (Latzel, 2007). Data for this thesis was taken from the ASEAN Secretariat historical documents, there was no detailed methodology.

Wittner et al described the ASEAN change management for post-approval variations (Wittner, Theisen and Metzner, 2019). They cite the ASEAN Variation guideline which outlines categories and supportive documentation but it excludes biologics, which is also outside the scope of this research (Wittner, Theisen and Metzner, 2019). The guidelines also do not cover timelines and procedures; the guidelines for the specific country in which the change is being filed have to be consulted. The change categories captured are Major (MaV); Minor (MiV-N) or Minor Prior Approval (MiV-PA) as confirmed by Sukumaran et al as well (Wittner, Theisen and Metzner, 2019; Sukumaran and Venkatesh, 2020). The change classification and document requirements are comparable with EU requirements. Singapore is noted to have clear guidance on timelines for the variations, but other member states have not issued clear guidance especially for MaV (Sukumaran and Venkatesh, 2020).

Regulatory harmonisation efforts in the ASEAN region are between alignment, harmonisation and implementation as reported by Teo et al (Teo, Foerg-Wimmer and Chew, 2016). Large strides have been made through the ASEAN Consultative Committee for Standards and Quality Pharmaceutical product Working Group (ACCSQ PPWG), which works to address the removal of technical barriers to trade in the ASEAN. However, they point out that the various NRAs implement in their own time according to their resources and capabilities, termed as the ASEAN-X approach (Teo, Foerg-Wimmer and Chew, 2016). This World Bank study report offers recommendations to overcome challenges in the region when it comes to implementation of the ASEAN standards/requirements/guidelines (Teo, Foerg-Wimmer and Chew, 2016). The report gives a general overview and review of harmonisation initiatives till date but is not specific to the area of post-approval variations.

To show the differences in CMC post-approval variation classification across the markets under study and the ASEAN guidelines, Table 3.3 captures the classification of three variations, considered as important as outlined in Chapter 1. The Thai guidelines could not be obtained at the time of the systematic review, therefore only Singapore and Malaysia are presented, comparing them to the ASEAN guidelines. The Thailand FDA website is presented in Thai and is not easily navigated, thus guidelines were not easily searchable on the website.

	Singapore	Malaysia	ASEAN
Variation	Addition or replacement of the manufacturing site of the drug product		

	Miv-1, prior approval, can be submitted by an abridged (120 days) or verification route (90 days). These timelines are not fixed, timelines could vary depending on whether they are grouped with other variations types; completeness of query responses	MaV- prior approval, 60 days review, 30 days for applicant responses, and 30 days for NRA to respond to query responses. After 3 rd correspondence with NRA where responses do not fulfil requirements the application can be rejected. Change of manufacturing site applications are categorised into 5 types with each requiring a different set of documentation.	MaV; review timeline specific to each country proposal. The 'timeline' and 'implementation of the variation' are subject to country-specific proposals and be made publicly available.
Variation	Change in Shelf Life		
	MiV-1	MaV	MaV
Variation	Change in storage condition		
	MiV-1	MaV	MaV

Table 3.3 Comparison between three CMC variation classifications based on Singapore, Malaysia and ASEAN Variation guidelines

MiV- minor variation; MaV- major variation.

The data presented confirms Sukumaran's observations of the differences in classification of variation categories cited earlier (Sukumaran and Venkatesh, 2020).

In Table 3.4, the ASEAN, Singapore and Malaysia requirements for the “change in DP manufacturing site”, one of the variations cited in Table 3.3 and which the research identifies as an important change for the markets under study, are compared.

Requirement	ASEAN^	MALAYSIA*	SINGAPORE**
GMP or CPP	√	√	√
Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batches) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).	√	√ (2,3,4)	√ (or CoAs)
Original CoA from proposed site		√ (2,3,4)	
Stability data as per ASEAN Guideline	√	√ (1,2,3,4)	√
Revised drafts of the package insert and labeling	√	√	√
Validation scheme and/or report of the manufacturing process of proposed site	√	√(1,2,3,4)	√
Comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dose form	√	2,3	√
A commitment to provide comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dose form (entitled for biowaver or for innovator products if applicable)		1,5	
Product Formula	√	√	√

Release and shelf-life specifications of drug product.	√	√	√
Batch numbering system	√		√
Specification of drug substance	√	√	-
Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).	√	√ (2,3,4)	√
In the case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable).	√		√
A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action).			√
For modified release oral solid dosage form, justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable the data shall be provided to the Health Sciences Authority upon request).			√

LoA from the product owner to authorize Product Registration Holder to submit the change of site application. In the case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.		√	
Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture.		√	
Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product are the same as already approved.			
Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post-change products		(1)	
Letter of commitment to submit stability data, certificate of analysis, process validation report (where applicable) and sample for laboratory testing within 6 months of approval of site change.		5	
A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.		1,2,4	

Table 3.4 ASEAN, Singapore and Malaysia requirements compared for the “change in DP manufacturing site” variation.

^For the ASEAN guidelines, the requirements do not apply to a batch release site, where manufacturing process is also affected, further requirements apply (ASEAN, 2012).

*The 5 types of manufacturing site changes in Malaysia (NPRA, 2018)

**For Singapore, these requirements only apply when there is a change to the site location, and do not cover any scale-up changes, change in manufacturing process, or changes in components or composition, for which other requirements may apply. Also do not cover batch release or packaging site (HSA website, 2020).

Again, the information presented here confirms previous observations of the ASEAN markets showing inconsistencies between the ASEAN guidelines and NRA-specific guidelines; even though they are supposed to be harmonized.

3.6 Discussion

In this systematic review 1368 articles including grey literature were screened. 17 articles were selected which provided information regarding the CMC post-approval landscape in Latin America and ASEAN with emphasis on convergence or harmonisation initiatives. 10 articles covered ASEAN data with 3 being NRA/Network guidelines. 8 articles covered LATAM information. 1 article provided a general overview of the global CMC landscape from the industry perspective (EFPIA, 2017).

From the few articles retrieved (a mix of grey literature and peer-reviewed journals and secondary data), it may be observed that research or discussion on the topic of streamlining CMC post-approval requirements in Latin America or ASEAN is yet to be explored more widely and not enough data has been published on the topic.

The review showed that no empirical studies have actually been conducted to confirm whether LATAM region had intentions of streamlining CMC requirements and whether this would be done via harmonisation or convergence, so a knowledge gap is confirmed. For ASEAN harmonization of CMC requirements, only one document mentioned how the harmonization of the CMC requirements occurred, though not in detail (Latzel, 2007).

Overall, the findings show that there is interest in streaming post-approval CMC variations to improve the safety and quality of medicines, but standardisation is not easy to achieve because of the ever-changing regulatory landscape, especially in LATAM. For LATAM, there remains a lack of clarity and visibility, of CMC post-approval variations guidance across markets. For ASEAN, a set of harmonised guidelines exist however individual market disparities remain.

ASEAN

The ASEAN region set out to standardize CMC post-approval requirements together with MAA requirements through agreed ASEAN guidelines. However, it can be noted that individual markets continue to have different variation categories, review timelines and even requirements though ASEAN aimed to completely harmonise requirements (Wittner,

Theisen and Metzner, 2019; Sukumaran and Venkatesh, 2020). The review highlights that the ASEAN allows a level of flexibility for market-specific requirements and timelines as stipulated in the guidelines. This flexibility was built into the harmonization process from the onset suggesting consensus by markets on this arrangement, and the value for market sovereignty (IPQ, 2010); still allowing markets to make final decisions based on their CMC landscape (IPQ, 2010). It also suggests that even though the ASEAN set out to harmonise requirements, the goal was not to have the exact same requirements for each market. This raises the question as to whether harmonization as defined by ICH was the initial goal, and if it was, what led to the current situation? The differences in classification and timelines increase the challenges and complexity of navigating post-approval CMC variation submissions for industry (Taneja, Chacko and Kedar, 2018). The review highlights the nature of ASEAN as an organization operating through member-state consensus and not through enforcement. Despite the above, it can be observed that ASEAN prioritizes standardization of CMC requirements as much as MAA requirements. It also highlights the desire for the markets to work together.

The apparent non-harmonisation in the ASEAN region is a knowledge gap that the thesis aims to explore through empirical evidence and hopefully explain why this has occurred.

LATAM

The review highlights that the region is taking steps towards convergence based on decisions to align regulatory guidelines to international standards and markets joining ICH (Hoey, 2017). There are also ongoing discussions through PANDRH aiming more for convergence than harmonization; though these discussions are not specific to CMC post-approval variations. However, there is no empirical evidence provided to support this hypothesis.

The review highlights regulatory cooperation, recognition and collaboration towards regulatory convergence as varying ways of addressing challenges such as divergent decisions, duplication and increased workload as well as variable timelines in the region. Tominaga set out to clarify and define the meaning of these terminologies based on internationally accepted definitions by WHO/FDA/APEC/ICH, as there has been ambiguity in the use of these terms as they have emerged (Tominaga, 2020).

In spite of these various pathways, the review could not identify the most suitable pathway that LATAM would benefit from or would be more practical for the region. It is clear though, that an awareness exists that no single authority can claim to be fully resourced to tackle post-approval issues. This suggests that it would be practical and beneficial for markets in

the region to leverage resources and knowledge to enhance efficiencies either by harmonizing within the region or converging to international standards.

The thesis seeks to first, explore if standardising CMC variation requirements is a priority for the region. It will also help to confirm or refute whether there are various processes or pathways through which convergence might be occurring in the region and how they may potentially interlink.

ASEAN versus LATAM

Based on the review, both regions have a type of regulatory body pulling the efforts of the markets together. PANDRH for LATAM stands out as the main organization enabling discussions about standardization but just like ASEAN, PANDRH's role is more of guidance and not enforcement. The review suggests that through the ASEAN, the member states have reached some level of consensus with requirements compared to LATAM. As at the time of this review, no other review or article was comparing LATAM streamlining initiatives to ASEAN initiatives.

Quality of data/review

In terms of quality, there was more grey literature than peer-reviewed journals, the grey literature provided insight from an industry and NRA perspective. Almost all the articles did not provide detailed methods or sampling (Lorenc, Petticrew and Whitehead, 2014), which minimises the replicability and reliability of the data. The quality of the selected articles was not uniform because many of the articles did not have detailed reporting on methods, data collection and hence a proper comparison could not be carried out as would be required in a systematic review (Harden *et al.*, 2009). For this reason, no attempt was made to weigh the findings by quality rating (Lorenc, Petticrew and Whitehead, 2014).

Strengths and weaknesses of the systematic review

The review was done over varying time points which highlighted any general movement or updates in the information, but this was observed to be minimal. The review, however, was able to provide the relevant information to answer the research question or to at least highlight the gap in knowledge about the research question (Harden *et al.*, 2009) which this thesis aims to address.

Comparison to the wider field

So far no articles have been identified comparing initiatives to streamline CMC requirements within LATAM, nor comparing LATAM to ASEAN markets. There are, therefore, undeniable gaps in knowledge that this research seeks to explore and fill. Interestingly, there are currently on-going discussions around streamlining of requirements for post-approval changes for biologics, biosimilars and vaccines but the same doesn't seem to be happening uniformly for small molecules (EFPIA,2019; Dellepiane *et al.*, 2020, CASSS 2015). The research aims to find out if discussions on CMC requirements for small molecules are a priority for the LATAM region. Biologics, biosimilars and vaccines are outside the scope of this thesis.

There are no previous systematic reviews on harmonization or convergence of post-approval CMC variations for LATAM or ASEAN so this systematic review is potentially the first to be carried out in this area.

There are also no reviews covering harmonization or convergence in the wider field of MAA submissions and requirements, though there are many articles covering the subject in general in differing contexts (Vogel, 1998; Lakkis, 2010; Molzon *et al.*, 2011; Timmermans and Tavory, 2012; Singh, 2015; Pezzola and Sweet, 2016).

As observed by the dates of these publications, harmonization is not a new topic in the pharmaceutical industry, especially in relation to MAA submissions.

The most extensive work completed on harmonization initiatives, at the time of this review, is a book by PL Lezotre entitled *International Cooperation, Convergence, and Harmonization of Pharmaceutical Regulations: A global perspective* (Lezotre, 2014a). It highlights worldwide harmonization initiatives, benefits of harmonization in general and challenges still being faced. Little is mentioned about post-approval CMC requirements in the publication.

Overall, the objective of the systematic review was to find any evidence of harmonisation, convergence or streamlining activities of post-approval CMC variations in LATAM or ASEAN. The review highlighted that there are common guidance documents for the ASEAN markets in the ASEAN guidelines, however, each ASEAN market has their own variants of the ASEAN guidelines. There was no discussion on whether the region was truly harmonised or not and what exactly ASEAN set out to achieve initially as pertains to standardisation of CMC requirements; a gap this thesis seeks to explore and try to answer.

For the LATAM markets, there is discussion of the benefits of streamlining but no concrete evidence of the region moving in the direction of convergence or harmonisation. No research work has compared ASEAN streamlining initiatives to LATAM initiatives, which

this thesis seeks to explore. It could be that there are notable principles that LATAM can learn from the ASEAN.

3.7 Limitations

Since there were only a limited number of peer-reviewed articles on the topic, the use of the grey literature (i.e., material that has not been through a peer-review process) was used to supplement the peer-reviewed articles. In these cases, however, the information was usually backed up by several sources (triangulation) (Adams *et al.*, 2015). The included articles were highly heterogeneous in terms of population (not always specific to markets under study); setting (sometimes within a global context and not regional) and aims (not necessarily focusing on streamlining initiatives) (Lorenc, Petticrew and Whitehead, 2014). However, information could be extracted from each article which related to the research question.

Most articles/grey literature did not state the methodology used, however, from reading them it appears authors accessed publicly available guidelines and regulations regarding requirements which they reviewed. A thesis database such as Ethos could have been used to search for relevant theses to ensure these were captured instead of relying on Google Scholar alone. The Google Scholar search did however yield one unpublished thesis; without searching a thesis database, it cannot be confirmed that other theses on the subject could be available.

The systematic review reveals that there is still a knowledge gap to confirm with empirical evidence whether LATAM is seeking to streamline CMC post-approval variations and which process will be appropriate or practical for the region. This thesis seeks to address this gap. The next Chapter explores the ASEAN CMC landscape and factors that have aided implementation of CMC streamlining initiatives in Singapore, Malaysia and Thailand.

The next chapter (Chapter 4) reviews the results of the ASEAN case study.

4 RESULTS FROM ASEAN INTERVIEWS

4.1 Introduction

The ASEAN region stands out for its progress in harmonizing post-approval CMC variation requirements for pharmaceutical companies to make amendments to existing drugs. Formed in 1967, with the signing of the Bangkok declaration, its aim was to create a common community to protect its members from external or foreign threats; to alleviate intra-ASEAN tensions and to promote the socio-economic development of its members (Narine, 2008). ASEAN's founding members were Indonesia, Malaysia, the Philippines, Singapore, and Thailand, three of which are being studied in this research. Over the years, other countries joined, namely, Vietnam, Brunei, Lao, Myanmar and Cambodia making up what is today the ten member states of ASEAN. Heads of state/Government and foreign ministers meet to deliberate and agree on issues pertaining to the region. One of the aims to establish an ASEAN economic community led to the agreement of eleven priority sectors that needed to be liberalised and integrated, these were: wood-based products, automotives, rubber-based products, textiles and apparel, agro-based products, fisheries, electronics, e-ASEAN, healthcare (pharmaceuticals), air travel and tourism (Latzel, 2007). Working groups under each sector were set up to facilitate discussions and decisions. The Pharmaceutical Product Working group was charged with accelerating the economic integration of the priority sector healthcare, which covers pharmaceuticals (Latzel, 2007; ASEAN website, 2022).

It is perhaps surprising that the ASEAN region was able to make such study progress. The region has diverse cultural, political and economic systems, as well as different histories and governance styles, which can hinder consensus and regional cooperation (Ishikawa, 2021).

To the researcher's knowledge, there are only a few published papers which have sought to investigate the processes that led to harmonization in ASEAN. One investigation was an unpublished Master's thesis from 2007, which provided a summary of the ASEAN regional integration with a focus on pharmaceutical harmonisation (Latzel, 2007). In 2010, Mason School of Business published a general assessment of 8 ASEAN markets and their level of interaction with and implementation of the ASEAN guidelines in relation to the healthcare market based upon their political, economic and social conditions. Pettman (2013) also reviewed technical barriers to trade in the ASEAN region and found that multiple barriers remained, including lack of strong leadership and political will at both regional and national levels (Pettman, 2013); and lack of well-established structures e.g.

ASEAN secretariat only has limited powers and sway over the member states (Pettman, 2013). Finally, Lezotre (Lezotre, 2014c) speaks about harmonisation and its role in improving the region's market attractiveness to industry.

Yet, it remains unclear how harmonisation of CMC requirements was achieved and how effective CMC harmonisation is in practice. The existing studies also tend to draw heavily on the perspectives and opinions of a few selected experts, rather than aim for a broad representation of the entire market and players involved.

To address these gaps, this Chapter explores the views of key stakeholders in pharmaceutical companies to ask three main related questions. How did ASEAN achieve regional harmonization? What were the motives and incentives for doing so? What are the current major barriers to effective implementation in the ASEAN region, if any?

4.2 Method

Full details of the qualitative methods are described in Chapter 2, Section 2.7 to 2.8.

Briefly, here the main interviewee characteristics, semi-structured interviews and secondary data analysis are reviewed.

Due to the mention of technical terms and regulatory processes from participant responses, otherwise not explained elsewhere, grey literature was used to clarify concepts and terms, providing context for greater understanding and awareness.

4.2.1 Interviewee characteristics

Participants were recruited through purposive and snowball sampling. In total, nine RA participants agreed to be interviewed out of a potential fifteen. Six participants did not respond to email follow up and hence interviews could not be scheduled. Out of the nine, none withdrew consent.

Table 4.1 lists the characteristics of the participants and identifiers (n=9). The sample included four males and five females. On average, participants had 10 years' experience. Most participants had regulatory experience across ASEAN as well as other regions, for example LATAM or Middle East. The definitions of the company type are also provided.

Date of Interview	Identifier	Regions/markets of regulatory experience	^Company type	Years worked in Regulatory	Experience specific to the research	Duration of interview
29.11.17	AS1	Asia, Japan	Medium sized pharmaceutical company	12yrs	Regulatory strategy, compliance	1hr 13 minutes
22.6.18	*AS2	Singapore	Small generics company	4 years	Regulatory strategy, CMC regulatory strategy, generics	12 minutes
29.01.19	AS3	Asia, EU and LATAM	Free-lance Consulting	20 years	Regulatory CMC experience	38 minutes
27.5.20	AS4	Asia including ASEAN markets	Consultancy	25 years Reg, 20 years ASEAN	Regulatory strategy	23minutes
5.6.2020	AS5	Asia including ASEAN markets, Middle East and Africa	Medium sized pharmaceutical company	23 years, 15 years ASEAN	Regulatory strategy, Medical devices	50 minutes

6.6.2020	AS6	Asia region including ASEAN markets	Small sized pharmaceutical company	11 years	Regulatory strategy	1hr 8 minutes
9.6.2020	AS7	Asian including ASEAN markets, Middle East, Latin America	Large sized pharmaceutical company	21yrs	Regulatory strategy	38 minutes
15.6.2020	AS8	Asia, Africa, Middle East	Large sized pharmaceutical company	25yrs	Regulatory strategy, policy, medical device	56 minutes
6.7.2020	AS9	Asia markets including Malaysia, Singapore, Thailand	Medium Sized Pharmaceutical company	9-10 years	Regulatory CMC experience	1hr 5min

Table 4.1 Characteristics of ASEAN participants

*As per section 4.2, AS2 was not used in the data analysis

^small pharmaceutical company on average has about 500 employees with a revenue of less than \$1B (UPM Pharmaceuticals, 2020)

^mid-sized pharmaceutical company on average does between \$1B-\$4B in annual sales. They are often concentrated in a smaller number of therapeutic areas than their larger peers, and while they're typically ^multinational, they often have a specific geographic as well (Startuphealth, 2019).

^Large pharmaceutical company usually refers to the very largest employers, those with tens of thousands of workers and billions of dollars in revenue (UPM Pharmaceuticals, 2020).

^Generic companies manufacture medicines where patent protection has expired from the innovator company (Dunne *et al.*, 2013).

^ Consultancy Pharmaceutical consultants advise companies on the development and sales of drugs and pharmaceuticals. They have expert knowledge on industry regulations so that they can aid and better enable companies to effectively deliver medical treatments to those in need (Ascent, 2023).

4.2.2 Semi-Structured Interviews

All interviews were conducted via Zoom. Online interviews did not diminish the quality of the interview process, especially with the use of the video. The researcher and participants were able to develop rapport and have clear communication, just like a face-to-face interview (Lobe, Morgan and Hoffman, 2022). Participants undertook the interviews in their workplaces in closed offices, after work colleagues had gone home in the case of open offices, or at home in a quiet environment away from others in the home to maintain privacy and avoid disruptions (Maldonado-Castellanos and Barrios, 2023). The researcher interviewed mostly from a private room at home. Interviews covered three major areas, including what were the drivers and history of harmonisation in the ASEAN region; the effectiveness of harmonisation to date; and any barriers and enablers to the harmonisation process. A major area explored was whether participants believed harmonisation of post-approval CMC variations had been achieved in the region and to what extent.

Upon interview completion, one participant (AS2) was excluded, due to inadequate internet connectivity and difficulty in understanding their accent. The researcher chose not to reschedule because the short interview made it clear that AS2 lacked the requisite knowledge. This left a total of 8 interviews completed for subsequent analysis. Interviews were transcribed verbatim with Rev (*Rev*, 2020).

The transcripts were provided to all participants for their review by email. No participants sent back any amendments to their individual transcripts, however, three transcripts had sections requiring clarification to make the responses clearer or had typos or inaudible

words to be clarified. For those three participants, the emails sent with the transcripts highlighted these areas for participants to respond to them. One participant requested a Zoom call to better understand the clarifications needed and to answer them via Zoom. The participant signed a second consent form for this call; however, this call is not captured in Table 4.1 as it was not another interview but a clarification call. The Zoom call was conducted within a week of the request and lasted ten minutes. All amendments were incorporated into the transcripts, and the transcripts were analysed. One such correction is highlighted below, as an example, with the updated section in bold and the original text in brackets:

AS8 “I should say, both Malaysia, and Thai FDA, Malaysia is the agency NHPA right? [So they, uh, they, uh, not as settled to be honest, as settled that in Singapore.] So they, uh, they, are not as open to be honest, as than Singapore.”

In this example, the participant’s meaning would have been lost if the researcher had assumed the meaning of ‘settled’ or tried to interpret it in their own understanding, even within the context of the wider response. Here, the participant was using the word ‘settled’ to denote the ‘openness’ of the NRA. As explained by McMullin, transcription can be influenced by the transcribers’ own assumptions and biases, hence, to limit this, participants were asked to provide their own clarifications to remain as true to the data as possible (McMullin, 2023).

The second participant responded to the clarifications by email within one week, and also commented that sending the transcripts back to participants was not good use of the participants’ time. The researcher clarified via email that the reviewing of transcripts was explained in the participant information sheet as necessary, since participants were not first-language English speakers and sometimes, due to connectivity issues, words may have been missed or rendered inaudible and, since the researcher was unable to transcribe the interview word for word whilst the interview was going on, these lapses were expected. The review was a way to overcome this hurdle and improve the validity of the transcript (Mero-Jaffe, 2011). Mero-Jaffe gives further benefits to the review of transcripts by participants such as: to overcome the researcher’s lack of hearing; clarifying unclear statements (as was the case for these 3 transcripts); as a courtesy to the participant; to uphold research ethics; and to avoid significant errors that may impact on the quality of the transcript (Mero-Jaffe, 2011).

The third participant did not respond to the email. The areas requiring clarification were put in square brackets i.e. [unclear] or [inaudible] and the transcript was analysed.

4.2.3 NRA Questionnaires/Interviews

The second group of stakeholders, the NRA personnel from the 3 markets were contacted via the use of a gatekeeper as outlined in Chapter 2. The gatekeeper was provided with the link to the online questionnaire, and the information sheet to provide to the NRAs. Initial contact was made, and follow-up occurred within 2 weeks as per the instructions provided to the gatekeeper. The gatekeeper received responses from all three markets and provided a summary by email on the 11th of March 2022. One NRA responded that they were unable to participate in the research. For the second NRA, the gatekeeper was advised to forward the information sheet to a higher official but did not receive a response following that. The third NRA responded positively and partially filled in the questionnaire (responded to General Information section only). The partial responses were unusable, i.e. responses were insufficient to perform any form of analysis. The NRA did not respond to the request within the questionnaire for a follow-up interview. None of the questions in the questionnaire were mandatory so the NRA was at liberty to answer those questions they were comfortable or able to answer. It was anticipated that NRA participation might be low, hence the use of different approaches and populations/stakeholders for data collection for the ASEAN markets were employed. One such approach was the use of secondary data to support triangulation and fill in gaps that other stakeholders could not address (Carter *et al.*, 2014).

4.2.4 Secondary Data

Based on the research objectives to learn the history and influences of CMC harmonisation in the ASEAN region, the researcher first searched the ASEAN website for any PPWG meeting minutes or ASEAN secretariat reports, which yielded no results.

During the systematic review, the researcher came across an unpublished Master's Thesis by Ruth Latzel, (Latzel, 2007) which discussed the 'Development of the ASEAN pharmaceutical harmonisation scheme.' The thesis pulled information from the PPWG meeting reports. In the thesis, it stated that all PPWG reports and presentations could be requested from the ASEAN Secretariat. Based on that information, the researcher

emailed the ASEAN Secretariat to request the PPWG meeting reports for historical insight and background information to ASEAN pharmaceutical harmonisation, especially concerning post-approval CMC requirement harmonisation. A response was received in February 2016 citing that the reports were confidential and could not be shared. Since Latzel's thesis covered the general history of the ASEAN pharmaceutical harmonisation process, even though not specific to post-approval CMC harmonisation, the researcher selected this thesis as one of the secondary documents to analyse for historical context on the ASEAN harmonisation process (Latzel, 2007). The thesis had no methods section so how the data was collected and analysed could not be verified. From the ASEAN, Malaysia and Singapore NRA websites, the researcher obtained the Post-approval CMC variation guidelines. These were also used in Chapter 2, the Systematic Review. The Thailand variation guideline (English) was provided by one of the ASEAN interview participants as the NRA website is in the Thai language and the researcher was unable to access the document directly. The guidelines provided comparative information across the 3 markets on their CMC post-approval variation requirements. The historical information gathered and data on the CMC requirements provided the researcher with valuable insights to help formulate some of the interview questions and follow-up prompts.

Analysis

The researcher read through the documents, looking for patterns and themes (inductive approach). Relevant information pertaining to the research question was extracted. Also any themes generated from the interviews and questionnaires were deductively searched for within the secondary data. Information from the secondary data was used within the results and discussion sections to triangulate information from the interviews and questionnaires (either corroborating or providing an alternative view).

4.2.5 Thematic Analysis

Interviews

As interviews were completed, they were provided to Rev transcription service for transcription with an average turnover of 24-48 hours depending on the level of interview data. In the reflexive journal, the researcher made notes of patterns that were emerging about the research objectives. The researcher also highlighted data that was different to the views they held due to their experience as a Regulatory Affairs Professional and any prior regulatory engagement with these markets (reflexivity). The researcher coded the interview transcripts manually using Braun & Clarke's Thematic Analysis method (Braun

and Clarke, 2006), as described in Chapter 2. Through reading the transcripts, the researcher immersed themselves in the data after which codes were generated to capture interesting features of the data which were of potential relevance to the research question (Clarke and Braun, 2014). 'Generated' because the researcher had to make active interpretive choices in generating the codes. The codes also analytically captured both semantic (surface) and latent (underlying) meanings from the data (Clarke and Braun, 2014). These codes were generated through the process of induction where no prior knowledge or theories were referenced in the process of coding. The codes came out purely from the data with no external influence apart from the researcher's own background knowledge, which they were aware of, and minimised, through the use of the reflexive diary (Nowell *et al.*, 2017). Even though inductive transcription analysis is always shaped to some extent by the researcher's standpoint, disciplinary knowledge and epistemology (Nowell *et al.*, 2017), by keeping a reflexive diary, the researcher was able to note ideas that differed from their experience or differed from what they thought they knew, to further alleviate any bias and keep the codes as true to the participant voices as possible. As a way of testing bias in the coding process, the first few pages of the first transcript were coded by a supervisor, Louise Hughes (LH), who has no prior knowledge or experience in Regulatory Affairs. It has been shown that the analysis of another person without the researcher's background could yield different results (Nowell *et al.*, 2017). The researcher's initial codes aligned with LH's codes which added some validity to the codes generated, concerning them coming from the data alone and not any preconceived notions or external influence of the researcher (Nowell *et al.*, 2017).

Codes with similar context/meanings were highlighted in the same colour within the transcripts. The codes were then collated in a separate Word document according to their colour highlights. As patterns emerged from the codes, the researcher created themes (these capture broader patterns of meaning) and assigned the groups of codes with similar context/meaning to these themes (Clarke and Braun, 2014). Themes were given definitions or contexts as a guide on which codes should be assigned to which themes. A screenshot of one of the themes and related codes as captured in Word is provided below:

Theme 6. Lack of coordinated leadership from ASEAN

AS4. p. 10 Who is ensuring or asking or mandating implementation of harmonized guideline? No one.

AS8 p.5. ASEAN has been established for approximately 20 years if I'm not there wrong, or even more than that, more than 20 years. And the PPWG meeting, if also I'm not wrong, it's more than 10 years. The working mechanism for PPWG is trying to harmonize the ASEAN guideline. So, but to be honest, the progress of such harmonization is it's way slower than what I expected. You can see how many, how many, uh, uh, guidelines they have published since 10 years. So more than 10 years ago, it's only like five, six guidelines. Variation could, is one, uh, BE study is one, GMP is one, this time, I even didn't see any significant guidelines.

Motivation and incentives for harmonisation- market attractiveness

AS1 pg 12 ...And the good thing about being harmonised right now for us young countries, I mean most of it is harmonised, not exactly all ... between these three countries is that you just repeat that one set of documents and you can file in all three countries

AS3 pg 15...actually, one of the things that drew them is that they wanted to be an attractive market, so that the people there, the local people, could benefit from having innovative products.

This process continued till all relevant codes had been identified and no new themes emerged from the data, at which point saturation could be said to have been achieved within the data set (Guest, Namey Emily and Chen, 2020). Full data saturation cannot be claimed due to the small dataset, however, as no new themes emerged from the data at that point, it is safe to conclude that a measure of saturation was achieved. Some themes were broken down further into subthemes. The researcher particularly noted any specificities/characteristics of the Singaporean, Malaysian or Thai markets and of the harmonisation processes in these markets.

Inductive studies produce theories or generalisations (Thomas and Harden, 2008); based on the synthesis of the interviewee responses, inductive analysis was therefore used to highlight characteristics of the ASEAN processes which formed a basis of comparison against the LATAM region. This will help ascertain whether LATAM could learn any lessons from ASEAN to enhance their own streamlining efforts (to be taken up in Chapter 6).. These characteristics were highlighted through the resulting themes hence the comparison was data-induced (Thomas, 2006)

A similar approach has been used by McMullin whereby the researcher's experience, participant data and a literature search were used in an inductive study to form recommendations against which study outcomes were compared (McMullin, 2023).

The researcher theorised that if LATAM characteristics show similarities to the ASEAN characteristics of harmonisation, then it showed a general movement towards harmonisation and if not, then movement towards convergence would be the alternative approach.

4.3 Results

The thematic analysis performed on the eight semi-structured interviews and document analysis from the secondary data, identified five major themes, laid out in Table 4.2 below. For one of the themes, ‘challenges to effective harmonisation, additional five sub-themes were identified, further described below.

Themes	Subthemes
i) How ASEAN countries achieved harmonisation	
ii) Motivation and Incentives for harmonisation	
iii) Real-world effectiveness of harmonization	
iv) Challenges to effective harmonization	
	a) Not following harmonised guidelines
	b) Lack of legally binding framework
	c) Level of agency transparency and coordination
	d) Level of agency maturity & expertise
	e) Lack of coordinated leadership from ASEAN

v) Ways to improve harmonization within ASEAN or to ensure better alignment	
---	--

Table 4.2 Themes generated from ASEAN qualitative interviews and secondary data

Each theme is covered in turn, with supporting evidence from the semi-structured interviews. Appendix 20 provides a full list of interviewee quotes for each theme.

4.3.1 How ASEAN achieved harmonization: the process and history of harmonising CMC requirements

One major theme was understanding how the ASEAN countries were able to transition from a patchwork of regulatory systems to a coherent and harmonized set of requirements, including CMC requirements.

Several participants, when asked about the process for achieving harmonization, expressed uncertainty and so did not give many details. However, one interviewee, AS1, gave more detailed information, reflecting more intimate knowledge of the ASEAN process of harmonisation.

Critical to the process was using an existing set of guidelines as a starting point or framework for developing harmonization. AS1 explains that the initial set of ASEAN guidelines was developed based on Singapore's guidelines:

AS1 "...So if I'm not wrong, its actually based on Singapore's guidelines..."

AS1 was, however, uncertain as to where Singapore's guidelines themselves had originated and stipulated that they were probably developed from the EU guidelines.

AS1 "...I'm not quite sure where it came from but most probably from the EU because Singapore guidelines are mostly mirrored from the EU guidelines..."

Two other participants believed that the basis of the ASEAN guidelines was the ICH or EU guidelines. Flear confirms that "compliance with ICH guidelines is a *de facto* requirement for the development and registration of pharmaceuticals in the EU" (Flear, 2017), hence the EU guidelines are based on the ICH guidelines. This means that at the core of the development of the ASEAN guidelines were the ICH guidelines. Latzel mentions that the ICH and WHO guidelines were taken into account in creating the ASEAN guidelines (Latzel, 2007).

At the outset of the harmonisation process, a Pharmaceutical Product Working Group (PPWG) was set up by regional government leaders and advisors. The group aimed to harmonise pharmaceutical requirements around the main areas required to approve the initial drug license for commercialisation. In addition, areas such as bioequivalence, stability and process validation were also targeted. To do so they created an ASEAN Common Technical Dossier (ACTD), a guideline of the agreed upon common format for the preparation of a well-structured application to ASEAN regulatory authorities for the approval and registration of pharmaceuticals for human use (Hutagalung, 2010). To accompany the ACTD, they also created a set of ASEAN Common Technical Requirements (ACTR) also confirmed by Latzel (Latzel, 2007), which included all the required documentation required to submit for review to ASEAN regulatory authorities for post-approval variations as explained by AS1:

AS1 “..the first task they [Pharmaceutical Product Working Group] had was ACTD [ASEAN Common Technical Dossier] and ACTR [ASEAN Common Technical Requirements]...So after the ACTD and ACTR [were] harmonized for registration, then of course they looked at the various sections that make up the ACTR. So things like stability was harmonized, bioequivalence was harmonized. What else, process validation was harmonized. Some of the big pockets of requirements are harmonized...”

Once the ACTD and ACTR were developed by the PPWG, these documents were then signed off by government officials across the ASEAN countries. This was an important piece of the harmonisation process, as it highlighted senior government official buy-in regarding the harmonisation process.

AS1 “...So they [PPWG] agree by mutual recognition...on like for example, some directives or whatever, they have to get it signed by the higher level. So once the working group is done with their review and everyone's happy, they get it signed by the leaders, the leader team of each country and then the ministers [Ministers of Health] actually do have to sign on it...”

It is important to note, however, that even though the health ministers agreed upon the regulatory documents and pathways, each ASEAN country could make modifications based on their local requirements and local peculiarities. This meant each market had a

level of flexibility and autonomy in terms of how they were to implement the harmonised requirements and processes.

AS1 *“...So then it's agreed that they will follow it. But of course, in every directive, they will have sort of a disclaimer that ... you know the country can make changes based on their local situation...”*

To summarise, the process that led to harmonisation within ASEAN included:

a set of guidelines that formed the basis of requirements; a dedicated Working Group that discussed and put together common ASEAN requirements and dossier format and senior government official buy-in. Lastly, markets were given a level of flexibility/autonomy on implementation.

4.3.2 Motivation and Incentives for Harmonisation

Next, interviewees were asked about the motives and incentives for harmonisation. They identified several reasons, as outlined below.

Increasing free trade was identified as a major, if not the main motivating factor for harmonisation and was cited by four interviewees. Free and easy movement of goods and human resources required harmonisation of certain industries, one being pharmaceuticals. Participants mentioned the desire to have a similar set up like the European Union where free trade is one of the important drivers and benefits of the Union, generating growth and jobs within the region (Salm and Andre, 2017).

AS4 *“... So they wanted to make the ASEAN market in line with how the European Union..... More than guideline I would say trade...”*

AS1 *“...So they want to do like a ASEAN community where there will be free movement of goods and human resources. So for that they realized that they have to harmonize some of the industries in these countries. And pharmaceuticals was identified as one of the key areas...”*

Again, Latzel confirms that the ultimate goal of pharmaceutical harmonisation was to eliminate barriers to trade (Latzel, 2007).

Less duplication of effort was another incentive cited by participants; this would occur as pharmaceutical companies would only need to provide the same core documents for the

various ASEAN markets. Many participants voiced that having a core set of documents when preparing the CMC variation dossiers would prevent having to go through the dossier compilation process separately for each market because the core documents would be quite similar.

AS5 “..... So that's the good news that your five report go everywhere, the documentation requirement quite close, so you don't need to duplicate a lot of effort to do something extra for this country, this country very, very different, et cetera.

Market attractiveness was also seen as a motivating force for harmonising requirements. There was a common belief among participants that multinational pharmaceutical companies would find it easier and more convenient to submit registrations in the region when requirements were streamlined. This enables better use of pharmaceutical resources because it saves them time which can be used to consider submissions in other places. This would mean more pharmaceutical companies would want to register their products in ASEAN because of the ease of submission and also because of the market share due to the size of the harmonised region. For the ASEAN region, this attractiveness means access to innovative medicines for patients in the region to improve their well-being. The region also relies heavily on pharmaceutical imports due to the limited therapeutic scope of local manufacturers (Teo, Foerg-Wimmer and Chew, 2016); hence the importance for the region to strive for market attractiveness.

AS3 “...that was one of the thoughts for the harmonization, is that, if they achieve harmonization, they become a more attractive market because of the size of the harmonized area, and so, they can have access to innovative products...”

One of the other incentives that drew the region to streamline requirements was their common climatic zone. Even though the region is very different politically, culturally and economically as cited by one participant, 4 participants mentioned that one thing the markets shared is the drug stability testing at Zone 4B climatic zone. During stability zone discussions within the International Conference of Harmonisation (ICH), the ASEAN markets were not satisfied with the stability protocol set for the ASEAN region (Kopp,

2006). This drove the countries to come together to discuss and develop a stability protocol for Zone 4b, specific to their region (Latzel, 2007).

AS7 "...Based on the stability studies, they gathered together and suggest changing the climate zone for the stability study..."

AS3 "...Well, for the pharmaceutical regulation, I think it was also this climatic zone, 4B, because it's really the only common thing they have between them..."

One participant mentioned the level of Government official engagement to be one of the drivers. The engagement by Government officials helped to push the harmonisation agenda forward as it was a top-down approach, removing resistance from the lower ranks of the regulatory administrative system.

AS5 "...There is, in ASEAN they even, the Prime Minister sign ASEAN document. So, it's Prime Minister level. You can see it's very super senior buy-in..."

4.3.3 Real-world effectiveness of harmonization: realisation and implementation

After considering the motivation and incentives for harmonisation, participants were asked to comment on how they viewed the progress and success of harmonisation of CMC requirements in the ASEAN region to date. When asked if the ASEAN had gained a level of success when it comes to harmonization or not, there were mixed views. Some suggested there was a degree of success with the harmonisation initiative albeit the region remained to be fully harmonised. It was observed that the region may be harmonised on paper, but in reality, implementation has not been completed across all markets. Individual markets have used the allowed flexibility to amend the requirements to suit their local regulatory landscape. Some suggested that the harmonisation initiative had not been successful at all, so they didn't think there was a degree of success.

AS4 explained that even though on paper the region seems harmonised, implementation has not occurred for various reasons. One of the reasons AS4 cited for this lack of harmonisation was markets acting independently of each other which is not a characteristic of a harmonised region. Also, market expectations in terms of how registrations should be processed and what documentation should be provided for a particular change vary. They also cited NRA evaluators having different expectations

which is seen in how one evaluator will review the same CMC variation differently from another evaluator across NRAs and even within the same NRA.

AS3 explains that even though the ASEAN has agreed a common document for requirements (ACTR), the actual legislation and regulation to enact the implementation is not harmonised across the region, so in essence, the implementation of the requirements is not really binding.

AS4 "...No, not harmonize. I wouldn't say it is harmonized yet. I wouldn't say. Because each market behaves independently, each market agency has different expectations. Even evaluators have a different expectation. So no. Yes, on paper, it is harmonized in terms of guideline, but it is not being implemented in reality..."

AS3 "...It's in the middle, I would say. Because they have achieved the harmonization of the requirements, of what is needed in terms of content, in terms of technical data needed on your product to reach the standard. They have harmonized the standards. But they did not harmonize their legislation and their regulation in terms of variation..."

As an example of non-alignment in CMC requirements, AS1 cited an example of 'change in manufacturing site' variation in Malaysia where there may be different categories for the change. This depends on what kind of site is being changed, and specifically whether it was a local manufacturing site or overseas. Differing requirements would govern those different scenarios. A potential explanation for this is that local manufacturers are not accustomed to building dossiers in compliance with ICH guidelines which are similar to the ASEAN guidelines (Veravithayanan and Russell, 2009). More content is required to comply with the ASEAN guidelines that the local manufacturers have to generate but they do not have the resources or competency to do this. Another reason could be favourable government policy to support local manufacturers versus foreign manufacturers to boost local production (Teo, Foerg-Wimmer and Chew, 2016). This is further explained by participants in section 4.4.4.1.

In Thailand for example, the scenario exists that sponsor/applicant companies could end up with two separate licenses for the same medicinal product depending on the particulars of the change in manufacturing site.

Another example cited was how a 'change in formulation' variation – which typically would be a notification resulting in an update to the existing license in other jurisdictions, could

result in a completely new product license altogether in Malaysia, a process not in compliance with the agreed ASEAN variation guideline. The Malaysian Variance Guidelines corroborate this observation (NPRA, 2013).

One participant was even adamant that full harmonisation in the region would never happen. AS5 explained that if the region truly sought harmonization, then there should be some sort of timetable or action plan the ASEAN was working towards to achieve this harmonization. They went on to explain that no such timetable existed. So harmonization had become more of a historical goal that ASEAN had initially set out to achieve, but in the real sense of the word where harmonization meant a full alignment of the whole region to the same requirements, this was not going to take place.

AS5 “..Let me take it this way, harmonization won't happen, will never happen because, that's definitely my personal opinion...nobody talk about harmonization timetable. When? When will you harmonize? No, nobody talk about it...”

In fact, 3 participants mentioned that the process happening in the region was closer to convergence than harmonization. This meant that markets were positively moving towards the common ASEAN requirements but, because of the flexibility to adapt requirements to local situations, there would always be variations from one market to the next, this resembled convergence more than harmonization. Most participants insisted that there would always be local requirements outside the ASEAN requirements.

Participants also mentioned the non-alignment of review timelines, review pathways and categorisation of the variations as part of the areas that were not harmonized. For example, Singapore has two categorisations for major variations, namely MAV1 and MAV2, whereas in Malaysia and Thailand, there is just one major variation categorization ('Health Singapore Authority (HSA) website', 2022; 'National Regulatory Pharmaceutical Authority (NRPA) website', 2022). For the same variation, review timelines are very different. In Singapore, three review or evaluation pathways can be applied to a Major variation and two evaluation pathways for a Minor variation (HSA website, 2022). This is not the same for Malaysia and Thailand.

AS4 “...No, I don't think so. It's only, they [ASEAN] have a harmonized guideline. However, if you go to Malaysia, they have a long, detailed, a hundred pages guideline for approval. Singapore has its own guideline. The pathway, they have are different. Thailand is totally new medical, new drug, new generic, three

pathways. Malaysia has another pathway. Singapore has another pathway. Classification route is different...

One participant mentioned how the initial Marketing Authorisation (MAA) requirements may be the same across the region, however, when it comes to CMC variations, even if it is the same variation for the three markets, different requirements may be requested to assess the variation or change in the medicinal product. This again points to a lack of effectiveness in the harmonisation process where different requirements are requested for the same CMC variation, especially where the initial registration dossiers contained the same information.

AS3 "...They all requires the same thing in the dossier, in terms of study, technical data in the registration dossier. But, in terms of variation, they may require different things to support the change..."

When asked to explain why there seemed to be so much variance in terms of country-specific requirements, thus affecting the harmonisation process in the region, AS8 said it was actually very difficult to explain or summarise. Sometimes when data is generated in one market, it is not mutually recognized in another market within the region, due to a lack of trust or confidence in the data generated or information provided. However, other markets within the region are willing to accept that same data.

AS8 goes on to cite an example:

AS8 "...So for example, the BE (Bioequivalence) study requirement in Thailand, is Thai FDA, do not feel confident to utilize the study from other countries, but then from the other side, the data generated in Thailand can be accepted in Malaysia and Singapore. So it is not mutually recognized..."

This mutual recognition should actually be a product of true harmonisation and be evidenced with variation approvals in one market being accepted in all markets across the region, as cited by AS4.

AS4 "...they have to see how it is going to respect each other's approval and upon one country's approval, industry should be able to market [commercialise] in other markets as well within ASEAN. Then it will be helpful..."

AS8 then explained that unless one knows the historical background to that market-specific difference, it is difficult to explain why different approaches or differences exist.

Three participants made a comparison between the ASEAN harmonisation process and the European harmonisation process stating that in as much as the EU is a political block, even they have some country-specific requirements. The participants raised this as a way of highlighting that even with the EU's advancement in harmonization and having a good legal backbone which ensures requirements are implemented, the EU still has country-specific requirements. Moreover, the EU has been undertaking the harmonization process far longer than the ASEAN has. This was to point out that the ASEAN is therefore still young in its attempts to harmonise across the region.

AS3 "...but, even in Europe, it is not fully harmonized. You still have some specificities between the countries..."

One participant explained that the term 'harmonisation' may have been the best and only known term to describe streamlining efforts at a particular time. However, with hindsight, and with the emergence of other streamlining practices, like 'convergence', it can be argued that 'harmonisation' was not the best term to describe the streamlining efforts at a particular time period and is probably misleading. This, they stated, could be said of the ASEAN. 'Harmonisation' may have been a historical term to describe the ASEAN streamlining process at a point in time, but at present the term and its currently accepted definition do not reflect ASEAN's streamlining process. This seems to point out that for lack of a better term, 'harmonisation' may have been the goal in the past, however, over time, the process has evolved into something else, hence the effectiveness of the harmonisation process cannot be measured if the goal post has indeed shifted or was not even well-placed from the initial stages.

AS5 "...Everybody talk about convergence. No organization able to talk about harmonization. Sometime, maybe the core organization name maybe confusing, they will say 'something, something harmonization' happen, or '[harmonization] organization'. That may be the initial organization name, but when you look in the organization, there is no timetable, no action plan, nobody talk about harmonization timetable..."

AS5 “...So now they talk about convergence. That's another term that would relatively make some sense...”

Another participant stressed that if harmonization had worked then there would not be issues with country-specific requirements, so based on their experiences, harmonization had not worked at all. Country-specific requirements are detailed in the country-specific variation guidelines (Thailand, Malaysia, Singapore Variation Guidelines). Participants expressed bewilderment as to why the agencies could not share resources and capacity which would inevitably benefit the markets. This would shorten review timelines and markets would not receive questions that were asking the same thing but in a slightly different manner, which meant responses had to be tailored per market, instead of having the same response per question for each market.

AS9 “...Yeah. I, don't why we wouldn't, you know, be been struggling like to understand country's specific requirements, that, that wouldn't be a case if the harmonization has work... why wouldn't they, able to share the capacity to share the resources and things like that. Because I mean, from our nice thought, it will be wonderful if they can do that because it definitely cut short a lot, um, uh, requirements there will be a lot of convergence so that, um, the timeline can be shortened and...imagine submitting, uh, one, one variation to 10 agencies, and then you get 10 different sets of questions and some questions might be repeating just slightly different from each other...”

4.3.4 Challenges to effective harmonisation (effective/actual/full)

Following on from the discussion on the previous theme, participants expressed their views on challenges to effective harmonization and implementation of regional guidelines with some overlap. Five subthemes emerged which are: i) not following harmonised guidelines; ii) lack of a legally binding framework; iii) assessment of transparency and coordination iv) assessment of agency maturity and expertise; v) lack of coordinated leadership. These barriers have prevented the region from reaping the full economic benefits of harmonisation.

4.3.4.1 Subtheme Not Following Harmonised Guidelines

The ASEAN produced guidelines for CMC variations, within these guidelines are the requirements for the various CMC changes. One participant stated that the guidelines are just that, guidelines, they are not law, markets can therefore choose to follow them or not. Due to this, each market has produced its own specific guidelines, though similar to the ASEAN variation guidelines, they are different.

One participant explained that even though each market follows the guidelines, there is always something additional expected during review or during questions, outside the guidelines.

Other participants cited the fact that requirements to be provided for a CMC variation can also differ from one evaluator to another, hence there is no consistency in what is requested even for the same variation.

Aside from the ASEAN guidelines, markets also classify variations differently and pathways to submitting the variation can also be different which also poses challenges to the harmonisation process.

AS4 "... It [the requirements] does change from evaluator to evaluator..."

AS4 "... No, I don't think so. It's only, they have a harmonized guideline. However, if you go to Malaysia, they have a long, detailed, a hundred pages guideline for approval. Singapore has its own guideline. The pathway, they have is different. Thailand is totally new medical, new drug, new generic, three pathways. Malaysia has another pathway. Singapore has another pathway. Classification route is different..."

This observation is also seen in the individual country guidelines, where the different requirements and classifications for the same variations are clearly spelled out.

Two participants shared the view on how the NRAs need to balance how multinational companies have the capacity to deal with the harmonisation requirements versus the local industry. Sometimes the local requirements are less stringent than the harmonized requirements adding to the complexity of why the guidelines are not being implemented fully. National or local pharmaceutical manufacturers and developers are key stakeholders for the NRAs, hence they need to balance somehow the stringent internationally developed CMC requirements being implemented for multinational and foreign companies

versus the need to raise the standards of local industry without damaging its ability to supply to the national market in the short term. In these still-developing markets – the local pharmaceutical industry is still in its early infancy of establishment in their own national market and may not have sufficient resources or expertise to fully implement these harmonised requirements, this dichotomy of managing local strategic industry to raise their standards to benefit local patients and enable them to export to other countries is a fine balancing act and poses a challenge for governments in the ASEAN region and all developing markets.

AS8 "...But then their concern is the local industry. How about local industry? So they cannot, you know, let's harmonize the international standards to multinational company only. Right? So that is not the way for, for the legislator. And the new legislation should be applicable to all the players in the markets..."

AS6 "...While coming to implementation, every country has its own challenges. First of all, they should take care of their own manufacturing companies, so do they really upgrade their standards to arrange the documentation to that level or not?..."

Sometimes due to the fact that local government laws are not easy to amend or sometimes not possible to change at all, markets cannot implement the ASEAN guidelines or choose not to, due to the complexities in changing the law just so the guidelines or requirement can be implemented (Management Sciences for Health, 2012, Chp 6, section 6.1). Some of these laws are very old [historical] and have not been reviewed in a long time, however, to change them would be a very complex and long process (Management Sciences for Health, 2012, Chp 6, section 6.1).

Regarding flexibility in changing the variations categories, AS1 explains how the inability to amend local laws affects guideline implementation, thus affecting the extent of harmonisation within the region:

AS1 "...Yes, so the market has the right to change it. Of course, they try to, at the PPWG, they try to agree but most of the times because of some laws preventing them from doing it. Because to change their law, they have to go back. It's not so easy or legal process. So they just choose not to follow..."

4.3.4.2 Subtheme Lack of legally binding framework

Again, participants compared the legally binding agreement seen in the EU to the lack of a legally binding agreement in the ASEAN region. Participants explained that having a set of requirements to harmonise to is the easy part. The difficult part is when there is no legal framework which drives markets to implement the guidelines/requirements. Participants mentioned that markets did not want to compromise their sovereignty to accept an approval in one market without conducting their own review and approval of a CMC variation even though that is the general purpose of harmonization in the region - to enable free-flow of trade based on common review and approvals.

One participant brought up the example of reference markets like EU and US who are not harmonised with each other because of the burden of responsibility to protect their citizens. Without a political agreement or alignment, it is difficult for one country to compromise the safety of its citizens based on the approval of another country. They related this example to the ASEAN region where political alignment in terms of a legal backbone for harmonised requirements does not exist because one market does not want to compromise completely for the other.

AS5 "...Yes, the important reference, you can also look at the U.S. and Europe, they are here for so many years and doing their pharmaceutical regulation, are they harmonized? No. Will they harmonize? No ...But without political, there's very little motivation to harmonize the technical part like that because you need compromise. Why me compromise, not you?..."

AS8 "... I should say a fundamental problem for ASEAN country, from my perspective, uh, why the harmonization process is that slow is that the ASEAN organizations itself is not the same as the European region. If I can refer to, they don't have a legislation basis..."

4.3.4.3 Subtheme Level of agency Transparency and Coordination

Participants were asked to comment on 'transparency' in the region, especially as applied to these three markets. Transparency here refers to how open or closed (engaging) the NRA is to industry input on requirements or guidelines/guidance/regulation; how NRAs

invite and respond to feedback from industry partners i.e. do they readily accept comments or industry reasoning or do they stick with their preferences or reasoning (Qiaquinto *et al.*, 2020); and how NRAs readily share information/expertise with stakeholders in relation to harmonizing requirements, in an accurate, timely and accessible manner (Stedman-Bryce *et al.*, 2015). The relevance is that, where transparency is inconsistent across the region and each territory seeks to develop national guidance outside the ASEAN guidance without divulging the reasons, discussions with stakeholders (industry, patients, other NRAs) will result in differing outputs. When information on decisions regarding requirements are shared, it allows for better discussion and dialogue amongst the stakeholders, leading to better understanding and hence greater chance for harmonization. One participant mentioned 'industry-friendly' as another way to explain transparency. Interviewees discussed transparency for each market in the context of hindrances to the harmonisation process.

Singapore

All participants agreed that Singapore was the most transparent NRA out of the three ASEAN markets. They are open to industry comments, organise meetings to listen to industry feedback and respond in a timely fashion. They publish agency guidance and regulations on their website which is user-friendly i.e. easy to find information. It is easy to request clarification on guidance/regulations from the Health Authority.

One participant mentioned how Singapore put a lot of thought into their decisions to prevent them from changing them constantly, however, they can be flexible if industry has a major problem with its decision/regulation/requirement.

AS7 "... I feel personally, my impression, they listen to industry's voice very well. Before guideline and regulation implementation, normally they will have a public comment..."

AS5 "...Do they listen? I think they listen, but when Singapore want something, they really do a lot of study before that they seldom need change again and again, again, because of many people talking. So you won't see a huge change after that. Unless they see a crisis that 90% industry have problem, then they will do something..."

Malaysia

All participants cited and agreed that Malaysia was second after Singapore in terms of transparency and industry-friendliness. The Health Authority engages with industry even though responses may take a little longer than when dealing with Singapore.

AS4 "... So Malaysia, we do interact with them. However, the response comes with... it takes a little longer. In terms of promptness I think it is second to Singapore..."

One participant also mentioned that Malaysia being 'friendly' was actually 'dangerous' because, when asked to comment on a submission, it is usually done quickly and prematurely: without taking much notice of the specific nature of the submission or reviewing the submission. Sometimes on submitting the application, and realising the nature of the submission, the decision changes. So their 'friendliness' could also be seen as a 'downside'.

Participants cited that Singapore NRA though industry-friendly was also cautious in giving responses right away, they would stress on comments being on a 'case-by-case' basis unlike Malaysia which may give comments pre-maturely and then upon submission and actual review of the documents, realise that a wrong judgement was made.

This friendliness can cause other problems in that, because of it, a company could receive two different responses from talking to different people at the agency which is then subject to interpretation. Ideally, an answer should be given on a case-by-case basis and with some evidence or initial review of the documentation before giving a response on say a classification of a variation.

AS5 "...Singapore, we'll answer like the way I answer or normally like this, but in your case, we need to be specific on this. He's thinking of how to meet, let's review and will do the case by case basis. And the keyword is case by case end up like that. Well, they [Malaysia NRA] are not super helpful to say, "Your case, no need. You just do this, will be fine." Then at the end maybe not the correct answer. When they see the file, "Oh, you actually mean this? Oh, sorry. Actually you need to do a clinical study."

Thailand

Thailand was found to be the least transparent in terms of engaging with industry on guidance and accepting comments. They also mentioned Thailand had a more 'friendly' approach than Malaysia where conflicting messages can be given due to their eagerness to respond to queries. Participants mentioned the communication barrier where everything needs to be communicated in Thai which could have an indirect bearing on the harmonization process due to possible misinterpretation of information. One participant had a contradictory view in that they mentioned that it was difficult to obtain responses from Thailand, aside from the language barrier.

Participants expressed the need for a local representative in order to engage with the Thailand FDA in the local Thai language. This was mentioned as a language barrier and hindrance to effective communication, which indirectly affects harmonisation initiatives.

AS7 "... I feel Thailand is, compared with Singapore, a little conservative, but still open..."

AS4 "...Thailand is very difficult to even get a response. And another portion is the language barrier. You don't know to whom to coordinate. Even if you have some email, it becomes unclear and as you don't have a local representative, you can't generally get input from Thailand..."

4.3.4.4 Subtheme Level of Agency Maturity & expertise

Participants were asked to comment on the maturity and expertise of the National Regulatory Authorities (NRAs) based on their experience. Participants expressed their views in relation to how they thought maturity and expertise affected the harmonization process in the region. They identified the various levels of maturity and expertise as challenges to the harmonisation process.

Maturity can be defined as the extent to which a regulatory system has been formalized as stable, well-functioning and integrated as per the WHO Global benchmarking tool (GBT) (Khadem Broojerdi *et al.*, 2020) The GBT was developed in 2016 and is used to

assess NRA maturity based on certain criteria. Expertise is defined by the express and requisite scientific knowledge and built experiences the NRA assessors have to adequately review the submissions to ensure their safety, quality and efficacy (Khadem Broojerdi *et al.*, 2020).

AS3 described the importance of NRAs being mature in relation to their regulatory expertise. They explained that when expertise is lacking it poses a challenge to the harmonisation process. They cited the example of these lead markets actually thinking that having extra requirements outside the ASEAN requirements makes them look more mature. AS8 adds that the harmonisation process is unable to move at a faster pace because of the different levels of competency.

AS3 "...what is difficult in the ASEAN area is that the countries have very different levels of competency in terms of regulation and medicinal variation...I guess that's, the leading country feel that maybe they should have additional requirements to compare to what is currently discussed as harmonized regulation across the area..."

AS8 "...if all those authority and the industry are not on the same page at all, not at the same maturity level is one of the reason why the harmonisation is moving, not that fast..."

4.3.4.5 Subtheme Lack of coordinated leadership from ASEAN

A lack of coordinated effort from political leadership to truly harmonise requirements was also raised by participants. Even though the ASEAN exists to harmonise pharmaceutical guidelines, and there is senior government buy-in concerning the requirements, as mentioned in section 4.3.1, participants did not recognise clear and strong leadership in making it happen, that is, in relation to implementation.

One participant mentioned that there is some 'ego' at play, referring to markets still wanting to exercise sovereignty in their decision making in relation to requirements, this in turn makes it difficult to be truly unified.

AS4 "... Who is ensuring or asking or mandating implementation of harmonized guideline? No one..."

AS3 “...Apart from ego ... I don't really know, actually...”

4.3.5 Ways to improve harmonization within ASEAN or to ensure better alignment

Having discussed the challenges ASEAN is facing regarding full harmonisation, participants were asked to express their views on ways of improving harmonisation within the region.

Two participants expressed a few ways to improve alignment in the region. One was for individual markets to adhere totally to the ASEAN guidelines and not insist on having market-specific requirements. Another improvement would be mutual recognition of approvals from one market to the rest. This would make harmonisation a realistic goal and move more rapidly.

