



**EVALUATION OF THE REGULATORY REVIEW PROCESS OF
THE GCC CENTRALISED PROCEDURE: DEVELOPMENT OF
A MODEL FOR IMPROVING THE APPROVAL PROCESS**

A thesis submitted in accordance with the condition
governing candidates for the degree of

DOCTOR OF PHILOSOPHY

in

CARDIFF UNIVERSITY

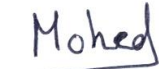
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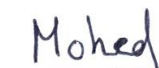
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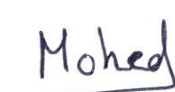
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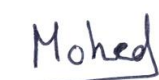
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ABSTRACT

The aim of this study was to evaluate seven GCC regulatory authorities and pharmaceutical companies active in the region in order to identify the strengths and weakness of the current GCC centralised procedure. The GCC regulatory authorities and the pharmaceutical companies who had registered their products through the GCC centralized registration procedure and the national registration systems were recruited into the study and asked to complete the questionnaires specifically designed for this study.

The regulatory review process in Oman was evaluated to identify areas for improvement in the system. Information on the total application numbers and approval dates were obtained directly from the Oman Ministry of Health archives. Another study was conducted to evaluate the regulatory review process and approval times of the remaining six GCC countries (Bahrain, Kuwait, Qatar, Saudi Arabia, UAE and Yemen) and the GCC central registration, with respect to review time for new and existing substances, to identify the strengths and weaknesses of the process and to propose strategies that could help the policy maker in the GCC to enhance the review process.

The results of the Omani regulatory system showed no significant increase ($p>0.05$) in the total number of registered pharmaceutical products from 2006 to 2010. The approval time in Oman showed that there was a significant increase in approval times for pharmaceutical products from 2006 to 2010 ($p<0.001$). The findings show that although there was an increase in the approval time for all pharmaceutical company products, the median approval time for the five year period was 117 days. This was within the time limit (4 months) fixed by the health authority for the overall registration time. The comparative study of the GCC States showed a downward trend in the median approval time for most of the GCC States, during 2008 to 2010. However, the approval time for all approved products in the GCC States during this period varied from 60 days in Qatar and Oman (2009 and 2010) to 609 days in Saudi Arabia (2008). The main reasons for the decrease in approval time in the Gulf States were due to the positive effect of the Gulf Central Registration, the rise in the number of reviewers in some GCC drug authorities, and the parallel procedure used in the regulatory approval review process. The study of the regulatory review process of the GCC central registration showed that a total of 413 products (96 NASs and 317 EASs) were approved during the period 2006-2010 with an overall significant increase in the EASs ($p<0.001$). The approval times increased from 107 calendar days in 2006 to 265 in 2010 ($p<0.001$). The lowest approval time was for EASs submitted by the Gulf companies (134 days) and the longest for NASs submitted by international companies (346 days) ($p<0.001$).

Both the regulatory authorities and the pharmaceutical companies agreed that the centralised procedure is an effective system for authorising medicinal products in all seven GCC countries in one procedure and is the way forward in the future but there is room for improvement in the procedure and the follow ups. They also agreed that clear guidelines, transparency of procedures, effective interactions between authorities and companies, increase in the number of the committee meetings per year, use of electronic on-line submissions will improve approval time for registration of new medicines, enhance the quality of review practice and encourage the pharmaceutical companies to use the GCC central registration system. This research has enabled development of a new model of the GCC central registration procedure to be proposed for the GCC Health Authorities which could improve patient access to medicines in the GCC states.

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LIST OF ABBREVIATIONS

AMRH:	African Regulatory Harmonization Initiative
APEC:	Asia Pacific Economic Cooperation
ADEC:	Australian Drug Evaluation Committee.
ATC:	Anatomical Therapeutic and Chemical code.
CACP:	Companies Assessment of Central Procedure
CATI:	Computer assisted telephone interviewing
CBER:	Centre for Biologics Evaluation and Research.
CIF:	Cost, Insurance and Freight
CIRS:	Centre for Innovation in Regulatory Science
CDER:	Centre for Drug Evaluation and Research.
CLADF:	Central Laboratory for Analysis of Drugs and Food.
CTD:	Centralised Technical Document
CHMP:	Committee for Medicinal Products for Human Use.
CMR:	Centre for Medicines Research
CPP:	Certificate of Pharmaceutical Product.
DGPA&DC:	Directorate General of Pharmaceutical Affairs and Drug Control
EMA:	European Medicines Agency.
EU:	European Union.
FDA:	Food and Drug Administration.
GACP:	Gulf Assessment of Centralised Procedure
GCC:	Gulf Cooperation Council
GCC-CP:	Gulf Cooperation Council Centralised Procedure
GCC-DR:	Gulf Cooperation Council Drug Registration committee.
GCP:	Good Clinical Practice.
GRP:	Good Review Practice.
HAS:	Health Sciences Authority of Singapore.
ICH:	International Conference on Harmonisation.
IND:	Investigational New Drug.
IT:	Information Technology.
KSA:	Kingdom of Saudi Arabia.
MA:	Marketing Authorisation.
MCA:	Medicines Control Agency.

MEB: Medicines Evaluation Board.

MERC: Middle East Regulatory Conference.

MERCOSUR: Mercado Comunal Sur

MHLW: Ministry of Health, Labour and Welfare.

MHW: Ministry of Health and Welfare.

MPA: Medical Products Agency.

NAS: New Active Substance.

NCE: New Chemical Entity.

NDA: New Drug Application.

NME: New Molecular Entity.

NGT: Nominal Group Technique

OCD: Office Centre Director.

PD: Pharmacodynamics.

PDUFA: Prescription Drug User Fee Act.

PANDRH: Pan American Network for Drug Regulatory Harmonisation

PK: Pharmacokinetics.

PMS: Post Marketing Surveillance.

PPRS: Pharmaceutical Pricing Regulation Scheme.

QA: Quality Assurance.

QCL: Quality Control Laboratory

R&D: Research and Development.

RC: Registration Committee.

RMS: Reference Member State.

SADC: Southern African Development Community

SOP: Standard Operating Procedure.

TCR&P: Technical Committee for Registration of Pharmaceutical Manufacturers & Their
Products & Pricing

TGA: Therapeutics Goods Administration.

TRIPS: Trade-Related Aspects of Intellectual Property Rights.

UAE: United Arab Emirates.

WHO: World Health Organisation.

WTO: World Trade Organisation.

GLOSSARY OF TERMS

Adverse event: Any untoward medical occurrence in a patient or clinical investigation of a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Africa, the Southern African Development Community (SADC): Angola, Botswana, Democratic Republic of Congo, Lesotho, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe.

Approval: The active substance has been approved for licence by a regulatory authority in one or more markets (when the authority grants a licence and subject to pricing/ reimbursement issues the product can be legally marketed).

Arab Central Registration (ACR): Jordan, UAE, Bahrain, Tunisia, Algeria, Djibouti, KSA, Sudan, Syria, Somalia, Iraq, Oman, Palestine, Mauritania, Yemen, Qatar, Comoros, Kuwait, Lebanon, Libya, Egypt and Morocco.

Asia-Pacific Economic Cooperation (APEC): Australia, Brunei Darussalam, Canada, Chile, China, Hong Kong, Indonesia, Japan, South Korea, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, Philippines, Russia, Singapore, Taiwan, Thailand, USA and Vietnam.

Association of Southeast Asian Nations (ASEAN): Brunei, India, Thailand, Philippines, Indonesia, Malaysia, Singapore, Myanmar and Cambodia.

Benefit/risk ratio: The benefit to risk ratio relates the potential or actual benefit that a patient derives from a treatment to the risks incurred by the patient through using the treatment. The benefit to risk ratio can be described in qualitative terms (high, low, equal, very low etc).

Binding: Advice provided by a regulatory authority prior to submission that is acknowledged and considered a regulatory agreement.

Biological: A substance isolated from animal tissues e.g. vaccines, hormones, antigens.

Biotech product: A naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or *in vivo* diagnostic use in humans. The only types of vaccines included in the biotech category are recombinant vaccines.

Centralised procedure: The Centralised procedure is used when marketing authorization covering the entire EU region is applied for, for example, for new biotechnological medicinal products and new innovative medicinal products. The applications for marketing authorization are then submitted to the European Agency for the Evaluation of Medicinal Products (EMA).

Clinical trial: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or to study the absorption, distribution, metabolism and excretion of an investigational product, with the objective of ascertaining its safety and/or efficacy.

Collaborative or sponsored research: The active substance is discovered as a result of research carried out in collaboration with, or sponsored by, another company, a university, government agency or an individual.

Co-operation Council of the Arab Gulf States (GCC): Bahrain, Kuwait, Oman, Qatar, United Arab Emirates and the Kingdom of Saudi Arabia.

Drug product: A finished formulation, for example, a tablet or capsule that contains the active substance, generally in association with one or more other ingredients.

Drug Regulatory Authority (DRA): The agency that develops and implements most of the legislation and regulation of medicines.

European Union Member States (EU): Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden The Netherlands and the United Kingdom.

Extrapolation of foreign clinical data: The generalisation and application of the safety, efficacy and dose response data generated in a population of a foreign region to the population of the new region.

Foreign region: Any region outside the new region where product authorisation is being sought.

ICH Regions: European Union, Japan and USA.

ICH: International Conference on Harmonisation.

Indication: The specific indication for which the active substance for the project is designed. This may represent the cure, alleviation, treatment, prevention or diagnosis of disease in humans.

Investigational New Drug (IND): An application that a drug sponsor must submit to FDA before beginning tests of a new drug in humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including structural formula, animal test results, and manufacturing information.

Launched: The active substance is made available for sale as an ethical prescription only medicine in the first market in any country.