AS4 “...I think first of all, they have to start using the same guideline across ASEAN, number one. Number two, they have to see how it is going to respect each other's approval and have one country's approval, industry should be able to market in other markets as well within ASEAN. Then it will be helpful...”

AS9 also suggested that the pharmaceutical industry in the region could build up case studies through the industry associations, highlighting a particular trend of misalignment in requirements. This could be used to train assessors in identifying the disparities that arise during review, hopefully leading to a strengthened enforcement of the written guidance.

AS9... “... this could be highly sensitive...implementation wise is very difficult, but in ideal world, if we have all the cases, um, um, presented and we try to find a trend and we try to, um, provide justification, uh, to, to look at the big picture and, and, and, uh, try to present this as an industry, as a one industry, to, to the health agency, perhaps if this can be accepted, then the health agency could, uh, have more, I mean, if the health agency is less mature in the way, they could provide more training to train their staff as well, to raise this sort of avenues to also strengthen enforcement of the, of the written guidance”

4.4 Discussion

This study set out to explore how harmonisation of CMC requirements was achieved in the ASEAN region and how effective CMC harmonisation is in practice using semi-structured interviews and secondary documents. Recruitment for the ASEAN participants peaked at n=9, Varying attempts were made to increase this number including: posting on specific ASEAN Regulatory LinkedIn groups (with permission) and not just the researcher's personal LinkedIn page; emphasising recruitment of ASEAN participants when posting; reaching out to colleagues with ASEAN experience within the researcher's professional network; asking them to reach out to colleagues in their network (snowballing), this extended to the supervisory team who also reached out to their network. Broadening the selection criteria also helped with recruitment, where flexibility of one of the exclusion criteria was allowed (i.e. RAs with medical device experience) because they still had experience which related to the research aims and objectives (Negrin *et al.*, 2022). These did not yield positive results and the researcher acknowledges this as a potential limitation to the ASEAN arm of the study. In hindsight, and in the researcher's experience, they have observed that ASEAN RAs may not be as comfortable with open conversation due to the language barrier. The researcher could have employed the use of email interviews to possibly increase the participation of ASEAN participants instead of semi-structured interviews (Negrin *et al.*, 2022). Despite the challenges with recruitment, the objectives were met with some further observed limitations discussed later in this section. Interviews of eight Regulatory Affairs professionals (RAs) revealed several important observations. The use of semi-structured interviews was advantageous in allowing participants to share their views and opinions openly and richly, expressed in their own words (Knox and Burkard, 2009). The secondary data was used to corroborate participant responses, for example, the ASEAN guidelines confirmed there were indeed market-specific requirements (Carter *et al.*, 2014). Latzel's unpublished thesis provided supporting information on the history of the ASEAN network (Latzel, 2007). The use of online interviewing did not affect the quality of the data collection in the researcher's opinion as participants provided enough information to answer the research question. There is a perception that online interviewing can reduce code density (i.e. level of depth and detail) (Lobe, Morgan and Hoffman, 2022). For the ASEAN participant group, the level of detail given could be due to the discomfort with open conversation as mentioned above and not necessarily due to the use of online interviewing. On average the duration of interviews was 46 minutes including AS2 who had the shortest duration due to poor internet connection.

Through the interviews, it was discovered that having a starting point guideline, in this case, Singapore's, helped move the discussions towards harmonization and achieve consensus. Secondly, establishing a joint Pharmaceutical Product Working Group through which all member countries could discuss and agree upon CMC requirements also accelerated the progress. Thirdly, a series of powerful motivating factors which helped power these activities was observed. Harmonisation was seen to help promote free trade, reduce duplication of effort and improve the region's market attractiveness to industry. The observations that addressing barriers to trade was a key motivating factor is consistent with various published papers on why the region has been undertaking efforts towards harmonization (Veravithayanan and Russell, 2009; Wileman and Mishra, 2010; Lezotre, 2014c). In spite of the above, interviews also revealed that, despite their best efforts towards harmonization of requirements, several challenges remained for effective implementation. Participants were divided as to whether ASEAN had really achieved success in harmonization of CMC requirements. They felt it was not yet fully harmonized, because the markets behaved differently and maintained market-specific requirements. Participants believed that the streamlining process was more akin to convergence than harmonisation. In an online article by Prof John Lim, he explains how the region has been committed to harmonisation since the 1990s, however, coordination of approvals of medicines across the region is still developing. He went on to state that convergence is also occurring as another avenue for cooperation amongst the member states, observed in the way the countries worked together during the COVID-19 pandemic to acquire the necessary vaccines for the public, yet still expressing their national sovereignty in which vaccines they used and how they acquired them - this flexibility being afforded through the process of convergence (Lim, 2021). In a recent ASEAN publication, the ASEAN Pharmaceutical Regulatory Policy established in 2022, is explained (ASEAN Secretariat, 2022). The policy exists to facilitate ASEAN harmonisation as well as convergence of NRA structures to enhance a single market and aid rapid access to essential medicines across the region (ASEAN Secretariat, 2022). This suggests that the region desires to use both harmonisation and convergence to achieve its aims whilst still maintaining a level of sovereignty as country-specific requirements are still desirable (Cairns, 2018). Hence participants' observations do indeed align with industry experience, however while industry is citing both harmonisation and convergence being in operation, participants felt convergence was the process being practised over harmonisation. The researcher postulates that the participants, who are mostly locally based RAs, interact daily with the

NRA and their regulatory processes and hence their view of convergence being the dominant practice is probably based on their experiences of what is happening in reality. Participants explained how the guidelines for harmonization were also not enforceable, as no legal framework existed at the regional cooperation level to enforce them. Reggie (2017) agrees with the absence of a legal framework, however, he highlights at least one benefit of the ASEAN harmonisation process being the agreeing of a single set of requirements and technical guidelines (Reggi, 2017). This suggests that until a legal framework is in force, true harmonisation cannot be claimed in the ASEAN region. A World Bank report also echoes the challenge of staggered implementation of harmonisation initiatives across the region (Teo, Foerg-Wimmer and Chew, 2016). The findings further corroborate observations from other studies which dictate that cooperation is challenged by the region's diverse cultural backgrounds and political systems (Ishikawa, 2021).

Interviewees often compared the ASEAN to the EU in relation to its desire for free trade across the region. These responses from the Regulatory Affairs professionals seem to suggest that the region looks up to the EU as a 'good model' to replicate in the ASEAN. The history section of the ASEAN website ('ASEAN website (history)', 2022), however, does not state an initial desire to mirror the EU framework. In an interview with the former ASEAN Secretary-General Surin Pitsuwan in 2016, he stated that the "ASEAN saw EU as an inspiration and not a model" (Asian House, no date). The referral to the EU as a passive reference point was also expressed by other researchers (Reggi, 2017; Ng, 2021). Also, Ng and Asian House report that both institutions (EU and ASEAN) were established with different governance models and objectives; therefore, it is in principle not appropriate to conclude if one is more successful than the other or even compare them (Ng, 2021; Asian House, no date).

The lack of a legal framework, also mentioned by participants, allows country sovereignty and flexibility in the implementation of the ASEAN CMC guidelines. This means that countries decide how much of the guidelines they implement and when they implement (Ng, 2021). This has ultimately led to a slowing down of the whole harmonisation process within the region.

One of the ASEAN founding members at the onset of ASEAN formation, sounded a potential warning of NRAs maintaining sovereignty whilst trying to work together on achieving oneness.

For his part, S. Rajaratnam, a former Minister of Culture of multi-cultural Singapore who, at that time, served as its first Foreign Minister, noted that two decades of nationalist fervour had not fulfilled the expectations of the people of Southeast Asia for better living standards. If ASEAN would succeed, he explained that, then its members would have to marry national thinking with regional thinking ('ASEAN website (history)', 2022).

Rajaratnam said the following:

"We must now think at two levels. We must think not only of our national interests but posit them against regional interests: that is a new way of thinking about our problems. And these are two different things and sometimes they can conflict. Secondly, we must also accept the fact, if we are really serious about it, that regional existence means painful adjustments to those practices and thinking in our respective countries. We must make these painful and difficult adjustments. If we are not going to do that, then regionalism remains a utopia." ('ASEAN website (history)', 2022).

Palatino (Palatino, 2013) expressed a similar view by stating that, in his opinion, the member states in reality view their association with ASEAN as a means to pursue their national interests and they are not necessarily eager to sacrifice the national agenda for the 'regional good'.

Even though participants aspired to the EU model, they also highlighted that EU market-specific requirements still exist, even though the EU is harmonised and has been for a long time. This is to suggest that it should not be surprising to also have market-specific requirements in ASEAN, being a younger initiative. The main contention, however, being that the EU is driven by a legal framework, plus member states voluntarily give up part of their sovereignty within a supranational organisation (Ng, 2021). ASEAN, in contrast, is an inter-governmental organisation in which each member state keeps its own sovereignty (Management Sciences for Health, 2012; Ng, 2021). In fact, one participant cited how Malaysia for instance can even have more stringent CMC requirements than the EU or ICH guidelines. So even though the ASEAN may aspire to the EU, they still have the final decision on what they require for their CMC variation requirements. This approach hinders total harmonisation in the region.

Markets also have historical reasons for some of the requirements or approaches they take in assessing CMC variations. These historical reasons can be based on historical laws that may not be easy to modify (Management Sciences for Health, 2012); a further hindrance to implementation.

AS9 mentioned that even with the harmonisation initiative, sometimes pharmaceutical companies needed to convince NRAs to update their own guidance based on updates made to the ASEAN guidelines. This should not be the case if the harmonisation process is working appropriately. It may also suggest that markets are more focused on their market-specific needs and not necessarily the regional guidelines which is the premise of harmonisation in the region.

Participants also recognized Singapore, Malaysia and Thailand as leading harmonization efforts in the region and this agrees with the literature as well (Ishikawa, 2021). Possibly, if these three markets can agree CMC requirements in totality, they could potentially drive the rest of the region to harmonise as the less mature markets try to catch up.

Participants expressed that the disparity in maturity and expertise amongst the markets was currently acting as a hindrance to harmonisation. However, sharing of expertise and resources by these lead markets, could be a potential way to improve the implementation of harmonised requirements in the region, if there is a political will to do so (Giaquinto *et al.*, 2020). This could be another area to investigate, being outside the specific scope of this research study.

Another issue preventing total harmonisation in the region is the apparent disparity between CMC requirements for Local manufacturers versus overseas or foreign manufacturers. There are less stringent requirements for the local manufacturers, this goes against the harmonisation principles, as all manufacturers should be made to adhere to the same set of requirements. One reason cited for this was local manufacturers not having the resource to take on the harmonised requirements. It would be interesting to see if this practice is also evident for the LATAM markets; it could be a pattern which could be explored for other international regions (regions outside US, EU).

Overall, the researcher believes there has been a level of success in streamlining CMC requirements in the region. Findings on the history of the ASEAN harmonisation process and motivations were consistent with Latzel's unpublished thesis (Latzel, 2007). As to whether the original purpose set out by ASEAN for 'pharmaceutical harmonisation' of CMC requirements has been achieved, this cannot be fully measured through the few participant responses received within this study. Secondly, the assertion that the streamlining model being operated by the ASEAN is one of 'convergence' rather than 'harmonisation' as mentioned by some participants, could also be a further topic of exploration. From the data presented, there is clearly a strong 'political and economic will' driving the ASEAN to work together. This 'will' does not seem to be weakening (Asian

House, no date). In addition, there is also a clear respect for each country's interpretation of the guidance and the need for other local requirements outside the ASEAN guidelines (Asian House, no date). This independent nature within the network stems from country sovereignty which is allowed to function and is even seen as a way of fostering resilience and flexibility within the organisation (Asian House, no date). It is the researcher's view that this independent way of working, whilst trying to achieve harmonisation of requirements and processes, can be a challenging balancing act and a hindrance to true harmonisation in the region. However, it seems that true harmonisation is not the goal, but rather a mixed model of harmonisation and convergence.

4.5 Strengths and Limitations

Before further interpretation of the findings, it should be noted that there are several limitations to the research. First, the sample size was very limited due to the difficulty in recruitment (Vasileiou *et al.*, 2018). Snowballing did not work well in this group of participants, so the researcher relied heavily on participants recruited through LinkedIn. Second, at one point the researcher deviated from the study protocol, in that participants from a medical device background were interviewed even though the research focuses more on RAs with a background in small molecules. The information shared, however, was still relevant as the medical device participants had knowledge of the ASEAN harmonisation process and current status (Vasileiou *et al.*, 2018). Third, to provide context for readers to understand the participants' responses, as they often dealt with specialized, technical processes, the researcher drew upon grey literature. Inevitably this creates potential to distort interpretation of the respondents' quotes, although in so doing the researcher attempted to only report factual interpretation about the context. Some themes were based on feedback from only one or two participants, due to the low sample size, a higher sample size could have provided further weight to those themes. For those themes, the grey literature was also used to either support or refute those claims, an example being the theme on the history of the ASEAN harmonisation process where grey literature and secondary data supported the narrative of AS1.

One major strength of the ASEAN study was that the use of interviews allowed flexibility in exploring the views of the participants. To the best of the researcher's knowledge it is the first study to explore the drivers of ASEAN harmonisation of CMC requirements through the perspective of RA stakeholders and secondary data. The interviewees had diverse regulatory experience which enabled broad coverage and avoided potential weaknesses

from limited perspectives. Interviewees had many years of experience (10 years on average) and had worked with all three markets under study as well as other geographical regions, which helped them focus on the specificities of the ASEAN region (Vasileiou *et al.*, 2018). The use of thematic analysis allowed flexibility in exploring emerging themes through inductive means and was also used deductively where needed, i.e. in the use of secondary data ((Nowell *et al.*, 2017). Thematic analysis is not tied to any specific theoretical framework unlike other qualitative analytical approaches; hence themes can be generated via many approaches (Braun and Clarke, 2021). This allowed the researcher to observe patterns in the data and use the patterns to develop general conclusions which are explained in the next section (Braun and Clarke, 2021) .

4.6 Implications for future research

Several important gaps were identified for future research to address. One is that there is a need to understand better how to achieve effective harmonization and, specifically, why market-specific requirements persist. Several participants noted that countries are maintaining barriers to attaining full harmonization. Further studies could perform additional semi-structured interviews to identify the causes of these market-specific requirements and strategies for overcoming them. A potential area of investigation would be to explore further the reasons for different requirements in filing CMC variations introduced by local versus foreign manufacturers as mentioned by one of the participants and whether this would change over time. Another area to explore would be the current framework of the ASEAN, will they consider a more robust structure with a defined legal backbone to ensure implementation across all markets?

One missing perspective in the study was from the National Regulatory Authorities as the researcher was unsuccessful in recruiting them through the gatekeeper. The timing of the recruitment being during the COVID pandemic could have played a major role in the failure in recruitment. While this could not be anticipated or avoided, in future, the timing of the research or recruitment should be considered when reaching out to ASEAN NRA participants in order to maximise uptake (Bonisteel *et al.*, 2021). Ultimately, the researcher is always at the mercy of participant motivations towards participation in a study (Negrin *et al.*, 2022). The NRA perspective would have potentially helped elucidate the objectives and roles of health ministries in harmonization. It is possible that resistance to full harmonization can be traced to these NRAs, who may wish to sustain control of

requirements in their countries. Health protections are often valid exceptions to free trade agreements, and ministries of health may be leveraging these to maintain sovereignty. Additionally, there is a need to extend this approach to other regions beyond ASEAN, such as LATAM (see the following chapter), where harmonization remains elusive, as well as African and Middle Eastern regions, where harmonization efforts are underway.

As one participant explained, there are areas that LATAM could explore in their quest to harmonise CMC requirements such as: having government buy-in, with senior government officials leading the agenda; access to finances for training, which would draw markets together; a singular platform where harmonization could be discussed. The LATAM region could also look at widening their scope and seeking help from other Regional Harmonisation Initiatives (RHI) such as the Global Harmonisation Task Force (GHTF) which looks at medical device regulation.

4.7 Implications for policy

For ASEAN, the findings show an ongoing gap from the original charter to achieve full harmonization of CMC requirements and remaining market-specific barriers. It is clear that trade is a powerful rhetorical factor in driving progress forward. This could build upon the Asian Free Trade Agreement charter that ASEAN member states signed attempting to create an EU-style free-trade bloc in 2015 which they have now begun to implement (Ishikawa, 2021).

By drawing on the themes emerging from the data about the motivating factors and steps to harmonization in ASEAN, a general conclusion on characteristics of harmonisation, that could apply to regions such as LATAM which have yet to achieve harmonization, can be developed. This includes five characteristics:

- Framing the benefits: Advertise the benefits of free trade or community cohesiveness or becoming an economic bloc.
- Mobilising an organizing body: Set up a joint body like the PPWG that will drive harmonisation discussions and initiatives
- Consensus: Agree upon which country's document could be the starting point
- Legal backbone and robust framework: This is to ensure it is actually effective from the outset
- Government buy-in: A top-down approach to facilitate progress and minimal resistance

The assumption here is that, if the 6 LATAM markets under investigation are exhibiting these above-mentioned characteristics, this would denote a move towards harmonisation within the 6 largest markets in the region and, in extension, a possible move towards harmonisation across the region, as opposed to convergence. Figure 4.1 provides an overview of the ASEAN characteristics of harmonisation.

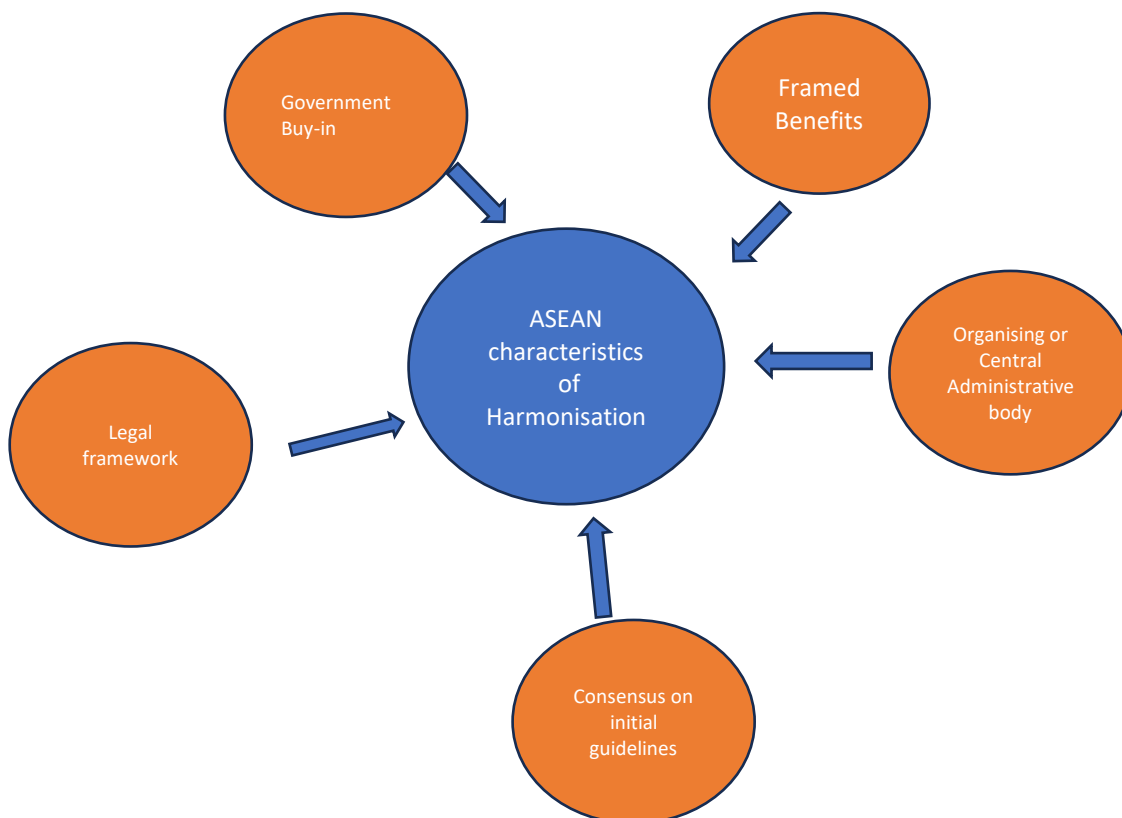


Figure 4.1 Characteristics required for harmonisation from the ASEAN perspective

4.8 Conclusion

This chapter set out to explore the reality of harmonisation of CMC requirements in the ASEAN region by interviewing key stakeholders in pharmaceutical companies. The objective was to seek answers to the following three main related questions:

- How did ASEAN achieve regional harmonization?
- What were the motives and incentives for doing so?
- What are the current major barriers to effective implementation in the ASEAN region, if any?

The objectives of the study have been met in that through the participant interviews, the history of ASEAN and harmonisation of CMC requirements has been explored. The researcher has been able to ascertain that there has been some level of success in harmonising CMC requirements with the creation of an ASEAN CMC guideline; others identify the process as convergence or a mixture of both. Implementation of the guidelines and harmonised requirements has met with some barriers which the region is trying to push through to establish free trade within the region. Singapore, Malaysia and Thailand are major players within the region and hence studying them throws light on where the region is headed in terms of harmonisation of post-approval CMC requirements.

The next Chapter (5) explores current efforts, if any, to streamline CMC post-approval variations in LATAM. Following that, the researcher will look at the extent to which the characteristics drawn out in this Chapter (ASEAN results) could help LATAM in standardising CMC requirements in their region by doing a comparative analysis.

5 RESULTS FROM LATAM INTERVIEWS & QUESTIONNAIRES

5.1 Introduction

The Latin America region has been described as a very evolving regulatory landscape with highly active health authorities (Chapman, 2020). Requirements and Health Authority expectations are continuously evolving and changing (Chapman, 2020). Countries such as Brazil and Argentina, are seen as large growing markets and the region has massive commercial interest for the pharmaceutical industry. (Sackman, 2013; Valverde, 2014) Latin American NRAs are interested in knowing / receiving data submitted and approved by health authorities of reference such as EMA and FDA for new drug applications (NDA)/ Marketing Authorisation Applications (MAA), however on most occasions they require some level of additional local specific CMC data known as ancillary documents (Chapman, 2020). There is some level of interest in greater harmonization across the region, yet there still remains great divergence between individual countries (Sackman, 2013). In Latin America, the Pan American Health Organisation (PAHO) designated the following countries as Level IV national regulatory authorities of regional reference (NRAr) based on their competence and efficiency in carrying out the regulatory functions recommended by PAHO / WHO to guarantee the efficacy, safety and quality of medicines:

- the National Administration of Drugs, Foods and Medical Devices (ANMAT) of Argentina;
- the National Health Surveillance Agency (ANVISA) of Brazil;
- the Center for State Control of Drugs, Equipment, and Medical Devices of Cuba (CECMED)
- the Federal Commission for Protection against Health Risks (COFEPRIS) of México;
- the Public Health Institute (ISP) of Chile;
- the National Food and Drug Surveillance Institute (INVIMA) of Colombia (Rodriguez and De Lucia, 2021)

Level IV is the highest designation that can be awarded to an NRA, indicating regulatory systems operating at an advanced level of performance with procedures in place to ensure continuous improvement. This designation does not give an indication of the region's willingness or efforts to streamline requirements for post-approval CMC changes, which is the focus of this research.

The research will thus focus on these countries due to their regulatory designation status. The research seeks to explore current and future perceived attitudes to streamlining of requirements for Post-approval CMC changes (PACs).

Studies have suggested the benefit of aligning PAC requirements to reduce NRA workload, provide timely access to medicines and help reduce review timelines. One such paper suggested a convergence model to help reduce NRA workload in reviewing and approval of PACs (Rodriguez and De Lucia, 2021). A further paper also suggests possible more timely access to vaccines if there is alignment in PAC guidelines where 33 markets including Brazil, Colombia, Cuba, Chile were studied (Dellepiane *et al.*, 2020). An unpublished Master's thesis investigated opportunities for alignment of the post-approval changes categories of Central America and Dominican Republic NRAs with the risk-based categories of FDA and EMA as encouraged by the ICH to help reduce review times (Vasquez, 2021). To date, there have been no studies exploring whether the LATAM region is indeed making efforts towards streamlining PAC requirements or whether there is an intent to. There are also no published studies, based on empirical data, confirming the possible direction of travel this streamlining process would take, if any.

This exploratory research therefore seeks to identify and understand two areas/objectives for these six NRAs:

- Are the LATAM markets progressing activities to streamline CMC requirements?
- If yes, are they doing this via convergence or harmonisation or some other means?

The research will explore the general CMC variation landscape; explore what relationship exists between markets i.e. do they collaborate? The research will investigate whether there is a level of global engagement i.e. are they reaching out to other international harmonisation networks or engaging with international standards; what perceptions do the NRAs, pharmaceutical industry associations and other regulatory bodies have about streamlining of CMC requirements in the region?

5.2 Method

Full details of the qualitative methods are described in Chapter 2, Section 2.8.

Briefly, the participant recruitment, main interviewee characteristics, semi-structured interviews and thematic analysis are reviewed.

Due to the mention of technical terms and regulatory processes from participant responses, otherwise not explained elsewhere, grey literature was used to clarify concepts and terms, providing context for greater understanding and awareness.

5.2.1 Interviewee characteristics

Participants were recruited through opportunistic, purposive and snowball sampling. In total, twenty-seven participants agreed to be interviewed out of a potential thirty-three; six participants did not respond to email follow up and hence interviews could not be scheduled. Out of the twenty-seven, none withdrew consent. The breakdown of the interviewees are as follows: eighteen RAs (LA1-LA18); one group interview with six participants who are FIFARMA members (LA16, FF1-FF5); one interview with a participant with working knowledge of a regional harmonisation network (RHN1); three participants with working knowledge of three of the NRAs under study (NRA1, NRA2, NRA3). RHN1, NRA1, NRA2, NRA3 provided their personal opinions based on their working knowledge, they were not being interviewed as official representatives of their organisations. The identities of the organisations are therefore not disclosed.

One participant (LA16) was interviewed twice (individual interviews on different days) and was also part of the group interview because of their level of expertise gained through several roles they had been employed in over the years. This is not uncommon for similar research studies (Knott *et al.*, 2022).

In total 27 participants took part in 23 individual interviews and 1 group interview, making 24 interviews in total, the breakdown is as follows:

- 1 Group interview comprising 6 participants (FF1, FF2, FF3, FF4, FF5 and LA16).
- 23 Individual interviews which included 1 email interview, comprised of 22 participants.

LA, FF, RHN and NRA are used to differentiate the types of participants based on their roles. A key to these abbreviations is given under Table 5.1 which lists the characteristics of the participants (n = 27). The sample had a greater number of females than males. On average, participants had 13 years' experience. Participants had regulatory experience across Latin America with Brazil being the most common market.

RA participant recruitment

The researcher posted the advert on LinkedIn and Facebook which yielded most of the participants. Once interviewed, each participant was asked to suggest a colleague (with permission) who may be interested in the research. The participants provided names and email addresses of colleagues who were then followed up by the researcher (snowballing).

FIFARMA participant recruitment

While it was originally intended to recruit just one individual with direct FIFARMA experience via snowball sampling, the key individual, being aware of the study spoke with other potential participants (snowballing) and proposed a group interview.

The individuals act in different capacities within FIFARMA with unique experiences of the phenomenon, which is the reason why the key person requested their input. The participants decided that a group interview would be better than individual interviews as they would collectively speak on behalf of the FIFARMA organisation, bringing their unique perspectives to bear as a holistic representation of the various ways FIFARMA interacted, or the roles played within the phenomenon being studied. A group interview was also logistically beneficial for the participants. As the researcher was offered this opportunity, via opportunistic sampling, to speak with these individuals in a way which suited them it was agreed to undertake a group interview for this particular set of participants.

The group was homogeneous in that it was made up of regulatory affairs professionals who were engaged with the trade association on behalf of their pharma companies and one direct employee of the trade association. They had similar regulatory experience; however, the group was heterogeneous in relation to the 'type' of experiences they brought to the discussion; hence certain questions were directed to specific participants by the group (Acocella, 2012). This was based on the fact that that each person in the group had a specific role in the organisation and the right person to answer a particular question was agreed by the group. Others contributed after the main person had responded, if they felt the need to do so.

The questions were given beforehand because the group requested for it and the researcher consented for the following reasons:

- 1) accessing that group of interviewees (expert) was rare and hence the researcher wanted to encourage their participation

2) they explained that as they were speaking on behalf of FIFARMA (not their own individual opinions unlike the RA individual interviewees) they wanted to ensure their responses were as accurate as possible, reflecting the organisation's position.

3) By seeing the questions beforehand, they could prepare to provide the correct information on behalf of the organisation.

Based on these reasons the researcher agreed to the questions being given beforehand, just for this participant group. As stated earlier, the option to give the questions out depends on what is considered appropriate for the research as defined by the researcher and what makes the participants comfortable (Knox and Burkard, 2009; Stanlick, 2011; Taherdoost, 2022).

There was no 'dominant' person in the group which can sometimes happen in group interviews, as each person contributed based on their recognised expertise and members within the group all deferred to the person best able to answer each specific question. This was also possible because questions were provided beforehand and therefore the group could identify who was best placed to answer each question in advance.

5.2.2 NRA Questionnaires followed by Interviews

Recruitment of NRA participants happened between 2018-2021 in parallel with RA recruitment. The researcher initially tried recruiting through their personal network, through the NRA websites, through direct emailing of potential participants and through snowballing using the RA participants. This initial recruitment strategy did not yield the desired results; the researcher then used gatekeepers in 2021 to recruit participants for this group. This yielded 2 NRA responses out of the potential 6 LATAM NRAs. A third NRA contact was obtained through snowballing from an RA that the gatekeeper had introduced to the researcher. The NRA participants were senior officials in the CMC departments of their NRAs.

NRA Questionnaires were distributed electronically via gatekeepers; responses were received from three out of the six NRA representatives, two followed up with an interview. The third participant agreed to be interviewed, but due to availability and connectivity issues, the interview was conducted via email. After review and analysis of their questionnaire responses, the follow-up questions arising from the questionnaire were

emailed to the participant and received by email within one week. The email interview was asynchronous, that is, not done in real time (Hawkins, 2018).

The other two NRA participants were interviewed via zoom after follow-up questions were generated based on the analysis of their questionnaire responses. NRA participants had the option to use interpreters during their interviews, but they declined the option in their questionnaire responses and confirmed the suitability of English as the medium for the interview.

As described in Chapter 2, data saturation was not the goal for this participant group but rather information power. Malterud et al express 'information power' as a concept or tool to assess sample size (Malterud, Siersma and Guassora, 2016). The larger information power the sample holds, the lower N is needed. They applied this tool in the context of qualitative interviews which can be related to this research for the NRA group. They elucidate that whereby a study concerns a very specific or rare experience, such as pertains to this research, this would limit the number of eligible participants or reduce the number of eligible participants/contributors needed. Sometimes only a small sample pool is available as is the case for the NRA and other expert participant groups (Malterud, Siersma and Guassora, 2016). Due to the small number of NRA officials working in the CMC department, therefore, it was felt that one senior official was enough to provide relevant information about their NRA CMC requirements and review processes.

5.2.3 Secondary data/reports

A regulatory consultancy was employed (paid service) to extract the LATAM NRA requirements from the various NRA websites. In some instances, the NRAs had to be emailed to obtain the requirements as they were not always easily accessible from the NRA website (Taneja, Chacko and Kedar, 2018). The researcher used their personal network to translate the requirements from Spanish/Portuguese into English where necessary, although some of the requirements were already in English.

The researcher reviewed the NRA guidelines in order to discuss the requirements of the five different variations across the markets. Participants provided rich responses to all other questions on the interview guide hence there was not enough time to thoroughly review and discuss the requirements as it would have prolonged interviews past the stipulated time. This did not change the focus of the research; however, it is cited as a limitation and a focus for possible future work.

Harmonisation network reports were analysed inductively to understand the history, structure and functions of the networks and used to support the formulation of questions as part of the interview guide for participants with expert knowledge of these networks (Agee, 2009)

Other secondary documents (PANDRH meeting reports, EFPIA white paper, CIRS reports) were used to either corroborate participant responses or provide alternative views to participant responses, in the discussion section of this chapter. The documents were also analysed deductively using themes generated from the interviews to see if similar themes were captured in the secondary data.

Date of Interview	Identifier	Regions/markets of regulatory experience	Company type (Large Pharma, generic, CRO, network, industry association)	Years worked in Regulatory	Experience specific to the research	Duration of interview
3.3.17	LA1	Latin America (excluding Cuba), Middle East, Africa, Eastern Europe, Asia	Large Pharmaceutical company	26 years	regulatory strategy, compliance	1hr 32 minutes
15.11.17	LA2	Brazil	Large pharmaceutical company	15 years	Regulatory strategy, post-approval changes, renewals	1hr 2 minutes
30.11.17	LA3	Latin America, Central South and Caribbean	Consultancy	20 years +	Regulatory consulting	1hr 21minutes
2.12.17	LA4	Europe, US	Generic Company	4 years	Regulatory CMC, quality assurance	1hr 20minutes

5.12.17	LA5	Brazil	Small pharmaceutical company	6 years	Regulatory strategy, regulatory compliance	1hr 15minutes
18.1.18	LA6	Mexico	Small pharmaceutical company	20 years	Regulatory strategy, medical devices, food supplements, cosmetics	58 minutes
23.6.18	LA7	Brazil	Large pharmaceutical company, API manufacturer	3 years	Regulatory Drug substance analysis, managing DMF	1hr 26 minutes
6.7.18	LA8	All Latin America, International regions	Large pharmaceutical company	10 years	Regulatory strategy	1hr 51 minutes
9.7.18	LA9	Latin America	Large pharmaceutical company	12 years	Regulatory strategy	56 minutes

31.7.18	LA10	Latin America, but majority of experience is with Brazil	Large pharmaceutical company	10 years	Regulatory CMC	1hr 13 minutes
5.09.18	LA11	Global experience, for Latin America main experience is in Brazil and Mexico	Large pharmaceutical company	15 years	Regulatory CMC	37 minutes
12.9.18	LA12	Latin America, Caribbean	Large pharmaceutical company	16 years	Regulatory strategy, labelling, generics	52 minutes
4.10.18	LA13	Latin America excluding Cuba	Large pharmaceutical company	9 years	Regulatory CMC	56 minutes
15.10.18	LA14	Latin America, minimal experience of Ciba	Large pharmaceutical company	20 years	Regulatory strategy and policy	41 minutes

7.2.19	LA15	Latin America (mainly Argentina, Brazil, Mexico, and Columbia) also US, Europe, Canada, Australia, and Japan.	Large pharmaceutical company	16 years	Regulatory CMC	55 minutes
9.6.20	LA16	Latin America, extensive Brazil experience	Large pharmaceutical, NRA and industry association experience	15 years	Regulatory policy	1hr 42 minutes individual
2.7.20	LA16	Latin America, extensive Brazil experience	Large pharmaceutical, NRA and industry association experience	15 years	Regulatory policy	2hrs 12 minutes
26.7.20	RHN	Latin America	Regional Harmonisation Network	6 years	Assists the Regional harmonization	1hr

					Network administratively	
19.9.20	LA17	Latin America, Africa, Middle East, Asia	Large pharmaceutical company	20 years	Regulatory strategy, pharmacovigilance, labelling, compliance	1hr 12 minutes
31.5.21	LA18	US, Latin America (including Cuba), Europe, Asia Pacific, Australia.	Consultancy	37 years	Regulatory strategy, market access	1hr 7minutes
10.9.21 (Group interview)	FF1 FF2 FF3 FF4 FF5 ^*LA16		All work with Large pharmaceutical companies	6 years 4 years 1 year 6 years 3 years ^time spent in this specific role	FIFARMA members	1hr 21 minutes

14.6.21 7.11.21	NRA1	Latin America	NRA	35 years in Regulatory 32 years in NRA	Regulatory affairs and policy	Conducted via email
17.9.21	NRA2	Latin America	NRA	12 years in Regulatory Affairs 6 months in NRA	Regulatory harmonization, intelligence	1hr 8 minutes
1.10.21	NRA3	Latin America	NRA	7 years in NRA	CMC Review, policy & intelligence, harmonization initiatives	1hr 44minutes

Table 5.1 Characteristics of the LATAM participants

*LA16 had experience working with different organisations so their multiple interviews covered those roles, They participated in 2x individual interviews and were part of group interview.

Key:

LA – Regulatory professional with Latin America experience

RHN – Participant with Regional Harmonisation Network experience

NRA – Participant with National Regulatory Authority experience

FF- Participant with FIFARMA experience.

5.2.4 Semi-Structured Interviews

Out of the 24 interviews 21 were conducted via zoom, 1 via Microsoft Teams, 1 was face-to face and 1 was conducted via email, based on interviewee preferences or ease of use (Sah, Singh and Sah, 2020). One group interview was employed for the FIFARMA group as previously outlined.

Participants undertook the interviews in their workplaces in closed offices, after work colleagues had gone home in the case of open offices, or at home in a quiet environment away from others in the home to maintain privacy (Maldonado-Castellanos and Barrios, 2023). The researcher interviewed mostly from a private room at home or, in the case of the one face-to-face interview, at the interviewee's place of work in a closed office.

For the RA group, the interview schedule was not provided in advance to participants whereas questions for the FIFARMA group was provided to them, for reasons laid out in Chapter 2. The RA group were providing their own opinions and hence providing question beforehand may have conditioned their responses which was not the objective for that participant group.

Interviews covered seven major areas, including, the general CMC landscape in each market, attitudes towards streamlining CMC requirements, perceived benefits and challenges to streamlining requirements; the impact or influence of industry associations and regulatory networks; global engagement; feedback from specialists with working knowledge of the NRAs. The last and major area was centred on exploring whether the region was converging to international guidelines/requirements or harmonising within the region; or if any other regulatory process was taking place.

Transcripts were provided to all participants for their review. One FIFARMA participant provided corrections via email on behalf of the group and the transcript was updated accordingly before analysis.

5.2.5 Thematic Analysis

Interview transcripts were coded with the help of NVivo; and themes identified inductively using Braun & Clarke's Thematic Analysis method (Braun and Clarke, 2006), as described in Chapter 2. This identified major themes and subthemes, noting any peculiarities for the six chosen countries. Questionnaires were coded manually, using the same analysis

method as the interview scripts. As described in Chapter 2, LH coded one transcript which was compared against the researcher’s codes to assess any bias.

Thematic data saturation was sought for RA participants. Additional interviews over 12 interviewees generated important and additional information relevant to the topic. The researcher therefore continued the recruitment, interviewing and analysis until additional interviews no longer provided new relevant information (i.e., thematic saturation) (Guest, Namey Emily and Chen, 2020). It can be confirmed that the sample size for the RA participants was enough to yield thematic saturation.

Based on the synthesis of the interviewee responses, themes explored the LATAM CMC landscape in relation to streamlining of CMC variation requirements. This will then form a basis to compare what is occurring in the LATAM region with the ASEAN region for any lessons to enhance LATAM’s own streamlining efforts. This will be taken up in Chapter six.

5.3 Results

Thematic analysis was performed on the 23 semi-structured interviews, 3 questionnaires and 1 email interview, from which seven major themes were identified, laid out in Table 5.2 below. Some themes had sub-themes described further below.

Themes	Subthemes
1. CMC Variation landscape;	<ul style="list-style-type: none"> i. General CMC landscape ii. NRA transparency, maturity, and expertise iii. Political landscape iv. Market specifics/peculiarities v. Guideline Review and triggers
2. Attitudes towards streamlining	
3. Perceived benefits of streamlining CMC requirements	

4. Perceived challenges to streamlining in CMC requirements	
5. Industry Associations & Networks and their influence or impact in the region on streamlining initiatives	i. FIFARMA
	ii. PANDRH
	iii. MERCOSUR
6. Global engagement from the region and implication on streamlining initiatives	
7. What process is being used to streamline CMC requirements?	Convergence or Harmonisation? Reliance

Table 5.2 Themes generated from LATAM qualitative interviews and questionnaires

Each theme is covered in turn, with supporting evidence from the semi-structured interviews and questionnaires. Where applicable, responses are shared for all participant groups, that is, RAs, FIFARMA and NRA participants. Appendix 19 provides a full list of interviewee quotes for each theme whilst Appendix 21 provides questionnaire responses from the NRA participants.

Based on how the conversation developed, some themes may occur only once, however, as an exploratory study, those themes were still taken to be relevant to the research.

5.3.1 CMC Variation landscape and NRA characteristics

RA participants were asked to provide comments on the general CMC landscape of the region and in relation to the Agency's maturity, expertise and openness to industry (transparency). Participants also commented on market peculiarities, challenges in the region and instances of guideline review, triggers and implementation. The majority of participants had more experience working with Brazil, Mexico and Argentina compared to Cuba, Chile and Colombia, subsequently responses for these last three markets were fewer and less rich than for example response for Brazil.

5.3.1.1 General CMC landscape

Two RAs mentioned that harmonizing CMC variation requirements in the region would be difficult to achieve. They did not have much hope that streamlining requirements in the region would be feasible especially as each market had their own laws and regulations.

LA12 *“... This is the most challenging by the way, for variations, in terms of harmonization...”*

LA3 *“...To me, I think it's very difficult to get a harmonization because of the, each country having their own individual laws and regulations...”*

LA12 went on to mention that most markets do not have a classification system describing which variations are major or minor which would support regulatory harmonisation if it existed. They mentioned at least two markets, Brazil and Argentina, having a post-approval CMC regulation for small molecules, which is a start to something more robust in future. LA13 cites the example of Colombia not having a post-approval CMC regulation in place at all.

LA12 *“..., they don't have, like I was saying, a classification system in terms of minor or major, uh, you know, variation. What they have is that for a small molecule, yes, they have a regulation mainly Brazil has and now ANAMAT Argentina also ...”*

LA13 *“...For Colombia, specifically for this topic, the post approval, they don't have a specific regulation for that.”*

In terms of review timelines, LA12 also mentioned that review of CMC variations can be delayed by up to one year due to the bureaucracy of not presenting a specific document which does not impact the safety or efficacy of the product in any way. This has potential to reduce patients access as non-approval of the change in a timely manner could affect the manufacturing and logistical supply of the medicinal product. Usually, the medicinal product is already available globally but not in Latin America due to this bureaucracy.

LA12 *“... And sometimes we take like six months, one year delay because one single CMC document which will not impact the safety and the efficacy of the product, it's just for bureaucracy to be fulfilled.”*

One participant cited their frustration at having to translate certain documents into Spanish for the NRAs e.g. scientific articles. They believed that the NRA should be able to employ assessors who, having a scientific background, can also read multiple languages and translate as they review. They felt some requirements were excessive and ultimately added to the overall delays in submission and assessment of the variations.

LA6 *“...They have people who speak English. Shouldn't it be acceptable, that these people would be able to translate as they read, when they review?...”*

There was also a notion from four participants that the NRAs can sometimes follow the legislation blindly without acknowledging the science behind the CMC change. This then impacts on the documentation a company is required to submit for a particular CMC change. For example, companies are still required to submit all stipulated documents even though some requested documents are not affected by the CMC change. Since classification systems are not in place, what may be deemed as a minor change in relation to the science, is still taken as a major change and hence attract long review times and unnecessarily complex requirements. By acknowledging the science, a better assessment could be made as to what is really needed to review the change and not just following a checklist.

LA11 *“...They're really focusing on one side, and not focusing on actually what has impacted that change or the quality impact to patient, and therefore actually that change, should it be at that level the amount of documentation that's having to be in place to support it.”*

One participant mentioned the need for local company representatives within the general landscape of the region. The local reps help with communication with the agency, fostering openness and transparency. By having access to and engaging with the NRAs, it can provide a bridge to discuss requirements and the science behind the product to

enhance review. Companies usually gather this intel to support interpretation of the NRA guidelines, sometimes however there is a language barrier in understanding the requirements or nuances of the requirements even after translation. A local RA professional who speaks the language can better understand what the NRA is trying to convey.

LA15 "...But in the past, I think very often, the way a lot of companies are structured is they have a local entity... And depending on their relationship with the agency, that can open up a lot of doors, because very often what it takes is finding someone who's willing to engage with you.

Two participants made mention of political whims in the region which affect the regulatory activities. This refers to changes in government which can subsequently affect or influence decisions made within the NRA. When there is a change in government personnel, especially higher government officials, depending on their political affiliations (USA or LATAM aligned), it can affect the general direction or decision making of the NRA.

LA9 "...Of course, they have a lot of influence when we have change in the politicians and when we have elections we suffer a little bit because of the requirements, ..."

Lack of resource was mentioned by three participants specifically for Brazil; however, it was inferred for the other markets who also spoke of backlogs due to lack of resource. This prevents NRAs from adhering to timelines which then leads to a backlog of reviewed applications. The same resource reviewing the CMC variations may be utilised for inspection of manufacturing sites and other regulatory activities. Recruitment of trained personnel is not frequent, and neither is it an easy task, as there is no government budget to open vacancies. Applicants are also required to write a test in order to work with some NRAs, such as ANVISA, which is also a barrier to recruitment and subsequently, sufficient resource within the NRA.

LA9 "...Yes. They are not recruiting... so they [the government] need to open vacancies and they need to have budget for that.

.. *Yeah, maybe* [to the notion that timelines can be adhered to once backlog is cleared]. *The point is that there is a backlog, but also they don't have enough people...*”

NRA participants also expressed their views on the general landscape of their markets. One NRA interviewee stated that there were no specific requirements for small molecules for human use for their market hence the responses provided covered generic drugs as well. This may be a limitation for the research as the research focuses on small molecules, however, the insights provided by the participant still provide insights into the market’s initiatives if any, to streamline CMC requirements. Their comment, however, confirms the response from RA participants about markets lacking specific post-approval CMC requirements or guidelines.

In terms of resource, the NRA participants provided the following staff numbers for post-approval in the questionnaire, shown in the table below.

	<i>NRA3</i>	<i>NRA1</i>	<i>NRA2</i>
<i>Number of staff who review CMC variations</i>	<i>20 * (did not provide the total number of drug product reviewers).</i>	<i>Unsure</i>	<i>15 out of 130 reviewers of drug products</i>

Table 5.3 Staff numbers of CMC reviewers in the NRAs

When asked about the stipulated timelines to review CMC changes versus the actual review timelines based on NRA statistics, the following responses were provided in the questionnaire, shown in Table 5.4 below.

	<i>NRA3</i>	<i>NRA2</i>	<i>NRA1</i>
<i>Published review time</i>	<i>180 days</i>	<i>150 calendar days</i>	<i>45 working days</i>
<i>Average review time (actual)</i>	<i>360 days</i>	<i>Statistics not available but within the established</i>	<i>11-18 months</i>

		<i>limits for all 5 changes</i>	
--	--	---------------------------------	--

Table 5.4 NRA published review timelines versus actual review timelines for the CMC variations under review

The responses confirm RA participant concerns about non-adherence to stipulated timelines. Based on responses and data from NRA 1 and 3, review timelines range from double to up to 10 times published targets. The long review times could indicate a disproportionate number (comparatively low) of evaluators to the number of CMC variations received by the NRAs.

NRA3 recognised the need for their NRA to modify their market CMC variation guidelines due to the conservative nature of the current guideline developed from combining the most restrictive practices/guidance from the Canadian and European (EMA) guidelines. This resulted in the majority of CMC variations being classified as major variations even though in many other markets, they are classified as minor variations.

NRA3 “... Because, we really have a complicated framework. So we'll probably change the resolution in the next year, because of the situation... So when we took the most conservative part of each, we ended up with the most conservative resolution, that classifies most changes as major...”

In the questionnaire, NRA participants were asked to confirm the classification of the five variations mentioned in the study. The classifications are laid out in Table 5.5 below.

	<i>NRA3</i>	<i>NRA2</i>	<i>NRA1</i>
<i>Classification</i>	<i>Other</i>	<i>Major change</i>	<i>Major change apart from 'change in manufacturing method' which has 'no classification.</i>

Table 5.5 NRA classification of CMC variations under review

The responses show a disparity in variation classification between NRA3 versus NRA1 and NRA2 even though they are all NRAs of regional reference. The type of classifications

(major variations require assessment before approval) combined with the long review times could be an indication of why review times are longer than stipulated.

To summarise, the participants mainly detailed general challenges or frustrations with the CMC landscape. These include: non-adherence to stipulated timelines; backlog of submissions; requests for ancillary documents; some requirements not being backed by science but just provided because it is mentioned in the guidelines; some markets not even having post-approval variation guidelines. NRAs are understaffed so have to try and prioritise the various regulatory activities, for example, GMP inspections, consequently, post-approval changes (PACs) are not a priority. In some countries updates or changes to guidelines can be affected by the political landscape. Most documents need to be translated into Spanish which is time consuming. NRA responses confirmed the negative outlook of the CMC landscape and agreed that more could be done within their remit to enhance the regulatory framework.

5.3.1.2 NRA transparency, maturity, and expertise

This section reviews the transparency, maturity and expertise of each market NRA and regulatory environment. These areas are indicators or measures of regulatory capacity, flexibility and know-how; either leading to a willingness, readiness and ability to streamline or not.

5.3.1.2.1 Brazil

Two participants advised that ANVISA was established in 1999 so it is a relatively new Agency, although eight participants cited Brazil (ANVISA) as the most mature and transparent country in the LATAM region. They are felt to be open to dialogue and to learn, pragmatic and outward looking i.e. willing to learn from outside the region. Participants cited that the assessors attend trainings which helps to improve their skills in evaluating dossiers. The NRA is open to receiving comments from industry and sometimes changes its position on requirements or a topic if the company or industry can provide a strong justification.

LA2 “... I have found that the agency has become more and more tough with the companies. They are asking more things they are also improving their skills to evaluate the dossiers that we have. ...”

LA14 “.... They facilitate for example, face-to-face meetings with the industry for pre-submission meeting. So anytime we have a file, and we have some doubts about the documents, we schedule a meeting and then they really provide their comments...”

Regulators can be tough in their assessment of small molecules as compared to others like biologics (which are considered quite complex, so a level of flexibility in reviewing is granted) and they have high standards and expectations of industry. One interviewee also mentioned that reviewers can often mix concepts between review of a generic versus small molecules as they often review both types of medicinal products in their role, causing them to be more stringent on requirements for small molecules:

LA12 “... ANVISA, however on biologicals they, they are more open mind for risky science, a risk based approach and but for small molecules; as they review generic and new product, they are more by the book, they have more local country, country specific requirements for small molecules because they mix up a little bit of the concept between generics and new products which are completely different; and they mix these because the same person that reviewed the generic, they also review the innovative product...”

On a positive note, however, one participant mentioned that Brazil is gaining respect among the other mature Agencies such as EMA and FDA as an agency that has competent technical staff and the ability to contribute to technical discussions / dialogues.

LA10 “... it's [ANVISA] already starting to have some kind of influence on these other agencies. I think that EMA and the FDA see ANVISA with, they're in the same level I think, in terms of technical staff, in terms of listening to ANVISA's technical staff, a technical point of view...”

LA7 however, raises a concern with transparency in relation to the recent/last change in post-approval guidelines (RDC73). The pharmaceutical industry was only consulted after

the guidelines had been completed. Multinational companies and local associations (SINDUS Pharma) made complaints about the lack of flexibility and transparency from ANVISA regarding the process. This prompted ANVISA to promise more transparency in subsequent updates according to the interviewee.

LA7 "... ANVISA didn't look at companies' side, so think from that moment they said, "okay I think we need to listen more before we write the guideline..."

In terms of expertise, three participants mentioned that sometimes information requested is not necessarily led by the science but rather by the legislation. Due to the requirement being hard written in the legislation, it needs to be provided regardless of whether it is adding anything to the quality, safety or efficacy of the medicinal product (the science). The participants advocated that the LATAM NRAs really need to understand the science behind the product which will help them understand the post-approval change being presented such that when a justification or rationale is provided as to why certain documents were or were not presented, the rationale would not be rejected based on it not being stipulated in the legislation. This is seen as a hurdle to enhancing streamlining and review processes. Participants commented that ICH guidelines allow for such flexibility and justifications, and hence LATAM NRAs should be able to assess variations in this manner. They, however, highlighted that evaluators in the various NRAs do not all have the same training and knowledge hence they are hesitant to apply different approaches not stipulated in the National regulations.

LA13 "...No. In fact, there are many situations that could the company has some scientific rationale or justification for some approach and ANVISA cannot accept this approach because in the regulation, it's clearly state that they need to provide some documents. So, if they needed to think about in a different way, in a different approach that it's not clear in the regulation, some evaluators are not comfortable to take this decision.

LA11 goes on to explain that multinational companies especially, should be given the opportunity to justify the science behind the documents they present. This is because they understand the intricacies of the innovator product compared to local generic companies and hence have better understanding of the science behind the CMC change. They would

appreciate if the NRA could hold that two-way conversation, engaging with them on the science, not just the legislation.

LA11 "...But it's allowing that two-way conversation. Sometimes you don't even get to be able to put your science and your technical evaluation across. It's just legislation..."

From participant responses, Brazil is seen to be a mature market with competent staff even though sometimes the requirements do not seem to be scientifically justified. The pharmaceutical industry could be consulted ahead of time before guidelines are issued to make them more transparent.

5.3.1.2.2 Argentina

In terms of transparency, maturity and expertise, there was a mixed reaction from the eight participants who commented on this theme. Three participants mentioned that the Argentinian dossiers tend to be very simple as they heavily reference the EU or US. Two participants mentioned that in 2018 the NRA published a draft guideline for post-approval changes for small molecules and allowed industry to comment. One other participant mentioned that they were not aware of any consultation with industry on the new guidelines whilst another said the NRA did not request any input from industry and that they were not really engaging industry. Participants gave a mixed reaction as to the openness and transparency of the NRA.

LA12 "... And for Argentina for instance, they just publish a draft guideline for Post approval changes for small Molecules and biotech. Recently they opened for comments and the, the Guidance was pretty much following the European variation guideline..."

LA1 "...They don't talk, really. They send out guidance but not requesting any input from industry..."

LA13 "...Yeah. The Argentina BOH are open for dialogue..."

In terms of maturity and expertise, one participant mentioned that Argentina was amongst the more mature NRAs within the region because they follow the EU and US guidelines, are more structured and have open dialogue with industry. LA9 placed ANMAT in the league of Brazil, Mexico and Colombia NRAs. However, another interviewee mentioned that the NRA was poorly regulated in that it had simpler CMC requirements. They stated the complete opposite to LA9, citing that ANMAT (Argentina) could not be compared to ANVISA (Brazil) or INVIMA (Colombia) or COFEPRIS (Mexico).

LA9 "...I think, considering these countries, especially the biggest four; can I say Brazil, Mexico, Argentina, and Colombia. Their health authority is getting more educated. They are following very well the U.S. and EMA..."

LA10 "... I can tell you in advance that Argentina, the regulatory aspect, ANMAT, it's poorly regulated, sort of, so to speak. We cannot even compare ANMAT to ANVISA or INVIMA or COFEPRIS. ANMAT, it's much simpler in terms of CMC requirements...."

5.3.1.2.3 Chile

Three participants commented on Chile's maturity. One commented that Chile NRA (ISP) was very strict and adhered to their published review timelines, making them a mature agency because a company can trust the published review timelines to plan their commercial and manufacturing activities.

LA8 "... Chile is a quite mature health authority from my point of view in terms of they're very strict with their timelines so if they say it will be approved within six months, within six months you have the answer, rejection or approval, so this is a very good point to trust in a health authority

One interviewee commented that even though the NRA was named as an NRAr, they wouldn't consider them as stringent as Argentina or Brazil. The other cited that their reviews were not in depth; their dossiers were simple, and they referenced CPPs from more mature agencies (like EU, FDA) to approve changes, which does not tally with the nature of a mature NRA from their perspective. They cited that Brazil for instance would

receive and review a full dossier; hence to call itself a mature Agency, Chile should be able to do the same. Among participants, there seems to be a divide or different understanding on how NRAs have been assessed as mature or reference agencies within the region.

LA15 “...Chile tends to be the one that, it’s not that in terms of sophistication. And so the review isn’t that in-depth...”

In terms of transparency, there were mixed views. Five interviewees said Chile was a transparent NRA, allowing for comments and discussion with industry on submissions and guidelines but maybe not as transparent as ANVISA. One of the 5 said Chile was very open whilst one said they were becoming ‘more open’. With that being said, there is still a lot of influence from a political and economic standpoint on the final regulations.

LA8 “...They are open to have meeting and discussions with the industry... they are not such open as to receive suggestions from the different industries even national or international. ...”

Two participants cited the opposite, saying Chile wasn’t open because of lack of human resources. They stated that the NRA may be open for face-to-face meetings if the product is to meet a rare disease or unmet medical need, but for a general medicine, the company would just join the queue and wait for the file to be accepted and reviewed.

LA14 “... Chile, it’s not so open, it’s difficult to have meetings...I think it’s also because of the lack of resources...”

5.3.1.2.4 Colombia

This study was unable to gain access to many interviewees with experience of Colombia. It was described as a simple and small market in terms of commercial interest to industry and relies on CPPs issued by mature markets (EU, FDA). One interviewee mentioned that it was a mature market but didn’t say anything else. One participant grouped it as a big market in the region together with Brazil, Mexico and Argentina.

LA2 “... I know that Columbia is mature...”

LA3 “... Again, Columbia is one of the, I would say, I would put that at almost at the same level as Mexico and Brazil as an agency...”

In terms of transparency, there were mixed reactions. One participant mentioned the NRA had been open to industry but due to changes in medical personnel at the NRA as a result of elections and arrests of some officials on alleged corruption charges, the NRA seems to be less open and remains so.

LA15 “...Columbia in the past was very open to influencing, and it seems to be less so of late. ...”

Four other participants absolutely agreed that transparency from INVIMA was very poor. They mentioned that INVIMA was not easily approachable, neither were they open to comments from industry on guidance and even if they received the comments, most were not considered in the implementation of the guidelines.

LA12 “...Columbia is the worst case in terms of openness for industry.. and they have very, very country specific requirements for CMC...”

Conversely, three participants mentioned that INVIMA from their perspective, was one of the more open NRAs, allowing meetings with industry and companies.

LA3 “...Columbia. I love that agency. So it's very easy going with them. You're able to meet with them. ..Columbia I would say is more open, they receive a lot more of the openness from the industry, ...”

5.3.1.2.5 Cuba

Again, most participants did not have experience with Cuba. Only 2 participants commented on maturity and transparency. In terms of transparency, they mentioned that Cuba was becoming more open, especially to international companies, as they look to align to ICH guidelines and look outward to more mature agencies like the EU. In the past, they would only allow pre-submission meetings for the national industry, but now they are accepting meetings with international companies. One participant mentioned that in the

past, companies were wary of being open with Cuba due to fear of confidential information/trade secrets about medicinal products being leaked because there were no confidentiality agreements. The fear was that generic companies would get hold of the information and flood the market before the innovator product had a chance.

LA9 “...*The times that I worked with Cuba, they were not so open to have dialogue between companies and Health Authorities...I know that at that time they were not open but maybe now they are...*”

In terms of maturity, one participant said Cuba adheres to their guidelines and timelines, so industry can be certain that a change will be approved in the specified time.

LA8 “...*They are really good... a new product you will have it approved within five to seven, eight months. And it is stated in the regulations and they stick to it...*”

LA8 mentioned that the NRA has well-prepared assessors who are able to engage with industry and discuss the submissions when a company wants to justify some information being provided. Due to their expertise, they are able to access information from the dossiers presented and do not duplicate requests for the same information. The same sentiment was shared by LA3.

LA8 “... *when you for example submit a dossier to the Cuban health authority you will never expect a strange question or a question that, Never expect a strange question, or a question that is already answered within the documentation.*

LA3 “...*Most of them [assessors], they're very high trained, very, very high trained professionals. They have two, three, four degrees, all of them...*”

5.3.1.2.6 Mexico

One participant mentioned a disconnect in CMC documentation provided in the MAA to what is provided and required for post-approval CMC changes. Ideally, documentation requested for a CMC variation should link back to the original MAA documentation for

alignment and continuity. Mexico, however, is more concerned with site registrations hence all the CMC documents to be provided for a change is mostly related to site registrations than the actual post-approval CMC change for the medicinal product and the scientific justification for the change. This relates to the expertise and maturity of the NRA in interpreting and assessing CMC variations.

LA11 *“.... So, when we talk about registration, we talk about the site registration. The enablement of that product to market, seems to be the stumbling block for Mexico, rather than the real CMC part of the dossier...then the quality part is being sort of looked across site registration, CMC, and not really focusing truly on the science behind that change...”*

Two other participants expressed that the NRA's expertise and capacity are not on the same level as Brazil even though other participants said the two NRAs have similar expertise and capacity.