Line extension: NASs which are already marketed but are being further developed for new indications, formulations, dosages, routes of administration, or novel drug delivery systems.

Local study: A study conducted in a single country with the primary aim of providing local experience with a compound.

Marketing Authorisation (MA): Legal approval granted to a company by a national (or regional) authority to market a medicinal product in that particular country (or region).

Marketing Authorisation Application (MAA): An application by a company for a marketing authorisation to be submitted to each country (or region) in which marketing approval is sought.

Mutual Recognition procedure: The Mutual Recognition (MR) procedure utilizes the marketing authorization granted for an active substance by another EU Member State, Norway, or Iceland. The Member State whose assessment is recognized as a basis for marketing authorization is called the Reference Member State (RMS).

National procedure: The national procedure is mainly used in cases where marketing authorisation is being applied for in a single member state within the.

New Active Substance (NAS): A chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product. The term NAS also includes: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously authorised; a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process; a radiopharmaceutical substance that is a radionuclide or a ligand not previously authorised as a

medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide that has not been previously authorised.

New Chemical Entity (NCE): An entity produced by chemical synthesis.

New Drug Application (NDA): An application requesting regulatory approval to commercially market a new drug for human use.

New Molecular Entity (NME): A product (including new chemical entities, biological products, vaccines and products of biotechnology) that has not been previously available for therapeutic use in man and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention or *in vivo* diagnosis of diseases in man. New salts, pro drugs and esters of existing products and certain biological compounds (e.g. antigens) are excluded. Combination products are also excluded unless one or more of the active constituents has never been previously marketed.

Pan-America Network for Drug Regulatory Harmonisation (PANDRA): Mexico, Costa Rica, Trinidad, Argentina and Colombia.

Pharmacodynamics (PD): Involves the study of the effect that a drug has on the body. This will include looking at what effect the amount of drug has, called a dose response, and will also look at the site of action of the drug, such as the kinetics of how a drug interacts with a receptor.

Pharmacogenetics: is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics: is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

Pharmacokinetics (PK): Involves the study of the manner in which the body handles a drug. It looks at the rate at which drug concentrations change in the body, and is involved with analysing the kinetics of absorption, distribution, metabolism and excretion of a drug.

Phase I: Initial safety trials on a new medicine, usually conducted in normal male volunteers. An attempt is made to establish the dose range tolerated by volunteers for single and multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g. in the field of cancer) or in less ill patients (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other epileptic medicines). Pharmacokinetic trials

are usually considered Phase I trials regardless of when they are conducted during the development of medicines.

Phase II: Clinical trials (pilot and well-controlled) to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose-response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy.

Phase III: Clinical trials conducted in patient populations for which the medicine is eventually intended. These generate additional data on both safety and efficacy in relatively large numbers of patients, in both controlled and uncontrolled trials. Clinical trials are also conducted in special groups of patients (e.g. renal failure patients) or under special conditions dictated by the nature of the medicine and disease. These trials often provide much of the information needed for the package insert and labelling of the medicine and also include trials that are conducted after the regulatory submission of a new drug application or other dossier, but prior to the medicine's approval and launch.

Phase IV: Phase IV clinical trials are (other than routine surveillance) performed after drug approval and related to the approved indication. They are not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose-response, or safety studies and studies designed to support an extended claim under the approved indication, e.g., mortality/morbidity studies.

Pivotal study: Well-controlled trial to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy.

Preclinical: *In vivo* and *in vitro* studies to support administration to man.

Pre-submission: The last patient visit for the last pivotal study to be included in the regulatory dossier is complete and the dossier is being prepared but has not yet been submitted to a regulatory authority.

Reference Member State (RMS): The EU member state that is chosen by a company to conduct the first review in the EU for marketing authorisation through the Mutual Recognition procedure.

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CHAPTER 1

General Introduction

BACKGROUND

Modern medicines regulations are the foundation of any country's drug policy. This ensures a viable pharmaceutical industry as well as a high standard for the drug approval process. Throughout history, governments have regulated food and drug products and in general, the focus of this regulation has been safeguarding the quality, safety and efficacy of these products. Drug regulation is almost universal in the industrialised nations of the world and is being progressively developed in third world countries. It is increasingly based on the hypothesis that regulation is needed to ensure that new medicines will be comparatively safe and effective, labelled accurately and marketed responsibly. In short, potential benefits and harms of modern medicines are too important to be left to the market place and the unregulated functioning of the pharmaceutical industry (Philip *et al* 1986).

Today, pharmaceutical products are highly regulated in most countries and need to comply with strict legislative requirements before being authorised for sale. Therefore, individual pharmaceutical regulatory bodies in each country are responsible for ensuring the safety and effectiveness of human and veterinary medicines in their jurisdiction, in compliance with local pharmaceutical legislation.

Regulatory Reviews Process, Approval Times and Patients' Access to Medicines

Anderson (2004) commented on the importance of timeliness for national regulatory authorities in order to approve new medicines, which may influence directly the stakeholders and patients during the process. A lengthy approval process results in a delay in marketing new approved medicines for patients. Normally, the length of the review process depends on the type of products being registered, the requirements of the approval process and the type of review carried out.

Governments are obligated to provide their citizens with access to new medicines and therapies when they are needed. In other words, conducting safety and efficacy reviews of marketing authorisation applications for new medicines and biotherapy products in a timely manner should be a major priority for safeguarding and enhancing public health, which is part of the core mission of health authorities. However, expediting the review process for new

medicines and biological products to ensure it is completed within predefined deadlines should never mean that regulatory standards can be compromised as they are essential to proving the safety, efficacy and quality of new medicines.

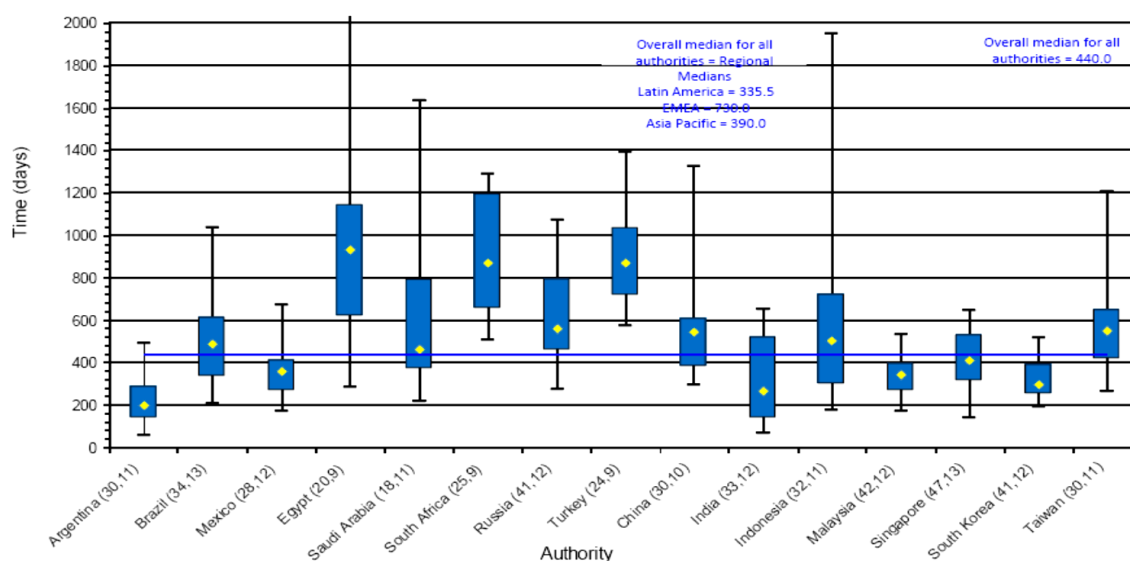
During the process of review and approval of new applications, the most important hurdles to the pharmaceutical industry is the length of the review time (CMR, 2001). Therefore, efforts have been made by several national authorities to allow patients' access to medicinal products in a timely manner by reviewing their strategies to monitor the efficiency of the review process, as well as the performance of the regulatory authorities (Mallia-Milanes, 2010).

Hill and Johnson (2004) suggested that in order to exploit the differences in registration requirements of different countries for manufacturers they should synchronize and streamline the registration process. Ultimately these unifying processes reduce the time lag for registering new products, as well as reinforcing the 'assurance of quality' of medicines. Furthermore, it is possible to complete and monitor the whole review process transparently within a reasonable time frame satisfying both the manufacturers and regulatory authorities. An effective review process is perceived through the overall approval times from submission to patients' access to new medicines (Rawson, 2000; Anderson, 2004).

Many countries have legislated maximum times allowed for the review of dossiers. For example, the target time-frame for completing the review process in the European Union centralised system is 210 days. This authorisation period has two points known as 'clock-stops' - at 120th day and 180th day. A time-scale of three months and one month, respectively, will now be mandated for applicants to respond and these periods may be doubled upon request (EMA, 2009). The longest review time usually occurs when the benefits of the product are not evident.

A study reported by the Centre for Innovation in Regulatory Science (CIRS, 2013) on New Active Substances (NASs) approved in the emerging markets between 2007 and 2011 indicated that there were considerable differences among countries in the time taken to review medicinal products with median approval times ranging from one to three years (Figure 1.1).

**Figure 1.1 Regulatory approval times from date of submission to date of approval
for New Active Substances (NASs) approved 2007-2011**



Data are shown for NASs that were approved between 01/01/2007 and 31/12/2011. (n1) = number of drug applications, (n2) = number of companies providing data. Box: 25th and 75th percentiles. Whiskers 5th and 95th percentiles ◆ = median

These study data (CIRS, 2013) for the median times for patients' access to NASs approved by the three major drug regulatory authorities namely, FDA, PMDA, and EMA from 2003 to 2012 showed that the median time for patients access achieved by the US FDA was the shortest among these three authorities (Figures 1.2 and 1.3).