LA8 *“...the capacity they have and the expertise they have at the health authority is not that prepared as, for example, in Brazil, or your reference countries...”*

One participant described a challenge in recruiting more experienced personnel due to lower salaries offered by the NRA in comparison to pharmaceutical companies; hence the preference is to work within the private industry.

LA6 *“...COFEPRIS has ... they don't have the best people working. They have very good people, but they could get people with more expertise, they don't have, because even though at some level they pay very high salaries, pharmaceutical companies paying more, so people would prefer to be employed in a pharmaceutical company for one...”*

In terms of transparency, there was a mixed reaction from the nine participants who commented. Five participants mentioned they were a closed NRA and difficult to deal with or get clarity from, while conversely, three stated that they were an open agency and easy to deal with. The ninth participant mentioned that the NRA is favourable and more open to large pharmaceutical companies but not smaller companies. A few participants mentioned that the NRA was trying to follow international guidelines i.e. being outward looking;

however. when it came to allowing industry to comment on guidelines, the process was confusing and not straight forward. The difference in opinions could be due to the type of companies the participants worked in: local versus multinational. The multinational may find it more difficult to engage with the NRA because they are not local and hence their rapport with the NRA may be more rigid.

LA8 So Mexico is also an ICH observer, and this is something that the industry is trying to use to negotiate more with them in terms of requirements, etc. However, in my experience, they are still very closed and they are not really accepting like negotiation, or they are not trying to align with ICH or with Europe, etc. They are still with requesting things like, you know, provide me with the trustability of all stability batches.

LA9 "...Mexico, they are more, I believe that COFEPRIS is getting more aligned with U.S. and EMA. They are very open for discussions. They have a nice way to work; it's quite easy to understand what they want and how to approach them. They have timelines but they don't follow them a lot, like Brazil, exactly timelines that they use. They have legislation, so sometimes they say, oh we'll approve in four months, and it's longer than that..."

LA6 "...COFEPRIS interact very much with the large pharmaceutical companies. That they do, and they have constant communication, but when you're the small guy trying to work here, you get into ... You feel like you're banging your head against a wall a lot. They're not the easiest agency to deal with..."

5.3.1.2.7 NRA perspective on transparency, maturity and expertise

NRA participants provided their perspectives on the six LATAM markets in terms of their transparency, maturity and expertise. They presented mixed views.

NRA1 believed the NRAs being studied in this research are all open, mature and well-resourced, citing PAHO's designation of the six NRAs as Level IV NRAs as proof. Level IV designation is given to NRAs in the LATAM region, that have been assessed and deemed competent and efficient in performing the recommended health regulatory functions to

ensure the efficacy, safety and quality of medicines (Svarch Perez, Sanchez-Henkel and Alcocer Varela, 2023).

NRA1 "...All the HAs of these countries, called in a generic way, National Regulatory Authorities (NRAs) are, in general terms open, well-resourced and mature enough. The PAHO's Program for Strengthening of NRAs has recognized them as National Regulatory Authorities of Reference for the Region of Latin Americas.

According to NRA3, industry comments (transparency) received by their NRA are taken seriously and reviewed by the board of directors and voted upon, but the majority decision is not always unanimous; in which case further discussions are had. There is a slight tendency to favour the national industry over multinationals and give them more time for instance to implement any decisions since they usually have fewer resources and expertise compared to the multinationals. It can still be a challenge to manage the various comments received from national and multinational companies. They also try to take the patient's interest as a priority. So, where a decision may be easier for the industry, even if industry says they will take full responsibility if anything goes wrong, the NRA does not allow it, as per the example cited below.

NRA3 "...first thing we do when we have differences between national and multinational industry is trying to solve it with timelines. So for instance, the CTD, okay. Then we sit specifically with national industry and we ask, "Okay, how long do you need, we want to arrive here but how long do you need?" And we discuss the timelines. So we try to conciliate, that's what we do in the office. Not take the conflict to the board of directors because it'll make the situation very stressful. It often involves timelines. So we give more time for adoption or something like that. And that's how we try to manage this. But it is very challenging indeed.

NRA2 speaks about a lack of transparency amongst the markets in the region because they do not trust their regulatory decision-making. They mentioned that the NRAs do not even have a real reliance procedure with the high surveillance agencies such as the FDA. Reviewers in one NRA are not open to other reviewers in the region, which works against reliance initiatives in the region. This is partly because NRAs are not familiar with another's

working procedures or SOPs, hence a form of training to expose the NRAs to their regulatory process may be needed to help build the trust.

NRA2 "...And I think it's because the people don't work together. The people that is reviewing the dossiers are not working together. There should be more networking with Latin American countries..."

When asked about receiving input from industry, NRA2 commented that the NRA actively seeks comments very often from industry through justification when deficiency letters are issued. When the justifications are provided, the NRA considers them. However, they commented on there being too many deficiency letters issued which could be avoided if there were more detailed guidelines on variations for the assessors to review the variations more accurately.

NRA2 "...the deficiency letters are because the reviewer didn't understand the papers that were submitted. But still, I think there's a problem there because there's a lot of deficiency letters granted by [NRA]. And this is because of the lack of guidelines..."

When asked if their NRA opened up to industry through forums / meetings for discussions, NRA2 said this occurred for medical devices and CTD implementation but there wasn't a specific group for CMC at the moment. However, they mentioned that they would not consider the NRA to be an open NRA as they do not willingly open up to industry, it is only by their invitation so there isn't much leeway to influence the NRA.

NRA2 "...Yes. Yes, this interaction exists. But for CMC, as I said before, it's not our priority right now. So there isn't any group for the CMC, but I think eventually will be..."

NRA2 "...I will say that in this administration, it is hard. No, it's only if [NRA] invites you to the group that you can propose new things..."

5.3.1.2.8 The FIFARMA perspective on transparency and maturity

The FIFARMA perspective on transparency and maturity and flexibility was that it differed from NRA to NRA in terms of dialoguing with industry regarding specific requirements. Some NRAs are not abreast of current regulations or discussions happening globally and other NRAs are set in their ways not wanting to change their requirements. The participant mentioned that NRAs need to develop a risk-based approach that goes beyond the written guidance and lean into the science when justifications or rationales are presented as to why industry may choose not to provide certain requested requirements.

LA16 "...Yeah. To add maybe what [FF1] and [FF2] have said, beyond that, I think that a good difficulty is also that we have different levels of openness from the regulators to dialogue with industry regarding those specific requirements. And some of them are not well versed in what's going on around the globe, and some of them seem that they don't want to be informed, they will stick to their requirements...So, it's not only the requirements but also the level of flexibility that the regulator would be able to give in case they're willing to hear from industry the rationale for a specific requirement to be presented on the way that it was. And unfortunately, this requires a risk-based mindset and a level of maturity that goes beyond whatever is written in the regulation..."

5.3.1.3 Political influence/landscape

5.3.1.3.1 Brazil

One participant mentioned that Brazil (ANVISA), even though pragmatic and outward-looking, tends to have governmental amnesia when there is a new government. Instead of carrying on from where the predecessor ended, there is frequently a re-start and any on-going plans or processes are started from scratch again, even if the same strategic plan is to be followed.

LA1 "... They don't really have a long-termism. You don't feel like there's a long-term plan, although it's all going in the right direction, it seems sometimes quite short-term..."

In terms of influence, ANVISA is autonomous to the Ministry of Health, however these two governmental arms can influence each other when it comes to public health.

LA10 "... So I think that the Ministry of Health has this power to influence ANVISA. ANVISA, at the same time, has the influence of, has enough strength to influence the Ministry of Health. For example, like [to] stop some kind of discussions about a regulation that does not make sense for the Brazilian market..."

LA7 gave an example where ANVISA influenced the government on the importation of a product that had not followed the due registration process even though the government wanted to authorise its import. LA7 described this as an 'ego fight' between the NRA and the government because patients were affected. The government eventually listened to ANVISA and the product was imported on a tender basis, however, patients went without medication for about two months during this period of disagreement.

LA7 "...Okay. So the company that won and got the chance to bring the product to Brazil, it was for a rare disease, okay and the company didn't have an authorization that is mandatory for ANVISA and the Ministry of Health came and said "Okay, No, for this case we don't want to follow this requirements" and it was a huge fight between the agency and the Ministry of Health because they want to, the Ministry wanted to cross ANVISA and take all the power basically on that case because ANVISA was saying no I won't agree, to them releasing customs, I won't agree. The company cannot sell here in Brazil, they cannot distribute this medicine here in Brazil and the Ministry of Health said "No, no".

So in this case we had political interview, directly political interview and after that the Ministry of health came back and said "Okay we'll go with ANVISA and we'll not accept this medicine here and we will pay annual tender" and they started the process again.

So what happened was the population that needs that medicine suffered without the medicine for I don't know I think one or two months. Yeah, because it was already missing here in the market and then you had this ego fight."

5.3.1.3.2 Mexico

As an example of political influence, LA15 describes how a change in government in Mexico halted planned updates to the CMC guidelines. The updates were seen as low priority by the new government.

LA15 "...With the recent election in Mexico, all of that got dissolved [CMC guidelines], because it wasn't seen as a high priority..."

5.3.1.3.3 Argentina

Three participants mentioned that the NRA (ANMAT) are very influenced by changes in government or politicians. This influence is the difference between the NRA being in-ward looking or outward looking i.e whether they align requirements within the region or align with external Agencies such as EU and US. The dynamic could also affect which types of products (international or national) are approved in the market or which industries (multinational or national) are allowed to comment on guidelines or be allowed pre-submission meetings.

LA8 "..... yes, the influence from political situation is really, really strong. I would say it's the stronger in Latin American countries ..."

5.3.1.3.4 Cuba

Cuba is mentioned as a socialist/communist government, where everything is run by the government hence the pharmaceutical industry is not so trusting of the NRA. One participant mentioned confidentiality issues leaving companies uncomfortable in providing the same level of information they would for Brazil for example. This meant that it was possible for medicinal product information to be easily accessed by generic companies, leading to a loss in commercial value for the pharmaceutical company. It could also negatively impact medication adherence for patients or even result in more adverse events (Straka, Keohane and Liu, 2017).

LA3 "...everything is run by the government and they have their own regulations. It's very hard to enter that market. The authorities, you have to meet with them..."

LA8 “.... So they will not provide the same level of details as they provide to major markets because of confidential issues...”

5.3.1.3.5 Colombia

From the few participants that had experience with Colombia, not much was said about the political landscape of the NRA apart from the fact that some believed they were a mature NRA like Mexico and Brazil. One participant who had mentioned that they used to be open but not so of late suggested this could be due to a change of government. They also mentioned cases of corruption within the NRA, cited earlier under maturity and transparency.

LA3 “...Again, Columbia is one of the, I would say, I would put that at almost at the same level as Mexico and Brazil as an agency...”

5.3.1.3.6 Chile

Participants didn't have much experience with Chile so there were no comments on the political status.

5.3.1.4 Market Peculiarities/specifics

5.3.1.4.1 Brazil

5.3.1.4.1.1 PATE document

One peculiarity to Brazil that most interviewees mentioned is the PATE document. In Spanish this is Parecer de Análise Técnica de Empresa, translating as Opinion of Technical Analysis of the Company or Company Technical Evaluation Opinion (Rodrigues, 2018; Amaral, 2021).

As explained by three participants, this document was introduced in 2019 during ANVISA's review of their CMC guidelines/requirements. The PATE helped both industry and NRA because it aided the categorisation of post-approval CMC changes as either major or minor. The PATE is given to companies to assess their CMC change and confirm to

ANVISA whether it's a major or minor change. In the past, that responsibility fell on ANVISA, as companies just presented whatever document they thought was necessary for ANVISA to review. ANVISA would then inform the company whether those documents were suitable for the CMC variation they had presented and whether that change could be implemented. Some companies would implement the change without waiting for ANVISA's feedback. There are times ANVISA would disagree with the company assessment hence the company would need to reverse the implemented action which could pose challenges in manufacturing leading to shortages of the medicinal product, affecting patient access. The PATE document is required for every post-approval CMC change, it is time-consuming and resource-intensive. No other market in the region requests for this document as part of post-approval CMC submissions.

LA7 "...Okay so PATE it's a very complicated system because the companies had to address themselves and create such kinds of committees to discuss every change because it has impact almost in every department of the company, you need to involve the quality unit, you need to involve pharmaco technical team, you need to involve everybody to discuss the impacts and write the PATE and submit to ANVISA and then implement so..."

LA2 ".....Sometimes we have facing difficulties to evaluate the change, I ask ANVISA for help. Because ANVISA told us, if we classify wrongly the change, we will be rejected. We will not have or receive a query or demand to be responded.

5.3.1.4.1.2 Annual reportable changes

One of the other peculiarities mentioned by five participants with Brazil is their 'Annual reportable change' document also known as Histórico de Mudanças do Produto (HMP). This document captures the medicinal product change history over the year for low-risk CMC variations that only required a notification to ANVISA. This is similar to the FDA's Annual reportable (BioPhorum, 2019). In the US, the post-approval manufacturing changes (PACs) have been determined to have a minimal potential to product an adverse effect on product quality. If a change is considered to be minor, an applicant may proceed with the change, but must notify FDA of the change in an annual report (FDA CDER,

2014). This is what happens in Brazil as well. The WHO guidelines also allow for this procedure stating that the NRA should be notified of a minor quality, but that it can be implemented “without prior review by the NRA” and also that “supporting data do not need to be provided with the notification.” (BioPhorum, 2019). In Brazil however, these minor changes and supporting documents are expected to be submitted prior to implementation using the HMP.

LA9 “... Yes, *this is like the annual report we have in the U.S. So you need to include in this document the low-risk variations like a notification...*”

5.3.1.4.2 Argentina & Chile

No peculiarities were mentioned apart from the fact that they have very simple requirements, do not conduct in depth reviews and are not very sophisticated NRAs.

5.3.1.4.3 Colombia

The only peculiarity mentioned about Colombia was their focus on GMP inspections sometimes over and above requirements for post-approval CMC variations. It seems the requirements for GMP inspections sometimes drive or overshadow the requirements for the post-approval CMC variations.

LA13 “...*Yeah. My experience with Colombia, it's more related to the GMP inspection...*”

5.3.1.4.4 Cuba

There were no peculiarities mentioned for Cuba.

5.3.1.4.5 Mexico

5.3.1.4.5.1 ATP process

Three RAs mentioned the Authorised Third Party Reviewers (ATPR) process. The process allows local regulatory companies authorized and audited by COFEPRIS to review medical device and drug applications on behalf of the NRA. They expedite the approval process as

they review the dossiers and present the dossiers to COFEPRIS as pre-approved (IPS, 2020). COFEPRIS then takes over and issues the final approval. The process is, however, very expensive, additional documents may be requested beyond the NRA requirements, but the review is quicker than COFEPRIS' stipulated timelines, so most companies opt for this process. Again, this is specific to COFEPRIS. Some participants referred to these companies as ATPC, which could be from the Spanish translation.

LA9 *".... So it's a third party company that can evaluate the dossier and when they do it, they will evaluate and they will prepare a report and this report given to COFEPRIS and then COFEPRIS will say it is approved or not..."*

LA8 *"... It is really regulated by COFEPRIS. So in the end it's, for me it's quite strange to work with them because it's like COFEPRIS, it's outsourcing some of the activities they have, and they are responsible for that. But they are not like checking...The peer review, let's say, it's really fast. So, yeah, the timelines are reduced, many for 24 months, that was the standard timing for COFEPRIS. You go up to 12 months. So it's really a lot..."*

LA3 *".... the agency should have a broader staff and more trained staff instead of having to pay \$20,000...because in Mexico, in order for you to get this third party reviewer, it costs like \$40,000. So it's not cheap..."*

5.3.1.4.5.2 Ancillary documents

Three participants mentioned that Mexico requested 'strange documents' and lots of ancillary ones. These being undesirable or not very popular with industry.

LA15 *"... To be honest, I think the good thing is, with some of these backlogs, it's forcing them to look at their requirements. The challenge for us is that, [for] the post-approval world if we look at Mexico, Mexico requires a lot of ancillary documents..."*

5.3.1.4.5.3 GMP inspections

Three participants also made mention of Mexico's insistence of GMP inspections, where the GMP inspection requirements seem to overshadow or drive the requirements for post-approval CMC variations, without necessarily assessing the CMC change in the light of the science behind the change.

LA11 *".....And I think what's happened is, there's been a convergence of those two priorities [site registration and MAA], and then it can impact on the approval. Because of that convergence, then the quality part is being sort of looked across site registration, CMC, and not really focusing truly on the science behind that change..."*

NRA perspectives

NRA participants provided insight into any NRA-specific requirements or processes and discussed whether these would be streamlined to international standards or to any regional initiatives. As this section speaks of market specifics, to maintain the anonymity of the NRAs, identifiers have been adjusted to NRAY, NRAX and NRAZ accordingly.

For one NRA, implementation of a market-specific document, required all companies (national and multinational) to assess any CMC changes duly and thoroughly before they submit it to the NRA. Since implementation, the quality of dossiers has improved. This has led to a significantly lower rate of regulatory rejection of CMC variations. The number of CMC variations submitted has also decreased because the document helps to identify whether the change needs to be submitted or not. So even though it is not an ICH document, it has helped the NRA and industry. In the past the Agency classified everything as major because of a lack of trust in the local industry's ability to assess PACs, now the NRA can review their classifications to be in line with international guidelines because companies are doing much better in assessing the PACs. When asked why the multinational companies had to fill in the document since they were already good at assessing a CMC change and presenting the right documentation, the NRA commented that different requirements to national and multinational companies would be considered illegal, because by law the registration requirements must be the same for every kind of industry.

NRAX “...We received, let's say, 3,000 post-approval changes a year, major changes. After new guideline, it was reduced roughly to 1000 and 500. So it's a half reduction roughly, and also, the quality of the documentation increased very much...and I think this is much because of [document]. It helped a lot of it in a sense...I think, now, we can be more liberal. We can be less conservative because now, we have more trust in what the companies are doing...”

NRAY's NRA has specific requirements for stability data for major CMC variations which is not a feature in other countries within the region or outside i.e. International guidelines. The NRA bases the review of the CMC variations on local guidelines which are not completely aligned to WHO or ICH guidelines, even though they are very similar to ICH.

NRAY “... [NRA] ask the traceability of the batches that we'd use for the stability, and I don't think that's a request in... well, in a few countries, but [market] has its own regulations.

When asked what drove the need for market specific requirements, the response was that the NRA does not have the capacity to conduct pharmacovigilance or site inspections, especially for local companies, instead, they request more information. They specifically mentioned that this was to ensure the local companies were presenting the right information in the dossiers.

NRAY “... instead of going to inspect the factory, they ask more documents. That's my perspective from the industry, and I also confirm it in [NRA]...”

RA and NRA participants both agreed that NRAs requested market specific requirements. NRAs had 'good' reasons for requesting these specifics, however, RA participants deemed these requirements as cumbersome and not always necessary.

5.3.1.5 Guideline Review and triggers

An area that came up in interviews was NRA review of national CMC guidelines and what triggered these reviews. It emerged that the main triggers were due to the NRAs seeking to align to international guidelines, recognising that their guidelines were either very old or no longer serving their purpose in relation to CMC post-approval variation submissions.

5.3.1.5.1 Brazil

Brazil reviewed their CMC guidelines in 2016 (RDC73), with implementation in 2017/2018. Prior to that the guideline was RDC 48 in 2009. It was triggered by Brazil joining ICH and also an awareness that their guidelines were not allowing the NRA to be as efficient in their reviews.

LA15 “...So Brazil is doing it right now. And it was triggered by them joining ICH...”

Due to the updated guidelines, there is a big push to reduce review timelines.

LA15 “... they revamped some of their post-approval with shortened timelines from 12 to 18 months to being done in three months...”

One participant mentioned that Brazil’s updated guidelines were based on the Canadian guidelines, moving away from ICH or WHO due to the flexibility it allows. LA15 explained that for Brazil, the EU guidelines seemed to be very stringent and outdated compared to the Canadian guidelines, however, if the EU guidelines had been updated a few years ago, Brazil would have probably aligned to that.

LA15 “.... They've sort of moved away from ICH, WHO, and essentially taken the Canadian model, the Canadian post-approval requirements holistically... I think the trouble is that they want to look for something that they can latch onto... If we look at the EU variation guidance, it's really helpful, but it's over specific, and it hasn't kept up with times. So I think if that had been released two years ago with an update, they probably would have taken that. But the Canadian one is relatively recently revamped. But yeah, it was surprise when ANVISA told us that...”

5.3.1.5.2 Mexico

Mexico had a planned update to their guidance which did not go through because of a change in government. The new government did not consider it as a high priority. In summary, a guideline review was triggered by one government but all activity on the review was dropped by another government. This political instability does not support a consistent agenda for streamlining activities.

LA15 "... And Mexico was talking about change, and they actually had put together an extension of COFEPRIS called Center of Excellence to help facilitate some of that. But that recently got disbanded....With the recent election in Mexico, all of that got dissolved, because it wasn't seen as a high priority..."

5.3.1.5.3 Argentina

Interviewees mentioned that in 2018, draft guidelines were published for post-approval changes in Argentina for the first time. These guidelines were based on the EU guidelines. Some participants mentioned these guidelines were for small molecules and not biologics whilst others did not specify. Participants also stated that they were not aware of any consultations with industry about the guidelines.

LA15 "...Argentina I've seen some stuff come through where they're starting to try and streamline some of their processes,. But I'm not aware of any consultation with the outside when they did that..."

LA14 "...For example, Argentina has now a draft legislation for post-approval changes, but it's the first one..."

The trigger seemed to be a change in government and the government trying to be more open to international industries as well as pressure from trade associations to have some form of guidelines. One participant mentioned that prior to the existence of the guidelines, interestingly, the NRA still had fees for different categories of variations. Without guidelines, assessors had no defined framework to work with, but variations were still being approved or rejected. The NRA recognised that to attract the multinational companies, they needed to implement guidelines to standardize the CMC review process.

LA8 "... I think, again, with the change of government they are trying to be more open to international industries.... They needed to standardize, somehow, their requirements to have a framework for the evaluators to decide whether they approve or not a change..."

5.3.1.5.4 Chile

There did not seem to be much clarity on the last time Chile reviewed their guidelines or the frequency with which they reviewed them. Three participants cited that there could have been a review of guidelines in 2014 or 2016 based on the time of the interview, but there were not sure. They also mentioned that it could have been for biologicals as opposed to small molecules because biologicals were more complicated. As to the trigger, one interviewee mentioned that as an NRA they probably act out of a sense of responsibility to keep the guidelines updated and hence that would be the reason for any guideline updates.

LA8 "...So in the end they have this sense of responsibility and they try to be updated. I think this is the main reason..."

LA9 "...For Chile, good question. Maybe 2014. I need to check, I'm not sure. I know that about biological medicines it was around 2014..."

5.3.1.5.5 Cuba

Only one participant had a comment about Cuba's CMC guidelines. They stated that Cuba's guidelines had probably not been changed in the last four to five years.

LA8 "...Cuba? I don't remember when was the last time they changed the regulation, to be honest. I would say that in the last four or five years, they didn't change anything. They changed the behaviour, but they didn't change their regulations, per se..."

5.3.1.5.6 Colombia

Two participants mentioned a review of stability guidelines but were not sure of the dates. One interviewee mentioned this could have been in 2016 or 2017 but again they were not sure if this related to post-approval CMC requirements or new marketing authorisations. One participant however mentioned that Colombia did not have their own post-approval CMC guidelines, hence it's possible that the stability guideline review was indeed related

to something other than the CMC post approval guidelines. The NRA has relied on regulations from WHO or other high surveillance markets. They mentioned that a lack of the guidelines could be a plus as it would be easier to implement harmonised requirements if there is no guideline currently in place. It would be easier for the NRAs' mindset to change if there was no existing precedent. No other participant mentioned a lack of post-approval CMC guidelines for Colombia.

LA8 "... Yes. For Colombia it was 2016, that they reviewed the stability, the stability requirements especially..."

LA9 "...I know that last year they had some change, I'm not sure if it's also for CMC..."

LA13 "...For Colombia, specifically for this topic, the post approval, they don't have a specific regulation for that. So they use some information for WHO or the information from other regulatory agencies ..."

Feedback from the NRA participant questionnaires confirmed where a review had been triggered, this was due to NRAs acknowledging outdated guidelines due to the evolution of the pharmaceutical industry. In the instance of no reviews, this could be due to low resource or the NRA not seeing the need to review guidelines at present.

The NRA participant responses corresponded with the opinions raised by RA participants over guideline review and triggers for the review or lack thereof.

5.3.2 Attitudes towards streamlining

Participants were asked to comment on general attitudes towards streamlining of CMC requirements.

LA8 and six other participants doubted whether harmonisation of CMC requirements within the region would occur any time soon, from their experience. They explained that the NRAs did not recognise other countries in the region or their practices as a reference point for them to learn from. Countries within the region were very proud about having their own regulation and their autonomy.

LA8 “... *It’s like every health authority in every country is really proud about having their own regulation and their own power of decision, let’s say. So in Latin America we are not yet in this stage.*”

LA13 comments on ANVISA looking outward to WHO guidelines for post approval submissions and hence it could be an opportunity for all the markets in the region to harmonise by aligning to the WHO guidelines.

LA13 “...ANVISA is about to review the current post approval regulation on bio products and we were told that ANVISA will use the WHO guideline Annex 3 and Annex 4 as a reference for reviewing the post approval regulation. ...”

One participant makes an observation that in as much as Brazil has become a member of ICH, Brazil would not go out of its way to influence the other LATAM countries to do the same, implying that there may not be a leading market in the region that other markets follow or would want to follow. Each market basically sets their own course when it comes to collaboration and there is not much collaboration when it comes to streamlining activities within the region.

LA14 “...Now that ANVISA is ICH member. They have to harmonize and internalize some ICH guidance, but it does not mean that they will influence the other agencies in Latin America to do that...”

LA13 also commented that the NRAs are trying to think about harmonisation and adoption of ICH guidelines because they know this is the future. If they want to remain relevant and have influence outside the region, then they would need to be part of harmonisation initiatives. There is sometimes a fear of the NRAs not being as confident in their assessment and process compared to markets like the EU and US; nevertheless, the LATAM NRAs would still like to make their own judgements outside of reference market approvals. The participant also mentioned that the NRAs would still expect companies to respect requests for country-specific requirements.

LA13 “...[The NRAs are]Thinking about harmonization, thinking about adopting ICH as a guideline, become a member because this is the future. If they want to have

more influence, have more dialogue with international associations and other regulatory agencies, they need to be part of this harmonization.

LA5 mentions that relations within the region are not politically strong so the countries within the region are not very integrated. This hinders any discussions on streamlining. Agreements they have had in the past have not worked and hence there is no incentive to carry on working together. They also go on to mention that even though Brazil tried to get closer to Argentina, Brazil essentially thinks they are better than Argentina hence they would not find anything worthwhile to learn from Argentina. This implies looking outward to agencies they believe they can learn from.

LA5 "...And I can tell you that the markets are not talking much from Latin America. They are not very integrated... if you are bad you are not going to look for another bad country to be with you. You are going to look for something better for you to improve...We cannot call ourselves a Latin America group. We are more like countries of Latin America. We are not working together like we are supposed to be. Probably because of the political part ..."

Four other participants mentioned that there was some form of country collaboration within the region in the form of training and mutual agreements on other topics outside alignment on CMC requirements and outside of PANDRH's streamlining efforts in the region. The participants were signifying a possible desire for markets to work together within the region.

LA12 ". So they have a bilateral eh, agreements for inspections for other topics. So the countries are collaborated to each other. They do not simply depend on PANDRH..."

One other interviewee mentions a scenario where it would be ideal to have a reference market within the region for other markets to follow in terms of review and approval, for example Brazil, being one of the mature NRAs. However, she commented that this may not be possible as it seems there is unhealthy competition amongst markets. They stipulated that it was almost childlike for the NRAs to behave this way. Argentina for instance would not want to approve an MAA or variation based on a previous Brazilian "reference" approval.

LA8 “... To be honest, we are in Latin America, we don't have this level of matureness in the different health authorities and in the different countries. They are competing with Argentina against Brazil. It's not just football. It's that they compete in all the things. It's a behaviour that you cannot imagine in terms of government, in terms of politics, in terms of different things...”

When asked if streamlining within the region was a focus or priority, there were mixed reactions. Two participants mentioned there was a desire to streamline requirements within the region, however it was not obvious. Two other participants mentioned that they did not think it was a priority to streamline CMC requirements within the region because the focus was on clearing the back log of reviews with the limited human resources they had. One participant believed that the region would like to achieve harmonisation and it was also desirable for industry, however they observed that each market was aligning to international guidelines in isolation to other LATAM markets. There was no collaborative effort even though they seem to be wanting the same thing, i.e. harmonisation.

LA13 “...Yeah. They're thinking about harmonization. This is something that they would like to achieve, and they are working towards to this but I cannot see many progress so far, except for the example that I provide you about the ANVISA that is trying to adopt the WHO guideline. But they are trying to adopt the WHO guideline but not aligned with the other Latin America market.. They are trying to harmonize but not working in Latin America as a whole group...”

LA14 “...It's not their priority at the moment, because they are so understaffed. They have a lot of pressure from the industry, so they are really trying to do their work...”

LA8 speaks of countries in the region exercising their sovereignty and not fully open to just relying on or trusting another market for review and approval of CMC variations.

LA8 “...they are not in the stage of fully reliance on other health authorities...”

LA3 and two other participants mention a collaboration between Mexico, Colombia, Chile and Peru called the Pacific Alliance which Mexico has used to release a wide range of medicinal products including medical devices into their market. The Pacific Alliance (Alianza del Pacifico) is a Latin American trade bloc, formed by Chile, Columbia, Mexico and Peru, which all border the Pacific Ocean. The alliance was formed with the express purpose of improving regional integration and moving toward complete freedom in the movement of goods, services, capital and people between the four member states. (Baker, 2017; Wikipedia, 2022)

LA3 "...What's happening now in Mexico is they're doing harmonization between Mexico and Colombia and Pacific Trade Agreement... that alliance really has been going on for a very long time now, and that's the work we're doing to facilitate and to get a larger variety of medications in Mexico.

Participants in the FIFARMA group interview explained that FIFARMA shared expertise on the current WHO post-approval change guidelines with local associations back in 2017-2018. The WHO guidelines are used as a basis for discussions on convergence or harmonisation with international standards in the Latin America region. The activities FIFARMA also engages in with PAHO, do not specifically deal with streamlining of CMC requirements as a separate project. There is constant messaging, however, through the materials shared with markets, driving at convergence with or harmonisation to international standards. So overall, FIFARMA's general goal is to drive markets to align with international standards as a whole, though there is no specific priority to do so for CMC variations.

FF2 "...More recently, because those guidelines I think, had been well communicated and understood, we haven't had CMC convergence as a priority topic related to any one specific guidance ..."

LA16 "...So currently we have a work plan with them [PAHO] that includes a series of activities. None of them is specifically in the area of CMC.

From the NRA questionnaires, a way to assess attitude towards streamlining CMC requirements was to look at the last time NRAs reviewed their CMC requirements:

NRA3 reviewed their requirements within the last 3-5 years leading to an updated post-approval CMC guideline. This shows an interest in keeping abreast with updates in the post-approval variation field. The NRA acknowledged that the review was triggered by out-of-date requirements, confirming a positive attitude towards updating their knowledge and becoming more flexible.

NRA1 and NRA 2 had not reviewed their CMC variations legislation for more than 10 years, citing other regulatory priorities or the need to clear the current backlog of variations as reasons for not reviewing their requirements for so long, during their follow-up interview.

In the questionnaire, NRA participants were asked to indicate if streamlining of CMC variations was a priority for their NRAs in their personal opinion.

NRA3 moderately agreed - their response aligns with the NRA's recent action of reviewed requirements. They went on to express their NRAs efforts to streamline by converging to ICH requirements, especially the Q12 post-approval guidelines as well as plans to align implementation types such as notifications or prior approvals for their small molecule guidelines.

NRA3 "...We are taking as priority the harmonization with ICH guidelines that refer to post-approval change, mainly ICH Q12 (that refers to Product Lifecycle Management, including post-approval changes). Other ICH guidelines that are also important for post-approval changes (e.g. Q8, Q9, Q10) are also being considered..."

However, NRA1 and NRA2 were non-committal in their opinion of the NRAs' priority to streamline CMC requirements within the questionnaire. Despite this, in their interviews, they mention that priority is low. This could indicate that they cannot confirm a clear direction from their NRA to streamline CMC requirements even though the NRAs have not reviewed their requirements for over 10 years. It is possible that the NRAs have a desire to review their CMC requirements but lack of resource or use of resource to clear backlogs or deal with other pressing areas has been more of a priority over the years.

With that being said, NRA1 in their follow-up interview, however, acknowledged that it was pertinent for their NRA to start focusing their efforts on post-approval CMC changes; shifting the priority from MAA and GMP. It can be noticed that the terms 'convergence' and

'harmonisation' are being used interchangeably. This probably refers to their desire to see the requirements being streamlined in general and not necessarily to be harmonised across LATAM markets.

NRA1 "...I believe that initiatives are currently focused to GMP and MA, not to CMC Changes, this is the priority. Nevertheless, I consider, that convergence of basic issues is quite advanced and that it is time to move the priority of harmonization to CMC changes, once that platform is reached..."

Based on the responses, attitudes towards streamlining CMC requirements are mixed. There is no political alignment and no desire to streamline requirements within the region. Markets want to exercise their own autonomy and there is no clear leader in the region that other markets can reference. From a FIFARMA and NRA perspective, streamlining CMC requirements does not seem to be a priority, though participants would like to see this happen. There is, however, a general consensus that the region is moving towards streamlining to international standards.

5.3.3 Perceived benefits of streamlining CMC requirements

Between twelve participants, five main benefits to streamlining requirements were cited. Firstly, if CMC requirements were streamlined, approval in a market with a scientifically robust but easy and quick review process, could be used as a reference for the other regional NRA. This would mean that the same information or customised dossier would not need to be re-submitted in the other markets for a full review before approval was obtained. As the requirements would be the same, the regional NRA could trust the review of the reference market and approve on the basis of the reference NRA assessment with no need for further translations or the use of 'authorised parties' such as in Mexico. This would particularly be useful with markets that have a complex/obscure registration process.

LA6 "...Well, my Latin American opinion the advantages would be registering the easiest country and use that as a spearhead for all the others..."

Two other benefits mentioned in regard to streamlining requirements were, the saving of time by removing duplication of effort and work to review the same information already reviewed by another NRA, basically following the reliance process. This would allow better use of limited human resources. The reviewer could utilise their time in reviewing other submissions that may have back-logs in the agency.

LA14 "... if a product is approved in Brazil, for example or in Argentina, it could be easier to be approved in central America or in the Caribbean region where the agency is lacking resource..."

One participant also explained how reliance has been used in Singapore to make good use of resource. At a training in [Country], LA16 presented an example of Singapore NRA using 51 reviewers to cover post-approval changes, new submissions, market surveillance, activities, adverse reactions. The delegates were surprised because they thought HSA had hundreds of reviewers and they considered HSA as a mature agency. LA16 was trying to convince the [country] NRA to consider reliance as it was possible to leverage reliance mechanisms for effective use of resources. HSA have various reliance pathways they use to review submissions which do not threaten their sovereignty. They went on to cite ANVISA having about 2000 reviewers but it was still struggling with back-logs. Reliance could really make a difference to LATAM NRAs if they would consider it.

LA16 "...I've been to [country] last year for a training, trying to sort of sell the idea of regulatory reliance for them because they are one of those countries that don't believe in regulatory reliance, that they are losing their sovereignty, et cetera. ...I was at some point try convincing ANVISA that there was some room for reliance. And we are talking about ANVISA, which is an agency with 2000 people..."

Streamlining requirements would establish a level playing field between local and multi-national companies. One participant cited unfairness in requirements for local versus multi-national companies; local companies having easier or less requirements than multi-national companies.

LA9 “...*Because sometimes in these countries, we have, for example, local companies, they have more advantages in comparison to multi-national companies, just because they are local...*”

Lastly, streamlining requirements means that the product specifications could be aligned and hence importers assured that the quality of the product is the same as everywhere else in the region or the same as compared to recognised markets like EU or FDA. When requirements are streamlined in this way, there is increased trust in the product being imported simplification of supply logistics on approval and this means that patients can have easier, quicker and continuous access to innovative medicines.

LA7 “...*If you have harmonized guidelines, it's much easier for the companies to export the products and for the population to have access faster and with better prices...*”

From an NRA perspective, participants had the following to say about benefits of streamlining CMC requirements:

NRA3 cited reduced risk of shortages to medicinal products and more flexibility in reviewing variations as benefits. They, however, explained that national manufacturers would have a steep learning curve as they would need to abandon checklist-type submissions and focus on science-based submission, making decisions on a case-by-case basis. This may be a big cultural shock as national manufacturers had not been used to preparing submissions against international guidelines.

NRA1 mentions that the regulatory system is a unit so modifying one aspect would normally impact the other areas hence applying a holistic approach is generally better, nevertheless, streamlining CMC variation requirements specifically would still have advantages.

Participants also mentioned the benefit of saving time, where companies do not have to prepare separate dossiers to submit; NRAs receiving standardised dossiers would enable quicker reviews. This would be beneficial because CMC changes can impact production

times and are required to avert certain risks. The ultimate benefit of the timely implementation of the change is to the patient.

NRA1 "...For the NRA to receive the information standardized due to harmonized requirements enables faster reviews...."

NRA2 "...To have faster and cheaper access to medical options that benefit the majority..."

Overall, all participants agreed that there are benefits to streamlining post-approval CMC requirements and that the region would definitely benefit from it whether harmonising within the region or converging to international guidelines.

5.3.4 Perceived Challenges to streamlining CMC requirements

During the interviews, participants cited numerous challenges they perceived would affect streamlining of post-approval CMC requirements.

Interpretation of guidelines was one such challenge mentioned by two participants. This is where the interpretation is different across countries and within the same countries by different reviewers. For the same change, different requirements are asked across countries within the region. Also, the reviewers at various NRAs vary in knowledge, resources and backgrounds and expertise which affects how the guidelines are interpreted. One participant cited how this even happens with EMA reviewers and ICH guidelines, that is, even the high surveillance, reference markets have issues with this, so it is not surprising for LATAM NRAs that are not as mature, having less resources and expertise to experience the same issue.

LA12 "... You know, sometimes we have exactly the same regulation among the countries and different people can interpret it differently...and even in ICH guidelines sometimes as it's sometimes it's high level, I think we have different ways to interpret. So this is a big challenge..."

Classification of requirements was also mentioned by one participant as a challenge in that in major reference markets (e.g. US, EU) a minor change could be seen as a major change in the LATAM markets which potentially delays the approval of that upgrade to the medicine in those markets. The minor variations could be a 'tell and do' meaning once the company notifies the NRA, they can go ahead and implement. The major variation, however, always requires a prior assessment in the emerging market. The delays could potentially be months versus days based on the classification and it is quite frustrating for multinational companies who have to manage the change across various markets. It becomes a very complex process balancing the different manufacturing operations and planning the implementation of the changes at different time points in different markets.

Another participant raised the issue of some NRAs being understaffed and not having the time to create post-approval CMC guidelines or review their existing ones to check if guidelines are still relevant based on science or what is current in the CMC space. They raised that this was because NRAs are understaffed and do not have the time to look at the guidelines. The lack of guidelines prevents companies from knowing what exactly to provide for the post-approval CMC changes.

LA14 "...It's not their priority at the moment, because they are so understaffed... They say that they don't have time to review the regulations. ..."

Another of the hindrances to streamlining of requirements is the need and insistence of market-specific requirements by NRAs. An example is cited below by Participant LA7 who describes ANVISA's need for different validation testing points to what is stipulated in the ICH guidelines, even though ANVISA is supposed to be a member of ICH. So a multinational company will prepare information based on ICH guidelines, knowing that Brazil adheres to ICH guidelines, they should not have to do any extra work. However, because of the market-specific requirements, the company has to go over and beyond the ICH requirements to fulfil these market-specific requests. This obviously goes against the purpose of the streamlining agenda.

LA7 "...I think the clearer example that we have now it's about the validation, okay about analytic methods. We use a guideline that it's 99% based on ICH guideline. But for linearity parameter that is established different concentrations, different points ..."

Many participants doubt ANVISA's ability to totally align with ICH requirements due to their insistence on local requirements. Industry is eagerly watching how Brazil will align to ICH as it becomes a legal requirement once a market joins the ICH. ANVISA argues that the local requirements are mainly to assist the local companies to comply with their regulations. However, it adversely affects the multinational companies who are conversant with ICH guidelines and do not need any further guidance. Regardless of that, as cited earlier, it is a legal requirement for local and multinational companies to provide what is required because they have experience with ICH guidelines and have been doing it for a while.

LA13 "...I think ANVISA is having some difficult to harmonize with ICH because of the details that they are usually include in the regulations. And ANVISA said that the details that they usually include in the regulations is required because the local companies needs more information to proceed with some stability or few other topic. ..."

Also, the use of market specific requirements such as the PATE document of ANVISA or the ancillary documents of COFEPRIS poses a challenge to streamlining requirements across the region.

LA2 "...And I heard a lot of colleagues from other companies telling the same, that the companies, maybe will not work with Brazil, will not change the product because of this, because of the difficult of the PATE document..."

LA15 "...Mexico requires a lot of ancillary documents..."

Adherence to the same or similar timelines is also a major challenge as explained by five participants. As one participant mentioned, it is all well and good to have the same requirements but ideally having similar timelines for review and approval would really help in terms of implementing the changes so the benefits can be derived by the patients at the same time. They went on to add that agreeing to the same timelines across the markets would be tougher as this heavily relied on what resource the NRA had to review and approve the submissions. In their opinion, streamlining of requirements should go hand in

hand with agreement of similar review timelines in order for the streamlining to have optimal impact in the region.

LA1 “...What tends to happen is that the timelines, if there are any set out, are exceeded... Let's agree that requirements are the same but the timelines would be more difficult. That's just based on resource...”

One participant explains the issue with country specific requirements where sometimes the NRA follows the guidance to the letter without any scientific consideration.

ANVISA was mentioned as an NRA that requests for more documentation than the ICH requirements they are trying to align to. This is mainly because they do not trust or have confidence in the local manufacturers/pharma companies and so request these documents to feel more confident in their review of the medicinal product. One participant put it this way ‘they are risk averse’.

LA13 also mentions that evaluators do not have the same knowledge or background so when information presented is outside the boundary of the guidelines they are not comfortable to take decisions i.e. approve or reject the variation submission. In order to streamline requirements, however, this flexibility or expertise in using good scientific judgement is required, especially when aligning to international regulations.

LA13 “.... ICH and other international guidelines, they allows for alternative approach if it technically justified. And it is a hurdle that we have in Brazil and any other Latin America countries because not all the evaluators have the same background, the same knowledge. So they rely on what's include in the regulation to approve the petition. So if they needed to think about in a different way, in a different approach that it's not clear in the regulation, some evaluators are not comfortable to take this decision...”

Six participants spoke about sovereignty being a challenge preventing streamlining of requirements because each NRA wants the autonomy to abide by what they believe is best for them and the ability to have their own local regulations.

LA3 So it's the same reason why they don't harmonize. It's the same reason why they won't say, okay, we'll accept that the same requirements can be submitted in Columbia

or in Peru because they...each agency wants to have their own laws, regulations, and the way they conduct affairs.

NRA participants expressed their views on challenges occurring in the region that may hinder streamlining initiatives. These ranged from social, cultural; political to local guidelines enshrined in old laws and markets wanting to keep their autonomy similar to the challenges raised by the RA participants.

NRA1 raised the fact that socio-cultural political contexts in markets can affect how companies are treated even though requirements should be driven by science. An example cited was the local industry being protected, having less severe requirements applied to them as compared to foreign companies, because the NRA has more control over the local companies.

NRA1 "...Regulation is the result of the evolution and the context of the country, then politics and culture are part of the context. It is written, that drug regulation is a public policy response to the perceived problems or perceived needs of society, so connexion exists ..."

NRA3 mentions that the political landscape is not conducive for collaboration within the region. There is a mix of left-wing and right-wing governments in the region which drives different political ideologies and fuels political tensions in the region.

NRA3 "...Yes. Currently at Latin America, we have some nationalist governments, such like [market] Government currently. And I think it's very unlikely that this government wants to approximate with other Latin American governments, especially left-wing governments like Argentina..."

Left-wing was explained by NRA3 as 'being liberal' whereas right-wing was explained as 'being conservative'. NRA3 also explained that each market would like to keep their autonomy hence a singular regulatory body would most likely be criticised politically across the region. This follow-up interview comment was given in response to the answer given in the questionnaire on whether the participant envisages LATAM having a singular regulatory body to help with streamlining activities.

NRA3 “.... At least at this moment, and I would say for the next 10 years, I don't really see it happening. I think it will be criticized, like we were about to lose [market] autonomy. ...”

NRA2 mentions a political scenario where a change in administration, changed a specific guideline that was in use and had been aligned to the ICH guidelines. The new administration reverted to the original local guidelines which were not as stringent as the retracted guidelines. Industry however still preferred to use the updated guidelines because it was more aligned to ICH requirements.

NRA2 “...But in this administration, they took it away, those [ICH-aligned] guideline because... Exactly, they said the requirements were more much than the local guidelines...”

NRA3 mentions lack of resource and a complex hiring process which is creating a back log of reviews for the NRA. The workload compared to the NRA workforce has always been disproportionate. The hiring of staff has to go through a whole public political process, on top of that, the NRA does not always have the financial budget for new staff. The little resource the NRA has is concentrated on clearing the backlog leaving little time to review requirements for streamlining initiatives.

Due to the guidelines being strict, it causes more work because most are classified as major changes meaning they need to be submitted and reviewed, unlike other markets where some changes only require notification, which are easier and quicker to process. Lastly the participant mentioned the behaviour of the companies as a challenge where companies take advantage to file early with non-commercial batches for instance, which necessitates a post approval change right after MAA approval as they now switch to production of commercial batches. The commercial batches need to be submitted for review.

NRA3 “.... Sometimes the registration takes some evaluations that make post approval changes necessary right after the registration...”

NRA3 “..... So in one side, workforce. In other side, workload and in some cases, also due to companies' and sponsors' behaviour....”

NRA2 raises the issue of markets having very old local guidelines and being comfortable with those guidelines, not wanting to change them which goes against any streamlining principles. NRAs must be flexible and willing to embrace change. NRA3 also raised the challenge of national companies not being used to scientific based guidelines like the ICH guidelines which sometimes requires case-by-case decisions. This is very different to the local guidelines they have been used to which is a more checklist approach.

NRA2 “.... That's why they haven't moved to another global guideline, for example, because the rules [NRA regulations] were made a long time ago, and they don't see the need to change them...”

Based on their experience working in industry and with FIFARMA, participants gave the below views on challenges or obstacles they believed the NRAs faced in implementing harmonisation or convergence.

One challenge mentioned was NRAs still choosing to have market-specific requirements. This would make streamlining to international standards difficult to achieve. This same challenge was mentioned by RA and NRA participants too.

FF3 “...if these countries are in the effort to agree to some level of harmonization, it's still being too country specific. ...”

Secondly, there is a language barrier when translating ICH or WHO requirements, some understanding and interpretation is lost whilst translating to Spanish or Portuguese. FIFARMA or PAHO will try to facilitate the translation, so the interpretation stays true to the original guideline. Lack of training on the ICH guidelines was another challenge mentioned by FF1 however the ICH has become more aware of this and provides training materials to guide willing markets through the convergence process.

FF1 “...I would say one of the key challenges we face is the language barrier. So every time there's a new guideline from WHO or even ICH, we try to facilitate the translation ...”

FF1 “...The other thing is, in the past we know there was limited training on ICH. ...”

The level of openness, transparency, flexibility and maturity differs between NRA to NRA in terms of dialoguing with industry regarding specific requirements, this can also hinder streamlining activities. The participant mentioned that NRAs need to develop a risk-based approach that goes beyond the written guidance and lean into the science as justifications or rationales are presented as to why industry may choose not to provide certain requested requirements.

LA16 "...So, it's not only the requirements, but also the level of flexibility that the regulator would be able to give in case they're willing to hear from industry the rationale for a specific requirement to be presented on the way that it was. ..."

Another challenge is also having the CMC information in the MAA dossiers being aligned to post-approval guidance so it doesn't trigger complex PACs after the MAA approval. This was also supported by one of the NRA participants.

FF2 "...So, for us I think that's one of the reasons why a lot of our messaging at the current time, and historically has been focused on the post-approval space, because we also want to make sure that that allows us to keep our dossiers up to date in a timely fashion and can prevent any impact on supply within the region..."

5.3.5 Industry Associations & Networks and their influence or impact in the region on streamlining initiatives

RA Participants were asked to express their views on industry associations and 'harmonisation' networks and how these organisations influence or impact streamlining initiatives on the countries. Three main organisations were spoken of, namely, PANDRH, MERCOSUR, FIFARMA. Some other organisations were mentioned in passing, namely: SINDUSFARMA, INTERFARMA, ALIFAR, EPFIA, IFPMA, MANIFAR One participant had specific working knowledge of a network and hence their comments are presented more for this organisation. They spoke in an unofficial capacity and shared their own opinions based on their working experience with the network.

5.3.5.1 Industry Association: FIFARMA

5.3.5.1.1 Structure and function

Members in the group interview presented a cross industry view of how FIFARMA operates and works in the region, based on their experiences. FIFARMA only represents innovator companies within the LATAM region such as INTERFARMA in Brazil, Argentina is CAEME; in Chile, they have CIF and AFRIDO in Columbia. There is no industry association in Cuba. MANIFAR represents the generic companies within the region. During the group interview, participants shared the history and structure of FIFARMA, and work the organisation is doing in influencing the CMC landscape if any.

One participant explained the structure and function of FIFARMA. It is a federation of pharmaceutical companies in the Latin America region with the role of being the voice of the pharmaceutical industry in the region. It consists of sixteen research and development pharma companies and eleven local associations. They have a working group model through which they drive their activities.

FF4 "...The idea of FIFARMA is to be the voice of the pharmaceutical industry in the region.....with the working groups, we have three working groups. One is on value of innovation, the other one is on health policies, and the other one is in regulatory and biologics..."

Two participants shared on how FIFARMA influences the LATAM landscape. FIFARMA does not engage directly with regional regulators, however, it works by sharing regulatory expertise with local pharma associations, through external conferences and webinars. FIFARMA does this by developing positions or key messages which the regional local associations can then share with regulators. FIFARMA also brings in company experts to share at regulator meetings and also organise webinars for regulators/NRAs.

LA16 "...I think it's worth noting here that we don't interact usually as FIFARMA with the regulators..."

FF2 "..... We have direct engagement occasionally with PAHO, but we would tend to start with very much a communicative style through sharing expertise, through bringing in company experts, for example, to speak at regulator meetings..."

As a group they sign post to other international training support initiatives such as communication from IFPMA. These are then shared with local associations which can be passed on to NRAs for their consideration. This is the extent of their influence within the region.

FF2 “.... So, we would obviously support signposting to these more international training support initiatives...”

Another activity that sometimes the group participates in, is to support local associations to comment on national guidelines by providing their expert opinions through feedback. Some of the comments will be to identify if a national guidance is aligned with international guidelines or not.

FF2 “... And in those cases, usually some of those comments will be to identify, for example, if a national guidance is not aligned with international best practices, or where unique country requirements may cause additional challenges. But we would do that only in partnership with the local association who would lead the commenting on that particular guidance...”

5.3.5.1.2 Impact or influence of FIFARMA within the region regarding streamlining initiatives

FIFARMA’s goal has been to encourage NRAs to focus on and adopt WHO or ICH guidelines in general, not for CMC requirements specifically but in general. FIFARMA’s aim is to support the LATAM markets to converge to international guidelines which could be seen as the first step towards harmonisation in the region.

FF2 “...our key focus is really trying to drive thinking towards adoption of these more international guidance or convergence with them, but we don't have any dedicated work stream that's focused specifically on CMC.

...Yes. I think it's fair to say FIFARMA supports regional convergence to align with international best practices in CMC...”

FF2 "...as we're fully aligned with the WHO, who in their definitions of these, as part of good regulatory practices, talk about convergence being the first step towards harmonization..."

Another participant explained that FIFARMA being a part of PANDRH, supports PANDRH's revised statutes which also focuses on convergence in the region. Even though the organisation's name includes 'harmonisation', PANDRH realised that harmonisation would not be as easy to achieve as it requires commitments that go beyond the scope of PANDRH. Harmonisation would require markets with different legal frameworks and health systems in the region, to agree on a common standard (PAHO, 2019). PANDRH does not have any legal authority over the various LATAM NRAs so it cannot facilitate true harmonisation within the region. Hence, they realised that convergence to international standards, would probably be more feasible for the region due to its flexibility.

LA16 "...So if you go to the statutes of the PANDRH network, you will actually see that they want to deliver on convergence and not exactly on harmonization...So this is our commitment as FIFARMA inside PANDRH is to support regulatory convergence, even though in the name it is harmonization..."

5.3.5.1.3 Interaction with other associations

Participants mentioned other pharma organisations and trade associations that FIFARMA collaborated with to build consensus and to influence positive change in the region. To promote convergence, it is vital for the same message to be sent across to the various NRAs. It also makes it easier for the NRAs to receive the message as it is being delivered from one consolidated source as opposed to many sources. FIFARMA therefore works with local, regional and global trade associations such as IFPMA which also prevents duplication of effort.

LA16 "... Put yourself in the shoes of a regulator. Um, you are ANVISA. Now you have, I don't know, hundreds of companies, you issue a guideline. You take it to public consultation. You take it to public hearings. Imagine having to hear a hundred, 200, 500, 2000 different opinions and getting, you know, so it's, uh, it's

easier and it's more efficient for industry if they agree among themselves some positions and bring them in a uniform manner to the regulator.

FIFARMA, however, does not interact with MERCOSUR. They do interact with IFPMA, which has a CMC/GMP working group. They share IFPMA materials to the local industry. They also work with ALIFAR which is the association of national companies for Latin America. Another organisation they interact with is EFPIA, by enforcing EFPIA's position to the local industry. By working with various trade organisations, they can strengthen their position and amplify their voice to the NRAs.

LA16 "...So, MERCOSUR. I don't think that historically FIFARMA has interacted with MERCOSUR"

FF2 "...Because they have this group [GMP/CMC group] that is quite focused in that space, and it is not an area that FIFARMA has a dedicated work stream on, we will often look to IFPMA for materials ..."

LA16 "...FIFARMA is a member of PANDRH, the Pan American Drug Regulatory Harmonization Network was created in early 1990s, and it included FIFARMA from the beginning, alongside ALIFAR..."

LA16 "...We share many members, EFPIA does not contain the associations that are represented in FIFARMA, but many companies and many people in those companies that participate in the Regulatory and Biologics group in FIFARMA are the same who join the meetings of the EFPIA Latin network ... as topics emerge, we as members discuss what the best strategy would be, and if there's an opportunity of a joint action, we will promote this approach but on an ad hoc basis. So we try not to duplicate each other's efforts, and when possible we try to reinforce each other's position..."

5.3.5.2 PANDRH/PAHO

Ten participants provided information about PANDRAH as an organisation including those from the group interview; out of the ten, two of the interviewees had working knowledge of the organisation and provided most of the information on the history and structure of the

organisation. One participant had not heard of the organisation, whilst another participant had heard of PANDRH but did not know enough to provide comments. The remaining five participants and group interviewees provided comments on PANDRH's influence or impact in the region in relation to streamlining post-approval requirements.

5.3.5.2.1 Historical Background and structure

LA16 gave the background to PANDRH. Of note is the fact that PANDRH started out with harmonisation as its aim by creating technical guidelines for markets to adhere to, but later PANDRH switched to convergence, recognising the global community going in that direction and convergence being more ideal for the region. This decision was made in a PANDRH conference in Brazil in 2011 where the direction changed from harmonisation to convergence.

LA16 "...So this was one of the suggestions that emerged in 2011, as a recommendation from the PANDRH conference in Brazil, was that we should move from a paradigm, a regulatory paradigm that moves away from trying to reach harmonization and our realization that, uh, we have more to win with convergence what is actually happening around the world is less harmonization and more convergence, you know, so that's why we adopted, the nomenclature..."

PANDRH initially used working groups to deliver their activities, but they switched to using projects, because the working groups model was not working effectively even though groups were given priorities and specific deadlines. Some groups went on for years; others were more effective than others; each group had their own agenda, so the activities were not streamlined. Projects however were more defined, they had clear objectives, milestones and deliverables. All members can submit a project, but a project needs to be agreed and approved by members before it is implemented.

LA12 "...currently I think there are some projects going on well, so I think it, this is the new way. Uh, I think it's working well..."

5.3.5.2.2 PANDRH as a potential governing body in the region

When asked if they saw PANDRH becoming a governing body in the region like EMA with a legal backbone, one participant said maybe in the future, however, NRAs would still want to maintain their autonomy for decisions regarding requirements. PANDRH helping and assisting the NRAs with streamlining activities instead of governing would be more practical at this point in time.

LA13 Yeah. The second option, more helping and assisting but not governing. Yeah, maybe the maturity of the Latin America region increase in a certain point that we can have PANDRA, as you said, as an EU organization in the future. But not for now, this is sore topic for now.

Participants explained that the organisation did not have any legal basis to enforce change in the region, they only provide recommendations but they cannot interfere in NRA outcomes. It is still down to the markets to implement any agreed outcomes coming out from their dialogues.

RHN “.., you cannot enforce anything, but you bring them together to discuss and then amongst themselves they agree. So, PANDRH is not an influencing force...”

5.3.5.2.3 Influence in the region regarding streamlining initiatives

Participants saw PANDRH as an organisation that assists the region with regulatory convergence and harmonisation.

LA12 “.... They are in charge of the regulatory harmonization among the Latin America and actually among the Americas, which also include the FDA, Canada. Okay. So they have a very important role to drive harmonization and convergence in those countries...”

None of the projects submitted so far to PANDRH relates to streamlining of CMC requirements.

LA7 “...So currently we have no active project on the area of CMC requirements ...”

One participant explained that since harmonisation activities had not worked very well, due to the amount of effort and time it would require, PANDRH started promoting reliance. Reliance had another function of supporting the improvement of NRA capabilities. Through reliance, the NRAs would learn how to leverage the work of other more mature NRAs and study their regulatory practices to improve their own. Another participant agreed that PANDRH’s objective was not to create technical guidelines but to focus on convergence by implementing international guidelines. RHN also mentions that the region is trying to do both convergence to international guidelines and harmonisation within the region (citing the example of CRS Caribbean Regulatory system that is harmonising their requirements within their bloc). The network is supporting NRAs to understand how to harmonise, how to converge, when they can exercise their sovereignty and also exposes NRAs to regulatory practises and processes happening outside the region as well.

LA14 “.... they now are focusing more in promoting the reliance and to improve the capabilities...”

LA16 “... It's not the objective of PANDRH to create technical guidelines. It's the objective of PANDRH to work on convergence by implementing international guidelines...”

RHN “...Working in both directions, so we have process that are fully harmonized, like the CRS is a, it's a harmonized process. CRS is the Caribbean region, uh, Caribbean regulatory system...”

...I think that the country, the region has evolved a lot, uh, towards both harmonization and convergence....”

5.3.5.3 MERCOSUR

Eight Participants commented on MERCOSUR and its ineffectiveness in the region. One participant gave the background to MERCOSUR as a body which had the aim of bringing

the region together as an economic bloc, potentially allowing for the free flow of goods, services and people. The organisation encompassed four LATAM markets, namely Paraguay, Uruguay, Brazil and Argentina. They however mentioned that the organisation never had any guidelines drafted or any topics presented or discussed for post-approval CMC submissions within the region. One interviewee said that the organisation could have been the best avenue to possibly harmonise requirements in the region, however, this hasn't been the case as the organisation is falling apart possibly due to political reasons. They also mentioned that there is a lack of integration or interaction amongst the countries in the region, so any agreements put in place under MERCOSUR could not hold.

LA16 “..... initially the, the intention of MERCOSUR is to create a common market, meaning that you have free flow of people in goods for you to have free flow of goods, you have to have common standards.

And also to be quite honest, I don't think that MERCOSUR agenda in the pharmaceutical area today includes any specific discussions on CMC related topics for harmonization. ...”

LA5 “...And it [MERCOSUR] is also falling apart. So I think it could be also political....”

One other participant explained how MERCOSUR did not have any political or economic bearing on the region. MERCOSUR exists only on paper and markets are working in silos which should be the opposite effect if the organisation was working well. Rarely is there any information or news about MERCOSUR and its activities in the region.