Figure.1.2. Number of NASs approved by ICH agencies (EMA, FDA, PMDA) by approval year (2003-2012)

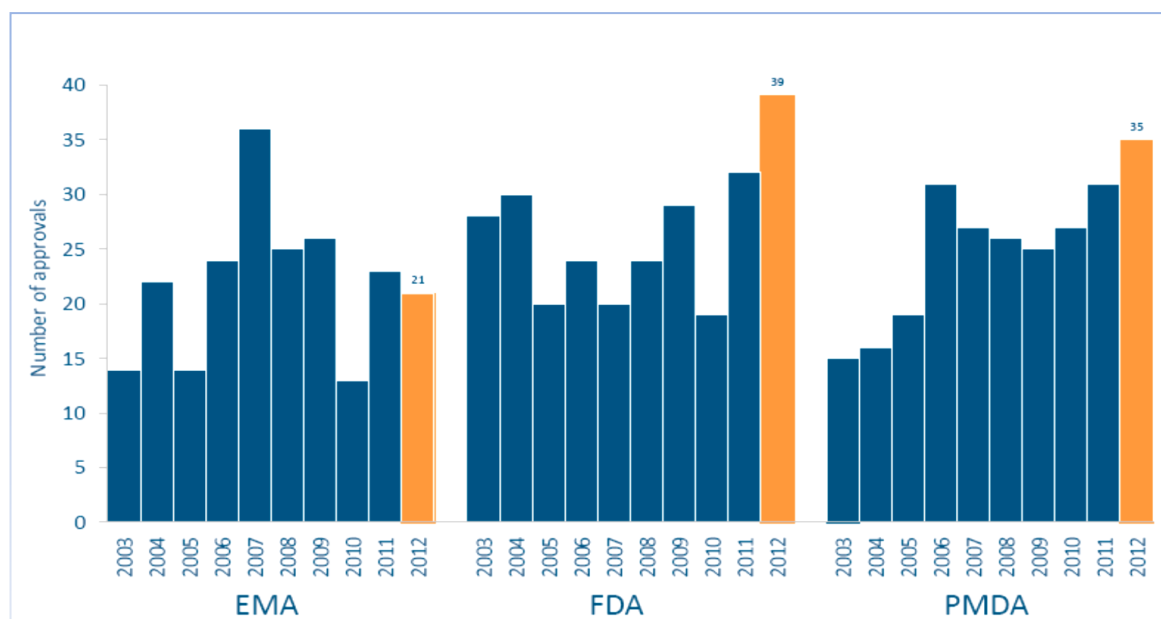
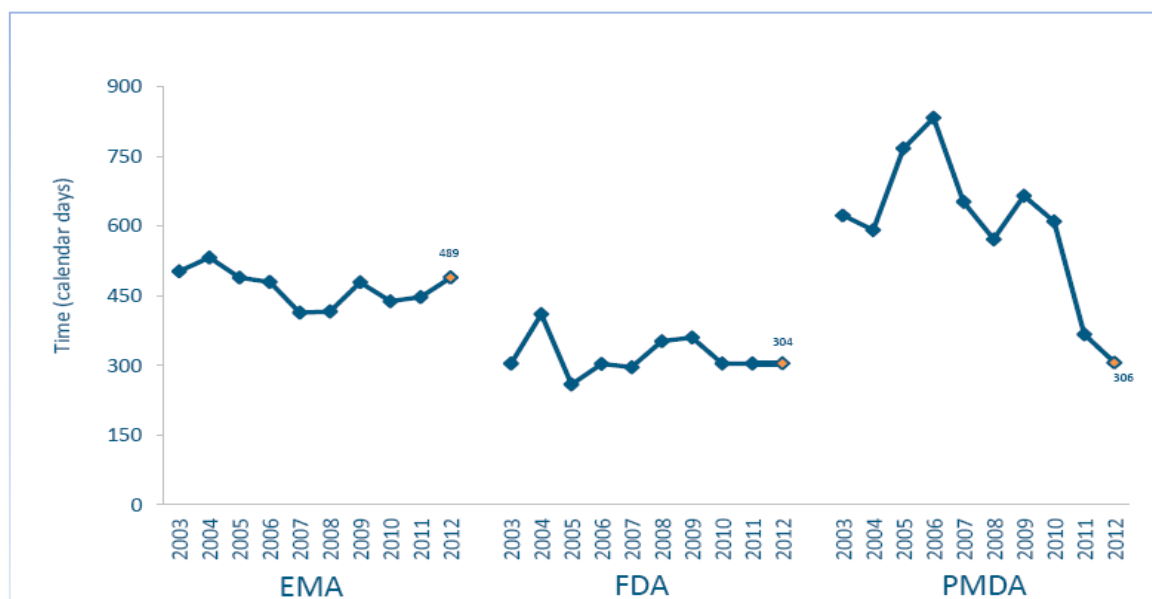


Figure.1.3. Median approval time of NASs approved by ICH agencies (2003-2012)



Quality of the Review Process

It is a recognised fact that the efficiency of the drug regulatory review process does not depend only on the speed of the review. In reality, the effectiveness of the regulatory process should be measured in terms of the approval time and the quality of decision-making. Both pharmaceutical companies and patients require a rapid registration process, but they should understand that this must not be at the expense of the quality of the review (Jefferys, 1997; Lumpkin, 2000).

In the case of new drug applications (Lumpkin, 2000) the quality of the review depends mainly on (i) the competence, consistency and experience of the reviewer and (ii) the scientific soundness in communication, transparency, consistency and adequacy of the process and feedback to the industry. Ultimately, the regulatory authority's primary responsibility to the public is to expedite the availability of safe and effective new therapies, however, pressure is also exerted on the authorities to constantly improve the efficiency and quality of their review processes. On the other hand, dossier quality, as well as the robustness and quality of the data submitted, are critical factors for achieving successful registration and expediting market access (McAuslane et al, 2004). Furthermore, companies and regulatory authorities have established open and frequent dialogue as regulatory factors that may

invariably result in enhancing the review process and review time (Cocchetto et al, 2000). Normally, the drug review process (Jefferys, 1997) depends on the following parameters:

The review input: In order to ensure the availability of safe and effective medicines in the market, governments usually have both legal requirements and guidelines. The assessment of quality involves identifying and defining the role of legal requirements and how they can be uniformly met with consistency. The clarity of information and communication between the regulatory agency and the pharmaceutical companies about the expected quality will influence the efficiency of the review process.

Clarity of roles: The credibility of the review process depends largely on the experts involved although conflicts of interest undermine the process. The scientific review must be independent of conflicts with suppliers of technology and they must also be protected from political influence. An independent scientific review process will hold both suppliers and purchasers accountable for decisions in the light of the scientific data.

Quality of data: Setting high standards of evidence are essential to the integrity of the drug review process. However, it is often uncertain whether all of the data from the available trials are being provided for the review. Requiring public registration of clinical trials and protocols will enable agencies to know which findings are not being reported by manufacturers.

The scientific assessment: It is the responsibility of the reviewing personnel to establish the consistency of the review and to maintain the quality and rigour of the scientific analysis. The scientific basis on which a decision is made must be underpinned on up to date scientific knowledge, procedures and expertise.

Transparency of rationale: Accountability in drug coverage decision-making requires that all stakeholders understand the reasons for decisions. One of the major obstacles to such transparency is currently the commercial confidentiality imposed by manufacturers (Morgan et al 2006).

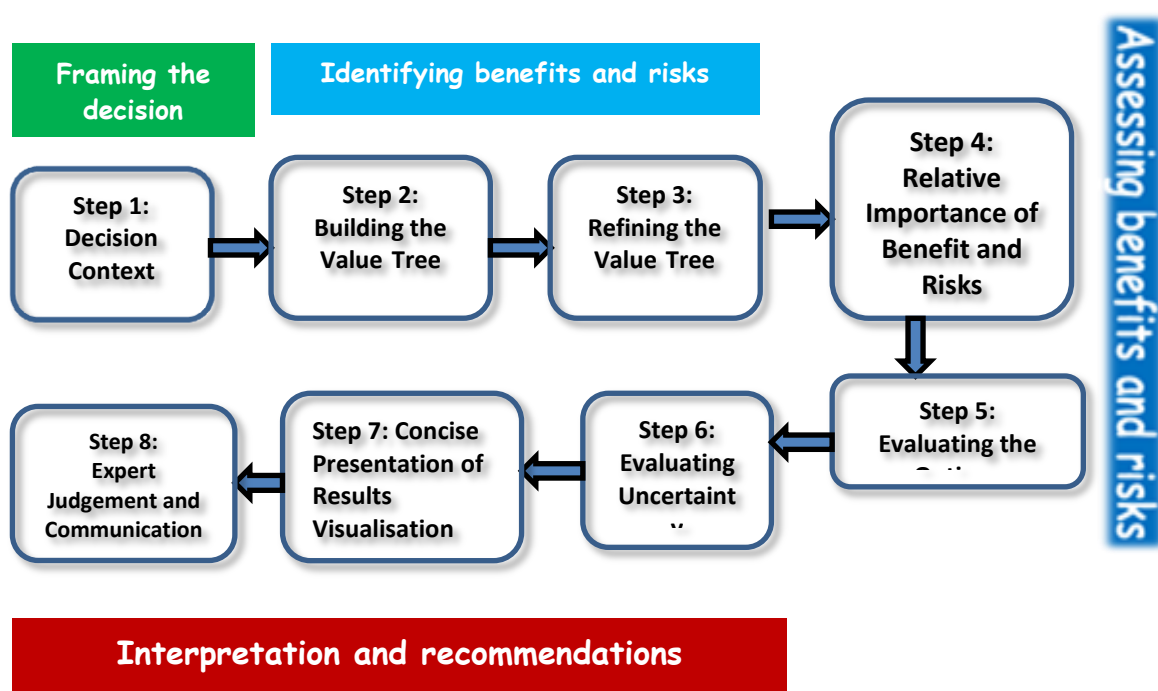
The output: The review process should help to ensure greater accountability of both decision-makers and manufacturers by requiring full disclosure of all reasonable evidence relevant to a medicine's potential coverage. The final decision and its communication to the