LA7 “...here we have the Mercosur that it has no political force, no economic force, it's almost as if it not existed, so it's a very weak bulk of countries. ...”

Another participant explained that even though there is a MERCOSUR agreement, markets still refused to accept the reviews and approvals of their colleague countries within the organisation due to rivalry. Hence the idea behind MERCOSUR has not really taken off as planned.

LA3 “...Just look into the MERCOSUR agreement. The MERCOSUR agreement is tying between Brazil, Argentina, Uruguay, and I think Paraguay, or Paraguay and not

Uruguay. In any case it's that end of the continent. But nevertheless Argentina does not accept just because Brazil approved it. And Brazil does not approve it just because Argentina approved it. There is rivalry..."

5.3.5.4 NRA Collaboration with Industry associations and other NRAs and impact on streamlining activities.

All three NRA participants responded negatively in the questionnaire with regard to collaborating with other NRAs specifically on CMC variations.

Questionnaire responses revealed that there was a level of collaboration and engagement among NRAs within the region, but it was not widespread, or it was less of a priority compared to engagement with international initiatives outside the region. NRA3 mentioned high-level discussions with NRAs through MERCOSUR, but nothing specific for CMC requirements. In the follow up interview, NRA3 speaks of the fact that their NRA prefers to collaborate with ICH and align to their guidelines rather than engaging with markets in the region.

NRA3 "...I mean, there are some meetings, for instance in MERCOSUR, there are some collaborations...So sometimes we discuss regulations, drug regulations, but it's not specifically for CMC. It's more a general discussion..." [questionnaire]

NRA3 ".... For instance, we do not really look at the regulations of other American agencies [LATAM Agencies]. We always prefer to align to ICH guidelines. ..."[interview]

NRA1 responded affirmatively in the questionnaire to collaborating with other NRAs with no further explanation.

NRA 2 mentioned collaboration with two other NRAs in the questionnaire. They exchanged technical information with these other NRAs, but no shared guidelines or regulatory framework had been established. This was an on-going process.

In their follow-up interview, NRA2 further explained that even though their NRA was looking to establish agreements or harmonise with other LATAM NRAs, most times, their guidelines were so different that it makes any form of alignment very difficult. They cited

the example of GMP inspections, ideally, they should be able to accept GMP certificates of other LATAM NRAs, however they still organise site inspections.

They also mentioned a lack of trust for the other NRAs in the region even though they are supposed to be seen as being on the same level of maturity and expertise.

Even though market collaborations exist, NRA2 explained that agreements had not progressed to any alignment specifically for CMC variations. There is no priority at present to streamline CMC variations. Even when agreements exist with high surveillance markets, the NRA still performs full evaluations of the CMC variations.

NRA2 “.. even if the agreement exists, for example, with EMA and FDA, the evaluation is full. And with the other two, Cuba and Argentina, as they are new, we haven't gone to the CMC part. That's why we don't still have that CMC reliance.

NRA1 mentioned interaction with FIFARMA on a PANDRH project related to the use of Certificate of Pharmaceutical Product (CPP) in convergent regulatory approaches. There was no project for CMC streamlining initiatives.

Overall, all three NRA participants responded negatively in the questionnaire to collaborating with other NRAs specifically on CMC variations.

5.3.6 Global Engagement

Fourteen RA participants including RHN had comments about how the markets are engaging with initiatives such as ICH and organisations such as the WHO and EMA. Engagement with the US was also mentioned several times by participants. Brazil, Mexico and Cuba were the most talked about markets in relation to global engagement.

5.3.6.1 Brazil

Several participants mentioned the clear desire for Brazil to align with markets outside the region, not seeing themselves as partners with markets within the region. Their desire is to align to ICH and to take the lead in doing so. Not every market within the region has this mindset, but Brazil is very certain of the direction it wants to travel.

LA16 "...the message was quite clear. So, we [ANVISA] want to be part of ICH. We want to take a lead in the international arena. We do not see ourselves as the natural partners of Argentina or Colombia. We see ourselves as the natural partners of Singapore, or Canada, or Switzerland. And that change in the mindset ...".

One participant mentioned ANVISA's willingness in using WHO guidelines to also review their biologics post-approval guidelines, further suggesting a move towards convergence. However, the participant thought it would be a good opportunity for the region to harmonise; that could only be possible if other markets planned to align to the same WHO guidelines. Harmonisation would then occur through the act of convergence.

LA13 "...And I think another good point that I missed, I think it's good to inform you, that ANVISA is about to review the current post approval regulation on bio products and we were told that ANVISA will use the WHO guideline ..."

Even though there is a willingness to align to international guidelines, Brazil especially still has the tendency to request and insist on country-specific documents as cited by LA13. ANVISA argues that the extra details are to support the local industry in their submissions. These requirements are enshrined in the local guidelines and hence companies need to adhere to them to gain approvals of their submissions. Being a member of ICH, however, requires that members align to the ICH guidelines which LA13 believes Brazil will struggle to do this as ANVISA's requirements sometimes go beyond ICH guidelines.

LA13 "...I think ANVISA is having some difficulty to harmonize with ICH because of the details that they are usually include in the regulations. ..."

One participant speaks of ANVISA's hidden desire to be like EMA or FDA though they will not admit it openly, in order to protect their sovereignty or pride. However, they acknowledge the FDA/EMA are mature agencies that they can learn from and be trained by as mentioned by other participants.

LA10 "..... I think that ANVISA wants to be very good and a highly health agency for Brazil. I think it wants to preserve its identity..."

One participant explained how industry was able to positively engage and influence industry on ANVISA's new post approval guidelines because of ANVISA's willingness to engage with ICH. The engagement with ICH acted as a stepping stone and foundation upon which they could discuss and justify certain requirements as not being realistic for innovator products over generic products as an example.

LA11 "...They were more accepting I would say, than previous interactions maybe over the last 10 years, because of their movement into the ICH environment, and everything that goes with that..."

5.3.6.2 Mexico

COFEPRIS was described as having a lot of agreements with international health authorities. They are known to attend international conferences and trying to align to countries though they still maintain country-specific requirements. The NRA is also known to aspire to agencies such as FDA and EMA.

LA1 "..., they're always looking to try and align where best they can with other agencies. They do try and partner with other agencies but when they do implement stuff that's as common to other regions, they still tend to have a country slant on it..."

5.3.6.3 Cuba

Participants had mixed reactions concerning Cuba. Two participants perceived Cuba to have a desire to engage with and align to international standards (ICH), mentioning that CECMED was more open now to the international industry than it had been in the last four to five years. They believed that CECMED was recognising they could have easier regulatory processes if they started to trust other regulations. One participant, however, described Cuba as not having an international outlook.

LA3 "... they do not have an international view so they cannot compare themselves. So they're like, this is our world and that's it..."

LA9 “...They are now observers in ICH, if I'm not mistaken. So for me they are following the same journey as Brazil, for example...”

5.3.6.4 Global engagement [NRA perspective]

NRA participants commented on the level of engagement with international networks or organisations such as WHO, ICH and other high surveillance markets/regions like the EU and US.

NRA3 cited that their regulatory actions were more focused on ICH activities than within Latin America or any streamlining initiatives Latin America were doing. They were more concerned about activities on the ICH front and engaging in conversations there. They also confirmed that they were less active with MERCOSUR or other regional harmonisation discussions.

NRA3 “...All the actions that we take internally are always focusing on ICH. For instance, we do not really look at the regulations of other American agencies [meaning LATAM Agencies]. We do not really discuss with them, not in the first place...”

NRA1 mentions in the questionnaire that their NRA has adopted 35 ICH guidelines so far. They are also an ICH observer.

Based on the NRA and RA responses, it is clear that the markets desire more engagement with global initiatives and organisation than within the region, giving a clear direction of where their focus is.

5.3.7 What process is being used to streamline CMC requirements?

Fifteen RA participants, the FIFARMA interviewees, RHN and the three NRA participants all explicitly agreed that the six markets were working more towards convergence with international standards rather than harmonising within the region.

5.3.7.1 Harmonisation within the region

The majority of the participants stressed that the markets were not ready to come together as a region to streamline requirements or harmonise due to many factors mentioned earlier, political reasons, each market wanting sovereignty, rivalry and so on. Even though an advanced market like Brazil would like to push harmonisation in the region, other less advanced markets do not have harmonisation as a focus. Also, each market is collaborating with organisations like WHO in isolation. This emphasises the drive towards convergence and the lack of desire to collaborate as a region. One participant had the following to say:

LA13 "...They are trying to harmonize but not working in Latin America as a whole group..."

In the questionnaire, NRA participants were asked whether their NRAs would prefer harmonisation in the region and whether it would be beneficial with the following results, captured in Table 5.6:

	NRA3	NRA1	NRA2
Prefer to harmonise within the region	Slightly disagree	Slightly disagree	Strongly disagree
Would it be beneficial to harmonise within	Slightly disagree	Strongly agree	Slightly disagree

Table 5.6 NRA responses about preference of harmonisation occurring in the region

From the questionnaires, it seemed there were mixed views about harmonisation occurring within the region. The follow up interviews made it clear that harmonisation in the region would be ideal and helpful, however, NRAs could not envisage it actually happening i.e. LATAM NRAs working together to formulate their own regulations and adhering to them as a collective group,

When asked if the NRAs would consider forming an economic bloc to support or push for the streamlining of requirements within the region, NRA3 and NRA2 said there is no interest to form an economic bloc within the region so this, in turn, hinders any drive for harmonisation within the region. One of the reasons cited for this was the fact that most

medicinal products are imported from the EU, US or Asia or locally produced, hence the markets would prefer to align their guidelines/requirements to their importing countries. NRA2 goes on further to explain a future desire for CELAC to drive harmonisation in the region in with the aim of promoting economic growth in the region.

The following phrases were summarised [due to poor internet connectivity] as what the participant said to which they confirmed the understanding was right:

NRA2 "...The rest of Latin American countries don't seem to be interested in harmonization..."

*Researcher: "So basically, if there's no driver economically, then it becomes a bit more challenging to do things within the region. And that there's no market that's actually leading the way but you're hoping that maybe [NRA] will lead the way with *CELAC..."*

NRA2 "...Yes..."

*CELAC is the Community of Latin American and Caribbean States (CELAC), initiated in February 2010. Made up of 33 Latin American and Caribbean states, CELAC aims to unite all Latin American and Caribbean States in order to create a political, economic and socio-cultural integration to advance social welfare, the quality of life, economic growth and promote independent and sustainable development. It includes all the six markets being studied in this research (ASEAN Secretariat, 2021).

Harmonisation within the region is also complicated because there are many trade associations (serving local or multinational companies), which leads to many different discussions and suggestions on what should be done or how things should be done in the region. The activities of these trade associations are not coordinated. This also affects plans to implement any convergence initiatives as well e.g. CTD implementation. In the case of CTD implementation, multinational companies already provide documentation in that format, national companies do not and are resistant to it even though from the NRAs' perspective, it would be beneficial for them.

NRA3 ".....We often receive different opposite suggestion from national and multinational industry associations..."

When asked in the questionnaire if they could envisage a singular regulatory body to unite and harmonise requirements within the region, all three NRA participants responded in the negative, due to political and cultural differences. MERCOSUR had not been successful for the last 30 years in bringing the markets together and there is no indication of this changing in the future. One participant went on to state in the questionnaire, that reviewers even perceived harmonisation within the region as more of a burden because of the political challenges in the region.

Participants had this to say in the follow up interview:

NRA3 "...MERCOSUR, it only works by consensus. So it's very difficult to achieve a consensus in many cases. I don't see this political proximity between [NRA] and other Latin America countries, I don't see even a cultural proximity that would be sufficient to make a single regulatory body..."

NRA2 "...[Market] is not part of MERCOSUR and has no plans to join. ..."

In the questionnaire, one participant mentioned that PANDRH could be more likely to hold such a role than MERCOSUR in relation to their specific NRA as PANDRH embodied some of their main business partners.

5.3.7.2 Convergence

One participant explained that whenever harmonisation or convergence is mentioned, it is in their opinion, always in relation to streamlining to international standards or more established countries such as US (FDA), EU (EMA), Health Canada, Australia or Japan. This leans more towards the definition of regulatory convergence than it does harmonisation. The reason given is that harmonization requires markets to subscribe to the same guidelines within a legal framework, however, Latin America markets have their individual legal frameworks making it tough to harmonize, hence convergence is more in tune with what is happening in the region. Another participant confirmed the same notion with the below quote:

FF3 "...convergence is where both regulators and local associations feel more comfortable too..."

Four participants expressed the view that the region is moving towards harmonisation as a whole, however, it is happening in stages with convergence being one of the steps.

LA5 “...*They are trying to harmonize within the region but they are doing it in steps...*”

LA6 “...*They're looking for harmonization, ... but right now I think we're just at the convergence stage...*”

NRA3 believes that the region will become harmonised as each NRA converges to international standards for example, ICH. There is a desire to have a form of harmonisation within the region because this will facilitate easier commercialisation across the region. This form of harmonisation will occur by the markets converging to international standards. Consequently, markets will eventually align to very similar requirements and guidelines but not through regional collaboration or amending their legal frameworks to suit each other. In most responses, there is the use of both terms interchangeably (harmonisation and convergence) but there is a clear direction towards streamlining to international standards mainly ICH, which denotes convergence. NRA1 commented that the region mainly uses WHO guidelines as a reference, this again leans towards convergence, with the use of both ICH and WHO guidelines.

NRA3 “...*There seems to be more effort in harmonization and convergence with ICH requirements, and not so much effort in harmonization with regional requirements.... So, we are prioritizing harmonization among ICH authorities...*”

NRA1 “...*WHO is the reference for the NRAs in our region....*”

Again, in the questionnaire, when NRA participants were asked about the preference of convergence and its benefits, they responded as follows, shown in Table 5.7

	NRA3	NRA1	NRA2
The Agency would like to align CMC requirements to international	Strongly agree	Strongly agree It means updating	Slightly agree

guidelines (convergence)			
The Agency believes it will be beneficial to align CMC requirements to international guidelines	Moderately agree	Strongly agree. It means updating.	Strongly agree

Table 5.7 NRA responses concerning convergence as a preference in the region

Overall, these responses denote a stronger desire to converge to international standards compared to the responses given for harmonisation in the region.

FIFARMA participants also cited that their focus has always been to encourage NRAs to focus on and adopt WHO or ICH guidelines in general, not for CMC requirements alone. Working with PANDRH, they realised that convergence to international standards would probably be more feasible for the region due to its flexibility and practicality in that convergence would not require the region to sit under one legal framework which would be very difficult to achieve.

FF2 “...Yes. I think it's fair to say FIFARMA supports regional convergence to align with international best practices in CMC...”

5.3.7.3 Regulatory reliance, cooperation and recognition – vehicles of regulatory convergence

Apart from convergence and harmonisation, some other terms or streamlining processes were mentioned by participants as outlined below. One participant tried to elaborate on the confusion that sometimes occurs in trying to explain how reliance, cooperation and recognition fit in with regulatory convergence. They explained that they were all vehicles through which regulatory convergence could be achieved. Different markets will use different ways to reach regulatory convergence.

LA16 “...I will say that it is a little bit confusing, but I guess there's not established archetypes of convergence and convergence is a concept and how you reach this

convergence is what we work on. It's information sharing, best practices, building case studies, participating in conferences...

5.3.7.3.1 Reliance

Five participants introduced the term 'reliance' into the discussions about streamlining CMC requirements. The term refers to “the act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others” (FIFARMA, 2020a). Reliance can also be used at all the regulatory phases making it a versatile approach. Reliance is another process happening in the region in relation to convergence.

LA14 “...Now they are focusing more on the concept of reliance. When agency relying on the evaluation of others and then they make their own decision...”

FIFARMA interviewees also heavily discussed the concept of reliance and how it fits into regulatory convergence. One participant expressed reliance as follows:

FF1 “.. reliance is built off the back of convergent regulatory standards. So agencies that practice reliance are prepared to acknowledge that the standards used to undertake that task within the reference authority are sufficiently converged with their own national standards (ie the market practicing the reliance), that they're willing to rely on that work. As agencies perhaps practice reliance, and they see more, other ways of agencies working, that will drive convergence, because they'll have a better understanding of other agencies' practices.”

They saw reliance as a way of driving efficiencies and building capacity and capability of NRAs in addition to supporting the streamlining process. They recognised that every market trying to have the same requirements would not be feasible. Reliance gives that flexibility to companies, allowing them to justify differences when there is misalignment on regulatory requirements. It also acknowledges that due to different regulatory frameworks, some local requirements would still remain but the reliance process is adaptable to cater

for that. The reliance process also recognises that not all LATAM NRAs can complete full quality, safety and efficacy reviews like FDA or even ANVISA, so through this process, other less mature NRAs are able to rely upon a major NRA, and can use the resource released to build their capacity, for local activities and assessments and to consolidate ICH /international standards into their processes. This ultimately would benefit local industry and its ability to manufacture and meet ICH requirements, permitting potential export to major markets.

FF1 "...because there're so many different regulatory frameworks for variations for post-approval changes, then there is a need to adapt the information to that local requirements, so then, of course the information will not look identical, and that's something that needs to be taken into consideration when practicing reliance for post-approval changes..."

When asked how reliance related to regulatory convergence, FIFARMA interviewees explained it as a way to achieve or support greater regulatory convergence but not a form or type of regulatory convergence.

FF1 "...Reliance can support regulatory convergence, because when you're using information from another regulator, then convergence within the same standards and regulations will facilitate reliance..."

5.3.7.3.2 Cooperation and recognition

Regulatory cooperation, another streamlining term, was seen as another vehicle for delivering regulatory convergence. Cooperation is defined as the process of interaction among drug regulatory authorities in regulating medicines in the forms of information sharing, work sharing, reliance, and recognition (WHO, 2021).

Recognition can be defined as the routine acceptance of the regulatory decision of another regulator or other trusted institution (WHO, 2021).

From the questionnaires, NRA participants also mentioned what regulatory processes they believed their NRAs were using to aid regulatory convergence in their markets, the results

are provided in Table 5.8. There is a mix of reliance, cooperation and recognition processes being employed by NRAs to support regulatory convergence.

NRA3	NRA1	NRA2
<i>Reliance, Cooperation</i>	<i>Cooperation</i>	<i>Reliance, Recognition</i>

Table 5.8 Regulatory processes being used by NRAs to support convergence in their market

This corresponds with the earlier comments that markets can use different vehicles to achieve regulatory convergence.

5.3.7.4 Challenges of adopting international guidelines by NRAs

The NRA participants were asked if there were any obstacles or challenges hindering them from achieving regulatory convergence.

NRA3 affirmed there were challenges, but saw them as temporal; not deterring them from moving on to streamline to international guidelines. One of the challenges was that some of the ICH guidelines were old and hence hard to interpret in the light of new approaches. These would need to be revised by ICH in order for the NRA to align to them. For the newer guidelines, some stumbling blocks to implementation were relevant facilities to implement them or legal frameworks that needed updating before those guidelines could be implemented.

NRA3 "...Q1, Q2. I think because they are old. There are so many new thinkings, so many new approaches. And it makes it difficult to have deep harmonization [convergence to the ICH guideline].

And we also have the other side, the newest guidelines, Q12 for instance, in this case we just have different ways to implement among the agencies. So we have some agencies like the FDA that have more facility to implement it. And some other agencies like the European agencies, the EMA and national agencies, that have some legal problems and need to treat them before implementation, let's say.

..."

NRA2 commented that their NRA works in isolation, not acknowledging how other NRAs are working; nor evaluators or reviewers interacting with evaluators in other NRAs. This

makes the convergence process difficult as the NRA is not actually engaging with Agencies. So they speak about convergence, but it is mostly on paper and not a reality.

NRA2 “... And one part of this convergence will be to work more directly with the agencies that will be beneficial for [NRA] because I think they are very isolated. They don't work much with other agencies ...”

In terms of the problem of individual reviewers asking for different documents during assessment, NRA1 said that their NRA reviews were standardised across assessors because assessors in their NRA followed an SOP when assessing. This may apply mainly for generics though which can be less complicated than assessments for small molecules.

NRA1 “...There are also Standardized Operational Procedures (SOP), as internal methodologies for the staff performing the assessment...”

NRA3 and NRA2 believed that the issue with assessors may not be solved completely because reviewers are susceptible to different opinions since they have different backgrounds and expertise. However, they acknowledged that the current disparity is quite high. NRA3 suggested a review guide and more training could help provide a suitable boundary for these differences and ease the challenge.

NRA3 “...There will always be some difference, but I think if we have a reviewers guide and solid trainings, the difference will be reduced to a minimum, but it'll always exist...”

NRA2 also mentioned training being a good intervention, however, they also said time for training would be an issue as reviewers needed to concentrate on clearing the backlog of submissions that exists.

NRA2 “...I mean, the problem with the backlog is severe because they don't have time to do training or to look together for answers...”

Another perceived challenge of aligning to international guidelines for NRA3 is that they feel that at the moment companies are not penalised enough when something goes wrong

which could put patients at risk. So NRA3 explained that companies may take advantage of the flexibility that comes with the ICH guidelines. They explained that the penalty fees for company errors were quite low; there are also many chances to appeal decisions, so the reviewers feel that companies are let off easily. On top of that, due to lack of resource, it takes a long time for a decision to be made on penalties so not many are meted out. This is one of the reasons why the national guidelines are very conservative, to prevent too much wriggle room for company mistakes which may go unchecked and also could put patients at risk.

NRA3 “...

...So ICH guidelines are much built based on flexibility and patient-focused analysis. And that's good, but it's also a risk because we can be flexible and company may take this flexibility on the wrong way and make, for instance, make variations with no good evaluation, and it may take to a risk for patients. And if this happens, we feel that a company will just not be punished enough. So that's how this is linked to the adoption of international requirements...”

In relation to market specific requirements, NRA3 was asked if their NRA will keep [document] now that they are members of ICH. They believed that the NRA would discuss it and possibly change it to a Product Lifecycle Maintenance document in line with ICH Q12 guidelines. They believed the document may change from its current format but the underlying self-evaluation aspect of the document should be kept

NRA3 “...*We do not want to create regional-specific documents, but there's a part of the [document B] that we think it's very important and it's that self-evaluation. Actually, we think it is part of the CTD, maybe not a specific document but the self-evaluation is among all the CTD documents...”*

Another major challenge that NRA3 expressed was difficulty in obtaining assessment reports from reference markets for reliance procedures. The reports in the public domain are often redacted and the NRA requires the full information for their assessment. NRA3 mentioned that their NRA was working on a solution which involved contacting the reference market directly to obtain the report having confidentiality agreements in place with these reference markets.

NRA3 "... Sponsors told us that it's difficult for them to obtain this evaluation report, and the public evaluation report is not sufficient because some data, for instance, specifications, some production details, it's something we need to make the reliance and it's not available in public report because of confidentiality..."

5.4 Discussion

In this study covering six Latin America markets, namely: Brazil, Argentina, Cuba, Colombia, Chile and Mexico; the views of three stakeholder groups were obtained via semi-structured interviews and questionnaires. These stakeholder groups were the Regulatory Affairs professionals (RAs); the industry association personnel (FF, RHN) and the personnel with working knowledge of the NRAs (NRA). They all presented very useful and varying experiences and perceptions of the CMC landscape in the Latin America region, specifically in relation to streamlining regulatory requirements for post-approval CMC variations.

The use of semi-structured interviews successfully provided participants the room to share rich accounts of their experiences (Brinkmann and Kvale, 2015). The LATAM participants were very comfortable and open in sharing their views which confirms the researcher's personal experience of working with LATAM RAs. The use of Gatekeepers to access NRA participants was partially successful as only 3 out of 6 NRA participants were recruited (Dahlke and Stahlke, 2020). It is possible that the other NRAs did not respond due to resourcing capabilities. The questionnaires worked well in obtaining initial data from NRA participants and to invite further participation through interviews (Kuter and Yilmaz, 2001). For the FIFARMA group, giving out interview questions beforehand, minimised an apparent disadvantage of group interviews where less time is utilised per participant as compared to individual interviews. Each participant came prepared to answer questions specific to their role in FIFARMA. Since participants worked together through the association, there existed a natural rapport among the group which prevented any 'awkwardness' and hence each participant was able to speak freely and share their views, resulting in rich responses (Rubin and Rubin, 2005). One observation made by the researcher was the positive effect of using video during the group interview. It was easier to identify who was speaking at any given time, similar to a face-to-face interview. If only audio were used, the researcher would have asked participants to identify themselves before answering a question to overcome that potential challenge. Care would be taken to remove such information when transcribing to maintain confidentiality and anonymity

(Lobe, Morgan and Hoffman, 2022). The use of Zoom, Microsoft Teams and email was very comfortable for participants and practical for the research (Archibald *et al.*, 2019). LATAM participants were eager to provide rich accounts of their experiences and this showed in their engagement with the researcher and the duration of the interviews (Lobe, Morgan and Hoffman, 2022). One participant even interviewed three times (two individual interviews and was part of the group interview); this also shows the level of interest and passion they have for the topic under discussion.

Regarding data saturation, Tran *et al* accurately point out that determining the point of saturation is a difficult endeavour (Tran *et al.*, 2016), because “researchers have information on only what they have found” (Guest, Namey Emily and Chen, 2020). However, for the LATAM RA group, based on the researcher’s experience and judgement (Guest, Namey Emily and Chen, 2020), no new themes emerged based on the sample size. The NRA participants yielded the necessary information to answer the research questions for their specific NRAs even though the sample size was n=1. The quality of data generated through the questionnaire and supporting interviews was enough to give a detailed view from the NRA perspective about the research question ((Malterud, Siersma and Guassora, 2016)

From participant responses, it becomes apparent that the CMC regulatory landscape is very active with many moving parts as stated by Chapman (Chapman, 2020).

Participants seemed to have more experience with Brazil, Mexico and Argentina in comparison with Chile, Colombia and Cuba; Cuba being the market where participants had least experience. This could be due to some RAs working in multinational companies where regulatory activity in Cuba was low due to international sanctions (Shahidi, 2010). Participants also mentioned the concern regarding lack of confidentiality agreements (PAHO, 2022b) which posed a threat to innovator products as most products in Cuba are manufactured locally (Hechavarría Núñez *et al.*, 2011; PAHO, 2022b). Most local-based RAs also did not have much experience with Cuba possibly due to political tensions in the region which participants have mentioned.

Reviewing participant responses, there is a definite move towards regulatory convergence with the desire to streamline requirements to ICH or WHO guidelines. Brazil became a member of ICH in 2016, with Mexico recently becoming a member in November 2021 (ICH Press release, 2021). All other NRAs (excluding Chile), are observers (ICH website, 2020; ICH Press release, 2021; PAHO, 2022b). Of the six markets, Cuba expressed a greater tendency to align with WHO guidelines (PAHO, 2022b).

Overall, the markets in the region are engaging more in international streamlining initiatives such as ICMRA. This observation aligns with the convergence model suggested by Rodriguez et al (Rodriguez and De Lucia, 2021) for CMC post-approval variations. They believed that the NRAs would have much to benefit from implementing convergence and indeed these benefits were confirmed by the participants.

Participants spoke of insufficient human resources at the NRAs due to various reasons, which has contributed to the backlogs for the review of PACs. Competent and sufficient resources are critical for robust regulatory systems (PAHO, 2022b). Convergence procedures such as reliance would greatly help in optimising resource, reducing review times and clearing backlogs as NRAs could opt to rely on reviews performed by more competent high surveillance markets that they reference (PAHO, 2022b). For comparison, the FDA had 17,468 full-time equivalent staff reviewing new marketing authorisations as at 2018, compared to a market like Brazil which had about 1769 centralised workers (PAHO, 2022b); a similar ratio could be extrapolated for PAC reviewers. Interestingly a report by CIRS cited Brazil as 'well-resourced' (CIRS, 2015) however, the number of reviewers for PACs cited by the three NRAs in this research shows there could indeed be an inadequacy of reviewers compared to the number of post-approval variations received annually (Rodriguez and De Lucia, 2021).

Participants agreed that another benefit of convergence was the expertise and knowledge sharing available to markets in the region which would boost their own regulatory capacities as they seek to work towards the highest international standards (Smith, 2023; Tami, 2023). Duplication of effort would be avoided by industry and NRAs (Mota Pina, 2021). In addition, most of the medicinal products are imported from these high-surveillance markets, hence NRA participants confirmed it being more practical and pragmatic to concentrate efforts in aligning to these market requirements to ensure the same quality for patients in the region.

Concerning harmonisation within the region, there was a clear understanding that no 'political will' existed for markets to engage with each other within the region, even economically (PAHO, 2022b). There rather seems to be distrust and rivalry amongst the countries in Latin America as confirmed by RA and NRA participants (Merke, Stuenkel and Feldmann, 2021).

Even though the region is facing outward, there is no urgency or priority for the markets to specifically streamline post-approval CMC variation requirements, regardless of the potential benefits (Rodriguez and De Lucia, 2021). The notion is that as the region converges to international guidelines, they assume that over time, the streamlining of CMC

requirements will automatically follow. A concept paper by BioPhorum makes mention of the absence of global harmonisation of post-approval change (PAC) requirements which aligns with the lack of priority in the LATAM region (BioPhorum, 2019).

In terms of maturity and transparency, participants expressed different views across the markets. There was consensus on Brazil being the most mature and transparent agency amongst the six markets and even the region as a whole (CIRS, 2015). One complaint made against ANVISA, however, was their inability to receive justifications when companies presented requirements outside the stipulated guidelines, even when based on the science. As a Level 4 designated NRA, one would expect that ANVISA's level of expertise would be able to cater for scientific justifications, but this does not seem to be the case.

For the other markets, there were also mixed reactions about maturity and expertise despite all six markets having been designated Level IV NRAs as well, this being the highest designation for an NRA by PANDRH. This observation could be attributed to participants working in different types of pharmaceutical companies i.e. multinational or local and their relationship or level of rapport with the various NRAs. NRA participants cited differences in expertise and experience of reviewers as a potential cause and further training required to help reviewers take a risk-based approach. Perhaps if the pharmaceutical industry was allowed to provide input into the designation of the NRAs, the outcome would have been different as it seems they hold the NRAs to a particular standard which they are not meeting (WHO website, 2023). As NRAs, however, they are expected to support the strengthening of other NRAs, be an example for best practice and support reliance activities in the region (PAHO, 2022b), hence the industry's high expectations may be warranted given the NRAs' remit and their current capacities.

It is interesting to note that even though there is a willingness to adhere to international guidelines, even the NRA participants observe that it may take some time due to cultural norms and current ways of working which are very strict and having to potentially learn how to assess with a risk-based approach which involves moving away from checklist approaches, but following the science (Tami, 2023). ICH members have a timeline by which they need to implement the ICH guidelines but the need for a change in mindset might delay this convergence process (ICH, 2020). Challenges that may slow down the convergence process in the region include markets wanting to maintain sovereignty and continued insistence on market-specific requirements. The reliance process, however, is known to offer a level of flexibility as it takes into account various regulatory frameworks

and it also allows for markets to maintain sovereignty in their regulatory decisions (Gomes and Lessa, 2022).

Acknowledged challenges like backlogs and lack of resources (Rodriguez and De Lucia, 2021) which could potentially act as catalysts or should act as a catalyst for change in the region or the drive towards harmonisation/convergence do not seem to be the case. In fact, assessors are not always in favour of convergence to international requirements because they feel it affords multinational companies too much flexibility sometimes, which does not always favour the patient.

There does not seem to be a coordinated effort across the region even with their willingness to converge to international standards and with PANDRH trying to be a unifying force (Gomes and Lessa, 2022), It seems that each market wants to move at their own pace and in their own way mostly due to political tensions. This may be an opportunity lost as markets could potentially leverage their knowledge and expertise instead of working in isolation (Mota Pina, 2021). One of the good practices of regulatory reliance being work-sharing.

There is a level of leniency for local companies versus multinational companies in the region, due to their lower level of expertise compared to the multinational companies. This could potentially slow down the convergence process as local companies would need time to adjust to the new requirements and processes and risk-based approach required to build their submission dossiers. This shows a disparity between the legal requirements and the situation on the ground; leading to potential unfairness or lack of parity in the process.

NRA3 raised a concern about varying comments and opinions from the many trade associations in the region regarding new guidelines. FIFARMA participants, however, mentioned that they were there to coordinate the discussions amongst associations so a singular voice could be presented from industry. The many voices could be other associations that FIFARMA does not represent, as mentioned in section 5.3.5.1.1. FIFARMA only coordinates initiatives amongst the innovator companies. This dynamic could also pose challenges if the associations outside FIFARMA are not focused on convergence like FIFARMA.

There are also different harmonisation initiatives ongoing in the region i.e. MERCOSUR, CELAC, PANDRH, all engaging a select number of markets (PAHO, 2022b). This could hinder or slow down streamlining initiatives in general as each initiative has a slightly different goal. PANDRH with the support of FIFARMA is encouraging the region to move towards convergence whilst MERCOSUR for instance, was set up to harmonise

requirements within the region but has been ineffective for many years. MERCOSUR now exists only as a customs union and free-trade area (Castilejo *et al.*, 2022) and there are calls to review its structure entirely as members still have divergent views .

One of the biggest challenges mentioned in relation to reliance was access to the assessment reports of reference markets. These reports were not always available when needed or certain sections were redacted due to confidentiality which makes it difficult for the LATAM NRAs to fully rely on. Accessing the reports directly from the reference markets agencies has not always yielded positive results (PAHO, 2020, CIRS 2015).

Many participants used harmonisation and convergence interchangeably. Harmonisation has been a historical word in relation to streamlining so it may be easier for people to relate to that term (Institute of Medicine, 2013b). But as new terms are arising, it is imperative for the right concepts to be stated and definitions provided within context. During the interviews, once participants were reminded of the working definitions for harmonisation or convergence in the context of the research, participants would use the right concept for whatever they were explaining. A possible explanation could be that participants have not fully understood or grasped the concept, the term harmonisation is a historical term and had a broader meaning at the onset but now with terms like reliance, cooperation, recognition and collaboration, markets can use better terms to describe their regulatory practices and processes. (Tominaga, 2020).

The findings in this study indicate that the six Level four designated markets are moving towards convergence to international standards, however, the streamlining of CMC post-approval variations is not a priority at present. Benefits to streamlining CMC post-approval requirements were, however, acknowledged yet, there are many challenges to overcome in the journey towards reliance and convergence to international standards.

This study may not be generalised to the whole of the Latin America as only a few select number of markets were chosen and not all NRAs responded to the questionnaire. It, however, gives a general indication of how markets in the region might behave in relation to streamlining post-approval CMC requirements.

5.5 Limitations

As the sample sizes were small, especially for the NRAs, it is difficult to generalise the data. However, given that these markets are the NRAs of regional reference, it is

anticipated that the common themes coming out of the research may be applicable to other markets in the region.

Some themes were only mentioned once yet have been cited, as the experiences of each NRA are unique and may not apply to another. Since this is an explorative study, any themes outside of the norm can be captured to show the variety and complexity of responses. Participant quotes were sometimes lengthy possibly due to the language barrier, making it hard to capture quotes succinctly, where meaning and context could be lost.

The use of gatekeepers shows the difficulty in reaching out to personnel from NRAs. Even with the gatekeeper's intervention, only three personnel out of the six NRAs could be recruited.

At the start of the research, there was no way of knowing that a global pandemic would occur. The pandemic probably made it harder to recruit from the NRAs due to their busy workloads which probably increased due to the pandemic's impact on the healthcare sector.

Due to lack of time, the researcher was unable to analyse and compare the individual market CMC requirements, however, useful data has been obtained that shed a light on how LATAM is progressing with regards to streamlining CMC requirements in general. If time had permitted, the researcher could have recruited another set of RAs just for the purpose of reviewing and discussing the CMC requirements which would have provided a different perspective as to why those different requirements existed in each market per PAC.

Responses from one of the NRA reps were mainly based on generics manufacturers which have slightly different challenges to dealing with novel products. The research focus was not on generics, it was an exclusion criterion, however, responses from that one NRA tied in with other NRA responses. They also highlighted some other challenges which are specific to them and throw more light on NRA challenges in the region.

Causality for some of the disparities in the responses on the same theme cannot be established with this qualitative data. Quantitative data with a larger data set would have enabled such an analysis to be conducted.

5.6 Future studies

A future study that could be embarked on is reviewing the success or failures in the implementation of international guidelines as the markets converge to them. How are they

overcoming the internal challenges raised in this study? This could be targeted at mainly the NRAs through interviews, or questionnaires for easier access. The research could be a longitudinal one as it will take some time for markets to converge to international guidelines.

5.7 Conclusion

The aims and objectives of this part of the study were met. Although recognising the limited sample size, through exploring the views of various stakeholders, a holistic summary of the six markets in relation to streamlining of CMC post-approval variations was given. It was evident that the markets in question are converging to international standards i.e. ICH and WHO guidelines though this is not coordinated across the region with each agency following this path in isolation. The priority to streamline CMC post approval variations at this current time is low. The major influences for this direction of travel are a lack of political will to harmonise within the region and a desire to raise standards to meet international expectations. Challenges exist to the convergence process which will slow down progress in this area, affecting all stakeholders (patients, NRA, industry).

The findings of Chapters Four and Five are compared in Chapter Six to see if any learnings can be gleaned from ASEAN towards LATAM's perceived convergence journey. Chapter Seven seeks to situate the findings into the global perspective, whilst offering suggestions for further work.

6 COMPARISON BETWEEN ASEAN AND LATAM RESULTS

6.1 Introduction

This chapter seeks to explore the differences and similarities between drivers of progress towards harmonisation or convergence across ASEAN and LATAM markets. What, if anything, can LATAM learn from ASEAN, in view of ASEAN's success in streamlining their post-approval CMC requirements?

To date only a handful of studies have attempted to draw comparisons in pharmaceutical regulatory processes across regions. Of these few, most studies focus on single region case studies, which have limited generalisability. Although studies have compared international cooperation initiatives (Lakkis, 2010; Lezotre, 2014b, 2014a; European Medicines Agency, 2015), they have not looked at CMC requirements specifically. Recently an unpublished Master's Thesis attempted to compare post-approval CMC requirements for a change in drug product manufacturing site variation, between Russia, China, FDA, EU, Brazil and South Africa (Hoey, 2017). However, it did not cover regional markets, which is arguably the important level of governance.

Comparing the ASEAN and LATAM regions is not straightforward. The two regions have very different cultures, systems, political set-ups, medical practices, infrastructure and levels of development, which can limit comparability across regions (Lezotre, 2014a). Hence, to facilitate cross-regional comparisons, this chapter draws upon the emergent characteristics of the ASEAN streamlining process from Chapter Four which identified a series of motivating factors and steps to harmonization that were prevalent in ASEAN. This can help bring clarity as to the potential reasons why LATAM is struggling not only to aspire towards harmonisation but even to achieve an effective degree of regulatory convergence.

These characteristics of harmonisation include five components which appeared to play a role in driving forward progress in ASEAN. These were:

- i) framing the benefits;

- ii) mobilising an organizing body;
- iii) achieving consensus;
- iv) establishing a legal backbone; and
- v) real government buy-in.

Here we revisit the interview data from Chapters Four and Five to compare and contrast the two regions across each of these dimensions. For brevity the comparison draws upon representative quotes from Chapters Four and Five. For full results please refer to the various sections in Chapters Four and Five highlighted within Table 6.1

Outside the characteristics, data from each region also highlighted other areas for comparison such as ‘challenges faced in each region’ and ‘level of priority given to streamlining of CMC variations’ These areas of comparison will also be discussed in this Chapter.

6.2 Results and Discussion

6.2.1 Comparing ASEAN and LATAM

Table 6.1 highlights comparisons between ASEAN and LATAM in reference to the ASEAN characteristics of harmonisation.

	ASEAN markets	LATAM markets
Framing the benefits	Trade & security benefits, less duplication	No economic or political goal; less duplication, faster patient access, standardised requirements across local and multinational companies
Mobilising an organizing body	ASEAN	PANDRH but not currently engaged towards harmonisation, MECOSUR, CELAC.
Consensus	Singapore, EU guidelines	ICH, WHO guidelines and local guidelines
Legal Backbone	None	None

Government buy-in	Yes	No
--------------------------	-----	----

Table 6.1 Comparing key drivers of harmonisation

As shown in Table 6.1, there are substantial differences in how benefits are framed, the presence of an organisational body, consensus about guidelines and government buy-in. The only area of similarity was for legal backbone, which both lacked at the time of analysis. For framing the benefits, both markets also had players who emphasised the value of reducing duplication. It is also clear that the LATAM region is characterised by much greater fragmentation, in guidelines and in potential organising bodies.

It is likely that the absence of critical driving factors can account for why LATAM is struggling to move towards harmonisation within the region.

Next, each component is discussed in greater detail.

6.2.2 Framing the benefits

Below in Table 6.2 are presented various quotes comparing motivating factors or benefits of streamlining CMC requirements across the two regions. In terms of benefits, the ASEAN had trade and security as two of their main factors for harmonising in the region; whereas in LATAM there is currently no economic or political goal nor intention for the markets to align within the region, even though its benefit can be appreciated.

	Selected Quotes	
Subtheme	ASEAN	LATAM
Trade: Free flow of goods; being able to trade more easily	<i>AS4 "... So they wanted to make the ASEAN market in line with how the European Union, to have the trade easily in all these 10 markets, which is there in the ASEAN.</i>	<i>LA7 "...If you have harmonized guidelines, it's much easier for the companies to export the products and for the population to have access</i>

<p>Facilitates easier export, faster patient access</p>	<p><i>And with that objective, they started making the ASEAN..... More than guideline I would say trade..."</i></p>	<p><i>faster and with better prices..."</i></p>
<p>Less duplication, core technical documents; efficient use of resource:</p>	<p><i>AS5 "...So that's the good news that your five report go everywhere, the documentation requirement quite close, so you don't need to duplicate a lot of effort to do something extra for this country, this country very, very different, et cetera. So your core technical documentation will be quite similar because of this effort, ASEAN effort..."</i></p>	<p><i>LA14 "...When agency relying on the evaluation of others and then they make their own decision. So they will avoid the duplication of work, if a product is approved in Brazil, for example or in Argentina, it could be easier to be approved in central America or in the Caribbean region where the agency is lacking resource..."</i></p>
<p>Become attractive economically, gain access to innovative products</p>	<p><i>AS3 "...that was one of the thoughts for the harmonization, is that, if they achieve harmonization, they become a more attractive market because of the size of the harmonized area, and so, they can have access to innovative products..."</i></p>	<p>-</p>

Regional leverage in global discussions	AS7 <i>"...Based on the stability studies, they gathered together and suggest changing the climate zone for the stability study. Then they also think they should have their own common technical document, so ASEAN CTD..."</i>	-
Standardised requirements for local and multinational companies	-	LA9 <i>"...Because sometimes in these countries, we have, for example, local companies, they have more advantages in comparison to multi-national companies, just because they are local. So sometimes they have different requirements. So for me, would be an advantage and it would be nice to have it because we could have the same kind of requirements and a standard for all countries in Latin America..."</i>

Table 6.2 Comparing ASEAN and LATAM Themes: Benefits for streamlining requirements

In ASEAN, the desire for the free flow of goods and people and regional security is a key motivating factor for keeping the group grounded. In fact, it was the initial basis for creating the ASEAN and this foundation has kept the drive for harmonisation till date (Lee and Oh, 2020). The ASEAN markets have shown that despite differences in political, social, economic and culture spheres, it is possible for a region to work together towards a common goal (Russell, 2020). It is possible for governments to place their own interests aside to ensure patient access to good healthcare.

In comparison, Latin America markets acknowledged the benefits of harmonised requirements, in that they enable faster patient access and easier exports, however, they are not enjoying these benefits because they are fragmented as a region. This fragmentation is partly because they lack a common goal like the ASEAN. The ability to unite as a region is a critical factor for harmonisation to occur and regional cooperation has been seen as one of the ways to address health care issues across a region (Amaya and De Lombaerde, 2021). This lack of cooperation in LATAM is one of the factors why the region is unable to move towards harmonisation within the region.

Another benefit of ASEAN is its attractiveness as an economic block. In fact, ASEAN is seen as one of the top worldwide destinations for foreign direct investment (Khuong, 2020). LATAM cannot boast of this achievement, however, as there is no intention to become a unified economic bloc, partly because of political tensions and rivalries. As NRA3 highlighted in Chapter Five, 5.3.4 there are left-wing and right-wing governments whose political ideologies do not align hence the thought of a unified economic bloc in the near future is bleak. This further adds to the evidence against harmonisation within the LATAM region for CMC post-approval requirements.

Additionally, ASEAN's regional integration allows them to leverage their consensus at global meetings, when discussing issues pertaining to their region (Kopp, 2006; Latzel, 2007; Leelianou, 2021). An example is the specific drafting of stability guidelines for the ASEAN region because the climatic zone differed from other regions when discussed at an ICH meeting, as cited by AS7 in section 4.3.2 of Chapter Four (Hoey, 2017). This was vital to ensure that the stability guidelines for CMC post-approval changes favoured the region's temperature and humidity requirements. This leverage may not have happened if the individual South Asian markets approached the ICH without that regional cooperation. The regional cooperation possibly gave additional weight to the request. In LATAM, however, no such benefit exists in terms of leverage as there isn't any foundation to leverage from. In fact, LATAM is known to be one of the most polarised regions across the globe. The failure to leverage shared expertise and to enhance regional governance may have had a debilitating result on the region's health care sector (Riggiorozzi, 2020). For example, during the recent Covid-19 pandemic it was reported that LATAM was one of the regions most affected, this was in part due to a lack of regional cooperation (OECD, 2020; ECLAC-PAHO, 2021). In the ASEAN, however, there was a coordinated effort to exchange and share information to member states to help support them through the crises (Djalante 2020; Chong 2021). This was possible because they could use their leverage

through the ASEAN organisation to help member states. This is a major lesson that LATAM can learn from ASEAN - regional cooperation and collaboration. Participants in both regions agreed that one benefit of streamlining requirements would be less duplication of effort and efficient use of resource, mainly for the pharmaceutical industry as only one main core technical dossier would be required for submission. If the NRAs were to conduct joint assessments, they could also reap the benefit of sharing the outcome of their joint assessment, thus saving resource on their end. In 2017, the ASEAN actually started a pilot for joint assessments within ASEAN, supported by WHO. With the pilot now completed, the ASEAN joint assessment procedure is now available on a voluntary basis for ASEAN member states to apply to their new marketing authorisation procedures and CMC post--approval variations (Chong, 2021; HSA website, 2021). Only one Asian participant mentioned the joint assessment pilot during interviews, showing the procedure was relatively new to the region and participants possibly had little or no experience of it. In the LATAM region, no such assessment exists as there are no regulatory structures set up to enable this in LATAM. So ASEAN is steps ahead of LATAM in terms of harmonising requirements within the region. Hence this is an extra benefit that LATAM cannot reap in terms of streamlining CMC post-approval requirements.

6.2.3 Mobilising an organising body

Another key driving factor was the presence of an organising body to facilitate progress in terms of streamlining requirements. Table 6.3 presents the comparisons between ASEAN and LATAM for organising bodies.

	Selected Quotes	
Subthemes	ASEAN	LATAM
ASEAN as an organising body	<i>AS1...So they want to do like a ASEAN community where there will be free movement of goods and human resources. So for that they realized that</i>	

	<i>they have to harmonize some of the industries in these countries. And pharmaceuticals was identified as one of the key areas</i>	
PANDRH as a LATAM organising body		<i>LA16 "...The PANDRH was created in the nineties, in the beginning of the nineties as the harmonization network. And in 2011...one of the conferences...when we realized that one, we were not doing harmonization, we were actually going for convergence.</i>
CELAC as an organising body for LATAM	-	<i>NRA2 "...Mexico is more involved with CELAC and not necessarily MECOSUR, Mexico is leading CELAC..."</i>
MECOSUR as an organising body for LATAM	-	<i>LA16 "And, um, initially the, the intention of MECOSUR is to create a common market, meaning that you have free flow of people in goods for you to have free flow of goods, you have to have common standards. So</i>

		<p><i>this is where they came from.</i></p> <p><i>LA5 "...And it [MECOSUR] is also falling apart. So I think it could be also political.</i></p>
--	--	--

Table 6.3 Comparing Themes: Mobilising an organising body

ASEAN as an organising body is an inter-governmental organisation which has been successful in bringing the Southeast Asian markets together to progress harmonisation in the region (Russell, 2020). It is also evident that the ASEAN is growing stronger, with the introduction of joint assessments and a move towards strengthening their global position by making agreements with China, EU, and even with LATAM (Swee-Hock, Lijun and Wah, 2005; ASEAN Secretariat, 2021; Yue, 2022). PANDRH on the other hand, is a network that is an initiative of NRAs in LATAM and PAHO (which sits under the WHO (Weisfeld and Lustig, 2013). PANDRH is not an intergovernmental organisation even though PAHO is. Hence PANDRH as a network can only promote collaboration but may not influence individual markets like an intergovernmental organisation such as ASEAN can. PANDRH has not been able to mobilise the LATAM region in the same way ASEAN has; nor drive regulatory efforts across the region as progress very much depends on each individual market's desire to progress. Even though the LATAM region is working on various projects through PANDRH, the region is very much a fragmented one, each market wanting autonomy in their decisions and working in silos when it comes to streamlining CMC requirements. PANDRH also recognised the asymmetries existing between markets in the region - some NRAs were well established, some developing and others not having robust regulatory capacity to consider harmonisation efforts (Lezotre, 2014a, 2014b, 2014c). This fragmentation and asymmetries contributed to PANDRH's shift from the aim of regulatory harmonisation within the region to regulatory convergence to international standards. The process of harmonisation was not deemed to be practical for the region.

Another observation is that, whilst the Asian markets have one unifying body which is the ASEAN, in LATAM they have other organisations outside of PANDRH with different selection of markets, all trying to create a common market or economic bloc. Two of them

are mentioned in Table 6.2, namely 'The Common Market of the South' or in Spanish 'Mercado Común del Sur' (MECOSUR) and CELAC. MECOSUR has not been very successful as cited by LA5. MECOSUR is an economic and political bloc consisting of Argentina, Brazil, Paraguay, and Uruguay and Venezuela founded in 1991 (Chodor, 2021). 'Comunidad de Estados Latinoamericanos y Caribeños' or 'Community of Latin America and Caribbean states' (CELAC) is more recent, founded in 2011, consisting of 33 states including Mexico and Brazil (Kennedy and Beaton, 2016). CELAC is known to have a weak structure with members having conflicting interests, consequently it has not been able to facilitate cooperation amongst the markets (Kennedy and Beaton, 2016). CELAC included all the LATAM markets in this research, however, in 2020 Brazil suspended its membership (REUTERS, 2020). These additional organisations create further tensions in the LATAM region and cannot possibly feed into any harmonisation initiatives but rather add to the existing divide.

6.2.4 Consensus on guidelines

One key feature of harmonisation is consensus on a specific guideline which all markets in the region can adhere to or work towards adhering to. Participants in both regions listed the relevant guidelines that they subscribe to as outlined with participant quotes in Table 6.4.

	Selected Quotes	
Subthemes	ASEAN	LATAM
ASEAN guidelines developed from Singapore guidelines which had EU guidelines as a basis.	AS1 "...I'm not quite sure where it came from but most probably from the EU because Singapore guidelines are mostly mirrored from the EU guidelines..."	

LATAM region use a mixture of ICH, WHO and local guidelines		<p>From the NRA questionnaire: NRA 1: WHO guidelines NRA2: Local Guidelines NRA3: ICH guidelines NRA2 <i>“But I can tell you that they are very like ICH guidelines...”</i></p> <p>FF2 <i>“...And so we do encourage agencies to look towards either the World Health Organization guidance, or the ICH guidance when available</i></p>

Table 6.4 Comparing Themes: Consensus

The ASEAN guidelines were based on the Singapore guidelines and the Singapore guidelines were originally drafted from the EU guidelines or mirror the EU guidelines. The WHO guidelines were also consulted (Latzel, 2007; Leong, 2013).

Markets in the ASEAN region subscribe to these guidelines, though not always fully. However, there is a common set of CMC post-approval requirements binding the region together. Industry benefits because they know exactly what to provide and they have guidelines to readily refer to for clarification. The common guidelines also enable member states to have a basis for any joint assessments whilst giving them a common foundation upon which to build any additional local guidelines. In LATAM, however, there is a mixture of guidelines being used; markets are either converging to ICH and/or WHO guidelines, in addition to local guidelines. This mixture of guidelines can result in different requirements for each market. This approach cannot work for the process of harmonisation as markets need to be aligning towards a common set of guidelines. For convergence through reliance, the absence of a common set of guidelines may not be a real issue as the

reliance caveat factors in a level of flexibility for individual market requirements. Again, this goes to show that harmonisation within LATAM will not be a practical solution to streamlining CMC post-approval requirements as compared to ASEAN.

6.2.5 Legal backbone

In order for guidelines to be implemented effectively, ideally there should be a legal basis for guidelines to be enforced. Table 6.5 provides quotes highlighting the current situation in ASEAN and LATAM,

	Selected quotes	
	ASEAN	LATAM
Lack of legal backbone for both the ASEAN and LATAM streamlining networks	AS8 “... I should say a fundamental problem for ASEAN country, from my perspective, uh, why the harmonization process is that slow is that the ASEAN organizations itself is not the same as the European region. If I can refer to, they don't have a legislation basis...”	RHN “...Cause like you said, you bring them together, but you cannot enforce anything, but you bring them together to discuss and then amongst themselves they agree. So PANDRH is not an influencing force...”

Table 6.5 Comparing Themes: Legal backbone

As per the quotes, the ASEAN and PANDRH organisations do not have a legal basis to enforce any adopted guidelines in the member states. Asian participants usually compared ASEAN to EU explaining that, because the EU guidelines had a legal backing, each EU nation had a legal obligation to implement the EU guidelines in their countries, which was not the case for ASEAN. In ASEAN, member states voluntarily adopt guidelines and implement in their own timeframe. Sometimes due to local legislation, which is hard to change, some guidelines cannot even be adopted (Chapter Four, section 4.3.4.1).

Implementation is therefore based on consensus and the political will or desire of individual markets (Teo, Foerg-Wimmer and Chew, 2016). In future, maybe the ASEAN will develop a supranational system like the EU (Lezotre, 2014a). Even so, it can be observed that there is a general desire from the ASEAN markets to work together, there seems to be an attitude and mindset of oneness unlike in LATAM. An example being the recently introduced joint assessments mentioned in 6.2.2 that member states are embracing, even without a legal backbone.

PANDRH and other networking organisations in LATAM, like MERCOSUR and CELAC, also lack legal structures (Portales, 2012; Silva, Cabello and Gaban, 2018) to enforce streamlining initiatives. They are trying to build consensus among the LATAM markets but the political will and mindset of the LATAM markets does not seem to want alignment (CFR.org editors, 2021). Whereas ASEAN lacks a legal backbone but it has not prevented them from progressing as a bloc, LATAM markets are far behind in this regard and, until the political will aligns to a common goal and mindset, even if other networking organisations are formed, it may not heal the divide to enable any form of harmonisation to take place.

6.2.6 Government buy-in

Table 6.6 captures quotes detailing the level of government backing that ASEAN or PANDRH have. For effective harmonisation, governments would need to have vested interest in the initiatives.

	Selected quotes	
	ASEAN	LATAM
Government buy-in	<i>AS5 "...There is, in ASEAN they even, the Prime Minister sign ASEAN document. So, it's Prime Minister level. You can see it's very super senior buy-in</i>	<i>NRA3 "...And I think it's very unlikely that this government wants to approximate with other Latin American governments..."</i>

--	--	--

Table 6.6 Comparing Themes: Government buy-in

As seen from the quotes, ASEAN markets enjoy backing from their governments in driving the harmonisation agenda whereas in LATAM the case is very different. In LATAM, governments are not willing to work together hence harmonising within the region will be difficult. The ASEAN being an intergovernmental body has the backing of the individual governments, this obviously puts extra weight on the organisation to function as a bloc. This also speaks to the fact that individual markets are willing to align in order to achieve harmonisation in the region. This is essential if the ASEAN wants to remain as a united political and economic bloc.

PANDRH is a suborganisation of WHO with the LATAM markets voluntarily engaging in PANDRH projects (PAHO, 2022a). The governments due to political tensions are not necessarily pushing for regional alignment (Riggiorozzi, 2020). With this attitude, harmonisation within the region would be very difficult and organisations like PANDRH will not have a strong political backing to progress initiatives. This further hinders any streamlining initiatives within the LATAM region.

6.2.7 The priority in streamlining CMC requirements

Outside the suggested framework model, there are other areas of comparison between the ASEAN and LATAM markets, one of which is the priority level that streamlining of CMC requirements has in each region. What level of priority has ASEAN or LATAM placed on streamlining CMC post-approval requirements? Table 6.7 outlines some quotes in this area.

	Selected quotes	
	ASEAN	LATAM
High Priority	<p>AS1 “..the first task they [Pharmaceutical Product Working Group] had was ACTD [ASEAN Common Technical Dossier] and</p>	

	<i>ACTR [ASEAN Common Technical Requirements] [which included the post-approval guideline]...So after the ACTD and ACTR [were] harmonized for registration, then of course they looked at the various sections that make up the ACTR</i>	
Low priority		<i>LA7 "...So currently we have no active project on the area of CMC requirements</i>

Table 6.7 Comparing Themes: Priority in streamlining CMC requirements

The ASEAN had the post-approval guidelines in mind from the onset when drafting the ACTR, it was one of the first tasks of the PPWG. This shows that when it came to pharmaceuticals, the ASEAN took a holistic approach. They worked to incorporate not just new marketing authorisations into the ACTR, but to also consider the post-approval CMC variation phase of drug registrations (Latzel, 2007). Individual markets also took the CMC guidelines and incorporated their own local requirements which shows individual markets also placed priority on that exercise to make it beneficial for patient access in their individual markets. The LATAM currently do not consider streamlining CMC post-approval changes a priority, even though they are striving to converge to international standards as a whole. Participants explained the LATAM markets will get to it eventually, as they gradually move through the ICH guidelines based on individual market health care priorities. With the LATAM not having an immediate priority for streamlining CMC requirements, it means challenges faced by industry may persist for a while until individual markets are ready to converge to those ICH standards relating to CMC post-approval variations. Having said that, currently not all LATAM markets are members of ICH to even compel them to start aligning with the ICH guidelines. Brazil and Mexico are members, all others are observers apart from Chile which is neither a member nor an observer. Perhaps they lack resources to currently engage with ICH.

Again comparing LATAM to ASEAN, ASEAN is definitely far ahead of LATAM in terms of having streamlining CMC requirements as a priority; even if their requirements are not fully aligned from one market to the next.

6.2.8 General challenges to streamlining

Chapters Four and Five also highlighted challenges that the regions are facing. Quotes covering shared challenges are highlighted in Table 6.8

	Selected Quotes	
	ASEAN	LATAM
Market-specific CMC requirements	AS4 “... No, I don't think so. It's only, they have a harmonized guideline. However, if you go to Malaysia, they have a long, detailed, a hundred pages guideline for approval. Singapore has its own guideline. The pathway, they have is different. Thailand is totally new medical, new drug, new generic, three pathways. Malaysia has another pathway. Singapore has another pathway. Classification route is different...”	FF3 “...No. Well, and especially even if these markets, these countries are in the effort to agree to some level of harmonization, it's still being too country specific
Preferential treatment for local companies over multi-	AS8 “...But then their concern is the local industry. How about local industry? So they cannot, you know, let's harmonize the international standards to	LA9 “...Because sometimes in these countries, we have, for example, local companies, they have more advantages in comparison to multi-national companies,

<p>national companies</p>	<p><i>multinational company only. Right? So that is not the way for, for the legislator. And the new legislation should be applicable to all the players in the markets..."</i></p>	<p><i>just because they are local. So sometimes they have different requirements. So for me, would be an advantage and it would be nice to have it because we could have the same kind of requirements and a standard for all countries in Latin America..."</i></p>
<p>Inability to adopt guidelines due to local laws or old legislation; NRAs unable to accept scientific rationale in place of certain requirements</p>	<p>AS1 <i>"...Yes, so the market has the right to change it. Of course, they try to, at the PPWG, they try to agree but most of the times because of some laws preventing them from doing it. Because to change their law, they have to go back. It's not so easy or legal process. So they just choose not to follow...."</i></p>	<p>LA9 <i>"... legislations are very, very old, and they just keep asking [for the same requirements]</i></p> <p>LA13 <i>"...No. In fact, there are many situations that the company has some scientific rationale or justification for some approach and ANVISA cannot accept this approach because in the regulation, it's clearly state that they need to provide some documents.</i></p>
<p>Reviewers/evaluators asking for different requirements</p>	<p>AS4 <i>"... It [the requirements] does change from evaluator to evaluator..."</i></p>	<p>LA6 <i>"...You can have one guy reviewing and asking for certain additional requirements, and you can make the same submission that someone is reviewing and not get any other requirements. It's kind of unstable in that way..."</i></p>

<p>Market Autonomy/sovereignty</p>	<p>ASEAN interviews expressed that markets wanting to exercise their autonomy. This was a latent theme that emerged from the data.</p> <p><i>AS4 "...Because each market behaves independently, each market agency has different expectations. Even evaluators have a different expectation. So no. Yes, on paper, it is harmonized in terms of guideline, but it is not being implemented in reality..."</i></p>	<p><i>LA8 "...It's like every health authority in every country is really proud about having their own regulation and their own power of decision..."</i></p>
<p>Harmonisation or convergence not fully implemented</p>	<p>Implementation</p> <p><i>AS4 "...No, not harmonize. I wouldn't say it is harmonized yet. I wouldn't say. Because each market behaves independently, each market agency has different expectations. Even evaluators have a different expectation. So no. Yes, on paper, it is harmonized in terms of guideline, but it is not being implemented in reality..."</i></p>	<p><i>NRA2 "...Exactly. I mean, it's doing it in paper, because they say in a lot of agreements, but in real life, it is not complete [convergence in the region]..."</i></p>

Table 6.8 Comparing Themes: Shared Challenges to streamlining CMC requirements

Though the discussion until now has centred on differences, there are several challenges both regions face which are markedly similar regardless of the streamlining process.

These are country-specific requirements, inability to effectively implement guidelines, reviewers having different assessments of submissions and old legislation preventing adoption of guidelines.

It denotes that even though the regions are streamlining requirements via different processes, they can still have similar challenges. This means there are peculiar situations prevalent in these regions that are a characteristic of the individual markets – the choice of streamlining process does not alleviate the challenge.

One challenge which each region faced, was country-specific requirements. ASEAN has CMC guidelines out of which individual markets have drafted their own market guidelines with market-specific requirements. This phenomenon caused some participants to state that true harmonisation had not actually occurred in ASEAN and there was still more work to be done. In LATAM, even though there is a move to converge to ICH guidelines, they also have country-specific requirements. There could be several reasons for these market-specific requirements. The voluntary nature of implementation means some markets are ahead/behind of others hence, at any given time, some market-specific requirements will still exist. Another explanation is the presence of old legislation that is difficult to amend or will take much time to amend due to legal and administrative structures in government. This then makes amendments to guidelines very difficult or delays them. One other explanation is that local pharmaceutical companies, often generic companies, may be required to give extra information to prove quality of the product. Other times as well, when converging to ICH guidelines there may be region-specific scenarios, e.g. stability zones that would need to be adapted to suit the region. WHO recognises the need to sometimes have these market-specific requirements and hence pushes for reliance as a way of convergence which will allow that flexibility for the individual markets (BioPhorum, 2019). ICH members are expected to align with and implement ICH guidelines recognising that implementation stages will differ depending on when the member joined the ICH, sometimes an ICH guideline may not be applicable depending on the regulatory landscape and what the guideline is requesting (ICH, 2018, 2020). A report by Sinduspharma looking at how LATAM markets have accepted and implemented ICH guidelines, showed that most markets that had partially adopted ICH guidelines were either still in observer status and, if in member status, were still within their 5 year implementation period; or could only partially implement because of specific region-specific scenarios which were mainly about stability for the region (Silva, Cabello and Gaban, 2018). These market-specific requirements make regulatory operations complex for multinational companies, however, there is a sense of relief that there is movement towards regulatory convergence no matter

how slow or small (Silva, Cabello and Gaban, 2018). For Asian interviewees, they mentioned that if country-specific requirements still remained, then the process in ASEAN should be termed convergence and not harmonisation as their understanding is that for harmonisation to occur, everyone should have the same requirements, not 'similar'. Whereas for LATAM, interviewees mused that market-specific requirements meant that even the process of convergence was just talk and not something that could be achieved. General challenges of country-specific requirements faced by both harmonisation and convergence initiatives may be difficult to resolve. Markets have their own reasons, whether valid to industry or not, for keeping those specific requirements. Sometimes those requirements are there to better manage the local pharmaceutical industry, for example, the use of the PATE in Brazil. In Brazil, using the PATE has greatly reduced the number of post-approval CMC variations submitted to the NRA because local companies have to now properly assess whether the change should be submitted or not. This in turn also prevents a further backlog at the NRA. The quality of the submission is also improved because local companies assess the proper documentation required to submit the change. In Chapter Five, participants explained that, for LATAM, the process of reliance enabled a level of flexibility for these country-specific requirements, backed by WHO guidelines. While this may be favourable to the NRAs, it may not be favourable to industry who would like to have the same core dossier packages to submit, reducing the need for extra resource. For ASEAN, participants expressed that these market-specific requirements meant that the ASEAN was not actually harmonised but rather expressed a form of convergence. So, the question arises, can a level or form of harmonisation be achieved where requirements are not fully aligned? And where should the line be drawn for convergence in relation to requirements? Again, how does the WHO allowance of reliance align with ICH's process of guideline alignment? This means that in as much as both regions desire to streamline requirements, true harmonisation or convergence may not be achieved, hence industry may need to settle with the 'best' of what the regions can offer.

Another challenge which was similar for both regions was that local companies are sometimes given some leniency when it comes to adhering to requirements because they may lack the required expertise and resource to implement the guidelines. Secondly, NRAs are trying to favour the local companies over the multinational companies as they are key stakeholders in supplying to the national market and hence NRAs do their best to support the local industry. Again, this may favour the local companies, but multinational companies consider this as unfair and unbalanced. Whether this will change in the future is yet to be seen. This may be an opportunity to help the local companies by training them

to bring them up to the standard of multinational companies in mindset. The resource issue though, cannot be easily fixed or helped. This disparity between local and multinational companies may not be an easy problem to solve either. It will be interesting to observe whether this leniency towards local companies will continue in light of harmonisation or convergence initiatives. One reason given for this leniency is that most of these markets do not export their local manufactured medicinal products, but is this a sound reason? Could this mean that those local products cannot compete on the global market? Can the quality be guaranteed to the same global standard if the requirements are different? Also, for both LATAM and ASEAN some legislations are so old and cannot be easily changed as they are enshrined in local law, hence those requirements are difficult to change.

This definitely poses a challenge to harmonisation or convergence initiatives and may slow down the process. However, the specifics need to be assessed in terms of what impact this will have and whether it is worthwhile for markets to amend their laws, which can be very time-consuming and bureaucratic.

This section shows that both harmonisation and convergence initiatives are still experiencing challenges and it may take some time for both regions to settle into a state which is comfortable for all stakeholders as many discussions would need to be had over what are the critical factors for harmonisation or convergence - at which stage do they say this is the best they can achieve considering the challenges that may not be easy to overcome? That said, the ASEAN seems to be much more stable as a region in their harmonisation process than the LATAM region's efforts in moving towards convergence. In addition, outside the framework model, the LATAM markets also expressed specific challenges in their efforts to converge to international standards which are not applicable to ASEAN markets. These peculiar challenges are: outdated ICH guidelines; lack of leverage amongst markets; flexibility of international guidelines giving room for companies to be irresponsible; inability for NRA reviewers to adopt a risk-based approach.

Quotes covering several of these challenges are highlighted in Table 6.9

	Selected Quotes
--	-----------------

Challenges experienced for convergence	LATAM
Outdated ICH guidelines	NRA3 “...Yes. I can give an example. We have the ICH Q1 guidelines, they are stability guidelines. We had recent work to implement ICH Q1. We consider it implemented. However, when we go deeply in specific cases and when we discuss with the agencies, with EMA, with PMDA, FDA, they have different responses. So it seems to me that it did not fulfill 100% its aim to harmonize all the procedures. So this is more common for old ICH guidelines, Q1, Q2. I think because they are old. There are so many new thinkings, so many new approaches. And it makes it difficult to have deep harmonization.
Lack of leverage amongst markets	NRA2”... And one part of this convergence will be to work more directly with the agencies that will be beneficial for the NRA because I think they are very isolated. They don't work much with other agencies, except for the international area but the other... For example, the evaluators or the reviewers, they don't have contact with other agencies. And I think that is not good, because in this case, we're not doing the convergence really...”
Flexibility of international guidelines may make companies irresponsible with changes	NRA3 “...So ICH guidelines are much built based on flexibility and patient-focused analysis. And that's good, but it's also a risk because we can be flexible and company may take this flexibility on the wrong way and make, for instance, make variations with no good evaluation, and it may take to a risk for patients...”
Inability for reviewers to adopt a risk-based approach when reviewing to international guidelines	LA16 “...And unfortunately this requires a risk-based mindset and a level of maturity that goes beyond whatever is written in the regulation...”[adopting international guidelines]

Table 6.9 Themes: Challenges experienced in LATAM for convergence

One challenge was that some ICH guidelines are outdated in terms of current approaches hence even the reference markets (US, Japan, FDA) have different views on their implementation. This makes it difficult for new markets to align to those guidelines. Within the LATAM region there is a lack of knowledge-sharing because they work in isolation. This lack of leverage does not facilitate the convergence process. A consequence of this is that reviewers in each market have a different way of reviewing submissions which leads to extra requests for requirements which may not be necessary. It also means that reviewers do not upgrade their knowledge in reviewing techniques or do not grow in their understanding of the science behind certain medicinal products which also affects how they review the submissions. The flexibility of the ICH guidelines means reviewers have more leeway in interpreting them which is very different to the current approach which is similar to a tick box exercise where they follow very stringent and rigid requirements. Reviewers are challenged and encouraged to take a risk-based approach in reviewing to ICH guidelines. This means a higher level of accountability and responsibility which some are not willing to take. The possible implication of this is that it may take some time for reviewers to develop that risk-based approach and be comfortable with it, meaning convergence to ICH guidelines may take a while. So even though there is movement in that direction, the benefits may not be reaped by industry nor NRAs easily or quickly. These challenges may be minimised as the region engages with training and continues to learn from the high surveillance markets like US, FDA and Japan. It will also depend largely on the region's willingness, capacity and capability to change their mindsets and attitudes towards working together as a region, and their ability to adopt a risk-based approach in their regulatory assessments.

The ASEAN participants may not be facing these particular challenges because over time, the ASEAN have engaged with ICH guidelines, some of their ASEAN guidelines being harmonised to ICH guidelines (Lezotre, 2014a). ASEAN became a member of ICH in 2003 much earlier compared to Brazil (2016) and Mexico (2021). This means ASEAN has had the time to possibly discuss the guidelines with other ICH members and digest the guidelines to develop that risk-based mindset. As previously mentioned, the basis of the ASEAN guidelines was the EU guidelines which may have also embodied that risk-based approach, so they may possibly have had much practice and trainings through workshops to integrate and adopt the ICH guidelines with the ASEAN guidelines (Latzel, 2007). ASEAN also has the opportunity to leverage expertise among member states, possibly making them more robust as a group through knowledge sharing and discussion of guidelines. In addition, because the ASEAN is not aligning to ICH guidelines directly but

has its own guidelines, any challenges to do with implementation of ICH guidelines may not be so applicable to ASEAN.

6.3 Discussion

Summary of key findings

Across Chapters Four and Five, several similarities and differences are observed for ASEAN and LATAM. These are pulled together in this chapter and a simple comparison is drawn to highlight any learnings that LATAM can pick up from ASEAN. To reiterate, participants with working knowledge of the NRAs provided their own opinions and not that of their organisations.

It was observed that ASEAN was a functioning mobilising body which supported the markets to progress harmonisation in the region even though it does not possess a legal backbone. Secondly, the ASEAN had government buy-in to push the initiative and they started with a common guideline upon which they drafted the ASEAN guidelines. The ASEAN also had key motivating factors like trade and the desire to reduce duplication of effort.

LATAM also highlights the benefits of streamlining CMC requirements, however, the region is not as united as ASEAN. PANDRH, the main mobilising body in LATAM moved from supporting harmonisation within the region to convergence due to harmonisation's impracticality for the region because of political tensions and a general lack of desire to work together. LATAM markets are working towards convergence with international guidelines with some market-specific challenges.

Compared to LATAM, one can deduce that ASEAN has a clear goal, a sense of direction; coupled with an enabling mindset to match that goal. This also makes them less risk averse, they challenge themselves to do better. This common goal and enabling mindset are pushing the region to achieve harmonisation in the area of CMC post-approval variations, ultimately benefiting the patient, industry and member states, even though they are experiencing some challenges. LATAM markets on the other hand have to develop and embrace a risk-based approach, and an enabling mindset like ASEAN. This will enable individual markets to embrace the ICH guidelines more readily and move the markets forward. Unfortunately, the political rivalry and disunity prevents them from leveraging expertise and sharing resource in working towards convergence to international guidelines. This does not benefit the region as a whole, industry, and patient access to innovative medicines. Hopefully, future collaborations with ASEAN (like ASEAN-CELAC)

and other networking bodies may encourage the region to develop this mindset and move the region forward as a whole.

6.4 Limitations

There were several limitations identified with this comparison which are outlined below. The comparison did not start with an a priori conceptual framework, but it emerged, which limits the comparative analysis.

The regions are not directly comparable for several reasons. One being that LATAM is heading for convergence whilst ASEAN is aiming for harmonisation. These are different processes for streamlining CMC requirements so the parameters of those processes will be different.

The LATAM and ASEAN regions have differing political, social and economic structures which prevents a like-for-like comparison.

Also, the comparison only took two regions into account, hence it cannot be generalised to other regions undergoing streamlining activities like Africa or the Gulf.

6.5 Future Research

Although there is a lack of research previously comparing CMC streamlining initiatives in ASEAN and LATAM, this research has provided some initial thoughts on the topic. There is no obvious single next study that could be done in isolation and therefore future research will be covered in Chapter Seven at a higher level.

6.6 Conclusion

This Chapter achieved its objectives of comparing the two regions and highlighting what LATAM could learn from ASEAN in their efforts to streamline CMC post-approval requirements. Based on the simple comparisons conducted in this Chapter, it is fair to say that having a common goal as a key motivating factor, a mobilising body; a strong and unified political will; an enabling mindset and government buy-in are the main things that LATAM can learn from ASEAN in streamlining CMC requirements in the region. Having these factors in place will help the LATAM region to be patient-focussed, working towards every possible solution to enhance patient access to vital and innovative medicines.

Chapter Seven provides a general discussion and conclusion of the research by offering the wider global perspective of streamlining CMC post-approval changes in the pharmaceutical regulatory space. It will also seek to draw conclusions about the streamlining processes occurring in both regions whilst providing suggestions for further research.

7 GENERAL DISCUSSION AND CONCLUSIONS

7.1 Introduction

After a medicinal product receives its initial marketing authorisation and product license, any subsequent chemistry and manufacturing changes that occur to the medicinal product or information in the license, are referred to as post-approval CMC changes or variations. The term CMC changes or variations can be used interchangeably, however, in this research, the term post-approval changes or PACs has been used throughout. (Dellepiane *et al.*, 2020)

PACs are important and necessary to the life cycle of medicinal products for numerous reasons, these include: to enhance efficiency of manufacturing processes, implement new knowledge, maintain a state of control, and drive continual improvement; as a response to changes in regulatory guidelines; or for increased capacity to accommodate supply as well as to increase the quality of the medicinal product (Dellepiane *et al.*, 2020; Ramnarine *et al.*, 2020).

Many PACS require regulatory approval before implementation, and this is a complex operation trying to satisfy individual NRA data and documentation requirements. For multinational companies, the complexity is multiplied as the same changes need to be submitted across different regions globally to implement the change within a narrow timeframe globally. One change can sometimes take years for worldwide approval and can jeopardise patient access if not managed properly (Ramnarine *et al.*, 2020). Therefore, to ensure product supply and continuity, effective management of PACs is required (same documentation and data requirements, similar submission approval timelines) One way of effectively managing PACs is to look at opportunities to streamline PAC requirements and timelines globally or across a region (BioPhorum, 2019).

With the continued globalisation of supply chains the importance of CMC changes and the necessity to streamline PACs, possibly developing a global standard that regions can adhere to, is being highlighted (BioPhorum, 2019).

Streamlining PACs would enable industry and NRAs to receive the same or similar packages to cater for multiple markets, saving resources and reducing duplication of effort (Weisfeld and Lustig, 2013).

The ASEAN have had some success in streamlining PACs within the region as evidenced by their common post-approval CMC guidelines (IPQ, 2010). The process of harmonisation has been the route taken by the ASEAN to arrive at this common goal (Reggi, 2017).

In LATAM, however, it was unclear whether streamlining of PACs is a priority in the region and what process, if any, is being employed in the region to streamline if applicable.

The research chose to focus on three Southeast Asian markets, namely Malaysia, Thailand and Singapore. It also looked at and contrasted six LATAM markets, namely Brazil, Argentina, Chile, Cuba, Colombia and Mexico. These six are designated as NRAR (Level IV) by PANDRH as explained in Chapter 1.

In both regions, the research sought to explore the post-approval CMC landscape for successes and challenges. It also sought to explore whether any streamlining initiatives were being undertaken in LATAM and whether this was a priority for the region. The research then sought to compare and contrast the initiatives in ASEAN with LATAM and determine if LATAM could learn any lessons from ASEAN.

Lastly, the research also set out to explore whether harmonisation within the region or convergence to international standards would be the preferred process to streamline PACs in LATAM if applicable.

Until now, no studies have compared streamlining of CMC requirements in ASEAN to streamlining initiatives in LATAM. Also, there has been no definitive study to confirm which preference LATAM would take to streamline CMC requirements and whether streamlining post-approval CMC changes is a priority for the region. This research addresses those gaps and provide a greater understanding of the phenomenon which will be beneficial to industry and NRAs, as both types of stakeholders shared their respective views. When the thesis is openly available, each stakeholder will be able to see each other's points of view. Besides the regulatory industry viewpoint, which the researcher is familiar with due to their regulatory background, the research has provided greater insight and clarity into the ASEAN and LATAM contexts of harmonisation and convergence respectively. The researcher has also received a better understanding of the complexities of streamlining PAC requirements, especially from the NRA perspective which will be useful for their future work in regulatory affairs.

The research was in 4 parts. The first part was a systematic review of the literature to explore any initiatives to streamline PACs in LATAM and ASEAN and by which process (Chapter 3). The second part explored the ASEAN PAC landscape via stakeholder interviews and secondary data to learn more about harmonisation of post-approval changes, challenges and successes (Chapter 4). The third part was achieved through individual, group interviews and questionnaires to explore and evaluate the post-approval landscape in the six LATAM markets to confirm priorities and processes for streamlining PACs (Chapter 5). The fourth and final part focused on comparing and contrasting streamlining activities in ASEAN to LATAM to glean any learnings that could be beneficial to LATAM (Chapter 6).

The data collected from Chapters 3, 4 and 5 were analysed individually, then the data in Chapters 4 and 5 were compared in Chapter 6. The overall analyses were then combined for this Chapter, to draw conclusions about the streamlining processes occurring in both regions.

7.2 General discussion

The systematic review in Chapter 3 exposed the understanding of harmonisation and convergence at the time (Tominaga, 2020). Convergence was a relatively new term at the time and was being used more broadly to mean something more flexible than harmonisation. It is a process where markets look for common ground within the structure of recognized standards. During the course of the research which started out in 2013, it was observed that the discussion regarding streamlining requirements and notably, convergence had progressed. This was noticeable in the interviews with the LATAM NRAs and FIFARMA participants where terms such as reliance, cooperation and recognition were discussed. These were seen as ways by which convergence could occur, hence convergence has taken on a much wider context than it had a few years back (Tominaga, 2020). This broader context offers various positions that markets can take depending on their regulatory capacity and capabilities; one position not being better than another but just different ways of reaching convergence (Mota Pina, 2021; Gomes and Lessa, 2022). This also means more flexibility in terms of how agreements on requirements could be reached. An NRA could use a mixture of these approaches, hence the outcomes may not always be the same from one market to the next, even within the same region (Mota Pina, 2021).

The Systematic review showed at the time that there was no mention of streamlining CMC requirements in LATAM. The low priority given to streamlining CMC requirements in LATAM was further confirmed through participant interviews, despite the known benefits. As described in Chapter 5, streamlining of CMC requirements will happen over time as the markets gradually converge to ICH standards. This obviously is not favourable for industry, because extensive resource is still required to provide market-specific submissions. However, there is comfort in knowing that the region is taking steps to converge to international standards. In the long run this will benefit patients, industry and the NRAs. The follow-on question is how long will this take? Another thought is what the outcome of this convergence will be, as the LATAM markets through reliance, have the flexibility to incorporate local guidelines whilst also adopting WHO guidelines. This is also not advantageous to industry as the result could still be market-specific requirements and varying degrees of implementation of the guidelines. This is something that could be explored further as an extension to this research.

The systematic review also revealed that, even though ASEAN has managed to draft common PAC guidelines, there are still individual market requirements which do not give a true picture of harmonisation. (Seth, 2022). In fact, ASEAN participants cited that the ASEAN streamlining process was more comparable to convergence than harmonisation. (Cairns, 2018; Lim, 2021). The ASEAN, however, is forging ahead with their harmonisation efforts, with the introduction of the joint assessments (Ahmad *et al.*, 2021; HSA website, 2021). This will encourage markets to further leverage their expertise and strengthen reliance procedures within the region.

The outcomes of the research suggest that the focus here should not necessarily be on a particular term, that is harmonisation or convergence or the process by which these alignments are happening, i.e. reliance, cooperation, recognition. The focus should rather be on the fact that the regions are moving towards a common goal with the aim of streamlining requirements to benefit the patient and to leverage expertise and capacities. This would be more so for ASEAN than LATAM, however, at the current time.

Chapter 5 highlighted that in LATAM, political instability in the region and the unwillingness to work together means that convergence is the more practical and preferred process for the region. Further fragmentation in the region is observed through the different initiatives such as PANDRH, CELAC, MERCOSUR, covering different set of markets; but with similar agendas of medicines regulation amongst other things. Interestingly, a new regional body is under discussion for the Latin America and the Caribbean region, called AMLAC, (*Agencia Reguladora de Medicamentos y Dispositivos Médicos de Latinoamérica*

y el Caribe). This is to be a medicines and medical device agency currently covering 10 nations including Cuba, Colombia, and Mexico. Argentina, Brazil and Chile have declined to join at present. The body aims to strengthen mechanisms for harmonization and recognition of regulations, aiming to ensure that the registration of a drug or medical device approved by the agency is recognized by the rest of the member countries (GaBI online, 2023). This new addition may add to the existing complexity of markets trying to work together. The ideal would be to have one main regulatory body (possibly PANDRH); which would help preserve resources as well.

LATAM markets seek to align to high surveillance markets like the US and believe they will gain more by converging to international standards rather than harmonising internally. This move towards convergence should be welcomed as it will inadvertently cause the region to become harmonised as each market adopts the ICH guidelines. This in turn will enhance the regulatory capacities of the NRAs (Mota Pina, 2021).

Here, it is expedient to mention the need for a positive and unified mindset for regional alignment to be a potential goal. The LATAM region is far from having such a mindset hence patient access to innovative medicines will continue to be slower as compared to the ASEAN region, as evidenced in the ASEAN's response to the recent pandemic compared to LATAM's lack of coordinated effort as a region (Djalante, 2020; Amaya and De Lombaerde, 2021).

It is likely, however, that local requirements will still exist between international guidelines like ICH and LATAM/ASEAN due to local differences such as climatic zone as highlighted by Sindusfarma's report (Silva, Cabello and Gaban, 2018) where they assess the extent to which LATAM markets have currently aligned to ICH guidelines.

In addition, WHO guidelines on procedures and data requirements for PACs are intended to serve only as a guide. Hence, they offer flexibility in requirements and process, acknowledging that markets may need specific local requirements; however, the caveat is that it is done appropriately and with scientific justification (WHO, 2002). As identified in Chapter 5, NRAs are not always quick to accept scientific justifications from industry and the reasons for NRA market-specific requirements are not always based on a scientific viewpoint from industry's perspective. Secondly, who determines what requirements are appropriate and what are not? Industry is at the mercy of the NRA in terms of requirements to enable their submission to be assessed and approved so they will continue to have to provide whatever is being requested to the best of their ability, even if they do not believe it to be scientifically justified.

There is definitely a heightened interest in streamlining PACs, especially from industry as they recognise the backlogs that the NRAs are facing. In trying to offer possible solutions, an EFPIA position paper and Dellepiane et al stress the advantage of using reliance to shorten review times (Dellepiane *et al.*, 2020; EFPIA, IFPMA and Vaccines Europe, 2021). Reliance was extensively discussed in Chapter 5 by participants as the way forward for Latin America markets. Reliance was expressed as a way through which regulatory convergence could occur and not necessarily a form of convergence, but a vehicle of convergence. In reliance, NRAs consider or give significant weight to evaluations of another NRA whilst remaining responsible and accountable for their decisions (PAHO, 2019). Reliance in LATAM is seen to support the lack of regulatory resources and regulatory capacity of the NRAs; whilst maintaining their sovereignty (Gomes and Lessa, 2022). In embracing reliance, duplication of effort is reduced, and the region benefits from easier exchange of information thereby fostering greater levels of convergence. Through reliance, NRA capabilities can also be improved as NRAs learn from the practices of more competent NRAs (Gomes and Lessa, 2022). Another argument for reliance based on participant responses and the secondary data, was the fact that the region had initially tried to harmonise technical guidelines and requirements through PANDRH (PANDRH Secretariat, 2014) but this proved unsuccessful, paving the way for reliance which is working better in the region. Duran et al (Durán *et al.*, 2021) state that regulatory reliance has become a common practice in Latin America for new marketing applications. The Covid-19 pandemic also proved that regulatory reliance helped support regulatory preparedness and response and was widely adopted by many markets in the region during the pandemic (Mota Pina, 2021). In an article by Rodriguez et al, the authors propose the use of reliance for post-approval CMC changes for LATAM NRAs as an effective way to optimise resources whilst ensuring continuity of medicine supply to patients as the PACs have increased faster than NRAs can attend to (Rodriguez and De Lucia, 2021). This is one of the few articles that has specifically discussed the streamlining of PAC requirements in LATAM since the completion of the systematic review in Chapter 2 in 2020.

While reliance may be thought of as a good approach, the responses from Chapter 5 (5.3.7.4) showed that obtaining the assessment reports from high surveillance markets for the reliance process can prove challenging. Mota Pina agrees that the availability of assessment reports from reference agencies is a good practice which will aid reliance (Mota Pina, 2021). The NRA participants' opinion was that the NRA will not apply reliance

without a full unredacted assessment report and these full unredacted reports are not always available from the reference markets.

This issue highlights the challenges that LATAM NRAs are facing in regard to reliance, which may not be appreciated by industry as this research has identified. Industry may believe that the NRAs are not progressing fast enough with convergence; however, the truth is that the NRAs are trying to overcome particular challenges in order to converge to the international standards (Chapman, 2020).

One such challenge faced by the NRAs, and even local companies in LATAM especially, is the change in mindset required to work to the standard of ICH guidelines. There needs to be a shift and move away from rigid tick box requirements to being able to interpret guidelines and apply them flexibly to PACs whilst following the science. This shift could be referred to as regulatory agility which is the adoption of risk-based, context-driven approaches and regulatory cooperation based on sound scientific evidence and information (Lim, 2021). This change in the way LATAM assessors will need to work using the ICH guidelines will take time. Local companies are also under the same pressure to realign and generate data in line with ICH requirements, which will enable them to properly categorise PACs also assess the necessary documents they need to submit in support of the change. . This demands a whole culture shift which may not always be easy. How long this change in mindset will take and whether there is enough motivation from the NRAs is impossible to determine, but it is needed for effective convergence to international guidelines to happen (Salcedo, 2020).

The challenges of the disparity in regulatory capacities between regions like LATAM and the EU must not be overlooked. Regions such as the EU are highly regulated markets with robust health care systems as compared to the LATAM region where the disparity in regulatory capacity and health care delivery is very wide moving from one country to the next (Weisfeld and Lustig, 2013). It will take time for LATAM markets to enhance regulatory capacity to the level of these highly regulated markets, hence more effort should be focused on regulatory capacity building which PAHO and WHO is supporting markets to achieve. Convergence therefore for LATAM may happen, but gradually.

As discussed above, in a like manner with ASEAN, harmonisation, where all requirements are the same in each ASEAN market, may not be realistic even though they are aiming for it. The researcher advocates for industry to be patient and cautious of what they expect from regions outside the high surveillance markets.

To bolster that point, WHO guidelines even allow for flexibility in requirements, and this is also being embraced by ICH guidelines where a good scientific justification can be given for any deviations. Given this flexibility, it is possible that complete harmonisation may never occur in ASEAN in the researcher's opinion. This position is also shared by other experts in ASEAN pharmaceutical regulation such as Prof John Lim of the Centre of Regulatory Excellence (CoRE) at the Duke-National University of Singapore Medical School (Duke-NUS) (Lim, 2021).

In conclusion, if a global standard is developed for PACs in the future (BioPhorum, 2019), whilst a focus on patient care and access is essential, it will also need to take these challenges and viewpoints into consideration.

7.3 Limitations

The majority of the specific limitations were covered in depth in previous chapters, sections 3.7; 4.5; 5.5 and 6.4 so only more general ones are captured here.

- a) Participants were hard to recruit especially those with a working knowledge of NRAs, hence gatekeepers were brought in to facilitate the recruitment. Even with the support of gatekeepers, recruitment of participants with working knowledge of the ASEAN NRAs was not possible. This meant that the ASEAN section of the research lacked that extra stakeholder perspective which would have given a better understanding of the CMC landscape in the ASEAN region, and possibly addressed or countered some perceived disparities raised by ASEAN RAs.
- b) For most participants, English was their second language, hence some quotes were quite lengthy as participants tried to express their views. The researcher sometimes had to spend more time than originally anticipated trying to clarify a point so was not always able to ask the full array of questions on the interview schedule. Hence extra details could have been missed to add to the body of data. Future research could consider using interpreters to overcome this limitation (see Chapter 2 for a more detailed discussion of this).
- c) The pandemic played a role in limiting participant recruitment. RAs and NRAs had increased workloads during this time and hence may not have been as willing to participate in this research. This limited the variety of RAs interviewed, especially in the ASEAN section of the research where RAs mainly with medical device expertise were recruited via snowballing.

7.4 Future Work

Based on the overall research outcomes and the discussion above, several areas could be explored in greater detail as future work. These are outlined below:

- i) A 'regulatory convergence' project could be suggested to PANDRH where markets are encouraged to explore their PAC challenges together, offering solutions which may help to shift mindsets and speed up the rate of convergence in the LATAM region. Markets may begin to appreciate the benefits of leveraging knowledge and expertise no matter how limited they currently perceive it to be.
- ii) For ASEAN, a wider exploration of the joint assessment procedure for PACs could be conducted to ascertain how many ASEAN markets are using the procedure and what is its impact on the region.
- iii) A longitudinal study could be carried out on the various streamlining terms (harmonisation, convergence, cooperation, reliance, recognition) to assess how they change over time. This would include assessing any new emerging terms and how relevant they remain in the fast-paced regulatory environment. Questions would include: are these terms changing over time; should there be different levels to these terms; should industry focus on the process of convergence and not be too focused on a 'term' (harmonisation or convergence), but rather 'how' the process will be carried out?
- iv) A more in-depth comparison could be performed of regional integration in ASEAN versus LATAM in light of the COVID-19 pandemic to explore what difference regional integration in the latter would have made in battling the pandemic.

For iii) and iv), as recruitment was a challenge in the ASEAN group of participants, possibly due to their spoken English not being as fluent as the LATAM participants, use of an interpreter could help overcome the language barrier.

7.5 Conclusions

This programme of research has provided an improved understanding of the harmonisation initiatives for PACs in ASEAN whilst comparing it to the convergence initiatives for PACs in LATAM. This comparison between the two regions provides an initial foundation for further research in this area. Over the course of this research project, there

has been a shift in understanding of the term 'harmonisation' where it is seen now as a historic term in some instances, rather than being the reality. The findings suggest that convergence is the more achievable goal for international markets. In addition, it is recognised that regulators in each market have the option to choose various vehicles for convergence such as reliance, cooperation and recognition. A novel understanding of the NRA challenges as pertaining to convergence of PACs has also been uncovered. This understanding can contribute to solutions in this area which will have a positive impact on patient access to healthcare and quality medicines.

REFERENCES

- Abdul Rehman, A. and Alharthi, K. (2016) 'An introduction to research paradigms', *International Journal of Educational Investigations*, 3(8), pp. 51–59.
- Abelson, M. (2010) 'Drug Development: Old Drugs, New Formulas', *Review of Ophthalmology*. Available at: <https://www.reviewofophthalmology.com/article/drug-development-old-drugs-new-formulas> (Accessed: 16 May 2023).
- Acocella, I. (2012) 'The focus groups in social research: advantages and disadvantages', *Quality & Quantity*, 46(4), pp. 1125–1136. Available at: <https://doi.org/10.1007/s11135-011-9600-4>.
- Adams, J. *et al.* (2015) 'Effectiveness and acceptability of parental financial incentives and quasi-mandatory schemes for increasing uptake of vaccinations in preschool children: systematic review, qualitative study and discrete choice experiment.', *Health technology assessment (Winchester, England)*, 19(94), pp. 1–176. Available at: <https://doi.org/10.3310/hta19940>.
- Agee, J. (2009) 'Developing qualitative research questions: a reflective process', *International Journal of Qualitative Studies in Education*, 22(4), pp. 431–447. Available at: <https://doi.org/10.1080/09518390902736512>.
- AHC (2014) *APEC Harmonisation Centre (AHC) Annual Report*. Available at: https://www.apec.org/docs/default-source/Publications/2014/8/APEC-Harmonization-Center-Annual-Report-2013/APEC-Harmonization-Center-Annual-Report_final_120914.pdf.
- Ahmad, R. *et al.* (2021) 'Joint Assessment of Marketing Authorization Applications: Cooperation Among ASEAN Drug Regulatory Authorities', *Global Forum, DIA*. Available at: <https://globalforum.diaglobal.org/issue/september-2021/joint-assessment-of-marketing-authorization-applications-cooperation-among-asean-drug-regulatory-authorities/> (Accessed: 6 December 2023).
- Ahn, E. and Kang, H. (2018) 'Introduction to systematic review and meta-analysis.', *Korean journal of anesthesiology*, 71(2), pp. 103–112. Available at: <https://doi.org/10.4097/kjae.2018.71.2.103>.
- Albuquerque, M. and Theoduloz, S. (2023) 'MERCOSUR and its Partners. What to expect from the wider Atlantic? A situation to monitor', *Policy Center For the New South*, 3 October. Available at: <https://www.policycenter.ma/publications/mercosur-and-its-partners-what-expect-wider-atlantic-situation-monitor> (Accessed: 5 January 2024).
- Allen, K. (2023) 'How Zoom, Microsoft Teams, and Google Workspace Stack Up in 2023', *Acceleration Economy*, 1 May. Available at: <https://accelerationeconomy.com/cloud/how-zoom-microsoft-teams-and-google-workspace-stack-up-in-2023/#> (Accessed: 13 October 2023).
- Alvarez, A.L. *et al.* (2023) 'Establishing a core dossier for multiple regulatory submissions: a case study in the Latin America region.', *Frontiers in medicine*, 10, p. 1102452. Available at: <https://doi.org/10.3389/fmed.2023.1102452>.

Amaral, L.M. (2021) 'Parecer de Análise Técnica da Empresa (PATE) no registro de agrotóxicos Translation: Opinion of Technical Analysis of the Company (PATE) in the registration of pesticides'. Available at: https://planitox-com-br.translate.google.com/registro-de-agrotoxicos/?_x_tr_sl=pt&_x_tr_tl=en&_x_tr_hl=en&_x_tr_pto=sc (Accessed: 25 August 2022).

Amaya, A.B. and De Lombaerde, P. (2021) 'Regional cooperation is essential to combatting health emergencies in the Global South', *Globalization and Health*, 17(1), p. 9. Available at: <https://doi.org/10.1186/s12992-021-00659-7>.

Amri, M., Angelakis, C. and Logan, D. (2021) 'Utilizing asynchronous email interviews for health research: overview of benefits and drawbacks', *BMC Research Notes*, 14(1), p. 148. Available at: <https://doi.org/10.1186/s13104-021-05547-2>.

Anderson, C. (2010) 'Presenting and evaluating qualitative research.', *American journal of pharmaceutical education*, 74(8), p. 141. Available at: <https://doi.org/10.5688/aj7408141>.

APEC RHSC (2011) 'Regulatory Harmonization Steering Committee Vision 2020: A Strategic Framework - Regulatory Convergence for Medical Products by 2020'. APEC Regional Harmonisation Steering committee. Available at: https://www.apec.org/docs/default-source/satellite/RHSC/General-RHSC-Documents/APEC_RHSC_Strategic-Framework_vF.pdf (Accessed: 27 February 2023).

Archibald, M.M. *et al.* (2019) 'Using Zoom Videoconferencing for Qualitative Data Collection: Perceptions and Experiences of Researchers and Participants', *International Journal of Qualitative Methods*, 18, p. 1609406919874596. Available at: <https://doi.org/10.1177/1609406919874596>.

Argentina.gob.ar (2023) 'International Cooperation'. Available at: <https://www.argentina.gob.ar/anmat/anmat-en/international-relations-0/international-cooperation> (Accessed: 14 June 2023).

Argotti, U. *et al.* (2023) 'Comparison of the Latin America Regulation Landscape and International Reference Health Authorities to Hasten Drug Registration and Clinical Research Applications.', *Therapeutic innovation & regulatory science*, 57(6), pp. 1287–1297. Available at: <https://doi.org/10.1007/s43441-023-00565-7>.

Arzuaga Palomino, S. (2014) 'Generating Theory From Secondary Data: a Variation on Eisenhardt's Case Study Method.', *13th European Conference on Research Methodology for Business and Management Studies* [Preprint]. Edited by A. Brown *et al.*

Ascent (2023) 'Pharmaceutical Consultant Job Description', *Ascent Professional services*. Available at: <https://www.ascentpros.com/us/job-profile/pharmaceutical-consultant#:~:text=What%20is%20a%20Pharmaceutical%20Consultant,treatments%20to%20those%20in%20need.> (Accessed: 13 November 2023).

ASEAN (2012) 'ASEAN variation guidelines for pharmaceutical products'. ASEAN Secretariat.

ASEAN Secretariat (2021) 'Overview of ASEAN-CELAC relations'. ASEAN Secretariat Information Paper. Available at: <https://asean.org/community-of-latin-american-and-caribbean-states-celac/>.

ASEAN Secretariat (2022) 'ASEAN Pharmaceutical Policy'. Available at: <https://asean.org/wp-content/uploads/2022/12/ASEAN-Pharmaceutical-Regulatory-Policy-Sample-Print-REV-20122022-.pdf> (Accessed: 12 August 2023).

'ASEAN website (ACTD)' (2022). Available at: [2022https://asean.org/book/asean-common-technical-dossier](https://asean.org/book/asean-common-technical-dossier).

'ASEAN website (history)' (2022). Available at: <https://asean.org/about-asean/the-founding-of-asean/> (Accessed: 22 May 2022).

Asian House (no date) *Re-thinking ASEAN integration: European precedents and Southeast Asian futures*. Available at: <https://asiahouse.org/wp-content/uploads/2019/04/ASEANresearch0525.pdf> (Accessed: 22 May 2022).

Babbie, E. (2013) *The practice of social research*. 14th edn. USA:Wadsworth: CENGAGE Learning.

Baber, N. (1994) 'International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH)', *British journal of clinical pharmacology*, 37(5), pp. 401–404. Available at: <https://doi.org/10.1111/j.1365-2125.1994.tb05705.x>.

Baker, M. (2017) 'The Pacific Alliance | La Alianza del Pacífico Uniquely Positioned to Execute Your Business Strategy in Latin America', January. Available at: https://www.bakermckenzie.com/-/media/files/locations/latin-america/br_la_pacificalliance_jan2017_v2.pdf?sc_lang=en&hash=139B4E00A7D6EAEAOCF3F7869F7EE7.

Berman, R.C. and Tyyskä, V. (2011) 'A Critical Reflection on the Use of Translators/Interpreters in a Qualitative Cross-Language Research Project', *International Journal of Qualitative Methods*, 10(2), pp. 178–190. Available at: <https://doi.org/10.1177/160940691101000206>.

Bhattacharjee, A. (2012) *Social Science Research: Principles, Methods, and Practices*. Global Text Project.

Biolife Solutions (2019) 'The importance of temperature and pharmaceutical storage'. Available at: <https://www.biolifesolutions.com/blog/storage-services/the-importance-of-temperature-and-pharmaceutical-storage/#:~:text=If%20a%20pharmaceutical%20product%20or,the%20properties%20of%20a%20drug>. (Accessed: 16 May 2023).

BioPhorum (2019) *PAS concept paper Brazil* https://www.biophorum.com/wp-content/uploads/bp_downloads/PAS-concept-paper-Brazil-March-2019.pdf.

Boland, J. *et al.* (2022) 'Zoom disrupts the rhythm of conversation', *Journal of Experimental Psychology: General*, 151(6), pp. 1272–1282. Available at: <https://doi.org/10.1037/xge0001150>.

Bonisteel, I. *et al.* (2021) 'Reconceptualizing Recruitment in Qualitative Research', *International Journal of Qualitative Methods*, 20, p. 16094069211042493. Available at: <https://doi.org/10.1177/16094069211042493>.

- Bowden, C. and Galindo-Gonzalez, S. (2015) 'Interviewing when you're not face-to-face: The use of email interviews in a phenomenological study', *International Journal of Doctoral Studies*, 10(12), pp. 79–92.
- Bowen, G. (2009) 'Document Analysis as a Qualitative Research Method', *Qualitative Research Journal*, 9(2), pp. 27–40.
- Boynton, P.M. (2004) 'Administering, analysing, and reporting your questionnaire', *BMJ (Clinical research ed.)*, 328(7452), pp. 1372–1375. Available at: <https://doi.org/10.1136/bmj.328.7452.1372>.
- Bramer, W.M. *et al.* (2018) 'A systematic approach to searching: an efficient and complete method to develop literature searches.', *Journal of the Medical Library Association : JMLA*, 106(4), pp. 531–541. Available at: <https://doi.org/10.5195/jmla.2018.283>.
- Bramer, W.M., Giustini, D. and Kramer, B.M.R. (2016) 'Comparing the coverage, recall, and precision of searches for 120 systematic reviews in Embase, MEDLINE, and Google Scholar: a prospective study', *Systematic Reviews*, 5(1), p. 39. Available at: <https://doi.org/10.1186/s13643-016-0215-7>.
- Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative Research in Psychology*, 3(2), pp. 77–101. Available at: <https://doi.org/10.1191/1478088706qp063oa>.
- Braun, V. and Clarke, V. (2013) *Successful Qualitative Research: A practical guide for beginners*. London: SAGE Publications, Inc., London.
- Braun, V. and Clarke, V. (2021) 'Conceptual and Design Thinking for Thematic Analysis', *Qualitative Psychology*, 9. Available at: <https://doi.org/10.1037/qup0000196>.
- Brewer, E. (2022) 'The Andean Community: A South American Union?', 6 September. Available at: <https://theowp.org/the-andean-community-a-south-american-union/> (Accessed: 1 October 2023).
- Brinkmann, S. and Kvale, S. (2015) *InterViews: Learning the Craft of Qualitative Research Interviewing*. 3. USA: SAGE Publications.
- Brown, G. and Edmunds, S. (2010) 'Doing Pedagogical Research in Engineering'. Engineering Centre for Excellence in Teaching and Learning (engCETL), Loughborough University. Available at: <https://core.ac.uk/download/pdf/19417953.pdf> (Accessed: 12 December 2020).
- Bryman, A. (2016) *Social Research Methods*. 5th edn. London: Oxford University Press.
- Cairns, S. (2018) 'Regulatory convergence or divergence for Asian pharma', *Pharmaceutical Technology*, 20 September. Available at: <https://www.pharmaceutical-technology.com/pricing-and-market-access/regulatory-convergence-or-divergence-for-asian-pharma-html/?cf-view> (Accessed: 12 August 2023).
- Capen, R. *et al.* (2012) 'On the shelf life of pharmaceutical products.', *AAPS PharmSciTech*, 13(3), pp. 911–918. Available at: <https://doi.org/10.1208/s12249-012-9815-2>.
- Carter, N. *et al.* (2014) 'The use of triangulation in qualitative research.', *Oncology nursing forum*, 41(5), pp. 545–547. Available at: <https://doi.org/10.1188/14.ONF.545-547>.

- Castilejo, C. *et al.* (2022) 'Explainer: What Is Mercosur?', 23 August. Available at: <https://www.as-coa.org/articles/explainer-what-mercosur> (Accessed: 5 January 2024).
- Casula, M., Rangarajan, N. and Shields, P. (2021) 'The potential of working hypotheses for deductive exploratory research.', *Quality & quantity*, 55(5), pp. 1703–1725. Available at: <https://doi.org/10.1007/s11135-020-01072-9>.
- CFR.org editors (2021) *Mercosur: South America's Fractious Trade Bloc*, Council on Foreign Relations. Available at: <https://www.cfr.org/backgrounder/mercosur-south-americas-fractious-trade-bloc> (Accessed: 6 September 2022).
- CFR.org editors (2023) 'What is ASEAN?', *Council on Foreign Relations*, 18 September. Available at: <https://www.cfr.org/backgrounder/what-asean> (Accessed: 19 October 2023).
- Chapman, J. (2020) 'CMC Challenges and Opportunities in Latin America'. Available at: <https://redica.com/pharma-cmc-challenges-and-opportunities-in-latin-america/> (Accessed: 22 July 2022).
- Charmaz, K. (2003) 'Qualitative interviewing and grounded theory analysis', *En J. F. Gubrium & J. S. Holstein (Eds.), Handbook of interview research: context and method*, pp. 675–694. Available at: <https://doi.org/10.4135/9781452218403.n25>.
- Cheong, H. *et al.* (2023) 'Secondary Qualitative Research Methodology Using Online Data within the Context of Social Sciences', *International Journal of Qualitative Methods*, 22, p. 16094069231180160. Available at: <https://doi.org/10.1177/16094069231180160>.
- Chodor, T. (2021) 'The Changing Face of Mercosur: Legitimacy and the Politics of Scale in South American Regionalism', *JCMS: Journal of Common Market Studies*, 59(2), pp. 417–431. Available at: <https://doi.org/10.1111/jcms.13200>.
- Chong, S.S. (2021) 'Measuring Progress of Regulatory Convergence and Cooperation Among Asia-Pacific Economic Cooperation (APEC) Member Economies in the Context of the COVID-19 Pandemic', *Therapeutic Innovation & Regulatory Science*, 55, pp. 786–798.
- Chong, S.S.F., Lim, J.C.W. and Tominaga, T. (2018) 'Developing key performance indicators to measure the progress of regional regulatory convergence and cooperation in Asia-Pacific Economic Cooperation (APEC)', *AAPS Open*, 4(1), p. 4. Available at: <https://doi.org/10.1186/s41120-018-0024-2>.
- Choy, L.T. (2014) 'The strengths and weaknesses of research methodology: Comparison and complimentary between qualitative and quantitative approaches', *IOSR journal of humanities and social science*, 19(4), pp. 99–104.
- CIRS (2015) 'the changing regulatory environment in latin america'. Centre for Innovation in Regulatory Science. Available at: https://cirsci.org/wp-content/uploads/dlm_uploads/2021/01/RD-58-FINAL-for-distribution-LATAM.pdf (Accessed: 1 June 2023).
- CIRS (2023a) *A Roadmap for Regulatory Strengthening: CIRS Tools for Measuring and Optimising Regulatory Performance to Support Practices in Line with the World Health Organization Global Benchmarking Tool Indicators*. 87. London, UK: Centre for Innovation in Regulatory Science.

Available at: <https://cirsci.org/publications/cirs-rd-briefing-87-a-roadmap-for-regulatory-strengthening-cirs-tools-for-measuring-and-optimising-regulatory-performance/>.

CIRS (2023b) *Centre for Innovation in Regulatory Science (CIRSCI): About us*. Available at: <https://www.cirsci.org/about-us/> (Accessed: 2 May 2023).

Clarivate (2018) 'Clarivate Analytics Launches Cortellis CMC Intelligence to Expand Drug Availability in Low and Middle Income Countries', October. Available at: <https://clarivate.com/news/clarivate-analytics-launches-cortellis-cmc-intelligence-to-expand-drug-availability-in-low-and-middle-income-countries/> (Accessed: 7 November 2020).

Clarke, V. and Braun, V. (2014) 'Thematic Analysis', in *APA handbook of research methods in psychology*, pp. 1947–1952. Available at: <https://doi.org/10.1037/13620-004>.

Coe, R. and Waring, M. (2021) 'Focus Groups and Group interviews, Chapter 25', in *Research methods and methodologies in education*. 3rd edn. Los Angeles: SAGE Publications.

Cohen, D. and Crabtree, B. (2006) 'Qualitative Research Gudeines Project', *Robert Wood Johnson Foundation*, July. Available at: <http://www.qualres.org/HomeRefl-3703.html> (Accessed: 11 January 2024).

Collins, C.S. and Stockton, C.M. (2018) 'The Central Role of Theory in Qualitative Research', *International Journal of Qualitative Methods*, 17(1), p. 1609406918797475. Available at: <https://doi.org/10.1177/1609406918797475>.

Cooper, R.L., Chenail, R.J. and Fleming, S. (2012) 'A grounded theory of inductive qualitative research education: Results of a meta-data-analysis', *The Qualitative Report*, 17, pp. 1–26.

CRD (2009) 'Systematic Reviews, CRD's guidance for undertaking reviews in health care'. Centre for Reviews and Dissemination, University of York. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf#page=60 (Accessed: 5 January 2024).

Creswell, J.W. (2013) *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*. 4th edn. SAGE Publications, Inc., London.

Crotty, M. (1998) *The foundations of social research, Meaning and perspective in the research process*. 1st edn. SAGE Publications, Inc., London.

Cullen, M.M. and Brennan, N.M. (2021) 'Grounded Theory: Description, Divergences and Application', *Accounting, Finance & Governance Review*, 27. Available at: <https://doi.org/10.52399/001c.22173>.

Dahlke, S. and Stahlke, S. (2020) 'Ethical challenges in accessing participants at a research site.', *Nurse researcher* [Preprint]. Available at: <https://doi.org/10.7748/nr.2020.e1665>.

Dellepiane, N. *et al.* (2020) 'Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers', *Vaccine: X*, 6, p. 100075. Available at: <https://doi.org/10.1016/j.jvacx.2020.100075>.

Deloitte (2015) *Global Life Sciences Outlook, Adapting in an era of transformation*. The Deloitte Touche Tohmatsu Limited's life sciences and health care (LSHC) industry group. Available at:

<https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-life-sciences-report.pdf> (Accessed: 1 June 2023).

Delve, H. and Limpaecher, A. (2021) 'The Practical Guide to Grounded Theory. Practical Guide to Grounded Theory Research.', 17 September. Available at: <https://delvetool.com/groundedtheory> (Accessed: 7 October 2023).

Diem, K. (2002) 'Choosing a data collection method for survey research', *The State University of New Jersey, Desktop publishing by RCE/Resource Centre Revised: February* [Preprint].

Djalante, R. (2020) 'COVID-19 and ASEAN responses: Comparative policy analysis', *Elsevier* [Preprint].

Dragan, I.-M. and Isaic-Maniu, A. (2013) 'Snowball Sampling Completion', *Journal of Studies in Social Sciences*, 5(2), pp. 160–177.

Du, B. *et al.* (2011) 'Evaluation of physical and chemical changes in pharmaceuticals flown on space missions.', *The AAPS journal*, 13(2), pp. 299–308. Available at: <https://doi.org/10.1208/s12248-011-9270-0>.

Dunne, S. *et al.* (2013) 'A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study', *BMC Pharmacology and Toxicology*, 14(1), p. 1. Available at: <https://doi.org/10.1186/2050-6511-14-1>.

Durán, C.E. *et al.* (2021) 'Regulatory reliance to approve new medicinal products in Latin American and Caribbean countries', *Revista panamericana de salud publica = Pan American journal of public health*, 45, pp. e10–e10. Available at: <https://doi.org/10.26633/RPSP.2021.10>.

ECLAC (2022) 'The World Has 8 Billion People, 662 Million of Whom Live in Latin America and the Caribbean', 14 November. Available at: <https://www.cepal.org/en/news/world-has-8-billion-people-662-million-whom-live-latin-america-and-caribbean> (Accessed: 1 June 2023).

ECLAC-PAHO (2021) 'The prolongation of the health crisis and its impact on health, the economy and social development, COVID-19 report'. Economic Commission for Latin America and the Caribbean (ECLAC) and the Pan American Health Organization (PAHO)ECLAC-PAHO. Available at: https://www.cepal.org/sites/default/files/events/files/s2100593_en.pdf (Accessed: 14 September 2022).

EDANZ (2023) 'Systematic Review, Scoping Review, Narrative Review – What's the Difference?' Available at: <https://www.edanz.com/blog/systematic-scoping-narrative#:~:text=Systematic%20reviews%20differ%20greatly%20from,a%20focused%20but%20broader%20topic>. (Accessed: 16 September 2023).

Edwards, R. (1998) 'A critical examination of the use of interpreters in the qualitative research process', *Journal of Ethnic and Migration Studies*, 24(1), pp. 197–208. Available at: <https://doi.org/10.1080/1369183X.1998.9976626>.

EFPIA (2016) 'EFPIA LATAM CONCEPT PAPER RELATED TO THE PROPOSED COMPANY TECHNICAL ASSESSMENT CHANGE REPORT (PATE) FOR POST APPROVAL CHANGES OF SYNTHETIC PRODUCTS IN BRAZIL'.

EFPIA (2017) 'Optimising Post-Approval Change Management for Timely Access to Medicines Worldwide'. EFPIA. Available at: https://www.efpia.eu/media/25953/efpia-post-approval-change-position-paper_final_feb2017.pdf (Accessed: 4 May 2020).

EFPIA (2019) 'Post-approval Changes for Biologics in Latin American Markets'. Available at: <https://www.efpia.eu/media/413202/post-approval-changes-for-biologics-in-latin-american-markets.pdf>.

EFPIA (2020) 'Reference Document on Post-Approval Change Management Protocols (PACMPs)', in. Available at: <https://www.efpia.eu/media/554680/post-approval-change-management-protocols-pacmps-reference-document.pdf> (Accessed: 20 August 2022).

EFPIA, IFPMA and Vaccines Europe (2021) 'Industry Position Paper: Optimising Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide', in.

Egill, B. (2023) 'Interviewing through Interpreters'. Psykologisk Institut, Århus Universitet. Available at: https://psy.au.dk/fileadmin/site_files/filer_psykologi/dokumenter/CKM/NB23/EGIL.pdf.

EMA (2015) 'September 2015 EMA/CHMP/ICH/214732/2007 Committee for Human Medicinal Products ICH guideline Q10 on pharmaceutical quality system Step 5'. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf (Accessed: 8 May 2023).

EMA (no date) *International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*, European Medicines Agency. Available at: <https://www.ema.europa.eu/en/partners-networks/international-activities/multilateral-coalitions-and-initiatives/international-council-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-ich#:~:text=ICH%20achieves%20harmonisation%20through%20developing,are%20expected%20to%20implement%20them.> (Accessed: 1 June 2023).

Eriksen, M. and Frandsen, T. (2018) 'The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review.', *J Med Libr Assoc.*, 106(4), pp. 420–431.

European Medicines Agency (2015) 'Connecting the dots. Towards global knowledge of the international medicine regulatory landscape: mapping of international initiatives. ICMRA mapping report'. Available at: https://www.ema.europa.eu/en/documents/leaflet/connecting-dots-towards-global-knowledge-international-medicine-regulatory-landscape-mapping_en.pdf (Accessed: 1 September 2022).

FDA (no date) *Regulatory Harmonization and Convergence*, US Food and Drug Administration. Available at: <https://www.fda.gov/vaccines-blood-biologics/international-activities/regulatory-harmonization-and-convergence> (Accessed: 1 June 2023).

FDA CDER (2014) 'Guidance for Industry CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports'. Available at: <https://www.fda.gov/files/drugs/published/CMC-Postapproval-Manufacturing-Changes-To-Be-Documented-in-Annual-Reports.pdf>.

Fernandez, W. and Lehmann, H. (2011) 'Case Studies And Grounded Theory Method In Information Systems Research: Issues And Use', *Journal of Information Technology Case and Application Research*, 13, pp. 4–15. Available at: <https://doi.org/10.1080/15228053.2011.10856199>.

FIFARMA (2020a) '5RelianceFIFARMApostp.pdf'. Available at: <https://fifarma.org/wp-content/uploads/2020/12/Reliance-INGLES-AJUSTADO-.pdf> (Accessed: 8 August 2022).

FIFARMA (2020b) 'Webinar APEC Opportunities for LATAM'. Available at: <https://fifarma.org/wp-content/uploads/2023/06/WEBINAR-ENLACES.pdf>.

Flear, D.M. (2017) 'Brexit and Pharmaceuticals' Regulation: Optimising the UK's post-Brexit influence in global standards-setting', p. 4.

Flyvbjerg, B. (2001) *Making Social Science Matter: Why Social Inquiry Fails and How it Can Succeed Again*. Translated by S. Sampson. Cambridge: Cambridge University Press. Available at: <https://doi.org/10.1017/CBO9780511810503>.

Fox, N. (2009) 'Using interviews in a research project', *The NIHR RDS for the East Midlands/Yorkshire & the Humber*, 26.

Frith, H. and Gleeson, K. (2004) 'Clothing and Embodiment: Men Managing Body Image and Appearance', *Psychology of Men & Masculinity*, 5. Available at: <https://doi.org/10.1037/1524-9220.5.1.40>.

GaBI online (2023) 'AMLAC: regulatory agency for medicines in Latin America and the Caribbean established', *Generics and Biosimilars Initiative*, 13 June. Available at: <https://www.gabionline.net/policies-legislation/amlac-regulatory-agency-for-medicines-in-latin-america-and-the-caribbean-established> (Accessed: 17 January 2024).

Gehanno, J.-F., Rollin, L. and Darmoni, S. (2013) 'Is the coverage of google scholar enough to be used alone for systematic reviews', *BMC Medical Informatics and Decision Making*, 13(1), p. 7. Available at: <https://doi.org/10.1186/1472-6947-13-7>.

Giaquinto, A. *et al.* (2020) 'Improving access to quality medicines in East Africa: An independent perspective on the East African Community Medicines Regulatory Harmonization initiative', *PLoS Med*, 17(8). Available at: <https://doi.org/10.1371/journal.pmed.1003092>.

Global Data (2022) 'Thailand Healthcare (Pharma and Medical Devices) Market Analysis, Regulatory, Reimbursement and Competitive Landscape', 11 May. Available at: <https://www.globaldata.com/store/report/thailand-healthcare-regulatory-and-reimbursement-analysis/> (Accessed: 25 May 2023).

Gomes, C.H. and Lessa, F. (2022) 'Regulatory Convergence and Other Best Practices in Caribbean & Latin America', *DIA Global Forum*, June. Available at: <https://globalforum.diaglobal.org/issue/june-2022/regulatory-convergence-and-other-best-practices-in-caribbean-latin-america/> (Accessed: 5 January 2024).

González Peña, O.I., López Zavala, M.Á. and Cabral Ruelas, H. (2021) 'Pharmaceuticals Market, Consumption Trends and Disease Incidence Are Not Driving the Pharmaceutical Research on

Water and Wastewater.', *International journal of environmental research and public health*, 18(5). Available at: <https://doi.org/10.3390/ijerph18052532>.

Groves, M. and Mundt, K. (2015) 'Friend or foe? Google Translate in language for academic purposes', *English for Specific Purposes*, 37, pp. 112–121. Available at: <https://doi.org/10.1016/j.esp.2014.09.001>.

Guest, G., Bunce, A. and Johnson, L. (2006) 'How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability', *Field Methods*, 18(1), pp. 59–82. Available at: <https://doi.org/10.1177/1525822X05279903>.

Guest, G., Namey Emily and Chen, M. (2020) 'A simple method to assess and report thematic saturation in qualitative research', *PLOS ONE*, 15(5), p. e0232076. Available at: <https://doi.org/10.1371/journal.pone.0232076>.