pharmaceutical company generally and the wider public must be rational, well-documented, well-organised and transparent (Lumpkin, 2000). The quality of the review (Moss, 2004) will finally depend on the methodical assessment of the reviewers and the reliable evidence embedded in the data.

Benefit-risk assessment and Decision-making

Benefit-risk assessment is the basis of any regulatory authority's decisions in the pre-market and post-market review process (EMA, 2012). A framework for medicines' benefit-risk decision-making that summarises the relevant facts, uncertainties, and key areas of judgment, clearly explains how these factors influence a regulatory decision and can greatly inform and clarify the regulatory discussion. A universal eight step framework has been developed for the Benefit-Risk assessment of medicines (Figure 1.4). This consists of the decision context (step one), building the value tree (step two), refining the value tree (step three), assessing the relative importance of Benefits and Risks (step four), evaluating the options (step five), evaluating uncertainty (step six), a concise presentation and visualisation of results (step seven) and expert judgment and communication (step eight). Such a framework can provide transparency regarding the basis of conflicting recommendations made by different agencies using the same information. Benefits and risks or harms assessment provide a summary of the submitted evidence regarding the drug under review (Coplan et al, 2011). Key considerations of benefits include the results of the pivotal clinical trials as well as appropriate analyses of subpopulations for efficacy. Also the key considerations of risks include the robustness of the safety database, the severity and reversibility of adverse events, and the sub-optimal management of the post-market surveillance studies. In assessing benefits and risks, consideration is also given to some factors that may be significant for a particular drug review, including nonclinical pharmacology and toxicology data, pharmacodynamics and pharmacokinetics, chemistry, manufacturing and controls and clinical microbiology. Risk Management or ideally benefit risk management provides a summary and assessment of any efforts that could help to lessen the identified safety concerns, or in other words ensure that the medicine is prescribe for those patients for whom the risk or harm is considered acceptable in the light of the benefits. Measures to reform the drug approval process have focused increasingly on the decision bias that minimises unsafe or ineffective medicines but neglects the costs of denying safe and effective drugs.

Figure 1.4 The Eight Step of the Benefit Risk Framework



Role of harmonisation

Harmonisation involves the formation of effective networks between regulatory authorities (nationally, regionally and internationally) to facilitate the sharing of best practices, making the best use of scarce resources and eliminating duplication of effort. Such networks are an important element in building regulatory capacity and trust between different regulatory systems (WHO, 2008). In recent years, considerable efforts have been made to harmonise regulatory requirements in terms of scientific content and presentation of data in the registration dossier, across various regions and countries. The meaning of ‘harmonisation’ in terms of the regulatory point of view is the standardisation of technical requirements for medicines regulation. The policies of global standardisation (Trouiller, 2002) of regulatory requirements have been set up, with the most notable example being the initiation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This initiative has disseminated a common set of technical requirements relating to quality control (validation of procedures), drug safety and efficacy as well as certain aspects of manufacturing practice for active ingredients.

Since medicines are essential to healthcare they should be available to the population of every country. Medicines regulations remain an important component of promotion and protection

of public health because they help to ensure that patients have access to high quality, safe, and effective medicines. Investing in the regulatory harmonisation initiative provides an opportunity for strengthening regulatory capacity and the cost-effective use of limited financial and human resources. Today regulatory authorities are thinking in terms of regionalisation (Molzon.2010, 2011) through the efforts made by the International Conference on Harmonisation.

The Global Cooperation Group (GCG) now includes the European Medicine Agency (EMA), the African Regulatory Harmonisation Initiative (AMRH), the United States FDA, the Association of Southeast Asian Nations (ASEAN), the Pan American Network for Drug Regulatory Harmonisation (PANDRH), the Asia Pacific Economic Cooperation (APEC), Southern African Development Community (SADC) and Japan. The Mercado Comunal Sur (MERCOSUR) is the South American “Common Market” consisting of Brazil, Bolivia, Argentina, Chile, Paraguay and Uruguay. This organisation is highly structured among the Central and South American trade groups for regulatory harmonisation of pharmaceuticals (Marcelo *et al*, 1998).