Habeeb, L. (2020) 'Investigating the Effectiveness of Google Translate among Iraqi Students', *International Journal of Innovation, Creativity and Change*, 12(12). Available at: https://www.ijicc.net/images/vol12/iss12/121231_Habeeb_2020_E_R.pdf.

Haigh, F. *et al.* (2019) 'Developing a critical realist informed framework to explain how the human rights and social determinants of health relationship works', *BMC Public Health*, 19(1), p. 1571. Available at: <https://doi.org/10.1186/s12889-019-7760-7>.

Hall, H., Griffiths, D. and McKenna, L. (2013) 'From Darwin to constructivism: the evolution of grounded theory.', *Nurse researcher*, 20(3), pp. 17–21. Available at: <https://doi.org/10.7748/nr2013.01.20.3.17.c9492>.

Haradhan, M. (2018) 'Qualitative Research Methodology in Social Sciences and Related Subjects', *Journal of Economic Development, Environment and People*, 7(1), pp. 23–48.

Harden, A. *et al.* (2009) 'Teenage pregnancy and social disadvantage: systematic review integrating controlled trials and qualitative studies.', *BMJ (Clinical research ed.)*, 339, p. b4254. Available at: <https://doi.org/10.1136/bmj.b4254>.

Hartling, L. *et al.* (2017) 'Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews', *BMC Medical Research Methodology*, 17(1), p. 64. Available at: <https://doi.org/10.1186/s12874-017-0347-z>.

Harzing, A.-W. (2016) 'Publish or Perish Explains the use of Publish or Perish and its metrics'. Available at: <https://harzing.com/resources/publish-or-perish> (Accessed: 25 September 2023).

Hashan, H.M. *et al.* (2022) 'Evaluation of the Performance of the Gulf Cooperation Council Centralised Regulatory Review Process: Strategies to Improve Product Authorisation Efficiency and Quality', *Pharmaceutical Medicine*, 36(4), pp. 223–231. Available at: <https://doi.org/10.1007/s40290-022-00432-0>.

Hawkins, J. (2018) 'The Practical Utility and Suitability of Email Interviews in Qualitative Research', *Nursing Faculty Publications*, 24. Available at: https://digitalcommons.odu.edu/nursing_fac_pubs/24 (Accessed: 18 January 2024).

- Haynes, K. (2012) 'Reflexivity in qualitative research', *Qualitative Organizational Research: Core Methods and Current Challenges*, pp. 72–89.
- Heale, R. and Forbes, D. (2013) 'Understanding triangulation in research', *Evidence-Based Nursing*, 16(4), pp. 98–98. Available at: <https://doi.org/10.1136/eb-2013-101494>.
- Health Sciences Authority (2022) *HSA Singapore the First National Regulatory Authority Awarded the Highest Recognition for an Advanced Medicines Regulatory System by the World Health Organization*.
- 'Health Singapore Authority (HSA) website' (2022). Available at: <https://www.hsa.gov.sg/therapeutic-products/variation-application/overview> (Accessed: 22 April 2022).
- Hechavarría Núñez, Y. *et al.* (2011) 'The regulatory framework for similar biotherapeutic products in Cuba', *Evaluation of Similar Biotherapeutic products: Scientific and Regulatory Challenges*, 39(5), pp. 317–320. Available at: <https://doi.org/10.1016/j.biologicals.2011.08.005>.
- Herman, S.W. (2015) 'Google Scholar Could Be Used as a Stand-Alone Resource for Systematic Reviews', *Evidence Based Library and Information Practice*, 10(2), pp. 147–149.
- Hoath, C., Chang, L. and Ramalingam, I.K. (2016) 'Postapproval Changes for Biopharmaceutical Drug-Substance and Drug-Product Manufacture: Regulatory Complexity and Impact', *Bioprocess International*. Available at: <https://bioprocessintl.com/business/regulatory-affairs/postapproval-changes-biopharmaceutical-drug-substance-drug-product-manufacture-regulatory-complexity-impact/> (Accessed: 8 May 2023).
- Hoey, B. (2017) *A Comprehensive Study on the Global Regulatory Requirements for the submission of a Post-Approval Change, specifically a Change in Manufacturing Site*.
- HSA website (2020) 'Singapore MiV guidelines'. Available at: <https://www.hsa.gov.sg/therapeutic-products/variation-application/overview> (Accessed: 22 October 2020).
- HSA website (2021) 'ASEAN Joint Assessment Procedure for Pharmaceutical Products Public Announcement', December. Available at: <https://www.hsa.gov.sg/docs/default-source/gdo/international-collaboration/asean/asean-ja-procedure-for-pharmaceutical-products---public-announcement.pdf> (Accessed: 15 September 2022).
- Hubbs, D. and Brand, C. (2005) 'The Paper Mirror: Understanding Reflective Journaling', *Journal of Experiential Education*, 28, pp. 60–71. Available at: <https://doi.org/10.1177/105382590502800107>.
- Huynh-Ba, K. and Beumer Sassi, A. (2018) 'ANVISA: an introduction to a new regulatory agency with many challenges', *AAPS Open*, 4(1), p. 9. Available at: <https://doi.org/10.1186/s41120-018-0029-x>.
- ICH (2018) 'Definitions of terms in the context of the implementation of ICH Guidelines'. ICH. Available at: https://admin.ich.org/sites/default/files/2019-06/ICH_Implementation_Definitions_V1.1_2018_1002.pdf (Accessed: 15 September 2022).
- ICH (2019) 'TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT Q12 STEP 4'. Available at:

https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf ICH Q12 (Accessed: 8 May 2023).

ICH (2020) *ICH Guideline Implementation, ICH*. Available at: <https://www.ich.org/page/ich-guideline-implementation> (Accessed: 15 September 2020).

ICH Press release (2021) '<https://www.ich.org/pressrelease/press-release-ich-assembly-virtual-meeting-november-2021>', November. Available at: <https://www.ich.org/pressrelease/press-release-ich-assembly-virtual-meeting-november-2021> (Accessed: 31 August 2022).

ICH website (2020) *Current Members and Observers*. Available at: <https://www.ich.org/page/members-observers> (Accessed: 31 October 2018).

ICH website (no date a) *History, ICH, Harmonisation for better health*. Available at: <https://www.ich.org/page/history> (Accessed: 25 February 2023).

ICH website (no date b) *Quality Guidelines*. Available at: <https://www.ich.org/page/quality-guidelines>.

IFPMA (2016) 'IFPMA Position Paper on the Handling of Post-approval Changes to Marketing Authorizations'. Available at: <https://www.ifpma.org/wp-content/uploads/2016/11/IFPMA-LCM-Position-Paper-vNov-2016-Final.pdf> (Accessed: 7 November 2020).

IFPMA (2018) 'Case Studies to Illustrate Position Paper on the Handling of Post-Approval Changes to Marketing Authorizations'.

IMS Institute for Healthcare Informatics (2012) 'IMS Institute Global Use of Medicines: Outlook through 2016', *Future Prescriber*, 14(1), pp. 10–12.

Institute of Medicine (2013a) *International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary*. Washington DC: National Academies Press (US). Available at: <https://www.ncbi.nlm.nih.gov/books/NBK174229/>.

Institute of Medicine (2013b) 'Principles and Definitional Considerations (Chapter 2)', in *International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary*. Washington DC: National Academies Press (US). Available at: <https://www.ncbi.nlm.nih.gov/books/NBK174229/>.

Int Trade Assoc (2020) 'North American Free Trade Agreement (NAFTA)'. Available at: <https://www.trade.gov/north-american-free-trade-agreement-nafta> (Accessed: 14 June 2023).

Intellspot (2024) 'Secondary Data: Advantages, Disadvantages, Sources, Types'. Available at: <https://www.intellspot.com/secondary-data/> (Accessed: 11 January 2024).

International Trade Administration (2020) 'Market Intelligence Singapore Healthcare', *International Trade Administration*. Available at: <https://www.trade.gov/market-intelligence/singapore-healthcare#:~:text=Singapore%27s%20healthcare%20spending%2C%20comprising%20both,up%20to%209%25%20by%202029.> (Accessed: 13 May 2023).

International Trade Administration (2023a) 'Healthcare Resource Guide Thailand', *International Trade Administration*. Available at: <https://www.trade.gov/healthcare-resource-guide-thailand> (Accessed: 25 May 2023).

International Trade Administration (2023b) 'Market Intelligence Singapore Budget', *International Trade Administration*. Available at: <https://www.trade.gov/market-intelligence/singapore-budget-2023#:~:text=The%20ministries%20that%20will%20receive,total%20expenditure%20of%20%2412.59%20billion.> (Accessed: 23 January 2024).

IPQ (2010) 'ASEAN Effort Progressing on CMC/GMP Harmonization, But Differences Remain', *International Pharmaceutical Quality* [Preprint]. Available at: <https://ipq.org/asean-effort-progressing-on-cmcgmp-harmonization-but-differences-remain/> (Accessed: 10 October 2018).

IPS (2020) 'COFEPRIS Approval Regulatory Strategy & Submissions'. Available at: <https://www.insumosparasalud.com/regulatory> (Accessed: 25 August 2022).

Ishikawa, K. (2021) 'The ASEAN Economic Community and ASEAN economic integration', *Journal of Contemporary East Asia Studies*, 10(1), pp. 24–41. Available at: <https://doi.org/10.1080/24761028.2021.1891702>.

Jacsó, P. (2009) 'Calculating the h-index and other bibliometric and scientometric indicators from Google Scholar with the Publish or Perish software', *Online Information Review*, 33(6), pp. 1189–1200. Available at: <https://doi.org/10.1108/14684520911011070>.

Johnson, B.T. and Hennessy, E. (2019) 'Systematic reviews and meta-analyses in the health sciences: Best practice methods for research syntheses', *Social Science & Medicine*, 233, pp. 237–251. Available at: <https://doi.org/10.1016/j.socscimed.2019.05.035>.

Juillet, Y. (2003) 'Internationalization of regulatory requirements.', *Fundamental & clinical pharmacology*, 17(1), pp. 21–25. Available at: <https://doi.org/10.1046/j.1472-8206.2003.00118.x>.

Kable, A.K., Pich, J. and Maslin-Prothero, S.E. (2012) 'A structured approach to documenting a search strategy for publication: a 12 step guideline for authors.', *Nurse education today*, 32(8), pp. 878–886. Available at: <https://doi.org/10.1016/j.nedt.2012.02.022>.

Kapborga, I. and Berterö, C. (2002) 'Using an Interpreter in Qualitative Interviews: Does it Threaten Validity?', *Nursing inquiry*, 9, pp. 52–6. Available at: <https://doi.org/10.1046/j.1440-1800.2002.00127.x>.

Kennedy, D. and Beaton, B. (2016) 'Two Steps Forward? Assessing Latin American Regionalism Through CELAC', *Latin American Policy*, 7(1), pp. 52–79. Available at: <https://doi.org/10.1111/lamp.12090>.

Khadem Broojerdi, A. *et al.* (2020) 'The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage', *Frontiers in medicine*, 7, pp. 457–457. Available at: <https://doi.org/10.3389/fmed.2020.00457>.

Khuong, V. (2020) 'ASEAN ECONOMIC PROSPECTS AMID EMERGING TURBULENCE: DEVELOPMENT CHALLENGES AND IMPLICATIONS FOR REFORM', *Foreign Polict at Brookings* [Preprint]. Available at: <https://www.brookings.edu/wp->

content/uploads/2020/07/FP_20200715_asean_economic_prospects_vu.pdf (Accessed: 9 September 2022).

King's College London (2017) *Searching for Systematic Reviews & Evidence Synthesis: Drawing up your strategy*, LibGuides. Available at: <https://libguides.kcl.ac.uk/systematicreview/searchstrat#:~:text=You%20will%20need%20to%20ensure,singular%2C%20abbreviations%2C%20etc.>

Kirchherr, J. and Charles, K. (2018) 'Enhancing the sample diversity of snowball samples: Recommendations from a research project on anti-dam movements in Southeast Asia.', *PLoS one*, 13(8), p. e0201710. Available at: <https://doi.org/10.1371/journal.pone.0201710>.

Kirk, A. (2008) 'ICH seeks harmony on quality', January. Available at: <https://www.pharmtech.com/view/ich-seeks-harmony-quality>.

Knott, E. *et al.* (2022) 'Interviews in the social sciences', *Nature Reviews Methods Primers*, 2(1), p. 73. Available at: <https://doi.org/10.1038/s43586-022-00150-6>.

Knox, S. and Burkard, A.W. (2009) 'Qualitative research interviews', *Psychotherapy Research*, 19(4–5), pp. 566–575. Available at: <https://doi.org/10.1080/10503300802702105>.

Kopp, D.S. (2006) 'Stability Testing of Pharmaceutical Products in a Global Environment', p. 4.

Kruse, N.A. (2015) 'Manufacturing process changes, biologic product comparability and post approval changes'. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-manufacturing-process-changes-biologic-product-comparability-post-approval-changes_en.pdf (Accessed: 16 May 2023).

Kumar, R. (2014) *Research Methodology: A step-by-step Guide for Beginners*. 4th edn. London: SAGE Publications, Inc., London.

Kuter, U. and Yilmaz, C. (2001) 'Survey methods: Questionnaires and interviews', *Choosing Human-Computer Interaction (HCI) Appropriate Research Methods* [Preprint].

Labonté, R. *et al.* (2019) 'USMCA (NAFTA 2.0): tightening the constraints on the right to regulate for public health', *Globalization and Health*, 15(1), p. 35. Available at: <https://doi.org/10.1186/s12992-019-0476-8>.

Lakkis, M.M. (2010) 'Global and Regional Drug Regulatory Harmonization Initiatives', *Drug information journal : DIJ / Drug Information Association*, 44(3), pp. 289–297. Available at: <https://doi.org/10.1177/009286151004400311>.

Lange, S. (2014) *Systematic review of scientific literature published on the topic of public procurement between the years 1997 and 2012*. MSc. University of Twente.

Latzel, R. (2007) *Development of the ASEAN Pharmaceutical Harmonisation Scheme - An Example of Regional Integration* -. Available at: https://www.dgra.de/media/pdf/studium/masterthesis/master_laetzel_r.pdf.

Lavrakas, P. (2022) 'Encyclopedia of Survey Research Methods'. Available at: <https://doi.org/10.4135/9781412963947>.

- Leask, J., Hawe, P. and Chapman, S. (2001) 'Focus group composition: a comparison between natural and constructed groups', *Australian and New Zealand Journal of Public Health*, 25(2), pp. 152–154. Available at: <https://doi.org/10.1111/j.1753-6405.2001.tb01838.x>.
- Lee, J.-O. and Adam, S. (2022) 'ASEAN is poised for post-pandemic inclusive growth and prosperity – here's why', January. Available at: <https://www.weforum.org/agenda/2022/01/asean-is-poised-for-post-pandemic-inclusive-growth-and-prosperity-heres-why/>.
- Lee, J.W. and Oh, J. (2020) 'ASEAN or plus alpha? The effectiveness of regional economic cooperation', *Asia Pacific Management Review*, 25(1), pp. 48–53. Available at: <https://doi.org/10.1016/j.apmr.2019.07.001>.
- Leelianou, S. (2021) *Does ASEAN's Consensus Decision Making Remain Relevant?* Masters. Flinders University. Available at: https://flex.flinders.edu.au/file/1b0b82bd-e5bf-4b49-9680-3e2524cbb0a6/1/Leelianou2021_MasterCopy.pdf (Accessed: 15 September 2022).
- Leong, C.C. (2013) *Updates on Malaysian Variation Guideline for Pharmaceutical Products*. Available at: https://www.npra.gov.my/images/Announcement/2013/Slides-for-National-Regulatory-Conference2013/Track_2_-_Session_8_-_Updates_on_Malaysian_Variation_Guidelines_by_Mr._Chai_Che_Leong.pdf (Accessed: 15 September 2022).
- Levers, M.-J.D. (2013) 'Philosophical paradigms, grounded theory, and perspectives on emergence', *Sage Open*, 3(4), p. 2158244013517243.
- Lezotre, P.-L. (2014a) *INTERNATIONAL COOPERATION, CONVERGENCE, AND HARMONIZATION OF PHARMACEUTICAL REGULATIONS A global perspective*.
- Lezotre, P.-L. (2014b) 'State of Play and Review of Major Cooperation Initiatives.', *International Cooperation, Convergence and Harmonization of Pharmaceutical Regulations*, pp. 7–170. Available at: <https://doi.org/doi:10.1016/B978-0-12-800053-3.00002-1>.
- Lezotre, P.-L. (2014c) 'Value and Influencing Factors of the Cooperation, Convergence, and Harmonization in the Pharmaceutical Sector', *International Cooperation, Convergence and Harmonization of Pharmaceutical Regulations*. 2014/01/17 edn, pp. 171–219. Available at: <https://doi.org/10.1016/B978-0-12-800053-3.00003-3>.
- Liberati, A. and Altman, D. (2009) 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration', *Journal of Clinical Epidemiology*, 62(10), pp. 1–34.
- Lim, J.C. (2021) 'Whithr ASEAN regulatory agility and convergence in the ongoing COVID-19 pandemic?' DUKE-NUS Centre of Regulatory Excellence. Available at: https://www.duke-nus.edu.sg/core/think-tank/core-regulatory-perspective/whither-asean-regulatory-agility-and-convergence-in-the-ongoing-covid-19-pandemic/flipbook/?pdfUrl=https://www.duke-nus.edu.sg/docs/librariesprovider5/core-regulatory-perspective-pieces/2021_002_-_core_whither-asean-regulatory-agility-and-convergence-in-the-ongoing-covid-19-pandemic.pdf?sfvrsn=a1ea64e_0 (Accessed: 12 August 2023).

- Littig, B. and Pochhacker, F. (2014) 'Socio-Translational Collaboration in Qualitative Inquiry: The Case of Expert Interviews', *Qualitative Inquiry*, 20, pp. 1085–1095. Available at: <https://doi.org/10.1177/1077800414543696>.
- Lobe, B., Morgan, D.L. and Hoffman, K. (2022) 'A Systematic Comparison of In-Person and Video-Based Online Interviewing', *International Journal of Qualitative Methods*, 21, p. 16094069221127068. Available at: <https://doi.org/10.1177/16094069221127068>.
- Lokesh, M., Gupta, N.V. and Belagoankar, B. (2015) 'Comparative Study of Process of Post Approval Change Application Submission and Approval for Marketing Authorization Variations in EU, US, India, Saudi Arabia and Singapore', *Int. J. Drug Dev. & Res*, 7, pp. 0975–9344.
- Lorenc, T., Petticrew, M. and Whitehead, M. (2014) 'Systematic review of qualitative evidence: findings Chp 6', in *Crime, fear of crime and mental health: synthesis of theory and systematic reviews of interventions and qualitative evidence*. Southampton UK: NIHR Journals Library (Public Health Research, 2.2).
- Lowrance, W. (2012) 'Confidentiality', in *Privacy, Confidentiality, and Health Research*. Cambridge University Press, p. 33.
- Macrotrends (2023) 'Malaysia Population 1950-2024', *Macrotrends*. Available at: <https://www.macrotrends.net/countries/MYS/malaysia/population> (Accessed: 25 May 2023).
- Macrotrends (2024) 'Thailand Population 1950-2024', *Macrotrends*. Available at: <https://www.macrotrends.net/countries/THA/thailand/population> (Accessed: 25 May 2023).
- Maldonado-Castellanos, I. and Barrios, L.M. (2023) 'Ethical Issues when Using Digital Platforms to Perform Interviews in Qualitative Health Research', *International Journal of Qualitative Methods*, 22, p. 16094069231165949. Available at: <https://doi.org/10.1177/16094069231165949>.
- Malterud, K., Siersma, V.D. and Guassora, A.D. (2016) 'Sample Size in Qualitative Interview Studies: Guided by Information Power', *Qualitative Health Research*, 26(13), pp. 1753–1760. Available at: <https://doi.org/10.1177/1049732315617444>.
- Management Sciences for Health (2012) *MDS-3: Managing Access to Medicines and Health Technologies*. Arlington, VA. Available at: <https://www.gims-foundation.org/wp-content/uploads/2016/05/mds3-jan2014.pdf>.
- Mansoor, I. (2022) 'Zoom Revenue and Usage Statistics (updated Jan 8, 2024)', *Business of Apps*. Available at: <https://www.businessofapps.com/data/zoom-statistics/> (Accessed: 27 January 2022).
- Marshall, S.L. and While, A.E. (1994) 'Interviewing respondents who have English as a second language: challenges encountered and suggestions for other researchers', *Journal of Advanced Nursing*, 19(3), pp. 566–571. Available at: <https://doi.org/10.1111/j.1365-2648.1994.tb01122.x>.
- Mason School of Business (2010) 'Harmonization and Standardization of the ASEAN Medical Industry'. Available at: <https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.471.3014&rep=rep1&type=pdf>.
- McGrath, C., Palmgren, P.J. and Liljedahl, M. (2019) 'Twelve tips for conducting qualitative research interviews', *Medical Teacher*, 41(9), pp. 1002–1006. Available at: <https://doi.org/10.1080/0142159X.2018.1497149>.

- McMullin, C. (2023) 'Transcription and Qualitative Methods: Implications for Third Sector Research', *VOLUNTAS: International Journal of Voluntary and Nonprofit Organizations*, 34(1), pp. 140–153. Available at: <https://doi.org/10.1007/s11266-021-00400-3>.
- Merke, F., Stuenkel, O. and Feldmann, A. (2021) 'Reimagining Regional Governance in Latin America'. Available at: <https://carnegieendowment.org/2021/06/24/reimagining-regional-governance-in-latin-america-pub-84813> (Accessed: 1 May 2022).
- Mero-Jaffe, I. (2011) "'Is that what I Said?" Interview Transcript Approval by Participants: An Aspect of Ethics in Qualitative Research', *International Journal of Qualitative Methods*, 10(3), pp. 231–247. Available at: <https://doi.org/10.1177/160940691101000304>.
- Miller, S. (2001) 'Enhancing your practice through evidence-based decision making: PICO, learning how to ask good questions', *Journal of Evidence Based Dental Practice*, 1(2), pp. 136–141.
- Mittelstand Global (2016) 'PharmaUpdate Brasilien 11/2016', *mittelstand global exportinitiative gesundheitswirtschaft*. Available at: http://www.exportinitiative-gesundheitswirtschaft.de/EIG/Redaktion/DE/Publikationen/PharmaUpdate/2016-12-15-brasilien.pdf?__blob=publicationFile&v=7 (Accessed: 20 November 2017).
- Molzon, J. *et al.* (2011) 'The Value and Benefits of the International Conference on Harmonisation to Drug Regulatory Authorities: Advancing Harmonization for Better Public Health', *Clinical Pharmacology & Therapeutics*, 89(4), pp. 503–512. Available at: <https://doi.org/10.1038/clpt.2011.10>.
- Morgan, D.L. (2007) 'Paradigms Lost and Pragmatism Regained: Methodological Implications of Combining Qualitative and Quantitative Methods', *Journal of Mixed Methods Research*, 1(1), pp. 48–76. Available at: <https://doi.org/10.1177/2345678906292462>.
- Morrison, A.J. and Singh, R.B. (2012) 'Rethinking emerging markets for regulatory affairs with the creation of a Regulatory Authority Development Index', in.
- Mota Pina, M.C. (2021) 'Importance of Reliance to Support Strengthening Latin American and Caribbean Regulatory Systems', *DIA Global Forum*, April. Available at: <https://globalforum.diaglobal.org/issue/april-2021/#supportstrengthening> (Accessed: 5 January 2024).
- Munn, Z., Peters, M.D.J., *et al.* (2018) 'Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach', *BMC Medical Research Methodology*, 18(1), p. 143. Available at: <https://doi.org/10.1186/s12874-018-0611-x>.
- Munn, Z., Stern, C., *et al.* (2018) 'What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences', *BMC Medical Research Methodology*, 18(1), p. 5. Available at: <https://doi.org/10.1186/s12874-017-0468-4>.
- Murphy, E. *et al.* (1998) 'Qualitative research methods in health technology assessment: a review of the literature.', *Health technology assessment (Winchester, England)*, 2(16), pp. iii–ix, 1–274.
- Murray, C.D. (2001) 'Using an interpreter to research', *Community, work and family.*, 4(2), pp. 157–170.

Murteira, S. *et al.* (2013) 'Drug reformulations and repositioning in pharmaceutical industry and its impact on market access: reassessment of nomenclature.', *Journal of market access & health policy*, 1. Available at: <https://doi.org/10.3402/jmahp.v1i0.21131>.

Naderifar, M., Goli, H. and Ghaljaei, F. (2017) 'Snowball Sampling: A Purposeful Method of Sampling in Qualitative Research', *Strides in Development of Medical Education*, In Press. Available at: <https://doi.org/10.5812/sdme.67670>.

Nadin, S. and Cassell, C. (2006) 'The use of a research diary as a tool for reflexive practice: Some reflections from management research', *Qualitative Research in Accounting & Management*, 3, pp. 208–217. Available at: <https://doi.org/10.1108/11766090610705407>.

Narine*, S. (2008) 'Forty years of ASEAN: a historical review', *The Pacific Review*, 21(4), pp. 411–429. Available at: <https://doi.org/10.1080/09512740802294689>.

'National Regulatory Pharmaceutical Authority (NRPA) website' (2022). Available at: <https://www.npra.gov.my/index.php/en/frequently-asked-questions-faqs-veterinary-medicine/variation-vet.html> (Accessed: 22 April 2022).

Negrin, K.A. *et al.* (2022) 'Successful Recruitment to Qualitative Research: A Critical Reflection', *International Journal of Qualitative Methods*, 21, p. 16094069221119576. Available at: <https://doi.org/10.1177/16094069221119576>.

Neris, R.R. *et al.* (2023) 'Five tips for conducting remote qualitative data collection in COVID times: theoretical and pragmatic considerations.', *Revista da Escola de Enfermagem da U S P*, 57, p. e20220277. Available at: <https://doi.org/10.1590/1980-220X-REEUSP-2022-0277en>.

Netherlands Enterprise Agency (2022) *Market Insights: Opportunities in the Life Science and Healthcare Industry (Malaysia)*. Available at: <https://www.rvo.nl/sites/default/files/2022/03/Opportunities%20in%20the%20Life%20Science%20and%20Healthcare%20Industry%20Malaysia.pdf> (Accessed: 26 May 2023).

Ng, A. (2021) 'The ASEAN harmonization of technical standards on health supplements – An industry perspective'. Available at: <https://www.raps.org/news-and-articles/news-articles/2021/6/journey-of-the-asean-harmonization-of-technical-st> (Accessed: 16 May 2022).

Noble, H. and Heale, R. (2019) 'Triangulation in research, with examples.', *Evidence-based nursing*, 22(3), pp. 67–68. Available at: <https://doi.org/10.1136/ebnurs-2019-103145>.

Nowell, L.S. *et al.* (2017) 'Thematic Analysis: Striving to Meet the Trustworthiness Criteria', *International Journal of Qualitative Methods*, 16(1), p. 1609406917733847. Available at: <https://doi.org/10.1177/1609406917733847>.

NPRA (2013) 'Malaysia variation guidelines'. NPRA.

NPRA (2018) *Change Of Manufacturing Site (COS) Application*. Available at: <https://www.npra.gov.my/index.php/en/change-of-manufacturing-site-cos-application> (Accessed: 29 October 2020).

NPRA website (2023) *About US, Official Portal, National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health, Malaysia*. Available at: <https://www.npra.gov.my/index.php/en/about.html> (Accessed: 12 December 2023).

NSW (2021) *Evaluation resource hub Interviews and focus groups*. Available at: <https://education.nsw.gov.au/teaching-and-learning/professional-learning/pl-resources/evaluation-resource-hub/collecting-data/interviews-and-focus-groups#:~:text=Focus%20groups%20are%20a%20specific,than%20an%20interviewer%20asking%20questions>. (Accessed: 12 December 2023).

Nyanchoka, L. *et al.* (2019) 'Key stakeholders' perspectives and experiences with defining, identifying and displaying gaps in health research: a qualitative study protocol.', *BMJ open*, 9(8), p. e027926. Available at: <https://doi.org/10.1136/bmjopen-2018-027926>.

OECD (2020) 'COVID-19 in Latin America and the Caribbean: An overview of government responses to the crisis'. Organisation for Economic Co-operation and Development (OECD). Available at: https://read.oecd-ilibrary.org/view/?ref=129_129907-eae84sciov&title=COVID-19-in-Latin-America-and-the-Caribbean_An-overview-of-government-responses-to-the-crisis (Accessed: 14 September 2022).

OECD and Organization, W.H. (2014) *Health at a Glance: Asia/Pacific 2014*. Available at: https://doi.org/10.1787/health_glance_ap-2014-en.

O'Keefe, R. (2015) 'Harmonisation of variation requirements, categorisation and implementation: A global view', *Regulatory Rapporteur*, 12(4), pp. 8–11.

Oliveira (2016) 'The benefits of convergence with international standards', 19 October.

Olmos-Vega, F.M. *et al.* (2023) 'A practical guide to reflexivity in qualitative research: AMEE Guide No. 149', *Medical Teacher*, 45(3), pp. 241–251. Available at: <https://doi.org/10.1080/0142159X.2022.2057287>.

Onwuegbuzie, A.J. *et al.* (2009) 'A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research', *International Journal of Qualitative Methods*, 8(3), pp. 1–21. Available at: <https://doi.org/10.1177/160940690900800301>.

Padua, A. *et al.* (2020) 'Registration pathways to accelerate regulatory assessment of innovative medicines in Latin America', *Journal of Public Health Policy*, 41(4), pp. 481–495. Available at: <https://doi.org/10.1057/s41271-020-00245-y>.

Paez, A. (2017) 'Grey literature: An important resource in systematic reviews', *J Evid Based Med* [Preprint]. Available at: <https://pubmed.ncbi.nlm.nih.gov/29266844/>.

PAHO (2013) 'PANDRH Technical Document n.10. Requirements for Medicines Registration in the Americas.' PAHO. Available at: <https://www.paho.org/en/documents/pandrh-technical-document-n10-requirements-medicines-registration-americas-2013> (Accessed: 14 June 2023).

PAHO (2018) *The Pan American Network for Drug Harmonization commemorates 20 years anniversary in El Salvador IX conference*. Available at: <https://www.paho.org/en/news/27-10-2018-pan-american-network-drug-harmonization-commemorates-20-years-anniversary-salvador>.

PAHO (2019) 'Pan American Health Organization. Regulatory Reliance Principles: Concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). (San Salvador, 24 to 26 October, 2018). Washington, D.C.: PAHO; 2019.'

- PAHO (2022a) 'CSP30/11 - Policy to Strengthen National Regulatory Systems for Medicines and Other Health Technologies'. Available at: <https://www.paho.org/en/documents/csp3011-policy-strengthen-national-regulatory-systems-medicines-and-other-health> (Accessed: 14 June 2023).
- PAHO (2022b) 'Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference'.
- PAHO (2023) *Quality Control of medicines*. Available at: <https://www.paho.org/en/topics/quality-control-medicines> (Accessed: 1 April 2023).
- PAHO website (2020a) *About PANDRH*. Available at: <https://www.paho.org/en/pan-american-network-drug-regulatory-harmonization-pandrh> (Accessed: 2 June 2023).
- PAHO website (2020b) *PANDRH Technical Working Groups*. Available at: <https://www.paho.org/en/pan-american-network-drug-regulatory-harmonization-pandrh/pandrh-technical-working-groups> (Accessed: 21 June 2023).
- PAHO website (2023) *Who We Are PAHO*. Available at: <https://www.paho.org/en/who-we-are> (Accessed: 1 June 2023).
- PANDRH (2013) 'VII Pan American Network for Drug Regulatory Harmonization (PANDRH) Conference Report'. Available at: <https://www3.paho.org/hq/dmdocuments/2015/drug-harmonization-Report-VII-CPANDRH-2015.pdf>.
- PANDRH Secretariat (2014) 'Strategic Development Plan 2014-2020 of the Pan American Network for Drug Regulatory Harmonization (PANDRH)'. Available at: <https://www.paho.org/sites/default/files/drug-harmonization-Strategic-Plan-PANDRH-04-20-2015.pdf>.
- Panhwar, D.A.H., Ansari, D. and Shah, A. (2017) 'Post-positivism: An Effective Paradigm for Social and Educational Research', *International Research Journal Arts & Humanities (IRJAH)*, 45, pp. 253–260.
- Patton, M. (2014) *Qualitative Research and Evaluation Methods*. 4th edn. Thousand Oaks, California: SAGE Publications.
- Petticrew, M. and Roberts, H. (2006) 'How to Appraise the Studies: An Introduction to Assessing Study Quality, Chpt 5', in *Systematic Reviews in the Social Sciences: A Practical guide*.
- Pettman, simon (2013) *Standards Harmonisation in ASEAN: Progress, Challenges and Moving Beyond 2015*.
- Pezzola, A. and Sweet, C.M. (2016) 'Global pharmaceutical regulation: the challenge of integration for developing states', *Globalization and Health*, 12(1), p. 85. Available at: <https://doi.org/10.1186/s12992-016-0208-2>.
- Pharmalex (2022) *PharmaLex Group develops UK operations*. Available at: PharmaLex Group develops UK operations (Accessed: 18 September 2022).
- Pharmexcil (2020) *THAILAND PHARMA MARKET & REGULATORY REPORT*. Pharmaceuticals Export Promotion Council of India, pp. 188–210. Available at:

https://pharmexcil.com/uploads/countryreports/Thailand_Market_Regulatory_report2020.pdf (Accessed: 25 May 2023).

Piasecki, J., Waligora, M. and Dranseika, V. (2018) 'Google Search as an Additional Source in Systematic Reviews', *Science and Engineering Ethics*, 24(2), pp. 809–810. Available at: <https://doi.org/10.1007/s11948-017-0010-4>.

Polit, D. and Beck, C. (2017) 'Nursing research: generating and assessing evidence for nursing practice', in *Nursing research: generating and assessing evidence for nursing practice*. Tenth. Philadelphia: Wolters Kluwer Health, p. 739.

Popay, J., Roberts, H. and Sowden, A. (2006) 'Guidance on the Conduct of Narrative Synthesis in Systematic Reviews A Product from the ESRC Methods Programme'. Available at: <https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf> (Accessed: 17 September 2023).

Portales, C. (2012) 'CELAC: a voice for Latin America and the Caribbean? The complex challenge of giving the region a stronger voice despite its many different cooperation and integration projects'. Norwegian Peacebuilding Resource Centre (NOREF). Available at: <https://www.files.ethz.ch/isn/137613/CELAC.pdf> (Accessed: 6 September 2022).

Prat, A.G. (2013) 'A practical overview of requirements for drug registration in Latin America', *Regulatory Rapporteur*, 10, pp. 5–11.

Precisionadvisors (2023) 'What You Need to Know About Latin American Pharmaceutical Markets and Access Pathways for 2023 and Beyond'. Precisionadvisors. Available at: <https://www.precisionadvisors.com/wp-content/uploads/2023/02/PRECISIONadvisors-LatinAm-Introduction-1.pdf> (Accessed: 1 June 2023).

Preston, C., Freitas, D.M. and Peña, J. (2020) 'Addressing the challenges of regulatory systems strengthening in small states.', *BMJ Global Health*, 5, p. e001912. Available at: <https://doi.org/doi:10.1136/bmjgh-2019-001912>.

PRISMA website (2023) *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) website, Transparent reporting of systematic reviews and meta-analyses*. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1> (Accessed: 17 September 2023).

Quinney, L., Dwyer, T.A. and Chapman, Y.B. (2016) 'Who, Where, and How of Interviewing Peers', *SAGE Open*, 6. Available at: <https://api.semanticscholar.org/CorpusID:147931218>.

Ralph, N., Birks, M. and Chapman, Y. (2015) 'The methodological dynamism of grounded theory', *International journal of qualitative methods*, 14(4), p. 1609406915611576.

Ramnarine, E. *et al.* (2020) 'Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions', *PDA Journal of Pharmaceutical Science and Technology*, p. pdajpst.2020.011734. Available at: <https://doi.org/10.5731/pdajpst.2020.011734>.

- Rao, K. *et al.* (2022) 'Future Health Spending in Latin America and the Caribbean: Health Expenditure Projections & Scenario Analysis'. Inter-American Development Bank. Available at: <https://publications.iadb.org/publications/english/viewer/Future-Health-Spending-in-Latin-America-and-the-Caribbean--Health-Expenditure-Projections--Scenario-Analysis.pdf> (Accessed: 1 June 2023).
- Rashid, Y. *et al.* (2019) 'Case Study Method: A Step-by-Step Guide for Business Researchers', *International Journal of Qualitative Methods*, 18, p. 1609406919862424. Available at: <https://doi.org/10.1177/1609406919862424>.
- Reggi, V. (2017) 'Medicines Regulatory Harmonization: International Collaboration as a Key to Improve Public Health', *Medicine Access @ Point of Care*, 1, p. maapoc.0000001. Available at: <https://doi.org/10.5301/maapoc.0000001>.
- Research and Markets (2023) *Vietnam Healthcare Providers Market Summary, Competitive Analysis and Forecast to 2027*. Available at: <https://www.researchandmarkets.com/reports/5632600/vietnam-healthcare-providers-market-summary> (Accessed: 26 May 2023).
- REUTERS (2020) *Brazil sits out leftist Latin American nations' body on anti-democracy fears*, *Reuters*. Available at: <https://www.reuters.com/article/us-brazil-diplomacy-celac/brazil-sits-out-leftist-latin-american-nations-body-on-anti-democracy-fears-idUSKBN1ZF2U9> (Accessed: 6 September 2022).
- Rev (2020) *Rev, Fast, accurate transcription services*. Available at: www.rev.com.
- Rieger, K. (2019) 'Discriminating among grounded theory approaches', *Nursing Inquiry*, 26(1), p. e12261.
- Riggirozzi, P. (2020) 'The Sobering Reality of Unpredicted Scenarios: COVID-19, Health and Regional Politics in Latin America', *United Nations University, Institute on Comparative Regional Integration Studies (UNU-CRIS)*, April. Available at: <https://cris.unu.edu/covid19-health-and-politics-latin-america> (Accessed: 14 September 2022).
- Roberts, K., Dowell, A. and Nie, J.-B. (2019) 'Attempting rigour and replicability in thematic analysis of qualitative research data; a case study of codebook development', *BMC Medical Research Methodology*, 19(1), p. 66. Available at: <https://doi.org/10.1186/s12874-019-0707-y>.
- Rodrigues, V. (2018) 'ICH Q12 AND BRAZILIAN POST APPROVAL PROCESS', 30 April. Available at: <https://www.linkedin.com/pulse/ich-q12-brazilian-post-approval-process-vanessa-rodrigues/> (Accessed: 25 August 2022).
- Rodriguez, H. and De Lucia, M.L. (2021) 'A Proposal of a Combined Convergence Regulatory Strategy Applied to Post-approval Changes by Latin American Countries, Reducing Workload and Allowing Continuous Improvement to Guarantee the Quality, Safety, and Efficacy of Medicines.', *Frontiers in medicine*, 8, p. 768376. Available at: <https://doi.org/10.3389/fmed.2021.768376>.
- Rodriguez, H., De Lucia, M.L. and Liberti, L. (2022) 'Cooperation Agreements, Memorandums of Understanding, and Letters of Intent as Instruments to Facilitate the Implementation of Reliance in Latin America', *Clinical Therapeutics*, 44(8), pp. 1107–1128.

- Rousseau, D.M., Manning, J. and Denyer, D. (2008) '11 Evidence in Management and Organizational Science: Assembling the Field's Full Weight of Scientific Knowledge Through Syntheses', *The Academy of Management Annals*, 2(1), pp. 475–515. Available at: <https://doi.org/10.1080/19416520802211651>.
- Rowlands, J. (2021) 'Interviewee Transcript Review as a Tool to Improve Data Quality and Participant Confidence in Sensitive Research', *International Journal of Qualitative Methods*, 20, p. 16094069211066170. Available at: <https://doi.org/10.1177/16094069211066170>.
- Rowley, J. (2014) 'Designing and using research questionnaires', *Management Research Review*, 37(3), pp. 308–330. Available at: <https://doi.org/10.1108/MRR-02-2013-0027>.
- Rubin, H. and Rubin, I. (2005) *Qualitative Interviewing (2nd ed.): The Art of Hearing Data*. 2nd edn. Thousand Oaks, California. Available at: <https://doi.org/10.4135/9781452226651>.
- Rugkåsa, J. and Canvin, K. (2011) 'Researching mental health in minority ethnic communities: reflections on recruitment.', *Qualitative health research*, 21(1), pp. 132–143. Available at: <https://doi.org/10.1177/1049732310379115>.
- Russell, M. (2020) 'The Association of Southeast Asian Nations (ASEAN) The EU's partner in Asia?' European Parliamentary Research Service (EPRS). Available at: [https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/659338/EPRS_BRI\(2020\)659338_EN.pdf](https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/659338/EPRS_BRI(2020)659338_EN.pdf).
- Ryan, R. (2013) 'Cochrane Consumers and Communication Review Group. "Cochrane Consumers and Communication Review Group: data synthesis and analysis"'. Available at: <http://cccr.org/sites/cccr.org/files/uploads/AnalysisRestyled.pdf> (Accessed: 20 September 2023).
- Saarijärvi, M. and Bratt, E.-L. (2021a) 'When face-to-face interviews are not possible: tips and tricks for video, telephone, online chat, and email interviews in qualitative research'. Oxford University Press.
- Saarijärvi, M. and Bratt, E.-L. (2021b) 'When face-to-face interviews are not possible: tips and tricks for video, telephone, online chat, and email interviews in qualitative research', *European Journal of Cardiovascular Nursing*, 20(4), pp. 392–396. Available at: <https://doi.org/10.1093/eurjcn/zvab038>.
- Sackman, J.E. (2013) 'Report from Latin America', *Pharmaceutical Technology*, 37(4). Available at: <https://www.pharmtech.com/view/report-latin-america> (Accessed: 7 June 2017).
- SADC website (2020) *SADC, History and Treaty*. Available at: <https://www.sadc.int/pages/history-and-treaty> (Accessed: 19 September 2020).
- SADC website (2022) *SADC Regional Indicative Strategic Development Plan (RISDP)*. Available at: <https://www.sadc.int/pillars/regional-indicative-strategic-development-plan-2020-2030> (Accessed: 1 May 2023).
- Sah, L.K., Singh, D.R. and Sah, R.K. (2020) 'Conducting Qualitative Interviews using Virtual Communication Tools amid COVID-19 Pandemic: A Learning Opportunity for Future Research.',

JNMA; *journal of the Nepal Medical Association*, 58(232), pp. 1103–1106. Available at: <https://doi.org/10.31729/jnma.5738>.

Salcedo, R. (2020) 'Regulatory Convergence -2020 Perspective', *OcyonBio Making Medicines Affordable*, January. Available at: <https://ocyonbio.com/regulatory-convergence-2020-perspective/> (Accessed: 13 September 2022).

Salganik, M.J. and Heckathorn, D.D. (2004) '5. Sampling and Estimation in Hidden Populations Using Respondent-Driven Sampling', *Sociological Methodology*, 34(1), pp. 193–240. Available at: <https://doi.org/10.1111/j.0081-1750.2004.00152.x>.

Salm, C. and Andre, M.C. (2017) 'Benefits of EU international trade agreements'. European Added Value Unit. Available at: https://www.europarl.europa.eu/RegData/etudes/BRIE/2017/603269/EPRS_BRI%282017%29603269_EN.pdf (Accessed: 15 July 2023).

Saunders, M.N.K., Lewis, P. and Thornhill, A. (2019) *Research Methods for Business Students*. 8th edn. New York: Pearson.

Schembri, N. and Jahić Jašić, A. (2022) 'Ethical issues in multilingual research situations: a focus on interview-based research', *Research Ethics*, 18(3), pp. 210–225. Available at: <https://doi.org/10.1177/17470161221085857>.

Seawright, J. and Gerring, J. (2008) 'Case Selection Techniques in Case Study Research: A Menu of Qualitative and Quantitative Options', *Political Research Quarterly*, 61(2), pp. 294–308. Available at: <https://doi.org/10.1177/1065912907313077>.

Seixas, B.V., Smith, N. and Mitton, C. (2018) 'The Qualitative Descriptive Approach in International Comparative Studies: Using Online Qualitative Surveys', *International journal of health policy and management*, 7(9), pp. 778–781. Available at: <https://doi.org/10.15171/ijhpm.2017.142>.

Selcuk, A.A. (2019) 'A Guide for Systematic Reviews: PRISMA', *Turkis Archvies of Otorhinolaryngology*, 57(1), pp. 57–58. Available at: <https://doi.org/10.5152/tao.2019.4058>.

Seth, A. (2022) 'Achieving Vaccines Regulatory Convergence and Agility in ASEAN: The Way Forward', *Asia Pacific Immunization Coalition*. Available at: https://medicine.nus.edu.sg/apic/wp-content/uploads/sites/28/2022/05/APIC_Regulatory-Harmonization_Policy_Brief_Final.pdf (Accessed: 6 December 2023).

Shahidi, F.V. (2010) 'Globalization From Below: Health, Pharmaceuticals, Cuba and Red Scares', *Undercurrent Journal: The Canadian Undergraduate Journal of Development Studies*, 7(2), pp. 33–41.

Shapka, J.D. *et al.* (2016) 'Online versus in-person interviews with adolescents: An exploration of data equivalence', *Computers in human behavior*, 58, pp. 361–367.

Shenton, A. (2004) 'Strategies for Ensuring Trustworthiness in Qualitative Research Projects', *Education for Information*, 22, pp. 63–75. Available at: <https://doi.org/10.3233/EFI-2004-22201>.

Silva, G., Cabello, J.R. and Gaban, T. (2018) 'Overview of ICH guidelines acceptance in Latin America'. SINDUSFARMA, LATAM Regulatory Working Group, subgroup 4. Available at:

https://sindusfarma.org.br/cadastro/public/uploads/publicacoes/arquivos/135/Boletim_DAR_2018_ICH_GD_Layout_v5_28nov18.pdf (Accessed: 14 September 2022).

Singh, J. (2015) 'International conference on harmonization of technical requirements for registration of pharmaceuticals for human use.', *Journal of pharmacology & pharmacotherapeutics*, 6(3), pp. 185–187. Available at: <https://doi.org/10.4103/0976-500X.162004>.

Smith, J. (2023) 'Latin American Roundup: Regulators announce new training, convergence initiatives after Washington meeting', *Regulatory Focus, A RAPS Publication*. Available at: <https://www.raps.org/News-and-Articles/News-Articles/2023/7/Latin-American-Roundup-Regulators-announce-new-tra> (Accessed: 5 January 2024).

von Soest, C. (2022) 'Why Do We Speak to Experts? Reviving the Strength of the Expert Interview Method', *Perspectives on Politics*, 21, pp. 1–11. Available at: <https://doi.org/10.1017/S1537592722001116>.

Sofaer, S. (1999) 'Qualitative methods: what are they and why use them', *Health Service Research*, 34(5 (Pt 2)), pp. 1101–1118.

Squires, A. (2008) 'Language barriers and qualitative nursing research: methodological considerations.', *International nursing review*, 55(3), pp. 265–273. Available at: <https://doi.org/10.1111/j.1466-7657.2008.00652.x>.

Stanlick, S. (2011) 'Qualitative Research Series: Debating the Question Question', *Research Salad: mixed methods, tossed up fresh*, 10 December. Available at: <https://researchsalad.wordpress.com/2011/10/12/qualitative-research-series-debating-the-question-question/> (Accessed: 2 November 2023).

Stansfield, C., Dickson, K. and Bangpan, M. (2016) 'Exploring issues in the conduct of website searching and other online sources for systematic reviews: how can we be systematic?', *Systematic Reviews*, 5(1), p. 191. Available at: <https://doi.org/10.1186/s13643-016-0371-9>.

Startuphealth (2019) 'Mid-Sized Pharma Could Present a Unique Opportunity for Health StartUps Sizing Up the Market', February. Available at: <https://healthtransformer.co/mid-sized-pharma-could-present-a-unique-opportunity-for-health-startups-sizing-up-the-market-dddbdfef4301> (Accessed: 5 November 2023).

Statista (2023) 'Revenue of the worldwide pharmaceutical market from 2001 to 2022 (in billion U.S. dollars)'. Available at: <https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/> (Accessed: 1 June 2023).

Stedman-Bryce, G. *et al.* (2015) 'Medicines Transparency Alliance (MeTA) Evaluation', *e-Pact*. Available at: www.itad.com/wpcontent/uploads/2016/05/MeTA-Evaluation-Final-Report.pdf [Preprint].

Straka, R.J., Keohane, D.J. and Liu, L.Z. (2017) 'Potential Clinical and Economic Impact of Switching Branded Medications to Generics.', *American journal of therapeutics*, 24(3), pp. e278–e289. Available at: <https://doi.org/10.1097/MJT.000000000000282>.

Strauss, A. and Corbin, J. (1998) *Basics of qualitative research: Techniques and procedures for developing grounded theory, 2nd ed.* Thousand Oaks, CA, US: Sage Publications, Inc (Basics of qualitative research: Techniques and procedures for developing grounded theory, 2nd ed.), pp. xiii, 312.

Sukumaran, T. and Venkatesh, M.P. (2020) 'Regulatory requirements for post approval changes in Japan, Canada and Malaysia', *Research Journal of Pharmacy and Technology*, 13(6), pp. 2585–2590.

Svarch Perez, A.E., Sanchez-Henkel, A.N. and Alcocer Varela, J.C. (2023) 'Toward a Health Sovereign Latin America', *Progressive International*. Available at: <https://progressive.international/blueprint/ee5282c5-11df-4137-8f4e-d7fd050c02dd-cmo-construir-una-agencia-latinoamericana-de-medicamentos/en> (Accessed: 30 December 2023).

Swee-Hock, S., Lijun, S. and Wah, C.K. (2005) 'An Overview of ASEAN-China Relations', in *ASEAN-China Relations: Realities and Prospects*. ISEAS–Yusof Ishak Institute, pp. 1–18. Available at: <https://www.cambridge.org/core/books/aseanchina-relations/an-overview-of-aseanchina-relations/7D6F7C0A414F5ADD5D8BAFC95D625088>.

Taherdoost, H. (2022) 'How to Conduct an Effective Interview; A Guide to Interview Design in Research Study'.

Tami, C. (2023) 'Reliance- Towards a global regulatory standard', 17 July. Available at: https://www.casss.org/docs/default-source/cmc-strategy-forum-north-america/2023-summer-speaker-presentations/tami-cecilia-genentech-2023.pdf?sfvrsn=aabd211a_8 (Accessed: 5 January 2024).

Taneja, R., Chacko, C. and Kedar, G. (2018) 'An Assessment of Global Chemistry, Manufacturing and Controls (CMC) Regulatory Requirements in Low and Middle Income Countries', *WHO Drug Information*, 32(3), pp. 400–406.

Tanner Pharma Group (2022) 'A guide to the key pharma markets in Latin America'. Available at: <https://tannerpharma.com/wp-content/uploads/2022/10/LAC-A-Guide-to-the-Key-Pharma-Markets-in-LATAM.pdf> (Accessed: 1 June 2023).

Tawfik, G.M. *et al.* (2019) 'A step by step guide for conducting a systematic review and meta-analysis with simulation data', *Tropical Medicine and Health*, 47(1), p. 46. Available at: <https://doi.org/10.1186/s41182-019-0165-6>.

Tay, A. (2022) *Harzing's Publish or Perish tool 8.0*, Singapore Management University. Available at: <https://library.smu.edu.sg/topics-insights/harzing-publish-or-perish-tool-80> (Accessed: 25 September 2023).

Tellner (2020) 'ICH: Instilling harmony for 30 years and never more relevant than today', *The EFPIA View*. Available at: <https://www.efpia.eu/news-events/the-efpia-view/blog-articles/ich-instilling-harmony-for-30-years-and-never-more-relevant-than-today/> (Accessed: 13 January 2024).

Teo, H.S., Foerg-Wimmer, C. and Chew, P.-L.M. (2016) *Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia*. World Bank, Washington, DC. Available at: <https://doi.org/10.1596/26801>.

- theglobaleconomy.com (2023) 'Health spending per capita - South East Asia', *The Global Economy.com; Business and economic data for 200 countries*. Available at: https://www.theglobaleconomy.com/rankings/health_spending_per_capita/South-East-Asia/.
- Thomas, D.R. (2006) 'A General Inductive Approach for Analyzing Qualitative Evaluation Data', *American Journal of Evaluation*, 27(2), pp. 237–246.
- Thomas, G. (2019) *Case Study*. London: SAGE Publications, Inc., London. Available at: <https://doi.org/10.4135/9781526421036812890>.
- Thomas, J. and Harden, A. (2008) 'Methods for the thematic synthesis of qualitative research in systematic reviews', *BMC Medical Research Methodology*, 8(1), p. 45. Available at: <https://doi.org/10.1186/1471-2288-8-45>.
- Thorne, S. (2017) 'Metasynthetic Madness: What Kind of Monster Have We Created?', *Qualitative health research*, 27(1), pp. 3–12. Available at: <https://doi.org/10.1177/1049732316679370>.
- Timmermans, S. and Tavory, I. (2012) 'Theory Construction in Qualitative Research: From Grounded Theory to Abductive Analysis', *Sociological Theory*, 30(3), pp. 167–186. Available at: <https://doi.org/10.1177/0735275112457914>.
- Tominaga, T. (2020) 'Expert Commentary: Diverse Meanings of Regulatory “Convergence”', *Therapeutic Innovation & Regulatory Science*, 54(5), pp. 1138–1140. Available at: <https://doi.org/10.1007/s43441-020-00135-1>.
- Tongia, A. (2018) 'Landscape in the ASEAN Region', p. 2.
- TRAC services (2015) 'Individual Challenges and Harmonisation: The CMC Post approval Landscape in Argentina, Mexico and Colombia (TRAC is now part of Pharmalex)'.
- Tran, V.-T. *et al.* (2016) 'Point of data saturation was assessed using resampling methods in a survey with open-ended questions.', *Journal of clinical epidemiology*, 80, pp. 88–96. Available at: <https://doi.org/10.1016/j.jclinepi.2016.07.014>.
- Tranfield, D., Denyer, D. and Smart, P. (2003) 'Towards a Methodology for Developing Evidence-Informed Management Knowledge by Means of Systematic Review', *British Journal of Management*, 14(3), pp. 207–222. Available at: <https://doi.org/10.1111/1467-8551.00375>.
- Tudor, D. (2019) 'What does the future of pharmaceutical manufacturing look like?', *Centre for Process Innovation Limited (CPI)*. Available at: <https://www.uk-cpi.com/blog/the-future-of-pharmaceutical-manufacturing> (Accessed: 16 May 2023).
- Turney, S. (2022) 'Systematic Review | Definition, Examples & Guide. Scribbr.', 17 October. Available at: <https://www.scribbr.co.uk/research-methods/systematic-reviews/> (Accessed: 10 October 2023).
- Uman, L.S. (2011) 'Systematic reviews and meta-analyses.', *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent*, 20(1), pp. 57–59.
- University of South Australia (2023) *Keywords, Library Guide Systematic Review*. Available at: <https://guides.library.unisa.edu.au/SystematicReviews> (Accessed: 12 December 2023).

UPM Pharmaceuticals (2020) 'Which Big Pharma vs Small Pharma Companies Should You Work For?' Available at: <https://www.upm-inc.com/working-for-big-pharma-vs-small-pharma#:~:text=Big%20pharma%20usually%20refers%20to,with%20fewer%20than%20500%20employees>. (Accessed: 3 November 2023).

Valverde, J. (2014) 'Latin American pharmaceutical overview', *Pharmaceuticals Policy and Law*, 16, pp. 179–206. Available at: <https://doi.org/10.3233/PPL-140384>.

Vasileiou, K. *et al.* (2018) 'Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period', *BMC Medical Research Methodology*, 18(1), p. 148. Available at: <https://doi.org/10.1186/s12874-018-0594-7>.

Vasquez, A.G.T. (2021) *Risk based approach of Post- Approval changes in Central America and Dominican Republic, Identifying opportunities for Convergence with EMA and FDA*. Masters. University of the Western Cape. Available at: <http://hdl.handle.net/11394/8641>.

Veravithayanan, M. and Russell, P. (2009) 'THE EFFECT OF ASEAN HARMONIZATION ON PHARMACEUTICAL REGISTRATION', p. 1.

Vogel, D. (1998) 'The globalization of pharmaceutical regulation', *Governance An International Journal of Policy, Administration and Institution*, 11(1), pp. 1–22.

Wahyuni, D. (2012) 'The Research Design Maze: Understanding Paradigms, Cases, Methods and Methodologies', *Journal of Applied Management Accounting Research*, 10.

Ward, M. (2005) 'ICH Update, Developments and future directions, Pan American Conf. on drug regulatory harmonisation', March. Available at: https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=0CAQQw7AJahcKEwjAtavH0qH6AhUAAAAAHQAAAAAQAg&url=https%3A%2F%2Fwww3.paho.org%2Fenglish%2Fad%2Fths%2Fev%2FREDParf_IVConf-Annex2_Ward%2520-English-ICH.ppt&psig=AOvVaw2Rf2O_f8IZbgebtM9cx4FL&ust=1663704003045037 (Accessed: 15 May 2014).

Weisfeld, V. and Lustig, T. (2013) 'Overview of the Current Global Regulatory Landscape.', in *International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary*. Washington DC: National Academies Press (US). Available at: <https://www.ncbi.nlm.nih.gov/books/NBK174229/>.

Wellcome (2022) 'Strengthening regulatory systems in LMICs Improving the sustainability of the vaccine innovation ecosystem in Africa'. Available at: <https://wellcome.org/sites/default/files/2022-07/strengthening-regulatory-systems-in-low-and-middle-income-countries-improving-the-sustainability-of-the-vaccine-innovation-ecosystem-in-africa-final-compendium.pdf>.

WHO (2002) 'The Impact of implementation of ICH guidelines in non-ICH countries : report of a WHO meeting, Geneva, 13-15 September 2001'. Available at: <https://apps.who.int/iris/handle/10665/67272> (Accessed: 13 March 2014).

WHO (2015) *Guidelines on procedures and data requirements for changes to approved vaccines: Annex 4*. Technical Report 993, pp. 175–259. Available at:

<https://www.who.int/publications/m/item/procedures-and-data-requirements-changes-to-approved-vaccines-annex-4-trs-no-993> (Accessed: 1 May 2023).

WHO (2017) 'World Bank List of Economies'. Available at: https://cdn.who.int/media/docs/default-source/air-quality-database/aqd-2018/countryregion_2017.pdf?sfvrsn=e074a4bf_3.

WHO (2021) *Annex 11 Good regulatory practices in the regulation of medical products*. WHO Technical Report Series 55th. WHO. Available at: https://www.wto.org/english/tratop_e/trips_e/techsymp_290621/gaspar_pres2.pdf.

WHO website (2023) *A Framework for evaluating and publicly designating regulatory authorities as WHO Listed Authorities (WLA)*. Available at: <https://www.who.int/initiatives/who-listed-authority-reg-authorities> (Accessed: 1 November 2023).

Wikipedia (2022) 'Pacific Alliance', *Pacific Alliance*, July. Available at: https://en.wikipedia.org/wiki/Pacific_Alliance (Accessed: 24 August 2022).

Wileman, H. and Mishra, A. (2010) 'Drug lag and key regulatory barriers in the emerging markets', *Perspectives in clinical research*, 1(2), pp. 51–56.

Wittner, M., Theisen, D.M. and Metzner, B. (2019) 'The Asia Pacific region: Part 2: CMC requirements during new drug application and post-approval life-cycle-management in ASEAN member states', *Pharmazeutische Industrie*, 81, pp. 84–89.

Wojcicka-Swidarska, K. (2021) 'Understanding the regulatory complexities of Latin America [Interview] Article-Understanding the regulatory complexities of Latin America [Interview]'. Available at: <https://insights.figlobal.com/fi-global-connect-2021-programme/understanding-regulatory-complexities-latin-america-interview> (Accessed: 1 June 2023).

World Population Review (2023) 'Singapore Population', *Country Meter*. Available at: <https://worldpopulationreview.com/countries/singapore-population> (Accessed: 12 May 2023).

Yin, R.K. (2018) *Case Study Research and Applications: Design and Methods*. 6th edn. Thousand Oaks, California: SAGE Publications, Inc., London.

Yip, C., Han, N.-L.R. and Sng, B.L. (2016) 'Legal and ethical issues in research.', *Indian journal of anaesthesia*, 60(9), pp. 684–688. Available at: <https://doi.org/10.4103/0019-5049.190627>.

Yue, Y. (2022) *EU-Asean-China Relations: Focus on South China Sea and Climate Crisis*, Italian Institute for International Political Studies. Available at: <https://www.ispionline.it/en/pubblicazione/eu-asean-china-relations-focus-south-china-sea-and-climate-crisis-34180> (Accessed: 15 September 2022).

APPENDICES

Appendix 1: Systematic review search strings

Scopus

((TITLE-ABS-KEY (harmoni*e OR harmoni*ation OR streamlin* OR regionali* OR standardi* OR converg* OR globali* OR streamline OR "regulatory requirement*" OR pharmaceut* OR "pharmaceutical drug" OR medicine OR "pharmaceutical molecule" OR "small molecule")) AND ((TITLE-ABS-KEY ("post-approval variation" OR "post approval variation" OR "post approval change" OR "post-approval change" OR "chemistry,manufacturing and control*" OR "post approval" OR "post-approval")) OR (TITLE-ABS-KEY ("life cycle maintenance" OR "life-cycle maintenance" OR "life cycle management" OR "lifecycle management" OR "life-cycle management" OR "lifecycle maintenance" OR "lifecycle*")))) AND (TITLE-ABS-KEY (brazil OR argentina OR cuba OR mexico OR pandrah OR paho OR chile OR colombia OR latam OR "Latin America" OR cecmed OR anvisa OR anmat OR invima OR cofepris OR ispch OR asean OR malaysia OR singapore OR thailand)))

#31 - harmonisation terms

#32 markets incl ASEAN

#40 post approval terms

(#31 AND #40) = #43 444 articles

#43 AND #40 = 14 articles

Web of science

Harmonise terms (H)

harmoni*ation OR standardi*ation OR regionalisation OR globali*ation OR "regulatory requirement" OR pharmaceutical OR "small molecule" OR "pharmaceutical drug" OR streamline OR medicine OR "pharmaceutical product" OR converg* OR harmoni*e OR globali*e OR standardi*e

Markets (M)

brazil OR argentina OR cuba OR mexico OR pandrah OR paho OR chile OR colombia OR latam OR "Latin America" OR cecmed OR anvisa OR anmat OR invima OR cofepris OR ispch OR ASEAN OR Singapore OR Malaysia OR Thailand)

PAC (P)

"post-approval*" OR "post approval*" OR "post-approval variation*" OR "post approval variation*" OR "post approval change*" OR "post-approval change*" OR "chemistry, manufacturing and control*" OR "lifecycle management" OR "life-cycle management" OR "life cycle management" OR "life-cycle maintenance" OR "lifecycle maintenance" OR "life cycle maintenance"

(H AND P) = HP

HP AND M = 31

Medline is in web of science

Google scholar in Publish or Perish

"Latin America" OR LATAM OR Brazil OR Cuba OR Chile OR Colombia OR Mexico OR Argentina OR PAHO OR PANDRH OR ASEAN OR Malaysia OR Singapore OR Thailand OR "post approval" OR convergence OR harmonisation OR harmonization OR "regulatory convergence" OR harmonise OR harmonize OR regionalisation OR standardisation or "chemistry, manufacturing and control"

Google search

"Latin America" OR LATAM OR Brazil OR Cuba OR Chile OR Colombia OR Mexico OR Argentina OR PAHO OR PANDRH OR ASEAN OR Malaysia OR Singapore OR Thailand OR "post approval" OR convergence OR harmonisation OR harmonization OR "regulatory convergence" OR harmonise OR harmonize OR regionalisation OR standardisation or "chemistry, manufacturing and control"

Appendix 2: Template used in organising literature from systematic review

Article Title	Published Date	Abstract	Name of journal	Date of search	Comments

Appendix 3: LinkedIn and Facebook: Regulatory Affairs associated pages where advertisement was posted

LinkedIn Pages:

The Life Sciences Professionals Hub
Regulatory Affairs Professionals Society (RAPS)
Ex-Pfizer Employees
Professionals in the Pharmaceutical and Biotech Industry
GSK Employees and Alumni Network
Regulatory Affairs for Asia Pacific
ARPA- RAPanel
Pharmaceutical Executive Magazine
Latin America Biotechnology & Pharmaceutical Association
Reuters Events Pharma Latin America
Regulatory Affairs – Worldwide
Drug Regulatory Affairs
Global Regulatory
R&D Professional Networking
Regulatory Affairs Group (for Permanent and freelance professionals)
Latin America Biotechnology & Pharmaceutical Association
Regulatory Affairs, Drug Safety, Quality
Quality & Regulatory Network

Facebook Page:

Regulatory Affairs Reps

Appendix 4: Research Advertisement for LinkedIn and Facebook

PhD Research: Request for assistance

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

My name is Ivy Essiam I would like to invite you to take part in a PhD research study to be interviewed by Videoconference or Teleconference for up to an hour and half maximum at a convenient time, about your views and experience. If you are unavailable for interview, you can also email your responses to the questions. The research is jointly organised by The Organisation for Professionals in Regulatory Affairs (TOPRA) and Cardiff University.

I'm particularly interested in Regulatory Affairs professionals with submissions and strategy experience in Chemistry, manufacturing and control (CMC) and/or market experience covering Brazil, Argentina, Colombia, Cuba, Mexico, Chile, Singapore, Malaysia and Thailand. I am also interested in speaking to Health Authority Assessors/Reviewers from these markets.

The research focuses on streamlining regulatory requirements for 5 supply critical post-approval CMC variations relating to the Drug product, in the above-mentioned Latin markets.

The variations are: i) Change in manufacturing site (add or replace); ii) change in shelf life; iii) change in storage condition; iv) change in formulation (from tablet); v) change in manufacturing method all in relation to small molecules (exclusion: generics/biologics/biosimilars/vaccines/medical devices)

The research's aims are threefold:

- a) To compare and contrast successes in harmonisation in Singapore, Malaysia & Thailand with the Latin markets.
- b) To explore which approach will work better in the Latin markets: harmonisation or convergence.
- c) To subsequently engage the Latin Drug Regulatory Authorities towards agreeing requirements/review processes and review timelines for the 5 post-approval CMC variations.

Your insight in these areas is highly valued and your participation would be greatly appreciated.

Participation is completely voluntary and you may withdraw at any stage. Quotes and findings will be anonymised and your privacy will be protected at all stages of the research.

If you are interested in participating or would like further information please email [email]. I'd like to finalise this stage of interviews by 31st March 2021, so a quick response would be appreciated.

As part of the research or if you are unavailable for interview but would still like to contribute, I would appreciate if you could provide input into the regulatory requirements for any of the above listed variations of any of the listed markets. Kindly use this link to provide the information:

<https://www.surveymzmo.com/s3/4675589/PhD-Research-Drug-Product-CMC-Requirements-LATAM>

Thank you for your help.

Ivy Essiam

Appendix 5: Participant Information Sheet

PARTIPANT INFORMATION SHEET

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

You are being invited to take part in a research project. Before you decide whether or not to take part, it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish. Thank you for reading this.

What is the purpose of the research project?

In Latin America, there are on-going initiatives to support regional technical cooperation initiatives to strengthen national regulatory capacities, however not much is known regarding initiatives to streamline post-licensing Chemistry, manufacturing and control requirements. In the post-licensing area, pharmaceutical companies wanting to increase manufacturing efficiencies and enhanced supply chains, have to comply with various technical requirements in order to implement these changes in a particular market. The various regulatory requirements, coupled with different review timelines across the markets, can be very complex and challenging. These factors can delay patient access and burden both the pharmaceutical company and the National Regulatory Authority (NRA). This presents an opportunity for simplification to reduce the risks of non-compliance across markets and prevent shortage of supply to the patient, the end-goal being improved access by the patient.

The aims of this research are twofold:

- 1) To explore the priority and any initiatives to streamline CMC variations within Latin America via *harmonisation (same set of guidelines sometimes adopted as legislation) or *convergence (voluntary process where requirements become similar over time), focusing on the PAHO designated National Reference Agencies of regional reference (NRAr), namely: ANMAT (Argentina), ANVISA (Brazil), ISP (Chile), INVIMA (Colombia), CECMED (Cuba) and COFEPRIS (Mexico), for five supply-critical post-approval variations.
- 2) To explore the successes in streamlining post-approval variations in Singapore, Thailand and Malaysia through the ASEAN network and assess whether any lessons can be learnt and applied to the Latin America markets.

The post- approval variations to be explored are changes in drug product for small molecules in the following areas:

- manufacturing site
- formulation
- storage condition
- shelf-Life
- manufacturing method

(Exclusion: generics/biologics/biosimilars/vaccines/medical devices/veterinary medicines)

The estimated completion date of the research is September 2022.

*Full Definitions

HARMONISATION: The agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or region. May also influence the review process and assessment and can be adopted as legislation.

CONVERGENCE: Within the APEC context, can be defined as “a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures.

1. Why have I been invited to take part?

You have been chosen to participate in this study because you are a Regulatory Affairs professional or part of a Regulatory network or association with expertise and extensive knowledge in Chemistry, Manufacturing and Control (CMC) variations and/or knowledge of the regulatory landscape in the markets under review. By engaging with you, I hope to gain more insight into the challenges, opportunities and successes that these markets have had so far in working towards common requirements and processes for post-approval variations. Also to understand any changes in guidelines for CMC variations in these markets.

2. Do I have to take part?

No, your participation in this research project is entirely voluntary and it is up to you to decide whether or not to take part. If you decide to take part, we will discuss the research project with you and ask you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights.

You are free to withdraw your consent to participate in the research project at any time, without giving a reason, even after signing the consent form.

The information sheet will be emailed to you together with a consent form. You will need to sign the consent form to record your agreement to take part. This should be signed and returned within 2 weeks and before you participate.

3. What will taking part involve?

You will be asked to participate in a one-to-one or group interview, mainly via a web-based platform (Zoom or Microsoft Teams). The interview will be video or audio recorded, depending on your preferences. It can also be via telephone which will be audio recorded. The interviews will explore the participants' experiences in working with these markets or working on these CMC variations. The interviews may last up to an hour and a half. It is possible that after the interview, you may be contacted by email or telephone to provide brief clarification of any issues that remain unclear. You will receive either a full transcript or summary of the interview and may make edits to ensure correct interpretation.

If you are unavailable for interview, you can also respond to the questions via email, this should take about 30-45 minutes. Upon contact, participants will be asked whether they prefer an interview or would like to respond by email. If the preference is email, the questions

will be emailed to the participant. Participants are encouraged to respond within 2 weeks so the research timelines can be met.

4. Will I be paid for taking part?

No. You should understand that any data you give will be as a gift and you will not benefit financially in the future should this research project lead to the development of a new method/test/assessment.

5. What are the possible risks of taking part?

For Regulatory Affairs professionals, there are no identified disadvantages or risks of taking part in this study. A disclaimer will be included stating that the participant's views are their own and not those of the companies or organisations they work for or represent. All information given will be confidential and remain so in all reports arising from the research. Any quotes will be anonymised.

6. What are the possible benefits of taking part?

There will be no direct advantages or benefits to you from taking part, but the information we get from the study will help increase the understanding of the regulatory landscape of these markets in relation to CMC post-approval variations and inform National Regulatory Authorities and Pharmaceutical companies/bodies.

7. Will my taking part in the study be kept confidential?

All information which is collected from or about you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data' (below) for further information.

8. What will happen to my Personal Data?

The following personal data will be collected/used in the research study: name, job role; years worked in role; email. These details however, will be anonymized through the use of a research code for each participant.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. Further information about Data Protection, including:

- your rights
- the legal basis under which Cardiff University processes your personal data for research
- Cardiff University's Data Protection Policy
- how to contact the Cardiff University Data Protection Officer
- how to contact the Information Commissioner's Office

may be found at <https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection>

Copies of the above-mentioned documentation and privacy notices can be provided upon request.

Rev.com will be used as a transcription service for the audio only, hence your personal data will be transferred outside the European Economic Area. Rev.com adhere to data protection and GDPR guidelines, their confidentiality and security policy can be found here: <https://www.rev.com/security>

Within 2 weeks, the research team will anonymise all the personal data it has collected from, or about you in connection with this research project, with the exception of your consent form.

Your consent form will be retained for 1 year after publication of the final report, and may be accessed by members of the research team and, where necessary, by members of the University's governance and audit teams. Anonymised information will be kept for a minimum of 1 year after publication of the final report but may be retained indefinitely, where it is likely to have continuing value for research purposes.

If you withdraw from the study, we will keep the information about you that we have already obtained. It will not be possible to withdraw any anonymised data that has already been published or in some cases, where identifiers are irreversibly removed during the course of a research project, from the point at which it has been anonymized

9. What happens to the data at the end of the research project?

The data provided may be used in research publications however any personal data will be removed before any form of sharing takes place. All quotes will be anonymized.

10. What will happen to the results of the research study?

The results are likely to be published in 2022. It is our intention to publish the results of this research project in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation. Verbatim quotes may be used. A summary of the results will also be made available to participants after the study.

What if there is a problem?

If you wish to complain, or have grounds for concerns about any aspect of the manner in which you have been approached or treated during the course of this research, please contact any of the below listed supervisors or the associated body, TOPRA.

Supervisor 1: Dr James Coulson Cardiff University [Role/Title] [Address] Tel: E-mail: Signature	Supervisor 2: Fraser Stodart Biogen [Role/Title] [Address] Tel: Direct: Email: Signature
---	--

Associated bodies:

Samantha Alsbury, The Organisation of Professionals in Regulatory Affairs Ltd (TOPRA)
email:

If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action, but you may have to pay for it.

11. Who is organizing and funding this research project?

The research is jointly organised by The Organisation of Professionals in Regulatory Affairs (TOPRA) and Ivy Essiam (student researcher); Dr James Coulson (supervisor) of Cardiff University. It is sponsored by Cardiff University.

12. Who has reviewed this research project?

This research project has been reviewed and given a favourable opinion by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

13. Further information and contact details

Should you have any questions relating to this research project, you may contact us during normal working hours:

Supervisor : Dr James Coulson

[Role/Title]

[Address]

Tel: Direct:

Email:

Thank you for considering to take part in this research project. If you decide to participate, you will be given a copy of the Participant Information Sheet and a signed consent form to keep for your records.

Appendix 6: Informed Consent

CONSENT FORM

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

SREC reference and committee: 1617-36 Pharmacy Ethics

Name of Chief/Principal Investigator: Ivy Essiam

**Please
initial box**

I confirm that I have read the information sheet dated June 2021 v15 for the above research project.	
I confirm that I have understood the information sheet dated June 2021 v15 for the above research project and that I have had the opportunity to ask questions and that these have been answered satisfactorily.	
I understand that my participation is voluntary and I am free to withdraw at any time without giving a reason and without any adverse consequences (e.g. to medical care or legal rights, if relevant). I understand that if I withdraw, information about me that has already been obtained may be kept by Cardiff University.	
I understand that data collected during the research project may be looked at by individuals from Cardiff University (supervisors), where it is relevant to my taking part in the research project. I give permission for these individuals to have access to my data.	
I consent to the processing of my personal information [name, place of work, job title, years worked] for the purposes explained to me. I understand that such information will be held in accordance with all applicable data protection legislation and in strict confidence, unless disclosure is required by law or professional obligation.	
I understand who will have access to the personal information provided, how the data will be stored and what will happen to the data at the end of the research project.	
Please <u>circle</u> your preference: I consent to being audio recorded/video recorded for the purposes of the research project and I understand how it will be used in the research	
I understand that I have the option to partake in a group interview. ONLY INITIAL IF THIS APPLIES	

I consent to participating in a group interview. ONLY INITIAL IF THIS APPLIES	
If I partake in a group interview, I understand that I need to keep the discussion confidential and not disclose details of the group interview to others	
I understand that anonymised excerpts and/or verbatim quotes from the interview/group interview may be used as part of the research publication.	
For individual interviews I understand that I have the option to respond to the questions by email (in my chosen medium) and consent to this, if applicable.	
I understand that there will be no payment or benefit for my participation	
I will receive either a full transcript or summary of my interview and may make edits I feel necessary to ensure the effectiveness of any agreement made about confidentiality and to ensure correct interpretation	
I understand how the findings and results of the research project will be written up and published.	
I agree to take part in this research project.	

Name of participant (print)

Date

Signature

(Electronic signatures are acceptable)

IVY ESSIAM

Name of person taking consent
(print)

Date

Signature

RESEARCHER

Role of person taking consent
(print)

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

Appendix 7: Gatekeeper Recruitment email

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

Dear [Gatekeeper name]

My name is Ivy Essiam and I'm currently undertaking a research project for my PhD at Cardiff University, approved by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

The research project will use questionnaires and follow up interviews to gain information from personnel of the following National Regulatory Authorities (NRA) [researcher to state chosen Latin America or South East Asian markets] about the current regulatory landscape of Chemistry, Manufacturing and Control (CMC) variations and initiatives to streamline CMC requirements in these markets.

Due to your experience and extended network, I am writing to solicit your help in recruiting NRA personnel who satisfy at least one of the criteria listed:

- a) deal with review of CMC variations;
- b) are involved in policy & intelligence
- c) interact with [PAHO/PANDRH/ASEAN- researcher to amend as required] or harmonisation initiatives across the region or outside

to gain their personal insights into the topic.

Kindly send the attached recruitment email together with the attached participant information sheet to the participants.

A follow-up email has also been provided so participants can be reminded **a week** after ending the first email, however potential participants should not be coerced into partaking in the study. It is completely voluntary to participate.

Participants will give consent for the questionnaire as part of the questionnaire itself. The participant can then contact the researcher directly if they have any questions or if they are willing to take part in a follow-up individual interview.

Kind Regards,
Ivy Essiam
PhD Student
Cardiff University

Appendix 8: NRA Participant Recruitment email

Email subject: Invitation to participant in Research Study

Dear Sir/Madam,

I am sending this email on behalf of Ivy Essiam, a PhD Student at Cardiff University, UK.

Ivy is currently carrying out research relating to streamlining regulatory requirements for 5 supply-critical post-approval CMC variations within [Latin America/South East Asia] namely, [country name- **researcher to insert specific market for each letter**] is one of the chosen markets. The other markets considered in the research are [other countries to be listed by researcher]

The variations are:

- i) Change in drug product manufacturing site
- ii) change in shelf life
- iii) change in storage condition
- iv) change in formulation
- v) change in manufacturing method

The research's aims are twofold:

- 3) To explore the priority and any initiatives to streamline CMC variations within Latin America via *harmonisation (same set of guidelines sometimes adopted as legislation) or *convergence (voluntary process where requirements become similar over time), focusing on the PAHO designated National Reference Agencies of regional reference (NRAR), namely: ANMAT (Argentina), ANVISA (Brazil), ISP (Chile), INVIMA (Colombia), CECMED (Cuba) and COFEPRIS (Mexico), for five supply-critical post-approval variations.
- 4) To also explore the successes in streamlining post-approval variations in Singapore, Thailand and Malaysia through the ASEAN network and assess whether any lessons can be learnt and applied to the Latin America markets.

Regulatory Affairs professionals with submissions and strategy experience in Chemistry, manufacturing and control (CMC) and/or market experience covering the listed markets have been interviewed as part of the research.

Ivy is now seeking National Regulatory Authority officials who either review CMC variations or deal with policy & intelligence or interact with PANDRH or harmonisation initiatives across the region or outside, to gain their personal insights into the topic. Your experience and insight in these areas is highly valued and your participation would be greatly appreciated.

Participants are kindly asked to fill in the below questionnaire with a voluntary option to be interviewed as a follow-up:

[LATAM NRA questionnaire: <https://survey.alchemer.com/s3/6349360/Health-Authority-Responses-Streamlining-CMC-Requirements>]

[South East Asian NRA questionnaire: <https://survey.alchemer.com/s3/6377751/Health-Authority-Responses-Streamlining-CMC-Requirements-ASEAN>]

An email reminder will be sent in a week's time

Participation is completely voluntary and you may withdraw at any stage. Quotes and findings will be anonymised and your privacy will be protected at all stages of the research.

If you would like further information on the research study, please contact Ivy by emailing [email].

The information sheet for the research is attached, kindly take time to read it. Consent for the questionnaire will be given within the questionnaire.

Yours Sincerely,
[Gate Keeper]

Appendix 8.1 NRA Participant 2-week Follow up email

Email subject: Follow-up: Invitation to participant in Research Study

Dear Sir/Madam,

Last week, I sent you an email inviting you to partake in a Research Study relating to the regulatory landscape for post-approval CMC variations in [researcher to state markets].

This is just a follow up email to remind you to fill in the online questionnaire if you are interested in taking part:

[LATAM NRA questionnaire: <https://survey.alchemer.com/s3/6349360/Health-Authority-Responses-Streamlining-CMC-Requirements>]

[South East Asian NRA questionnaire: <https://survey.alchemer.com/s3/6377751/Health-Authority-Responses-Streamlining-CMC-Requirements-ASEAN>]

The Information sheet is re-attached for your kind information.

Please ignore this email if you have already filled in the questionnaire.

Yours Sincerely,
[Gate keeper]

Appendix 9: LATAM NRA Questionnaire

Health Authority Responses: Streamlining CMC Requirements

Introduction & Consent

Introduction to study

In the post-licensing area, pharmaceutical companies wanting to increase manufacturing efficiencies and enhanced supply chains, have to comply with various technical requirements in order to implement these changes in a particular market. The various regulatory requirements, coupled with different review timelines across the markets, can be very complex and challenging. These factors can delay patient access and burden both the pharmaceutical company and the regulatory agency. This presents an opportunity for simplification to reduce the risks of non-compliance across markets and prevent shortage of supply to the patient, the end-goal being improved access by the patient.

This questionnaire would like to understand the chemistry, manufacturing and control (CMC) landscape and explore any activities to streamline CMC variations within Latin America, focusing on the PANDRH designated National Regulatory Agencies of Regional Reference (NRAR), namely: Argentina, Brazil, Chile, Colombia, Cuba and Mexico. The study focuses on 5 Drug product CMC variations for small molecules, which are:

Change in manufacturer;

Change in shelf life;

Change in storage condition;

Change in formulation

Change in manufacturing method.

The main question to be explored is whether these markets seek to harmonise or converge for CMC variations.

***DEFINITIONS:**

HARMONISATION: The agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or region. May also influence the review process and assessment and can be adopted as legislation.

CONVERGENCE: Within the APEC context, can be defined as “a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures.

The opinions are solely the participant's and do not reflect the official position of the Agency.

The participant can be provided a copy of the report either by providing an email address or through the gatekeeper. Please indicate. The participant will be given a code with which they can use to request the report.**

Instructions for filling out this questionnaire

Kindly provide the best responses or use the free text fields to elaborate further.

Please note that where free text is allowed, participants can respond in their native language. The survey will take approximately 20-30 minutes to complete.

***This questionnaire can be saved and returned to at a later time.**

Researcher's name: Ivy Essiam Researcher's email:[email]

Consent

By filing in this questionnaire, I consent to the following:*

I have read the Information sheet and have had the opportunity to ask questions. I understand that I am free to contact the researcher with any questions I may have in the future (Researcher's email provided above).

I understand that my participation is voluntary and I am free to withdraw at anytime without giving any reason.

If I decide to withdraw, I give permission for any data gathered up to my withdrawal to be used in the study

I understand that there will be no benefit or payment for my participation.

I understand that I will be provided with a report of the results of the study is completed.

I agree to take part in this study

General Information

1) Please indicate the name of your National Regulatory Authority

Argentina - ANMAT

Brazil - ANVISA

Chile - ISP

Colombia - INVIMA

Cuba - CECMED

Mexico - COFEPRIS

2) Describe your role in the Agency. Does it involve working with CMC variations or dealing with policy & intelligence or harmonisation initiatives?

3) How many years have you worked in the Agency?

4) How many years have you been in this role?

About the Agency

5)

Indicate which of the following best describes this agency.

Autonomous agency, independent from the Health Ministry administration

Operates within the administrative structure of the Health Ministry

6) In the recent report on 'Regulatory System Strengthening in the Americas', the number of workers in the Agencies has been cited.

Please state roughly how many staff work to review CMC variations out of the total Agency staff (if known).

If unsure, please state 'unsure'.

7) Does your agency collaborate with other NRAR (Argentina, Brazil, Chile, Colombia, Cuba, Mexico)? (Collaboration means the exchange of technical information, existence of confidentiality agreements or Memorandum of understanding, share best practices etc)

8) Do any of these collaborations involve discussions on CMC variations? If yes, please elaborate (what specifically is being discussed, what outcomes are expected?).

Interaction with Regulatory Networks: MERCOSUR, PANDRH, WHO, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

Definitions: **1. MERCOSUR:** Mercado Común del Sur; **2. PANDRH:** Pan American Network for Drug Regulatory Harmonization; **3. WHO:** World Health Organisation; **4. ICH:** The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

9) What is the role of MERCOSUR in the region? Is the Agency actively involved with MERCOSUR or hoping to join in future?

10) In your opinion, does MERCOSUR have plans to streamline CMC variations within the region? Is the Agency part of this initiative, if applicable?

11) What is the role of PANDRH in the region? How is the Agency involved with PANDRH?

12) Proposed PANDRH projects

As per your knowledge, has the agency proposed a project to PANDRH for alignment of CMC requirements within the region?

Yes

No

If Yes, why?

If No, why?

13) The Agency and ICH

Which of the following applies to the Agency.

ICH observer

ICH member

In the process of becoming a member

In the process of becoming an observer

No plans to join ICH

In your opinion, does the Agency seek to adopt ICH guidelines and hence ICH CMC requirements?

Please answer Yes or No and give reasons why you believe the Agency seeks to adopt or not.

14) As per your knowledge, are there any WHO initiatives to streamline CMC requirements?

Yes

No

Not sure

15) If you answered 'YES' to Q14, in your opinion, is the Agency involved in WHO's initiative to streamline CMC requirements?

Yes

No

Not sure

16) In your opinion, would the Agency envision the creation of a central regulatory body for Latin America or in sub-regions of Latin America? (similar to EMA in Europe)

YES

NO

Not sure

17) In your opinion, would PANDRH or MERCOSUR be suitable for such a task ie central regulatory body? Please elaborate

About CMC Variations

This section will review 6 Drug Product CMC variations:

Change in Manufacturer, Change in formulation; change in manufacturing method, change in storage condition; change in shelf life.

18) How does the Agency categorise the listed variations (Major or minor as per your NRA's definitions)

	Change in Drug product manufacturer (addition or replacement)	Change in manufacturing method	Change in storage condition	Change in shelf life	Change in formulation
Category					

19) Review timelines

What is the stipulated/published review timeline for the following variations (in months):

Change in Drug product manufacturer (addition or replacement):

Change in manufacturing method:

Change in storage condition:

Change in shelf life:

Change in formulation:

20) What is the average review timeline (actual) for each of the listed variations (in months):

Change in Drug product manufacturer (addition or replacement):

Change in manufacturing method:

Change in storage condition:

Change in shelf life:

Change in formulation:

21) In your opinion, is the Agency working towards improving the current review timelines for CMC variations?

Yes No Maybe Not sure

22) In your opinion, are there any improvements that the agency is implementing / could implement to improve timelines?

23) In your opinion, the Agency's current CMC Requirements are more aligned to:

FDA guidelines

EMA guidelines

ICH guidelines

WHO guidelines

Local guidelines

Other

24) If 'Local guidelines' or 'Other' was selected from Q23, please elaborate:

25) The Agency's CMC variation requirements/guidelines have been updated within the last:

Within the last year

Within the last 2 years

Within the last 3-5 years

More than 5 years ago

More than 10 years ago

Never been updated since the Agency's inception

Not sure

26) In your opinion, what triggered the review of the requirements? eg out of date requirements, change in global landscape, local update with or without reference to the global landscape? Please elaborate.

27) If there have been no review of the requirements, please elaborate why this is the case in your opinion

28) Does the agency have any reliance pathways for reviewing CMC variations (using reference agencies such as US FDA, EMA, other NRAR, etc.)? If yes, please state which reference markets.

29) If you answered 'Yes' to Q28 , please elaborate on 'HOW' this reliance works (eg. use of approval letter, use of reference market package; review of questions raised by reference market etc)

30) Please choose a response based on your opinion.

Streamlining of CMC variations is a priority for the Agency:

Strongly disagree	Moderately disagree	Slightly disagree	Neutral	Slightly
agree	Moderately agree	Strongly Agree	Not applicable	

31) Please choose a response based on your opinion.

The Agency would like CMC requirements to be streamlined via harmonisation within the region (regulators across Latin America agree on the same requirements):

Strongly disagree	Moderately disagree	Slightly disagree	Neutral	Slightly
agree	Moderately agree	Strongly agree	Not applicable	

32) Please choose a response based on your opinion.

The Agency believes it will be beneficial to streamline CMC requirements within the region:

Strongly disagree	Moderately disagree	Slightly Disagree	Neutral	Slightly
agree	Moderately agree	Strongly agree	Not applicable	

33) Please choose a response based on your opinion.

The Agency would like to align CMC requirements to international guidelines (convergence)

Strongly Disagree	Moderately disagree	Slightly disagree	Neutral	Slightly
agree	Moderately agree	Strongly agree	Not applicable	

34) The Agency believes it will be beneficial to align CMC requirements to international guidelines

Strongly disagree	Moderately disagree	Slightly disagree	Neutral	Slightly
Agree	Moderately agree	Strongly agree	Not applicable	

35) Please elaborate on your answers to Q30 to Q34

36) Convergence can occur in various ways. Three processes are listed below.

Definitions:

Reliance: act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision

Recognition: the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. OR acceptance of regulatory result/decision from another NRA based on a legal framework

Cooperation: Process of interaction among drug regulatory authorities in regulating medicines in the forms of information sharing, work sharing, reliance, and recognition.

For your agency, which of these processes are they seeking to follow:

Reliance

Cooperation

Recognition

Other

Not applicable

If other, please state which other process the Agency is using

37) Drivers/Reasons

In your opinion:

What does the Agency consider to be the drivers or reasons for wanting to streamline within the region?

What does the Agency consider to be the drivers or reasons for wanting to streamline to international requirements?

38) Challenges with streamlining within the region

In your opinion:

Does the Agency envisage challenges with streamlining within the region

Yes

No

Not sure

Please elaborate

39) Challenges aligning with international requirements

In your opinion:

Does the Agency envisage challenges in streamlining with international requirements?

Yes

No

Not sure

Please elaborate

40) In your opinion, what is the Agency's view, on the likely direction of the LATAM region in terms of streamlining CMC Variations:

Harmonise within the region

Converge to international standards

Transparency

41) Industry comments are actively sought in relation to review of CMC requirements

Always Very often Sometimes Rarely/ Never

42) Please elaborate your answer to Q41

43) Industry comments are accepted in relation to review of CMC requirements
Always Very often Sometimes Rarely Never

44) Regulatory Affairs professionals with LATAM experience were interviewed and reported that the Agency requirements were sometimes over and beyond what is expected by ICH for example.

Do you agree with this observation?

Yes

No

Not aware

Do you still envision the need for local requirements outside the ICH requirements?

Yes

No

Maybe

What local factors do you think possibly drive the request for regional or market specific documentation not covered by international guidelines (such as ICH requirements)?

45) In your opinion, when different assessors in the Agency evaluate the same submission packages (same product type & variation), the results of the assessment will always be the same.

Agree (there is standardization among different assessors)

Disagree (similar submission packages can lead to different requests for documentation, depending on the assessor)

46) If you agree to Q45, how does the Agency ensure the standardized assessment?

47) If you disagree to Q45, what do you think causes these differences in assessment?

48) Interview Request

Would you be interested in being interviewed to elaborate further? *A Spanish/Portuguese translator can be made available for the interview upon request and by consent.

Yes

No

If yes, kindly provide your name and email address

Thank You!

Thank you for filling in the questionnaire. Your response is very important to us. If you indicated a preference to be interviewed, the researcher will be in touch in due course.

Appendix 10: ASEAN NRA Questionnaire

Health Authority Responses: Streamlining CMC Requirements ASEAN

Introduction & Consent

Consent

By filing in this questionnaire, I consent to the following:*

I have read the Information sheet and have had the opportunity to ask questions. I understand that I am free to contact the researcher with any questions I may have in the future (Researcher's email provided above).

I understand that my participation is voluntary and I am free to withdraw at anytime without giving any reason.

If I decide to withdraw, I give permission for any data gathered up to my withdrawal to be used in the study

I understand that there will be no benefit or payment for my participation.

I understand that I will be provided with a report of the results of the study when completed if indicated

I agree to take part in this study

General Information

1) Please indicate the name of your Health Agency

HSA - Singapore

FDA - Thailand

NPRA- Malaysia

2) Describe your role in the Agency. Does it involve working with CMC variations or dealing with policy & intelligence or harmonisation initiatives?

3) How many years have you worked in the Agency?

4) How many years have you been in this role?

About the Agency

5)

Indicate which of the following best describes this agency.

Autonomous agency, independent from the Health Ministry administration

Operates within the administrative structure of the Health Ministry

6) Size of agency - Please state how many staff work at the Agency.

7) Please state how many staff work to review CMC variations out of the total Agency staff.

ASEAN Common Technical Requirements (ACTR)

8) In 1999 PPWG was set up with the objective to develop a harmonisation scheme for pharmaceuticals. Did this initiative mean for markets to 'totally' align with the ACTR?

Yes

No

Not sure

9) Please elaborate on Q8

10) Was there a level of flexibility with the requirements? If yes, please explain why this flexibility was given and what that flexibility meant for an ASEAN member.

11) What was the basis for the ACTR CMC requirements?

ICH guidelines

WHO guidelines

EMA guideline

Other

12) if you answered 'other', please elaborate

13) Based on the initial PPWG objective, for harmonised CMC requirements/classifications, what level of success would you say has been achieved?

0 _____ [] _____ 100

14) Please elaborate on your response for Q13

15) How was agreement achieved on the CMC variation requirements & classifications?

16) Did a specific market initiate discussions on CMC requirements? If yes, was there a reason? Please elaborate the reason.

17) Has the ACTR been revised since initial agreement? If yes, when and what was the driver?

18) What drives the differences between ACTR and your local requirements & classifications?

19) How does the Agency categorise the listed variations?

	Change in Drug product manufacturer (addition or replacement)	Change in manufacturing method	Change in storage condition	Change in shelf life	Change in formulation
--	--	---------------------------------------	------------------------------------	-----------------------------	------------------------------

Category					
----------	--	--	--	--	--

20) Review timelines

What is the stipulated/published review timeline for the following variations in your market?

Change in Drug product manufacturer (addition or replacement):

Change in manufacturing method:

Change in storage condition:

Change in shelf life:

Change in formulation:

21) What is the average review timeline (actual) for each of the listed variations in your market?

Change in Drug product manufacturer (addition or replacement):

Change in manufacturing method:

Change in storage condition:

Change in shelf life:

Change in formulation:

22) In your opinion, is the Agency looking to enhance the 'actual' review timelines. If yes, how does the Agency plan to do this?

23) What challenges, if any, were overcome to implement the CMC guidelines in your market?

24) Does the agency plan to totally align the CMC variations requirements with the ACTR or will local requirements remain?

25) How has the ACTR especially CMC variation guidelines been beneficial to your market?

26) What lessons can other initiatives learn from ASEAN, ACTR and its processes?

27) Would you agree that CMC requirements are more converged than harmonised to the ACTR within the ASEAN region?

Interview Request

28) Interview Request

Would you be interested in being interviewed to elaborate further?

Yes

No

If yes, kindly provide your name and email address

Thank You!

PARTIPANT INFORMATION SHEET

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

You are being invited to take part in a research project. Before you decide whether or not to take part, it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish. Thank you for reading this.

What is the purpose of the research project?

In Latin America, there are on-going initiatives to support regional technical cooperation initiatives to strengthen national regulatory capacities, however, not much is known regarding initiatives to streamline post-licensing chemistry, manufacturing and control requirements. In the post-licensing area, pharmaceutical companies wanting to increase manufacturing efficiencies and enhanced supply chains have to comply with various technical requirements in order to implement these changes in a particular market. The various regulatory requirements, coupled with different review timelines across the markets, can be very complex and challenging. These factors can delay patient access and burden both the pharmaceutical company and the National Regulatory Authority (NRA). This presents an opportunity for simplification to reduce the risks of non-compliance across markets and prevent shortage of supply to the patient, the end-goal being improved access by the patient.

The aims of this research are two-fold:

To explore the priority and any initiatives to streamline CMC variations within Latin America via *harmonisation (same set of guidelines sometimes adopted as legislation) or *convergence (voluntary process where requirements become similar over time), focusing on the PAHO designated National Reference Agencies of regional reference (NRAR), namely: ANMAT (Argentina), ANVISA (Brazil), ISP (Chile), INVIMA (Colombia), CECMED (Cuba) and COFEPRIS (Mexico), for five supply-critical post-approval variations.

To explore the successes in streamlining post-approval variations in Singapore, Thailand and Malaysia through the ASEAN network and assess whether any lessons can be learnt and applied to the Latin America markets.

The post-approval variations to be explored are changes in drug product for small molecules in the following areas:

- manufacturing site
- formulation
- storage condition
- shelf-life

manufacturing method

(Exclusion: generics/biologics/biosimilars/vaccines/medical devices/veterinary medicines)

The estimated completion date of the research is September 2022

*Full Definitions

HARMONISATION: The agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or region. May also influence the review process and assessment and can be adopted as legislation.

CONVERGENCE: Within the APEC context, can be defined as “a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures.

Why have I been invited to take part?

You have been chosen to participate in this study because of your direct experience with the NRAs under study, plus your expertise and extensive knowledge in Chemistry, Manufacturing and Control (CMC) variations and/or your knowledge of the regulatory landscape in the markets under review. By engaging with you, I hope to gain more insight into the challenges, opportunities and successes that these markets have had so far in working towards common requirements and processes for post-approval variations. Also I want to understand any changes in guidelines for CMC variations in these markets.

What will taking part involve?

You will be asked to fill out an online questionnaire with the option to participate in a follow-up interview via a web based platform (Zoom or Microsoft Teams). The questionnaire will explore the participants’ opinions and experiences of working with their respective NRAs in relation to CMC variations. The questionnaire will take between 15-20 minutes to fill in and participants are encouraged to respond within 2 weeks of receiving it. The interview will seek to probe or further clarify responses given in the online questionnaire and may last up to an hour. Where the participant agrees to be interviewed and a medium other than English is requested, a Local Consultant can be provided during interview to translate on behalf of the researcher, with the participant’s express permission.

The Interview will be video- or audio-recorded, depending on your preference. It can also be via telephone which will be audio-recorded. You will receive either a full transcript or summary of the interview and may make edits to ensure correct interpretation.

Do I have to take part?

No, your participation in this research project is entirely voluntary and it is up to you to decide whether or not to take part. If you decide to take part, you will have the opportunity to ask questions about the research project and will be asked to provide your consent to complete the online questionnaire which will be the first section of the online questionnaire. If you decide to participate in the online interview, you will need to sign a separate consent form which will be provided to you. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights.

You are free to withdraw your consent to participate in the research project at any time, without giving a reason, even after signing the consent form.

The information sheet will be emailed to you together with the link to the online questionnaire and if applicable, the interview consent form. You will need to sign the interview consent form to record your agreement to take part. This should be signed and returned within 2 weeks and before you participate in the interview.

Will I be paid for taking part?

No. You should understand that any data you give will be as a gift and you will not benefit financially in the future should this research project lead to the development of a new method/test/assessment.

What are the possible risks of taking part?

There are no identified disadvantages or risks of taking part in this study. A disclaimer will be included stating that the participant's views are their own and not those of the Health Authority they work for or represent. All information given will be confidential and remain so in all reports arising from the research. Any quotes will be anonymised.

If you consent to interpretation by a Local Consultant during an interview, you may feel uncomfortable sharing your personal opinions in the presence of the Local Consultant. Please note that Local Consultants will not have access to recordings and will sign a confidentiality agreement not to share any information from the interview.

What are the possible benefits of taking part?

There will be no direct advantages or benefits to you from taking part, but the information obtained from the study will help to increase the understanding of the regulatory landscape of these markets in relation to CMC post-approval variations and inform National Regulatory Authorities and Pharmaceutical companies/bodies.

Will my taking part in the study be kept confidential?

All information which is collected from or about you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data' (below) for further information.

What will happen to my Personal Data?

The following personal data may be collected/used in the research study: name, job role; years worked in role; email. These details however, will be anonymized through the use of a research code for each participant.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation.

Further information about Data Protection, including:

your rights

the legal basis under which Cardiff University processes your personal data for research

Cardiff University's Data Protection Policy
how to contact the Cardiff University Data Protection Officer
how to contact the Information Commissioner's Office

may be found at <https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection>.

Copies of the above-mentioned documentation and privacy notices can be provided upon request.

If a Local Consultant is required to translate during an interview (with your consent), they will be privy to this personal data and the personal opinions of the participant only during the interview. They will not have access to the interview recording or transcript and have also signed a confidentiality agreement not to divulge any information shared during the interview.

Alchemer.com (formerly surveyGizmo) will be the platform used for the online questionnaire. Your data will be transferred outside the European Economic Area. Alchemer.com adhere to data protection and GDPR guidelines, their data privacy and protection policy can be accessed here: <https://www.alchemer.com/privacy/gdpr/>

Rev.com will be used as an interview transcription service for the audio recording only, hence your personal data will be transferred outside the European Economic Area. Rev.com adhere to data protection and GDPR guidelines, their confidentiality and security policy can be found here: <https://www.rev.com/security>

Within 2 weeks, the research team will anonymise all the personal data it has collected from, or about you in connection with this research project, with the exception of your consent form.

Your consent form will be retained for 1 year after publication of the final report, and may be accessed by members of the research team and, where necessary, by members of the University's governance and audit teams. Anonymised information will be kept for a minimum of 1 year after publication of the final report but may be retained indefinitely, where it is likely to have continuing value for research purposes.

If you withdraw from the study, we will keep the information about you that we have already obtained. It will not be possible to withdraw any anonymised data that has already been published or in some cases, where identifiers are irreversibly removed during the course of a research project, from the point at which it has been anonymized

What happens to the data at the end of the research project?

The data provided may be used in research publications however any personal data will be removed before any form of sharing takes place. All quotes will be anonymized.

What will happen to the results of the research study?

The results are likely to be published in 2022. It is our intention to publish the results of this research project in academic journals and present findings at conferences. Participants

will not be identified in any report, publication or presentation. Verbatim quotes may be used. A summary of the results will also be made available to participants after the study.

What if there is a problem?

If you wish to complain, or have grounds for concerns about any aspect of the manner in which you have been approached or treated during the course of this research, please contact any of the below listed supervisors or the associated body, TOPRA:

Supervisor 1: Dr James Coulson Cardiff University [Role/Title] [Address] Tel: Direct: Email:	Supervisor 2: Fraser Stodart, Biogen [Role/Title] [Address] Tel: Direct: Email:
Associated bodies: Samantha Alsbury, The Organisation of Professionals in Regulatory Affairs Ltd (TOPRA) email:	

If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action, but you may have to pay for it.

Who is organizing and funding this research project?

The research is jointly organised by The Organisation of Professionals in Regulatory Affairs (TOPRA) and Ivy Essiam (student researcher); Dr James Coulson (supervisor) of Cardiff University. It is sponsored by Cardiff University.

Who has reviewed this research project?

This research project has been reviewed and given a favourable opinion by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

Further information and contact details

Should you have any questions relating to this research project, you may contact us during normal working hours:

Supervisor : Dr James Coulson
[Role/Title]

[Address]

Tel: Direct:

Email:

Thank you for considering to take part in this research project. If you decide to participate, you will be given a copy of the Participant Information Sheet and a signed consent form to keep for your records.

Appendix 12: RA Interview Schedule

INDIVIDUAL INTERVIEW SCHEDULE FOR REGULATORY AFFAIRS PROFESSIONALS

Disclaimer: These views are the personal views of the participant and do not reflect the views of the companies they work for.

Before recording, thank them for their time in participating. Mention that you will start recording.

Questions are related to CMC variations for small molecules for human use, **NOT** veterinary, biologics, generics, vaccines, biosimilars, medical devices.

1. Personal Questions

- Kindly state your name and your current role
- How long have you worked in Regulatory Affairs?
- What has been your career/experience till date?
- What markets/regions have you had responsibility for?

2. Work with LATAM markets (Brazil, Chile, Colombia, Argentina, Cuba, Mexico)

- Have you worked with any of these markets, are you currently working with them?
- Can you describe your experience working with any of the listed markets?
- How would you describe the National Regulatory Authority (NRA) of each market (open, closed, mature or not, well-resourced or not, any others)?
- In your experience, are they open to industry in terms of dialogue on requirements, influencing decisions on harmonisation? Give examples if possible.

3. Streamlining

- What are their review processes for post approval CMC (do they have categories, is there a specific process for submitting & reviewing CMC variations)?
- Do you know the last time they reviewed their CMC requirements? How frequently do they review and what triggers it in your opinion?
- Have the reviewed requirements enabled them to improve their review process and review time?
- What in your opinion are the specific advantages of CMC harmonisation if any, compared to MAA requirement harmonisation
-Advantages to industry/companies/HA of CMC harmonisation

4. Regulatory Requirements (CMC Reg/ In-country & HQ Market Specialists)

I have chosen to look at these cmc requirements in relation to the Drug Product:

- Change/addition of manufacturing site
- Change in formulation
- Change in storage condition
- Change in Shelf Life

- Changes in manufacturing method (relates to oral solid dose ie tablet and change to oral solution for change in formulation). **The requirements are in the attached spreadsheet.**

- What are your views on my choice of these specific variations - relevance to industry? Advantage/disadvantage?
- In your view, what requirements would be essential or relevant for these variations. Requirements that would show that the efficacy, safety and quality have been maintained in doing the change? (please refer and comment on spreadsheet if that will help)
- Which of these do you think are unnecessary and why?
- Do you think some of the requirements are influenced by culture or politics?
- Do you think there are factors outside scientific reasons, affecting the choice of these requirements? What are they and why?
- How much influence does the Govt have over regulatory requirements?
- Is the Regulatory Agency able to influence govt?
- How open is govt/HA to industry or external influences like EMA/FDA?

5. Streamlining priority

- Where is the current status of harmonisation initiatives in each market for CMC variations?
- Any observations on their attitude towards harmonisation?
- Looking at the initiatives for MAA requirement harmonisation, has it been successful, is the region progressing? If not, why?
- In your experience, what is the priority in harmonising CMC post approval variations versus other harmonisation initiatives ongoing in these markets. eg MAA, GMP etc. (**what are the other harmonisation initiatives they are doing?)
- In your view, are the LATAM market requirements getting more harmonised or converged or rather drifting apart? (in light of the definitions)
- If drifting apart why do you say so and can you give examples? eg Brazil PATE document
- If drifting apart, what do you think is the main factor(s) and how do you think they can overcome it?
- Looking at the definition of convergence and harmonisation, which model do you think would be most suited to LATAM and why?

Definitions

HARMONISATION: THE AGREEMENT OF THE SAME SET OF GUIDELINES OR REQUIREMENTS, LEADING TO AGREED TECHNICAL OR SCIENTIFIC CONTENT AND DOSSIER FORMAT ACROSS A SET OF MARKETS OR REGION. MAY ALSO INFLUENCE THE REVIEW PROCESS AND ASSESSMENT TOWARDS OBTAINING A HEALTH AUTHORITY APPROVAL.

CONVERGENCE: WITHIN THE APEC CONTEXT, CAN BE DEFINED AS “A VOLUNTARY PROCESS WHEREBY THE REGULATORY REQUIREMENTS ACROSS ECONOMIES BECOME MORE SIMILAR OR “ALIGNED” OVER TIME AS A RESULT OF THE GRADUAL ADOPTION OF INTERNATIONALLY RECOGNIZED TECHNICAL GUIDANCE DOCUMENTS, STANDARDS AND SCIENTIFIC PRINCIPLES AND COMMON OR SIMILAR PRACTICES AND PROCEDURES.

6. PANDRH/PAHO questions (please answer if you have some knowledge regarding these organisations)

- What is the current set up of Pan American Health Organisation (PAHO) & Pan American Network for Drug Regulatory Harmonisation (PANDRH) within the region? How do these organisations interact with members?
- What is the current role/influence of PAHO/PANDRH in the region?
- How has PAHO/PANDRH influenced the regulatory environment towards streamlining of CMC variations?
- Have the markets been open to streamlining CMC variations?
- What is the current focus for PAHO/PANDRH within the region?
- Does PAHO/PANDRH see itself becoming a governing body with more control over requirements in the region like EMA?
- Do you know of any projects within PANDRH aimed at streamlining CMC variations?

7. Other questions

- Do you know of any other groups currently discussing harmonisation of CMC requirements within LATAM eg FIFARMA, MERCUSOR and what is the status?

8. Final Questions

- Anything else you'd like to add?
- Do you know or can you recommend any other Regulatory Affairs contacts from industry that may be interested in this research?
- Could you recommend any contacts from the LATAM Agencies who would be willing to provide information on the topic?

ASEAN markets

1. Kindly state your name and your current role
 2. How long have you worked in Regulatory Affairs?
 3. What has been your career/experience till date?
 4. What markets/regions have you had responsibility for?
- Experience with Singapore, Malaysia, Thailand Agencies? Are they open to industry (in terms of input/deliberation)
 - Categorisation/review process/guidelines for CMC variations?
 - Attitude towards harmonisation?
 - In your experience, have these markets gained a level of success, why do you say so? What do you think helped them have this success?
 - If they have local guidelines, when did these come about (outside of ACTR) and do they get reviewed? Often? When was the last time?
 - Why/what reasons do they request extra documents? What type of extra documents do they request?
 - Have they got more to do to harmonise requirements?
 - Can LATAM learn anything from them? Or what can you see or say are the differences in ASEAN's harmonisation process/initiatives versus LATAM?

Other questions

Miscellaneous

Any contacts in ASEAN or Singapore/Malaysia/Thailand Agencies who may be interested in this research?

Other Regulatory Affairs contacts from industry that may be interested?

- Anything else you'd like to add?

Appendix 13: FIFARMA Interview Schedule

FIFARMA GROUP INTERVIEW SCHEDULE

Disclaimer: The views shared are the personal views of the participants and not the direct views of FIFARMA. Participants have consented to a group interview.

Markets being studied: Brazil, Chile, Colombia, Argentina, Cuba and Mexico.

DEFINITIONS

HARMONISATION: The agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or region. May also influence the review process and assessment towards obtaining a Health Authority approval.

CONVERGENCE: Within the APEC context, can be defined as “a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual adoption of internationally recognized technical guidance documents, standards and scientific principles and common or similar practices and procedures.

Objective for this meeting:

For FIFARMA to share its understanding of or insights on streamlining initiatives for CMC variations happening in the region (if any).

To explore the role and influence (if any) of FIFARMA on the process of streamlining CMC variations in LATAM markets under study.

QUESTIONS FOR INTERVIEW

ROLE OF FIFARMA IN THE LATAM REGION - perceptions of the participants as per their experience working with FIFARMA

-

- What is the current set up of FIFARMA within the region? How does it interact with members?
- What is the current role/influence of FIFARMA in the region?
- What's FIFARMA's take on the importance of streamlining CMC requirements across markets. What difficulties does a lack of 'streamlining requirements across markets' cause.
- Do the markets have defined classifications eg major/minor for CMC variations?
- Has FIFARMA participated in discussions/projects/initiatives to influence the regulatory environment towards streamlining of CMC variations? If yes, how?
- Have the markets been open to discussions on streamlining of CMC variations? Have they progressed and what have been the road blocks? How would you define progress?
- Is streamlining CMC requirements a current focus for FIFARMA within the region? If not, why?

FIFARMA Interactions with Other Organisations

- Does FIFARMA interact with MERCUSOR? Any discussions on CMC?
- Interact with PANDRH?
- Does FIFARMA interact with outside associations like EFPIA on the topic of CMC? Any recent discussions?

QUESTIONS ON STREAMLINING REQUIREMENTS

- In your opinion, what has FIFARMA observed regarding attitudes towards 'streamlining requirements/(harmonisation) or 'processes' in these markets?.
- Looking at harmonisation of MAA requirements, has it been successful, is the region progressing? If not, what do you think the reasons are and why?
- In your experience, what is the priority in harmonising CMC post approval variations versus other harmonisation initiatives ongoing in the region. (**what are the other initiatives they are doing)
- In your view, are the LATAM market requirements getting more harmonised (within the region) or converged (towards international guidelines) or rather drifting apart/diverging (market specific requirements)? (in light of the definitions)
- If drifting apart why do you say so? And can you give examples of maybe recent updates to requirements which suggest so?
- If drifting apart, what do you think is the main factor(s) and how do you think they can overcome it? If they want to overcome?
- Is streamlining CMC requirements a current focus within the region in general? If not, why?
- Do these markets have a reliance model with traditional reference markets (EU/US) and/or local eg ANVISA etc
- Looking at the definition of convergence and harmonisation, which model/process do you think would be most suited to LATAM and why? What about other models like cooperation?
- Any other information you would like to share?

Appendix 14: NRA Consent Form

CONSENT FORM

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

SREC reference and committee: 1617-36 Pharmacy Ethics

Name of Chief/Principal Investigator: Ivy Essiam

**Please
initial box**

I confirm that I have read the information sheet dated June 2021 v15 for the above research project.	
I confirm that I have understood the information sheet dated June 2021 v15 for the above research project and that I have had the opportunity to ask questions and that these have been answered satisfactorily.	
I understand that my participation is voluntary and I am free to withdraw at any time without giving a reason and without any adverse consequences (e.g. to medical care or legal rights, if relevant). I understand that if I withdraw, information about me that has already been obtained may be kept by Cardiff University.	
I understand that data collected during the research project may be looked at by individuals from Cardiff University (supervisors), where it is relevant to my taking part in the research project. I give permission for these individuals to have access to my data.	
I consent to the processing of my personal information [name, place of work, job title, years worked] for the purposes explained to me. I understand that such information will be held in accordance with all applicable data protection legislation and in strict confidence, unless disclosure is required by law or professional obligation.	
I understand who will have access to the personal information provided, how the data will be stored and what will happen to the data at the end of the research project.	
Please <u>circle</u> your preference: I consent to being audio recorded/video recorded for the purposes of the research project and I understand how it will be used in the research	

I understand that with my express permission, a Local Consultant can act as a translator in the interview if the interview will not be conducted in English.	
I understand that if this is the case, the Local Consultant will not have access to the interview recording and has signed a confidentiality/data protection agreement, hence they cannot share any details of the interview to anyone.	
I consent for the Local Consultant to act as an interpreter in the interview if this applies.	
I understand that anonymised excerpts and/or verbatim quotes from the interview/group interview may be used as part of the research publication.	
I understand that there will be no payment or benefit for my participation	
I will receive either a full transcript or summary of my interview and may make edits I feel necessary to ensure the effectiveness of any agreement made about confidentiality and to ensure correct interpretation	
I understand how the findings and results of the research project will be written up and published.	
I agree to take part in this research project.	

Name of participant (print) Date Signature

(Electronic signatures are acceptable)

IVY ESSIAM

Name of person taking consent Date Signature
(print)

RESEARCHER
Role of person taking consent
(print)

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

Appendix 15 Interpreter Information Sheet

INTERPRETER INFORMATION SHEET

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

You are being invited to take part in a research project. Before you decide whether or not to take part, it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish. Thank you for reading this.

1) What is the purpose of the research project?

In Latin America, there are on-going initiatives to support regional technical cooperation initiatives to strengthen national regulatory capacities, however not much is known regarding initiatives to streamline post-licensing chemistry, manufacturing and control requirements. In the post-licensing area, pharmaceutical companies wanting to increase manufacturing efficiencies and enhanced supply chains, have to comply with various technical requirements in order to implement these changes in a particular market. The various regulatory requirements, coupled with different review timelines across the markets, can be very complex and challenging. These factors can delay patient access and burden both the pharmaceutical company and the National Regulatory Authority (NRA). This presents an opportunity for simplification to reduce the risks of non-compliance across markets and prevent shortage of supply to the patient, the end-goal being improved access by the patient.

The aims of this research are two-fold:

- 1) To explore the priority and any initiatives to streamline CMC variations within Latin America via *harmonisation (same set of guidelines sometimes adopted as legislation) or *convergence (voluntary process where requirements become similar over time), focusing on the PAHO designated National Reference Agencies of regional reference (NRAR), namely: ANMAT (Argentina), ANVISA (Brazil), ISP (Chile), INVIMA (Colombia), CECMED (Cuba) and COFEPRIS (Mexico), for five supply-critical post-approval variations.
- 2) To explore the successes in streamlining post-approval variations in Singapore, Thailand and Malaysia through the ASEAN network and assess whether any lessons can be learnt and applied to the Latin America markets.

The post-approval variations to be explored are changes in drug product for small molecules in the following areas:

- manufacturing site
- formulation
- storage condition
- shelf-life

- manufacturing method

(Exclusion: generics/biologics/biosimilars/vaccines/medical devices/veterinary medicines)

The estimated completion date of the research is September 2022

*Full Definitions

HARMONISATION: The agreement of the same set of guidelines or requirements, leading to agreed technical or scientific content and dossier format across a set of markets or region. May also influence the review process and assessment and can be adopted as legislation.

CONVERGENCE: Within the APEC context, can be defined as “a voluntary process whereby the regulatory requirements across economies become more similar or “aligned” over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures.

1) Why have I been invited to take part?

You have been invited to be an interpreter due to your experience as a Local Regulatory Affairs consultant and as someone who can speak Spanish and/or Portuguese as well as English.

2) What will taking part involve?

Your main role will be to act as an interpreter during interviews with National Regulatory Authority personnel in relation to the research project.

Your role will be a neutral one where you will follow the lead of the researcher during the interview to interpret questions and responses as the interview proceeds. The translations must be direct translations and questions/answers should not be modified without the researcher’s express knowledge during the course of the interview

You will be given training on what to expect and how to conduct yourself during the interview and the extent of your role during the interview interactions. You cannot interpret for the study if you do not attend the training. Training may last up to an hour. The interview questions will be shared with you prior to training and will be discussed during the training. The interview(s) may last up to an hour. They will be conducted online via telephone or a web-based platform such as Zoom or Microsoft Teams at a suitable time and date for the interviewee. There will be a pool of interpreters hence whoever is available at the interviewee’s preferred time will join the researcher for the interview.

The information shared during the interview will be the participant’s own opinions and will in no way reflect the opinions of the National Regulatory Authority they work for.

Please note that you will be under strict obligations not to divulge any information shared during the interview, whether verbally or in written form as per the University’s data protection guidelines.

3) Do I have to take part?

No, your participation as interpreter is entirely voluntary and it is up to you to decide whether or not to take part. If you decide to take part, you will have the opportunity to ask questions about the research and the role of interpreter and will be asked to provide your consent to

act as interpreter. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights.

You are free to withdraw your consent as interpreter at any time, without giving a reason, even after signing the consent form.

The information sheet will be emailed to you together with the interview schedule and interpreter consent form. You will need to sign the consent form to record your agreement to take part. This should be signed and returned as soon as possible and before any scheduled interview takes place.

4) Will I be paid for the interpreter role?

Yes. As an interpreter, the researcher will pay \$30/hour for any time spent in training and interpreting during the interview(s).

5) What are the possible risks of taking part?

There are no identified disadvantages or risks of taking part in this study, however you may be known to the interviewee which may or may not be comfortable for interpreter and/or interviewee. All information shared during the interview will be confidential and will remain so in all reports arising from the research.

As an interpreter, you will not have access to recordings and will sign a confidentiality agreement not to share any information from the interview with anyone.

6) What are the possible benefits of taking part?

The benefit to the interpreter is remuneration for time spent training and interpreting.

7) Will my taking part in the study be kept confidential?

All information which is collected from or about you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data' (below) for further information.

8) What will happen to my Personal Data?

The following personal data may be collected/used in the research study: name, job role; email. These details, however, will only be used for the purposes of anonymisation through the use of a research code for each participant.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. Further information about Data Protection, including:

- your rights
- the legal basis under which Cardiff University processes your personal data for research
- Cardiff University's Data Protection Policy
- how to contact the Cardiff University Data Protection Officer
- how to contact the Information Commissioner's Office

may be found at <https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection>

Copies of the above-mentioned documentation and privacy notices can be provided upon request.

Rev.com will be used as an interview transcription service for the audio recording only, hence your personal data will be transferred outside the European Economic Area. Rev.com adhere to data protection and GDPR guidelines, their confidentiality and security policy can be found here: <https://www.rev.com/security>

Within 2 weeks, the research team will anonymise all the personal data it has collected from, or about you in connection with this research project, with the exception of your consent form.

Your consent form will be retained for 1 year after publication of the final report, and may be accessed by members of the research team and, where necessary, by members of the University's governance and audit teams. Anonymised information will be kept for a minimum of 1 year after publication of the final report but may be retained indefinitely, where it is likely to have continuing value for research purposes.

If you withdraw from the role of interpreter, we will keep the information about you that we have already obtained. It will not be possible to withdraw any anonymised data that has already been published or in some cases, where identifiers are irreversibly removed during the course of a research project, from the point at which it has been anonymized.

9) What happens to the data at the end of the research project?

The data provided may be used in research publications however any personal data will be removed before any form of sharing takes place.

10) What will happen to the results of the research study?

The results are likely to be published in 2022. It is our intention to publish the results of this research project in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation. Verbatim quotes may be used.

11) What if there is a problem?

If you wish to complain, or have grounds for concerns about any aspect of the manner in which you have been approached or treated during the course of this research, please contact any of the below listed supervisors or the associated body, TOPRA:

<p>Supervisor 1: Dr James Coulson Cardiff University [Role/Title] [Address] Tel: Direct: Email:</p>	<p>Supervisor 2: Fraser Stodart, Biogen [Role/Title] [Address] Tel: Direct: Email:</p>
<p>Associated bodies: Samantha Alsbury, The Organisation of Professionals in Regulatory Affairs Ltd (TOPRA) email:</p>	

If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action, but you may have to pay for it.

12)Who is organizing and funding this research project?

The research is jointly organised by The Organisation of Professionals in Regulatory Affairs (TOPRA) and Ivy Essiam (student researcher); Dr James Coulson (supervisor) of Cardiff University. It is sponsored by Cardiff University.

13)Who has reviewed this research project?

This research project has been reviewed and given a favourable opinion by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

14)Further information and contact details

Should you have any questions relating to this research project, you may contact us during normal working hours:

Supervisor: Dr James Coulson

[Role/Title]
[Address]
Tel: Direct:
Email:

Thank you for considering to take on the role of interpreter for this study. If you decide to participate, you will be given a copy of the Participant Information Sheet and a signed consent form to keep for your records.

Appendix 16 Interpreter Recruitment letter

Interpreter Recruitment letter

Dear [Interpreter name]

My name is Ivy Essiam and I'm currently undertaking a research project for my PhD at Cardiff University, approved by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

Your name was passed on to me by (*X Consultancies*). I would like to solicit your help as an interpreter during research interviews involving National Regulatory Authority personnel in the medium of Spanish or Portuguese.

This will be a paid role and is completely voluntary.

Please refer to the attached information sheet for full details about the study, what role the translator will play and the training that will be provided for the research.

If you are interested in this interpreter role after reading the information sheet, please sign the attached consent form and return to me at [email].

Feel free to contact me should you have any questions about the study or the role of the interpreter in the research study.

Yours Sincerely,

Ivy Essiam
PhD Student
Cardiff University, UK

Appendix 17: Interpreter Consent Form

CONSENT FORM

Study Title: Regulatory Convergence or harmonisation? Exploring regional approaches for streamlining chemistry, manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia.

SREC reference and committee: 1617-36 Pharmacy Ethics

Name of Chief/Principal Investigator: Ivy Essiam

Please tick (✓) to confirm your understanding of the study, what is expected of you as an interpreter and to provide your consent to assist with translating based on your availability:

**Please
initial
box**

I confirm that I have read the interpreter information sheet dated July 2021 v1 for the above research project.	
I confirm that I have understood the interpreter information sheet dated June 2021 v1 for the above research project and I have had the opportunity to ask questions and that these have been answered satisfactorily.	
I understand that my participation in the research as an interpreter is voluntary and that I am free to withdraw at any time without giving a reason and without any adverse consequences (e.g. to medical care or legal rights, if relevant). I understand that if I withdraw, information about me that has already been obtained may be kept by Cardiff University.	
I understand that my personal data (name, email) and involvement as an interpreter will be anonymous and remain confidential	
I understand that there is remuneration for the role of interpreter for the study at \$30/hour for each hour spent on the research study.	
I agree to adhere to the Data Protection Act/University's GDPR requirements in relation to participant's personal data as laid out below.	
I understand that where I am unable to attend the training session, I cannot interpret	
I understand that I cannot share any information given during the interview(s) in the event I have to translate. Interview information shall remain confidential.	
I agree to take part in the study as an interpreter	

Name of interpreter:

Date:

Signature:

Name of Researcher:

Date:

Signature:

Attachments:

Information Sheet

NRA Interview schedule

THANK YOU FOR PARTICIPATING IN THE RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

Appendix 18 INTERPRETER TRAINING SCHEDULE (for researcher)

INTERPRETER TRAINING SCHEDULE

This checklist provides an overview of what the researcher will discuss with the Interpreters to prepare them for the NRA interviews.

1. Determine best date/time interpreters can meet. May have to organise more than 1 session to cover the pool.
2. On the day, take a register of those present
3. Check that all consent forms have been received
4. Go through interpreter information sheet & take questions on the research study
5. Discuss the interview procedure: their role & conduct; what to expect
6. Take any further questions
7. Inform them that time will be scheduled with NRA participants and the dates shared so that any interpreter available can confirm and be booked for that interview session.

Appendix 19: Table of generated themes and quotes on CMC requirement harmonisation in LATAM

Theme	Quotes
<p>CMC Variation Landscape</p>	<p>LA12... <i>and what they have is that for a small molecule, yes, they have a regulation mainly Brazil has and now now ANAMAT Argentina also I think all of them has a regulation for small molecules for post approval . changes, but it's not as robust as we have in Europe.</i></p> <p>LA12 <i>You know, I think the work you are doing, we will be effecting directly to patients because it will mean that the patient will get that medicine faster, because if you talk about the CMC requirements in Latina America, this is the most tough ones. And sometimes we take like six months, one year delay because one single CMC document which will not impact the safety and the efficacy of the product, it's just for bureaucracy to be fulfilled. So this is something very unfair for patients that are waiting and looking for the innovative medicine that is available everywhere and is not in Latin America. So this is something I really think that your research will help a lot of the patients. So it's, it's very beautiful to, to, to do this.</i></p> <p>LA6 <i>They have people who speak English. They don't need the scientific articles in Spanish, for starters. I'm okay, I'm on board with the need for translations. That's fine, but they are supposed to be hiring people with a scientific background, and I don't see any reason to ... If they're doing this, I don't see any reason to not ask these people to speak French, English, German, Spanish.</i></p> <p>LA9 <i>They are quite typical variations that we have for products. In my previous job,</i></p>

	<p><i>we were including new manufacturing sites for basically all medicines because you need to have a second option. You cannot just...I don't have the product...so I can't....you need to supply the product. And the same for the others. So manufacturing process, you are always looking to see how to improve something inside the manufacturing process. Packaging, the same. Maybe I would include new indication. Because it is something that...new presentation, I know that depending on type of products, but for OTCs for example, over-the-counter, they are always trying to include new presentations or new flavors, something that is not so complicated but that is bringing innovation to the product.</i></p> <p><i>LA15 I would say, Argentina and Chile would be the ones that I would say haven't. It's sort of more the general markets we're changing something, whereas what I see from Mexico, Columbia and Brazil is that they tend to have defined processes that, you're changing, say, a site, there's a distinct filing category for that.</i></p> <p><i>LA15 It actually allowed them to downgrade a lot of changes. So they're definitely yes. The Columbia and Mexico know it's still taking as long, and I think it's more toward resourcing. They've improved things on their end, but because they're not resourced to handle this, it just gets a big backlog as well.</i></p>
Political Influence	<p><i>LA9 I know that Argentina is very dependent on government. Every time we have elections or a new president, we have change inside ANMAT, Argentina's health authority.AS4 '...Yes. They have defined it [the CMC variations] as major and minor variation. So their classification is not aligned. The requirement, they have the national guideline. So I wouldn't say they're harmonized. Sorry. I don't think they are harmonized.</i></p> <p><i>LA2 No, it's not totally separated because it is a part of health minister. But he has his own structure. I think the chief of the director from ANVISA is the health minister. So there is impact of the government. There is no... Also the directors</i></p>

	<p>from ANVISA, they are nominees from the government. So there is impact of the government in ANVISA. the only thing that was approved by the government was the law, but this is different. There is a lot of laws that the government published. ANVISA have to follow. But they do not influence the guidelines from ANVISA.</p>
<p>Guideline review</p>	<p>LA8 ...<i>For Argentina? Well, last, yeah, in December last year they created from scratch the post-approval changes for regulation for large molecules. So it is still under evaluation at the health authority, but it was last year the last time when they analyzed this.</i></p> <p>LA12 <i>So we have Argentina now. Right? So Argentina errh what can I say for Argentina it's like for a small molecule, they pretty much rely on the reference countries for new products. The product that is approved in reference country, they, they can, they can use it, the reliance approach. So we can submit the an abbreviate package registration package to be approved. So in this way they are, they're considered international standards.</i></p> <p>LA14 <i>Well, they ... For example, now Brazil has legislation from 2016 if I'm not wrong for post-approval change for syntax in biologics. So they have revealed, it took five years for them to review. So we know that they will review again next year to try to find some convergence with ICH. But the other agencies do not have such thing, so they don't disclose when they are going to reveal. For example, Argentina has now a draft legislation for post-approval chase, but it's the first one.</i></p> <p>LA2 <i>Also in this guideline we have some changes that are, could be implemented immediately with the sign off of these documents are the proofs necessary to the change. Also we have some changes that it's prior approval changes. They are divided into some categories.</i></p>

	<p><i>LA3</i></p> <p><i>So my belief on what triggered is that they saw that there was a lack and need of additional regulations in order to make sure that the submissions that or the variations were secured. That's the only thing that I could believe.</i></p> <p><i>LA9 For Chile, good question. Maybe 2014. I need to check, I'm not sure. I know that about biological medicines it was around 2014.</i></p> <p><i>LA8</i></p> <p><i>Cuba? I don't remember when was the last time they changed the regulation, to be honest. I would say that in the last four or five years, they didn't change anything. They changed the behavior, but they didn't change their relations, per se.</i></p>
<p>Attitudes to streamlining</p>	<p><i>LA2 Brazil it's become a member of ICH so they are talking about a lot of ICH to harmonize some things but Brazil is not talking about harmonization but convergency with other regular affairs. They are talking a lot with other regulatory agencies to become to change the legislation but since Brazil it's becoming a part of ICH they will have to change a lot of current legislation. About companies and the dialogue we have a new director and resident director and president director in ANVISA</i></p> <p><i>LA5 ... I see more like these countries here trying to be equal to European countries or to American countries. Maybe I don't know if it would be an advantage to try to make a group again and to make them equal to European or ICH. But for now I think they are doing everything by themselves.</i></p> <p><i>LA3 That's one key thing, is to be able to accept if one agency has already done its homework and it's an agency, I can't expect the same thing for example, from Venezuela. Me personally if I am in Colombia and I wanna accept the post approval that they did in Venezuela, no way, because I know the type of agency that Venezuela is, right? But if it's an agency like Mexico, Colombia or Brazil they should ... The rest of the countries, Ecuador should be accepting the other countries'</i></p>

	<p><i>inspections, the other countries' approvals, so forth. But of course then that would minimize the role of the regulatory person, and they would evolve into a more leadership role and to a more strategical role of the regulatory instead of just being like they portrayed originally as a push of papers</i></p> <p><i>LA8 Especially outside but they have great forums that even they organize including other health authorities in Latin America: Cuba, Mexico, Argentina, and they participate from different conferences in Latin America and also international conferences where they send some members of ANVISA to get trained and to get what is the information that is moving around the world at the moment in terms of regulation. So they are really up-to-date in terms of what is happening around.</i></p>
<p>Perceived benefits to streamlining</p>	<p><i>LA1 Yes. How about specific advantages are that you're creating one data package effectively for all markets at the same time, if you can harmonize. There's a common understanding and this is where it gets really difficult because what you harmonize to, but there's a common understanding that a variation in Europe is the same variation or similar variation in other markets. You have a common understanding that timelines, so if you've got harmonized timelines across a region or across all regions, you can give guidance into development teams and into manufacturing organizations about when you believe this is going to be approved and just really an implementation, the easiest implementation, if you're able to submit, I know, to ... Let's take, if you have a common package what was going to Brazil, Chile, Mexico, Columbia, Argentina with a common timeline, you're able to advise the business that, "Yes, we've made the submission. We've got shared pack in Columbia and Argentina or Columbia and Mexico, that shared pipe will be approved at the same time in these two markets and we'll be able to implement at the same time." There's a little bit of this that sits outside that as well is implementation timelines. You've got the guidance that says, "Okay. It's the same variation and it's the same approval timelines." Ideally, what you probably want as well is some common understanding or common legislation on when these variations have to be implemented because, again, in different countries, that difference in some countries, its immediate implementation so you have to carefully manage your stock to make sure that when you get an approval, you haven't got too</i></p>

	<p><i>much of your old stock. In other countries, that can be three to six months. It's also what's sits outside the immediate legislation, what's your implementation dates as well.</i></p> <p><i>LA5 Now that the harmonization is arriving, I can tell you that is one part that is requirement, that is requiring more documents and more effort of the company. I think it's very good thing to improve the quality of the products and then I know that the quality of the products are more assured when this change occurred. There's manufacturing and formulation.</i></p>
<p>Perceived challenges to streamlining</p>	<p><i>LA9 I believe that it will be nice. Because nowadays we have a very different type of evaluation. If it is to be the same dosage, different people, they will evaluate in a very different way. So sometimes the legislation, you are following the legislation but the interpretation, can vary a lot. If you have high standards, they shouldn't. It would be much more, standard, these evaluations, inside the health authority. So it would be more fair to have an evaluation across technicians or across employees inside the health authority.</i></p> <p><i>LA15 Yeah. The biggest challenge that I would have with Latin America markets is that, a lot of their guidances, so to speak, are written legislation. They don't have true guidance. What this means is that, the legislation, it removes their ability to work in the gray zone. It has to be very black and white. You meet the legislation or you don't, not the spirit of it, in terms of guidance, or your ability to ask for a waiver from that are just by not having it. It reduces your flexibility.</i></p> <p><i>LA1 Yeah. Yeah. It's not necessarily they're putting their own twists. They're not deliberately putting a twist on it. "Okay," they're thinking, "Well, how can we implement this in our markets?" If you've got 15 different markets reading the same thing, you'll get 15 different results. That's what's happening is its been implemented ad hoc across all the different countries. Yeah.</i></p>

	<p><i>LA1 but even for CMC variations, a number of the countries still require evidence of approval in the markets. Again, that puts an in-built delay. If you've got a variation of EU and US, it takes 30 or 90 days, then you have to wait 30 or 90 days before you get your CPP. Then, you've got more than that because you've got to order it. That builds in a delay in many of the countries including all of these, Brazil and Columbia and Mexico and so forth. You've got an in-built delay there.</i></p> <p><i>LA3 So it's the same reason why they don't harmonize. It's the same reason why they won't say, okay, we'll accept that the same requirements can be submitted in Columbia or in Peru because they, each agency wants to have their own laws, regulations, and the way they.</i></p> <p><i>LA8 Hmm. I will not say specifically to regulatory requirements but to the health authority, per se. So the health authority may find ways to delay an approval or not to put a product into the market but to put other that is cheaper. So in countries, I would say, except Brasil, that is and besides independent of the government, I mean, they don't change the evaluators and the top positions of the health authority because of change in government. It is independent in that way. But with exception of Brasil, all the countries are impacted by governmental situations. They are not independent of the government.</i></p>
<p>Industry Associations & Networks and their influence or impact in the region on streamlining initiatives</p>	<p><i>LA10 We have a few pharma associations here. I live in São Paulo, so here in São Paulo is Sindusfarma. I can write down by mail. So it's the syndicate of the pharma industries. You have Interfarma, you have quite a few pharma associations, but the most famous ones are Sindusfarma and Interfarma.</i></p> <p><i>FF1 So I would say that this is a no. And also to be quite honest, I don't think that MERCOSUR agenda in the pharmaceutical area today includes any specific discussions on CMC related topics for harmonization. So I would have to double-check their agenda, but historically this is a topic that was not present there. If anyone knows about any MERCOSUR interaction, but I don't think so.</i></p>

	<p><i>LA3 Well, for example with MERCOSUR you have ... it's a regulation where it says that if it's registered in Argentina you should be able to accept the approval with a little bit of variations with just some small differences, but you should be able to accept that. But nevertheless when that happen it's like submitting a brand new dossier, so whatever is written in the medical suite agreement it's not relevant. But for example, with Mexico, Mexico has very cool agreements that Ecuador, El Salvador and Chile, so if the product is registered in Mexico they will accept the registration with very minimal information.</i></p>
<p>Changing local laws to accommodate harmonised requirement is difficult</p>	<p><i>LA10 Mercosur is the common market for the South American region and it's not only about trading stuff. It's like a common trading for the South American countries, but we also have some regulations that can be applicable to the countries that are members of this Mercosur. So countries that are members of the Mercosur, if I'm not mistaken, is; Argentina, Uruguay, Paraguay, and Brazil. I think these are the only countries that are part of Mercosur. So there are some regulations that are common to these four countries as well. But I am not that familiar with these regulations.</i></p> <p><i>LA14 No, I think I've covered that. There was really no efforts in the harmonization. It was not even possible with Mercosur doing that, plus the agency were really looking at each other. They were not looking at what was happening around the world, but this is changing. But this will not change so fast, but this is evolving.</i></p> <p><i>LA2 I never heard about anything about that here in Brazil about this PANDRH.</i></p> <p><i>LA12 As the projects are mainly done by the, by the members in Americas and uh, I know PANDRH as member of PAHO, they have an interaction with WHO as well. So, so they share, I guess they share, I'm not sure, Uh, but I think they share the projects with WHO for instance, what is going, on as a member of PANDRH</i></p>

	<p><i>LA13 I think it's really important for the region. In my company, we do have some people working in these or is being informed about this and cascaded this into the organization. I think this is, for Latin America, this is really important, this two organizations. We don't have so many initiatives like that. So, having this by a recognized organization, this is really important. And I think that they focus on the topics that we need to focus because they have the experts in the region so I only have good things to say about these organizations.</i></p>
<p>NRA involvement in streamlining CMC requirements</p>	<p><i>NRA3 I mean, there are some meetings, for instance in MERCUSOR, there are some collaborations. Often we respond to some doubts, but not discuss specifically a product. That's not happening. The collaboration is just on a high level, in the sense that sometimes we discuss regulations. Sometimes we discuss general actions, but not really product by product.</i></p>
<p>What process is being used to streamline CMC requirements?</p>	<p><i>LA1 Yeah. The reason is because they're not in political alignment like Europe or ASEAN. I think that's the main thing, they're not in a political alignment. They're all slightly going in different directions at the moment. The way they have to do support with them is to engage with them through PANDRH and PAHO, et cetera to try and get them to converge and to use all the other global organizations like ICH and WHO to encourage convergence. Harmonization, I think harmonization tends to be underwritten and underlined by certain political agreements.</i></p> <p><i>LA2 Brazil it's become a member of ICH so they are talking about a lot of ICH to harmonize some things but Brazil is not talking about harmonization but convergency with other regular affairs. They are talking a lot with other regulatory agencies to become to change the legislation but since Brazil it's becoming a part of ICH they will have to change a lot of current legislation. About companies and the dialogue we have a new director and resident director and president director in ANVISA</i></p>

	<p><i>LA8 Yeah. I think that they look apart from each other because they don't really trust other countries' decisions. They are really product [inaudible 01:37:45] themselves and they're competing with the other countries.</i></p>
--	--

Appendix 20: Table of generated themes and quotes on CMC requirement harmonisation in ASEAN

Theme	Quotes
<p><i>How ASEAN achieved harmonization: the process and history of harmonising CMC requirements</i></p>	<p><i>AS1... Yeah so PPW was formed in 1999 right because its main aim is for harmonization of the pharma regulations of ASEAN, all the ASEAN member countries. And it's because of ASEAN's economy pillar that they want to form something like a community of ... what do you call it. A community of ... let me see. Yeah, they want to do something like a EU kind of thing but maybe to that scale.</i></p> <p><i>AS1... So they want to do like a ASEAN community where there will be free movement of goods and human resources. So for that they realized that they have to harmonize some of the industries in these countries. And pharmaceuticals was identified as one of the key areas. So because of that, PPW was formed and they have meetings every once a year. PPWG typically does harmonization like I said. So they're working on ... I mean the first task they had was ACTD and ACTR. So after that, they have moved on to ... they're also doing some MRAs on GMP inspection. So after the ACTD and ACTR harmonized for registration, then of course they looked at the various sections that make up the ACTR. So things like stability was harmonized, bioequivalence was harmonized. What else, process validation was harmonized. Some of the big pockets of requirements are harmonized</i></p> <p><i>AS1... So they agree by mutual recognition and in the end it's actually the ... whatever they agree on like for example, some directives or whatever, they have to get it signed by the higher level. So once the working group is done with their review and everyone's happy, they get it [inaudible 00:39:43] by the leaders, the leader team of each country and then the ministers actually do have to sign on it.</i></p>

<p>Real-world effectiveness of harmonisation: realisation and implementation</p>	<p><i>'...No, they're not law...So they're just guidelines so you can choose to follow or not...So what happens in these three countries is following the variation guidelines they actually came out with their own guidelines. Very, very similar to the ASEAN variation guidelines, but they are, they have their own...'</i></p> <p><i>AS4 '...They do follow it, but there is something additional also they do expect later, that's the question. So you can submit a document based in ACTDR, however you have to also submit as and when they ask questions and as and when they evaluate...'</i></p> <p><i>AS9 '...and we do not have to explain to, you know, imagine submitting, uh, one, one variation to 10 agencies, and then you get 10 different set of questions and some questions might be repeating just slightly different from each other...'</i></p> <p><i>AS4 '...Yes. They have defined it [the CMC variations] as major and minor variation. So their classification is not aligned. The requirement, they have the national guideline. So I wouldn't say they're harmonized. Sorry. I don't think they are harmonized.</i></p> <p><i>AS8 '...But if you, you, from industry perspective, if you put so many countries specific requirements, it really creates the hurdle for the industry to enjoy the harmonization...'</i></p> <p><i>AS8 '...So those are the local, generic, pharmaceutical companies, which may have relatively small scale, which may use to those traditional way of working, which may not have, uh, you know, highest uh highest standard from GXP perspective. It doesn't also doesn't necessarily mean they don't want to be, but it just means they don't have sufficient revenue to support the investment...'</i></p>
---	--

AS1 '*...There are some specific CMC variations that they do not follow. The countries can choose not to follow the ASEAN variation guideline...*'

AS3 '*...they are the major countries [Singapore, Malaysia, Thailand], but they are not harmonized yet...because, for the pharmaceutical legislation, they are seeking harmonization, but they are not quite there yet...*'

AS4 '*...No, not harmonize. I wouldn't say it is harmonized yet. I wouldn't say. Because each market behaves independently, each market agency has different expectations. Even evaluators have a different expectation. So no. Yes, on paper, it is harmonized in terms of guideline, but it is not being implemented in reality...*'

AS3 '*...It's in the middle, I would say. Because they have achieved the harmonization of the requirements, of what is needed in terms of content, in terms of technical data needed on your product to reach the standard. They have harmonized the standards. But they did not harmonize their legislation and their regulation in terms of variation...*'

AS5 '*...Let me take it this way, harmonization won't happen, will never happen because, that's definitely my personal opinion, harmonization will never happen because of a few things...*'

AS4 '*...No, I don't think so. It's only, they have a harmonized guideline. However, if you go to Malaysia, they have a long, detailed, a hundred pages guideline for approval. Singapore has its own guideline. The pathway, they have are different. Thailand is totally new medical, new drug, new generic, three pathways. Malaysia has another pathway. Singapore has another pathway. Classification route is different...*'

AS4 '*... So their classification is not aligned. The requirement, they have the national guideline. So I wouldn't say they're harmonized. Sorry. I don't think they are harmonized...*'

AS4 '*...So ideally if you see now it's almost a decade I would say that, or more than a decade where they have harmonized guideline, but I don't think they have reached to somewhere...*'

AS8 '*... So, uh, theoretically all the ASEAN member States should following the ASEAN guideline. Um, however, uh, there are still some, you know, country specific requirements during the submission from each country...*'

AS4 '*... See, what is the objective of any harmonization? Finally you do harmonization to get the benefit in terms of trade. So if you are not able to replicate that harmonized guideline, implement those guidelines in each and every country uniformly, and then give a benefit to the applicant or benefit to the market or to have free trade, there's no use of having some paper which is aligned. So it has to result into some benefit. So there's no benefit...*'

AS3 '*...It's in the middle, I would say. Because they have achieved the harmonization of the requirements, of what is needed in terms of content, in terms of technical data needed on your product to reach the standard. They have harmonized the standards...*'

AS3 '*...And actually, the variation guidelines, you have an ASEAN variation guidelines, and this one has only been adopted by Thailand. And Malaysia and Singapore have their own guideline...*'

AS1 '*...So what happens in these three countries is following the variation guidelines most of them actually came out their own guidelines. Very, very similar to the ASEAN variation guidelines, but they are the, they have their own. It's name is like maybe Singapore variation guideline, Malaysia variation guideline. It is very easy. It's very similar to ASEAN variation except for a few categories that they choose not to follow...*'

AS3 '*...Exactly, yes. And it was the same in Europe some years ago, so it's not a specific process. They all requires the same thing in the dossier, in terms of study, technical data. In the registration dossier. But, in terms of variation, they may require different things to support the change...*'

'...So for example, the BE study requirement in Thailand, is Thai FDA, do not feel confident to utilize the study from other countries, but then from the other side, then the data generates in Thailand can be accepted in Malaysia and Singapore. So it is not mutually recognized...'

Convergence is happening rather than harmonisation

AS3 '... You are talking about convergence in your topic, and that's what they are trying to do, but you have two different levels. They are converging the standards for all the ASEAN common technical requirements in terms of content. The requirements, yeah, in terms of content and scientific, technical data. And, actually, they are harmonized there. But there is a sort of legislation on the format of the dossier, and variation...'

AS5 .So now they talk about convergence. That's another term that would be relatively make some sense...'

AS5 '....Everybody talk about convergence. No organization able to talk about harmonization. Sometime, maybe the core organization name maybe confusing, they will say something, something harmonization happen, or organization. That may be the initial organization name, but when you look in the organization, there is no timetable, no action plan, nobody talk about harmonization timetable..'

AS5'...And I hope I don't scare you when I say, no harmonization, it won't happen. I hope you don't break many people, my God, what is at least little hope or little dream one day it will happen. It will happen, but in a way of convergence...'

*'AS9... Yeah. I don't why we wouldn't, you know, be struggling like to understand country specific requirements, that, that wouldn't be a case if the harmonization has worked. So, yeah. And yeah. Yeah. It's also, it's also ongoing effort to try to understand as well. Um, like the challenges behind the agencies, why wouldn't they, you know, able to share the, the capacity to share the resources and things like that. Because I mean, from our nice thought, it will be wonderful if they can do that because it definitely cut short a lot, um, uh, requirements and a lot of, uh, **there will be a lot of convergence** so that, um, the timeline can be shortened and you know, and we do not have to explain to, you know, imagine submitting, uh, one, one*

	<p><i>variation to to to 10 agencies, and then you get 10 different set of questions and some questions might be repeating just slightly different from each other...'</i></p> <p><i>AS7 '...Yeah. Personally, so current system completely harmonize is difficult, is my impression. They have their own voice. I feel, of course they have ASEAN's, how do you say? They will decide their fundamental document, but still they want to have their own voice, maybe... My personal impression, maybe not harmonize like in EU...'</i></p>
<p>Motivation and incentives</p>	<p>Economic advantage/trade</p> <p><i>AS4 '... So they wanted to make the ASEAN market in line with how the European Union, to have the trade easily in all these 10 markets, which is there in the ASEAN. And with that objective, they started making the ASEAN..... More than guideline I would say trade...'</i></p> <p><i>AS1 '...And it's because of ASEAN's economy pillar that they want to form something like a community of ... what do you call it. A community of ... let me see. Yeah, they want to do something like a EU kind of thing but maybe to that scale...'</i></p> <p><i>AS4 '... See, what is the objective of any harmonization? Finally you do harmonization to get the benefit in terms of trade...'</i></p> <p>Reduce duplication of effort and documents</p> <p><i>AS5 '...But when they develop the requirement, at least they have a direction to follow, not to make it too different from the core requirement at least...'</i></p> <p><i>AS1 '...because ASEAN harmonization, the ASEAN variation guideline actually had ... they are quite specific. There's a broad range of the kind of variations that a drug can have. So it sort of cuts down the work that regulatory professionals have</i></p>

to do. Because previously you have to go to the authority to ask them, okay if I have this change, what are the documents I need to provide. But now with the ASEAN variation guidelines you can just flip and find the categories that fit and file the same variation package in each countries...'

AS5 '...But if you create document, let's say you have five reports, you go to Singapore, they accept it, that's good. Then you go Malaysia, they also accept it. So that's the good news that your five report go everywhere, the documentation requirement quite close...'

AS5 '...so you don't need to duplicate a lot of effort to do something extra for this country, this country very, very different, et cetera. So your core technical documentation will be quite similar because of this effort, ASEAN effort...'

AS1 '...And the good thing about being harmonized right now for us young countries, I mean most of it is harmonized, not exactly all ... between these three countries is that you just repeat that one set of documents and you can file in all three countries...'

Become an attractive market/candidate for innovative products

AS3 '...actually, one of the things that drew them is that they wanted to be an attractive market, so that the people there, the local people, could benefit from having innovative products...'

AS3 '..... that was actually recognized and written on their charter, it said, if there still exist as individual countries with each individual regulations, it **adds complexities** for pharmaceutical companies to get product registered in their market...' [to remove complexities or simplify registrations]

AS3 '....That was one of the thoughts for the harmonization, is that, if they achieve harmonization, they become a more **attractive market** because of the size of the harmonized area, and so, they can have access to innovative products...'

AS3 '*...Because they want to achieve a political harmonized area. That's why they can do it, it's because they share this wanting, they share this vision to be, yeah, an **economical** and **political** harmonized area...*'

AS8 '*....I do believe the harmonization will bring more business opportunity to the region...*'

climatic zone:

AS7 '*...Based on the stability studies, they gathered together and suggest to change the climate zone for the stability study. Then they also think they should have their own common technical document, so ASEAN CTD...*'

AS3 '*...Well, for the pharmaceutical regulation, I think it was also this climatic zone, 4B, because it's really the only common thing they have between them...*'

AS3 '*...ICH tried to set a specific stability protocol for climatic zone 4B, but the constant country were not satisfied with these standards, and so, they established a stability protocol which was really representative of their own climatic zone. It was also something that put them together. And to be able to build this standard which was not taken into consideration by the ICH*

Government buy-in

AS5... *There is, in ASEAN they even, the Prime Minister sign ASEAN document. So it's Prime Minister level. You can see it's very super senior buy-in.*

Challenges to harmonisation	
Not following harmonised guidelines	<p><i>'AS1..No, they're not law...So they're just guidelines so you can choose to follow or not...So what happens in these three countries is following the variation guidelines they actually came out with their own guidelines. Very, very similar to the ASEAN variation guidelines, but they are, they have their own...'</i></p> <p><i>AS4 '... They do follow it, but there is something additional also they do expect later, that's the question. So you can submit a document based in ACTDR, however you have to also submit as and when they ask questions and as and when they evaluate...'</i></p> <p><i>AS4 '... It does change from evaluator to evaluator...'</i></p> <p><i>AS9 '...and we do not have to explain to, you know, imagine submitting, uh, one, one variation to 10 agencies, and then you get 10 different set of questions and some questions might be repeating just slightly different from each other...'</i></p>
Classifying variations differently	<p><i>AS4 '...Yes. They have defined it as major and minor variation. (when asked about variation guidelines)...So their classification is not aligned. The requirement, they have the national guideline. So I wouldn't say they're harmonized. Sorry. I don't think they are harmonized.</i></p> <p><i>AS4 '... No, I don't think so. It's only, they have a harmonized guideline. However, if you go to Malaysia, they have a long, detailed, a hundred pages guideline for approval. Singapore has its own guideline. The pathway, they have are different.</i></p>

	<p><i>Thailand is totally new medical, new drug, new generic, three pathways. Malaysia has another pathway. Singapore has another pathway. Classification route is different...'</i></p> <p><i>AS8 '...But if you, you, from industry perspective, if you put so many countries specific requirements, it really creates the hurdle for the industry to enjoy the harmonization...'</i></p>
<p>Requirements for local manufacturers differ to foreign manufacturers</p>	<p><i>AS8 '...But then their concern is the local industry. How about local industry? So they cannot, you know, let's harmonize the international standards to multinational company only. Right? So that is not the way for, for the legislator. And the new legislation should be applicable to all the players in the markets...'</i></p> <p><i>AS8 '...So those are the local, generic, pharmaceutical companies, which may have relatively small scale, which may use to those traditional way of working, which may not have, uh, you know, highest uh highest standard from GXP perspective. It doesn't also doesn't necessarily mean they don't want to be, but it just means they don't have sufficient revenue to support the investment...'</i></p> <p><i>AS6 '...While coming to implementation, every country has its own challenges. First of all, they should take care of their own manufacturing companies, so do they really upgrade their standards to arrange the documentation to that level or not?...'</i></p>
<p>Changing local laws to accommodate harmonised requirement is difficult</p>	<p><i>'AS1...Yes, so the market has the right to change it. Of course, they try to, at the PPWG, they try to agree but most of the times because of some laws preventing them from doing it. Because to change their law, they have to go back. It's not so easy or legal process. So they just choose not to follow....'</i></p>

	<p>AS1 Sometimes it's due to a law, like they might have a law that prohibits them from following directly, like a wholesale and sometimes it might be just due to some legacy issues or some local domestic industry cannot fulfill these requirements</p>
<p>Lack of legal backbone and political reasons</p>	<p>AS4 ‘... Like I would say that EU, so you have a European Union. If you have a European Union, all countries are legally aligned with each other and their trade, and law wise, you are allowed to do that. If you have a harmonized guideline, but you are not legally or by law, if you're not allowed to freely trade within the market or register in each other market or respect each country's opinion, that's no harmonization....’</p> <p>AS8 ‘... I should say a fundamental problem for ASEAN country, from my perspective, uh, why the harmonization process is that slow is that the ASEAN organizations itself is not the same as the European region. If I can refer to, they don't have a legislation basis...’</p> <p>AS5... Number one, harmonization is super easy. If you have a definition, I have a definition, the word different, let's adjust let's agree one. That to me, super, super easy. The difficult, difficult part is the politics... You will never approved in Europe, then you'll be automatically be approved in U.S., never, because of the political reason</p> <p>Political will</p> <p>‘AS5... Yes, the important reference, you can also look at the U.S. and Europe, they are here for so many years and doing their pharmaceutical regulation, are they harmonized? No. Will they harmonize? No</p> <p>AS5... But without political, they're letting very little motivation to harmonize the technical part like that because you need compromise. Why me compromise, not you?’</p>

Assessment of agency Transparency and Coordination	
Transparency- Singapore	<p><i>AS4 ‘...Singapore is quite good in comparison to all three markers, they are open for comments and their transparency is good, their response is good. Whatever questions you have, you really get answers easily, even industry can comment. So yes, Singapore is quite ahead as compared to other two agencies’</i></p> <p><i>AS5 ‘... But they do listen, they do organize meetings to listen to your feedback...’</i></p> <p><i>AS5 ‘...Singapore of course I would say industry-friendly, if 10 is a full mark, I would give a eight. So they proactively publish all their regulations, guidance document if you don't understand, and they always have a hotline to answer your questions, you can schedule meeting with them</i></p> <p><i>AS7... I feel personal, my impression they listen to industry's voice very well. Before guideline and regulation implementation, normally they will have a public comment</i></p>
Malaysia transparency	<p><i>AS5 ‘...but when you come to Malaysia is relatively less and well established maybe, maybe infrastructure, et cetera...’</i></p> <p><i>AS5 ‘...Malaysia, I think they're more industry-friendly in the sense of communication. Now, when they talk, they give you advice, they tell you the answer maybe straight away...’</i></p> <p><i>AS5 ‘...You ask this, they say yes, ask that one, they say no. And then we sometime confuse. So they are friendly, but you end up you have two problem.</i></p>

	<p><i>One, you got different answer and two, actually you should not get answer from government because from my angle, a lot of times you're subjected to interpretation. You cannot just ask a question like over the phone or right now in front you, if this, this, this, what would be my product classification and do I need to do submission?...</i></p> <p><i>AS5 '...So they're friendly, sometimes friendly, dangerous'...</i></p> <p><i>AS4 '... So Malaysia, we do interact with them. However, the response comes with... it takes a little longer. In terms of promptness I think it is second to Singapore...'</i></p>
<p>Thailand transparency</p>	<p><i>AS4 '....Thailand is very difficult to even get a response. And another portion is the language barrier. You don't know to whom to coordinate. Even if you have some email, it becomes unclear and as you don't have a local representative, you can't generally get input from Thailand...'</i></p> <p><i>AS5 '...Thailand, even more helpful, even more dangerous. In their style. Thailand people, very nice people. So they are very nice...'</i></p> <p><i>AS5 '...So if you're a foreigner, you need to send your own local team member to listen what's going on maybe, but that is a language barrier, not their problem, but that's a challenge there...'</i></p> <p><i>AS7 '... I feel Thailand is, compared with Singapore, a little conservative, but still open...'</i></p>

Assessment of agency maturity and expertise	
Competency and maturity	<p>AS1 '<i>...Because Singapore is rich, they can afford to hire more qualified people. So you have people with PhD working in an evaluation committee and generally Singapore just because it's a more developed country...</i>'</p> <p>AS5 '<i>...Singapore government relatively, well, established, maybe the regulatory more experienced...</i>'</p> <p>AS3 '<i>...what is difficult in the ASEAN area is that the countries have very different levels of competency in terms of regulation and medicinal variation...I guess that's, the leading country feel that maybe they should have additional requirements to compare to what is currently discussed as harmonized regulation across the area...</i>'</p> <p>AS8 '<i>...So that, those, those, so that's, that's why I'm saying if all those authority and the industry are not on the same page at all, not at the same maturity level is one of the reason why the harmonisation is moving, not that fast...</i>'</p>
Lack of coordinated leadership from ASEAN	
	<p>AS4 '<i>.... Who is ensuring or asking or mandating implementation of harmonized guideline? No one...</i>'</p> <p>AS8 '<i>...ASEAN has been established for approximately 20 years if I'm not there wrong, or even more than that, more than 20 years. And the, PPWG meeting, if also I'm not wrong, it's more than 10 years. The working mechanism for PPWG is trying</i></p>

	<p><i>to harmonize the ASEAN guideline. So, but to be honest, the progress of such harmonization is its way slower than what I expected. You can see how many, how many, uh, uh, guidelines they have published since 10 years. So more than 10 years ago, it's only like five, six guidelines. Variation guide, is one, uh, BE study is one, GMP is one, this time, I even didn't see any significant guidelines...'</i></p> <p><i>AS5 '...but when you look in the organization, there is no timetable, no action plan, nobody talk about harmonization timetable. When? When will you harmonize? No, nobody talk about it....'</i></p> <p><i>AS3...Apart from ego [of NRAs] ... I don't really know, actually</i></p>
<p>Strategies to improve the implementation of harmonization</p>	
	<p><i>AS4 '...I think first of all, they have to start using the same guideline across ASEAN, number one. Number two, they have to see how it is going to respect each other's approval and have one country's approval, industry should be able to market in other markets as well within ASEAN. Then it will be helpful...'</i></p>

Appendix 21 LATAM NRA Questionnaire responses

Question	NRA3	NRA1	NRA2
Type of Agency	Autonomous agency, independent from the Health Ministry administration	Autonomous agency, independent from the Health Ministry administration	Operates within the administrative structure of the Health Ministry
Number of staff who review CMC variations	20	Unsure	15 out of 130 reviewers of drug products
Does your agency collaborate with other NRAr	Yes <i>I mean, there are some meetings, for instance in MERCOSUR, there are some collaborations. Often we respond to some doubts, but not discuss specifically a product. That's not happening. The collaboration is just on a high level, in the sense that sometimes we discuss regulations. Sometimes we discuss general actions, but not really product by product. Participant:</i>	Yes	Yes, [NRA] is currently working with Cuba and Argentina to exchange of technical information. Guidelines and regulatory framework is still on progress.

	<i>We do not make, for instance, collaborative analysis and these kinds of action is not made, at least not yet. And nothing that involves CMC. So sometimes we discuss regulations, drug regulations, but it's not specifically for CMC. It's more a general discussion.</i>		
Do any of these collaborations involve discussions on CMC variations?	Not specifically. Some collaborations involve CMC discussions on a high level, but not specific CMC changes.	No, as far as I know.	Not yet.
What is the role of MERCOSUR? Is the agency actively involved or planning to do so?	Not specifically for drugs CMC topics.	[NRA] isn't part of MERCOSUR.	[NRA] is not part of MERCOSUR and has no plans to join.
In your opinion, does MERCOSUR have plans to streamline CMC variations within the region? Is the Agency part of this initiative, if applicable?	Don't think MERCOSUR has specific plans for CMC variations. The Agency could be part of this initiative, but probably harmonization within ICH would be preferred, if we had to choose between them.	N/A	N/A
What is the role of PANDRH in the region? How is the Agency	We do not have any specific discussion for CMC topics.	What we see as the role of PANDRH is to share and facilitate, the implementation and	Practically all cooperation and convergence takes place within the

<p>involved with PANDRH?</p>		<p>adoption of scientific and regulatory advances in the field of human health, taking into consideration priorities and necessities in the Region of the Americas.</p> <p>Our agency, [NRA] has been involved in several projects and activities of PANDRH, several published technical documents have the contribution of [NRA], for example, the Technical Document No. 1 of PANDRH named Harmonized Requirements for Registration (MA) of Vaccines in the Region of the Americas and Guide for the preparation of an appliance of Sanitary Registration (Requisitos armonizados para el registro de vacunas en la Región de las Américas y Guía para la preparación de una solicitud de registro sanitaria), was coordinated by [NRA].</p> <p>2 projects [NRA] are involved in: Assessment of the requirements of the Certificate of Pharmaceutical Product (CPP) for registration processes of medicines in the region of the Americas towards a more timely</p>	<p>framework of the PANDRH, [NRA] is the</p> <ul style="list-style-type: none"> Antimicrobial Medical devices Regulatory Convergence (Equivalence Agreements) Risk management plans (Pharmacovigilance) Pharmaceutical Product Certificate [Market], through [NRA], is a member of PANDRH, which implies participating in projects that are of interest. Currently we are alternate representative of the Steering Committee As of the next PANDRH Conference, it will be made official that [NRA] is the representative of the North American Subregion on the Steering Committee.
------------------------------	--	---	---

		access to medicines and more convergent regulatory approaches; Containment of antimicrobial resistance; For Medical Devices: Strengthening of regulatory capacities for Medical Devices (Colombia and Cuba).	
As per your knowledge, has the agency proposed a project to PANDRH for alignment of CMC requirements within the region? Give reasons for your answer	No, It seems to me that harmonization among ICH agencies [<i>countries that are members, not observers</i>] is preferred, and due to limited human resources it does not seem feasible to run parallel harmonization works. <i>All the actions that we take internally are always focusing on ICH. For instance, we do not really look at the regulations of other American agencies [meaning LA Agencies]. We do not really discuss with them, not in the first place. We always prefer to align to ICH guidelines. So if Mexican or Argentinian regulation is different from ICH, we would definitely prefer to follow the ICH guidelines. And we</i>	No. We haven't receive information about any project with this objective.	No, No, CMC is not priority for PANDRH projects.

	<i>participate more on the ICH guideline and less actively on other MERCOSUR or other Latin American discussions.</i>		
ICH member or observer?	ICH member	ICH observer.	ICH observer
In your opinion, does the Agency seek to adopt ICH guidelines and hence ICH CMC requirements? Give reasons	Yes. The Agency is working to implement most of ICH "Q" guidelines, and has already implemented some of them, as it can be seen in ICH's website. We are taking as priority the harmonization with ICH guidelines that refer to post-approval change, mainly ICH Q12 (that refers to Product Lifecycle Management, including post-approval changes). Other ICH guidelines that are also important for post-approval changes (e.g. Q8, Q9, Q10) are also being considered. So, we are prioritizing harmonization among ICH authorities. Also, we intend to start in the next months a maintenance procedure for our post-approval changes resolution of small molecules (GUIDELINE), in order to	Yes, and there are evidences. For example, in Resolution [XXX] of [DATE], Regulation [XXX] Guidelines of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopted by [NRA]. There is a list of 35 guidelines of ICH adopted by [NRA]. Unfortunately, at the beginning ICH was focused in MA of new products and guidelines for CMC changes weren't included. Only Q5E guideline (for biological and biotechnological products) is related with CMC changes (Comparability of biotechnological/biological products subject to changes in their manufacturing process).	Yes, currently [NRA] is seeking to be a member of ICH. The main reason for [NRA] to be a member of ICH is harmonization and convergence with most of the world's regulatory agencies

	<p>implement some enablers that are present in ICH Q12 guideline and seek for harmonization with post-approval changes both for implementation type (notification, prior approval, etc.) and for tests required. However, we are facing some difficulties in this harmonization work, because both implementation types and requirements seem not to be fully harmonized amongst ICH regions. Anyway, we intend to issue a public consultation by the end of 2021 / beginning of 2022 in order to have an ample discussion with stakeholders and to have a Resolution that is as harmonized as possible with other ICH members.</p> <p><i>Yes. I can give an example. We have the ICH Q1 guidelines, they are stability guidelines. We had recent work to implement ICH Q1. We consider it implemented.</i></p>		
--	---	--	--

	<p><i>However, when we go deeply in specific cases and when we discuss with the agencies, with EMA, with PMDA, FDA, they have different responses.</i></p> <p><i>Participant:</i></p> <p><i>So it seems to me that it did not fulfill 100% its aim to harmonize all the procedures. There is some harmonization, but when you go... We still need to discuss and to harmonize some things. So this is more common for old ICH guidelines, Q1, Q2. I think because they are old. There are so many new thinkings, so many new approaches. And it makes it difficult to have deep harmonization. And the Q1 guideline for instance, even founder members of ICH had problems to adopt. And I think it's because some terms and some specific actions are not really covered by the guideline. And we also have the other side, the newest guidelines,</i></p>		
--	---	--	--

	<p><i>Q12 for instance, in this case we just have different ways to implement among the agencies. So we have some agencies like the FDA that have more facility to implement it. And some other agencies like the European agencies, the EMA and national agencies, that have some legal problems and need to treat them before implementation, let's say. I think this is temporary and should be solved. But for the old guidelines, I think they just need to be revised, because some things need to change in order to assure total harmonization.</i></p>		
<p>As per your knowledge, are there any WHO initiatives to streamline CMC requirements?</p>	<p>Not sure</p>	<p>Yes. There are some examples in favour to standardization of requirements of CMC, in more general contexts. One example is the approach of WHO about CMC included in Guidelines of WHO. For example, The Blue Book. Marketing Authorization of Pharmaceutical Products with Special Reference to Multi-source (Generic) Products. A Manual for</p>	<p>No</p>

		<p>National Medicines Regulatory Authorities (NMRAs)”, published in 2011. It includes a chapter for Variations (https://www.who.int/publications-detail-redirect/9789241501453).</p> <p>The WHO initiative about Benchmarking, related with the strengthening of Regulatory Systems and the Global Benchmarking Tool for the assessment of Regulatory Systems, in the Module of MA includes subindicators related to CMC. I think it is a very important initiative, which is not specific for CMC but that benefits the common approach. More recently, the guidance evaluating and publicly designating regulatory authorities as who-listed authorities (now in public consultation), gives more importance to the accomplishment of these indicators/subindicators of the GBT, and represents an incentive for to afford the Maturity Level 3 for national and regional regulatory authorities.</p>	
--	--	--	--

		Should be considered that these are common tasks for WHO and PAHO.	
If you answered 'YES' to Q14, in your opinion, is the Agency involved in WHO's initiative to streamline CMC requirements?	Not sure	Yes. We have for national guidelines WHO as the first reference and [NRA] is deeply involved in the GBT and WHO Listed Authorities (WLA)'s activities.	
In your opinion, would the Agency envision the creation of a central regulatory body for Latin America or in subregions of Latin America? (similar to EMA in Europe)	NO	NO. The initiative for the creation of the Drug Regulatory Centre (ALBAmed) as a tool for countries of ALBA, operating with the new Drug Grannational Registration (countries participating: Bolivia, Cuba, Ecuador, Nicaragua and Venezuela). [MARKET] was the coordinator of this Regional Project, but the development of the centre was interrupted. It was prepared and agreed a model guideline for Drug Registration which included a chapter for Variations.	No
In your opinion, would PANDRH or MERCOSUR be suitable for such a task ie central regulatory body? Please elaborate	There seems to be no movement in [NRA] to create a central regulatory body such as EMA in Latin America. This possibility seems very unlikely to me, both in short and in medium-term, both for internal	No for the moment. It is a very complex process and not only the technical point of view is involved.	PANDRH will be more likely to be a central regulatory body for [MARKET], because it also contains the main business partners of Mexico, USA and Canada.

	reasons (reviewers seem to have a trend to "prefer" harmonization among ICH authorities and often see regional harmonization more like a "burden") and due to the current political situation in the region.		
How does the Agency categorise the listed variations	All 5- Other	All 5 categorized as Type 1 According to the National Rules for Sanitary Registration of Medicines for Human Use (Reglamento para el Registro Sanitario de Medicamentos de Uso Humano), Resolution of MINSAP No. 321, from September 29, 2009, Section Fourth, Requirements for Modifications, Chapter VIII Article 80, there are two categories for post approval variations (CMC): those which require approval prior implementation (Type I) and those that could be notified only (Type II). Type I could be recognized as Major changes.	All 5 classified as major apart from change in manufacturing method which is 'no categorisation'
What is the stipulated/published review timeline for the following variations (in months):	Change in Drug product manufacturer (addition or replacement) : Category can be minor or major (refer to [GUIDELINE] – [DURATION]	According to the [GUIDELINES] Resolution of [NAME], from [DATE], Section [NUMBER], About [PROCEDURE], for all	[DURATION] working days

	<p>days on Agency's time (clock stops if deficiency letter is issued) - if change does not require in vivo data (e.g. bioequivalency study) it may be implemented if Agency does not respond in [DURATION] days / immediate notification if minor Change in manufacturing method : Category can be minor or major (refer to [GUIDELINE] – [DURATION] days on Agency's time (clock stops if deficiency letter is issued) - if change does not require in vivo data (e.g. bioequivalency study) it may be implemented if Agency does not respond in [DURATION] days / immediate notification if minor Change in storage condition : Category can be minor or major (refer to [GUIDELINE] – [DURATION] days on Agency's time (clock stops if deficiency letter is issued) - if change does not require in vivo data (e.g. bioequivalency study) it may</p>	<p>appliances of changes, [NRA] has till 150 calendar days.</p>	
--	---	---	--

	<p>be implemented if Agency does not respond in [DURATION] days / immediate notification if minor Change in shelf life : Category can be minor or major (refer to [GUIDELINE]) – [DURATION] days on Agency's time (clock stops if deficiency letter is issued) - if change does not require in vivo data (e.g. bioequivalency study) it may be implemented if Agency does not respond in [DURATION] days / immediate notification if minor Change in formulation : Category can be minor or major (refer to [GUIDELINE]) – [DURATION] days on Agency's time (clock stops if deficiency letter is issued) - if change does not require in vivo data (e.g. bioequivalency study) it may be implemented if Agency does not respond in [DURATION] days / immediate notification if minor</p>		
--	--	--	--

<p>What is the average review timeline (actual) for each of the listed variations (in months):</p>	<p>Change in Drug product manufacturer (addition or replacement) : FOR MAJOR CHANGES: about [DURATION] days (total time). Change in manufacturing method : FOR MAJOR CHANGES: about [DURATION] days (total time). Change in storage condition : FOR MAJOR CHANGES: about [DURATION] days (total time). Change in shelf life : FOR MAJOR CHANGES: about [DURATION] days (total time). Change in formulation : FOR MAJOR CHANGES: about [DURATION] days (total time).</p>	<p>Statistics are not available, but within the established limits for all of them.</p>	<p>Change in Drug product manufacturer (addition or replacement) : [DURATION] months Change in manufacturing method : Depends on the change involved up to [DURATION] months Change in storage condition : [DURATION] months Change in shelf life : [DURATION] months Change in formulation : Depends on the change involved up to [DURATION] months</p>
<p>In your opinion, is the Agency working towards improving the current review timelines for CMC variations?</p>	<p>Yes</p>	<p>Yes. The general policy is to accomplish the established times and to reduce them as possible.</p>	<p>Yes</p>
<p>In your opinion, are there any improvements that the agency is implementing / could implement to improve timelines?</p>	<p>Yes. We are working at: - Internal procedures for expedited and abridged reviews; - Change in some classifications (to increase</p>	<p>No response</p>	<p>Yes, currently [NRA] is seeking more reliance mechanism with the Agencies that are already covered by an equivalence agreement and expect to do more agreements with LATAM countries.</p>

	the number of minor changes).		
In your opinion, the Agency's current CMC Requirements are more aligned to which guidelines? Provide further details for 'other' or 'local guidelines'	EMA guidelines, Local guidelines and Other. Our CMC requirements were based in many different guidelines, including EMA, Health Canada and also keeping some requirements from an old Resolution, and this is actually one of the main problems. It ended up as a "mix" of many different conditions and tends to result in conservative classifications in many cases.	WHO guidelines	Local guidelines. Local guidelines, all major variation required stability and traceability of all raw materials and finished product used in the batches under stability. [cos ich or int guidelines do not ask for such detail]
The Agency's CMC variation requirements/guidelines have been updated within the last:	Within the last 3-5 years	More than 10 years ago	More than 10 years ago
In your opinion, what triggered the review of the requirements? eg out of date requirements, change in global landscape, local update with or without reference to the global landscape? Please elaborate.	The review of requirements that resulted in [GUIDELINES] was mainly due to out of date requirements. The new review that we intend to take in the next months considers Q12 and an internal need for more flexibility.	The incidence of certain types of changes, because of the development and evolution of the National Pharmaceutical Industry.	Until now, only format updates have been made without affecting the content. Stakeholders know well the regulation to submit CMC variations. The agency can make a better decision to grant authorization given the context of the request.

If there have been no review of the requirements, please elaborate why this is the case in your opinion		Regulatory priorities of the [NRA].	
Does the agency have any reliance pathways for reviewing CMC variations (using reference agencies such as US FDA, EMA, other NRAR, etc.)? If yes, please state which reference markets.	Yes. All ICH members are eligible, but it is analysed case-by-case.	No	Not yet
If you answered 'Yes' to Q28 , please elaborate on 'HOW' this reliance works (eg. use of approval letter, use of reference market package; review of questions raised by reference market etc)	We have a pathway [NAME], but it is very recent (April/2020) and we did not receive many submissions. The COMPLETE evaluation report is required (public evaluation report and approval letter are not sufficient because many CMC aspects are considered confidential).	-	-
Streamlining of CMC variations is a priority for the Agency:	Moderately agree	Neutral	Neutral
The Agency would like CMC requirements to be streamlined via harmonisation within	Slightly disagree	Slightly disagree because it is too ideal	Strongly disagree

the region (regulators across Latin America agree on the same requirements):			
The Agency believes it will be beneficial to streamline CMC requirements within the region:	Slightly disagree	Strongly agree	Slightly Disagree
The Agency would like to align CMC requirements to international guidelines (convergence)	Strongly agree	Strongly agree It means updating	Slightly agree
The Agency believes it will be beneficial to align CMC requirements to international guidelines	Moderately agree	Strongly agree. It means updating.	Strongly agree
Please elaborate on your answers to Q30 to Q34	There seems to be more effort in harmonization and convergence with ICH requirements, and not so much effort in harmonization with regional requirements. The harmonization with international requirements tends to be beneficial (reduce risk of shortages and confer more flexibility) but care should be taken, especially with national	* During the process of updating the national requirements for changes these questions will be answered.	Current priorities for [NRA] are COVID products, vaccines and drug product of national interest, the rest of the variations are reviewed according to first in first out. In order to maintain its position worldwide [NRA] finds necessary to have the most possible harmonization with the high surveillance agencies.

	manufacturers, because the harmonization requires a big change in culture (abandon "how-to-do" Resolutions and focus on scientific-based and guidelines and often case-by-case decisions).		
Convergence can occur in various ways. Three processes are listed below. For your agency, which of these processes are they seeking to follow: reliance, cooperation, recognition	Reliance, Cooperation	Cooperation	Reliance, Recognition
What does the Agency consider to be the drivers or reasons for wanting to streamline within the region?	Difficulty to deal with high workload due to limited resources; reduce the risk of product shortage; reduce regional specific requirements (especially the ones that result in regional-specific products).	Mutual interest.	To have faster and cheaper access to medical options that benefit the majority of the population.
What does the Agency consider to be the drivers or reasons for wanting to streamline to international requirements?	Difficulty to deal with high workload due to limited resources; reduce the risk of product shortage; reduce regional specific requirements (especially the ones that result in regional-specific products).	Maturity level of [NRA] and importance of Global market.	Being a more competitive country in terms of the supply of medical products as well as being better prepared for foreign investment in the manufacture of medical supplies.

Does the Agency envisage challenges with streamlining within the region	Yes	Yes.	
Please elaborate	Regional authorities have different cultures, and there seems to be a lack of political will to seek for regional harmonization	To be done with positive approach, and without doubts with potential benefit results.	With some countries like Cuba and Argentina the exchange of technical information is more accessible. The rest of the LATAM countries don't seem to be interested in harmonization.
Does the Agency envisage challenges in streamlining with international requirements?	Yes	Yes	Yes
Please elaborate	Need to change in culture and to improve enforcement, punishment and fiscalization activities.	It is always a challenge.	The agency is currently working in harmonization projects like implementation of CTD, being a member of ICH.
In your opinion, what is the Agency's view, on the likely direction of the LATAM region in terms of streamlining CMC Variations:	Converge to international standards	Converge to international standards	Converge to international standards
Industry comments are actively sought in relation to review of CMC requirements	Very often	Rarely	Very often
Elaborate	Industry comments are very important to consider the review of CMC requirements,	It is not common to have comments about CMC.	As part of the answer to Deficiency letter, industry can justify its answers.

	however we often receive different comments (sometimes in completely different directions) depending on the industry (small / big, national / multinational).		
Industry comments are accepted in relation to review of CMC requirements	Sometimes	Sometimes. When comments are received (about CMC, and about any subject, they are always review and also taken into consideration if applicable. The process for develop the guideline includes a phase of consultation with regulated, mainly with industry).	Very often
Regulatory Affairs professionals with LATAM experience were interviewed and reported that the Agency requirements were sometimes over and beyond what is expected by ICH for example. Do you agree with this observation?	Yes	No	Yes
Do you still envision the need for local requirements outside the ICH requirements?	Yes	Yes	No

<p>What local factors do you think possibly drive the request for regional or market specific documentation not covered by international guidelines (such as ICH requirements)?</p>	<p>Different climatic zone may lead to different stability requirements. Differences in taxation may lead to different procedures on lifecycle management.</p>	<p>ICH requirements haven't been addressed to generic products for many years, now it is changing, but there are not enough guidelines for not so new pharmaceutical products.</p>	<p>The amount of national or international producers is big in the market therefore asking additional documentation (traceability of batches for stability) mitigates lack of surveillance.</p>
<p>In your opinion, when different assessors in the Agency evaluate the same submission packages (same product type & variation), the results of the assessment will always be the same.</p>	<p>Disagree (similar submission packages can lead to different requests for documentation, depending on the assessor)</p>	<p>Agree (there is standardization among different assessors)</p>	<p>Disagree (similar submission packages can lead to different requests for documentation, depending on the assessor)</p>
<p>If you disagree to Q45, what do you think causes these differences in assessment?</p>	<p>Different depth in the review (due to a lack of a specific reviewer's guide), different levels of knowledge among reviewers.</p>	<p>Because in [NRA] we have guidelines, and Standard Operational Procedures (SOP), in order to standardize the assessments, even when they are performed by different assessors.</p>	<p>The lack of depth in the guidelines for CMC variations gives the reviewer much opportunity to use their own judgment.</p>