The structures of medicines regulation that exist today which include the drug laws, drug regulatory agencies, the drug evaluation boards, quality control (QC) laboratories, drug information centres, have evolved over time. Regulation of medicines encompasses a variety of functions including licensing, inspection of manufacturing facilities and distribution channels, product assessment and registration, adverse drug reactions (ADR) monitoring, laboratory testing for the quality control of promotion and advertising and control of clinical trials (Sauwakon *et al*, 2002). Each of these functions target a different aspect of pharmaceutical activity and act in concert for effective consumer protection.

The Gulf Cooperation Council (GCC) States

The Gulf Cooperation Council (GCC) was established by an agreement concluded on the 25th May 1981 in Abu Dhabi (UAE) among Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE in view of their special relationship, geographic proximity, similar political systems based on Islamic beliefs, joint destiny and common objectives (Figure 1.5). The GCC States are located in the Arabian Peninsula southwest of Asia, bordered by Iraq and Jordan in the North, the Republic of Yemen and the Arabian Sea in the South, the Arabian Gulf in the East,

and the Red Sea in the West. The total population of the six member states is 44,223,488 inhabitants in a total area of 2,572,954 square kilometres. Yemen is currently in negotiations for GCC membership and hopes to join by 2016. The GCC has already approved Yemen's accession to some areas such as the GCC Council of Health Ministers and the GCC Council of Labour and Social Affairs Ministers. The demographic characteristics of the GCC are shown in the table 1.1.

Figure 1.5 Map of the Seven Gulf Cooperation Council (GCC) States



GCC Drug Regulatory Authorities

The GCC authorities official names are as follows, Bahrain National Health Regulatory Authority; Kuwait Drug and Food Control; The Directorate General of Pharmaceutical Affairs & Drug Control Oman; The Pharmacy & Drug Control Department Qatar, Saudi Food & Drug Authority; The Registration & Drug Control Department UAE; and the Supreme Board of Drugs & Medical Appliances Yemen. These seven authorities form the membership of the GCC Centralised Procedure system (GCC-CP). Five authorities are under their respective Health Ministries and fully funded by their respective governments. Saudi Arabia and Yemen, however, are independent stand-alone authorities that rely on registration fees as the major source of their funding.

Table 1.1 The demographic structure of the Gulf Cooperation Council (GCC) States

Country	Area / sq Km	Population	Median age (years)	Life expectancy at birth (years)	GDP (\$)	GDP per capita (\$)
Bahrain	760	1,234,571	30.4	75.4	28.27 billion	17763
Kuwait	17,818	2,672,926	26.4	77.89	137.7 billion	46509
Oman	309,500	2,773,479	23.9	73.97	72.78 billion	21355
Qatar	11,586	1,715,010	30.8	75.51	100.8 billion	74839
Saudi Arabia	2,149,690	27,563,432	24.9	73.87	590.9 billion	16355
UAE	83,600	8,264,070	30.2	76.32	191.9 billion	36017
Yemen	527,968	23,495,361	17.9	63.36	57.95billion	2,500
Total	3,100,922	67,718,849	-	-	-	-
Average	-	-	26.4	73.76	168.47	30,762.57

Ref. The Cooperation Council for the Arab States of Gulf Secretariat General, Statistical Bulletin, Information Sector, Statistical Department (Volume Twenty, 2012).

The seven GCC authorities regulate pharmaceutical products for human use with their main activities such as marketing authorisation, post-marketing surveillance and quality control of pharmaceutical and health products (Al-Essa, 2011). They also have a variety of other responsibilities depending on the size and resources available for each regulatory authority (Table 1.2).

Evolution of GCC-DR

The harmonisation of regulatory processes in the GCC States was initiated following the consent of the GCC Health Ministers' Council Decree No. 8 in 1976 regarding the formation of a study group to report on how a centralised registration system should be set up to monitor medicines and establish common guidelines for the participating authorities (Hashan, 2005). In 1997, the State of Bahrain submitted a proposal for the formation of a Central Committee of Gulf States to register pharmaceutical companies and their products to ensure basic standards for the manufacture of good quality medicines and also to unify the regulations relating to export of medicines from the Council States.

Table 1.2 The structure, responsibilities and scope of activities within each of the seven GCC regulatory authorities*

Country		Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Name of Authority		National Health Regulatory Authority	Kuwait Drug and Food Control	The Directorate General of Pharmaceutical Affairs & Drug Control	The Pharmacy & Drug Control Department	Saudi Food & Drug Authority	The Registration & Drug Control Department	Supreme Board of Drugs & Medical Appliances
Independent stand-alone authority		X	X	X	X	√	X	√
Budget / GBP		NA	2million	NA	NA	85million	1.6million	2million
Fees / GBP		9	230	130	None	>5000	NA	470
Scope of registration responsibilities	Medicines for human use	√	√	√	√	√	√	√
	Veterinary medicines	X	√	X	X	√	√	√
	Medical devices and in-vitro diagnostics	√	√	√	√	√	√	X
	Cosmetic products	X	√	X	X	X	X	X
	Food supplements	X	√	X	X	X	X	X
	Herbal medicines	X	√	X	X	X	X	X
Scope of activities	Marketing authorisation	√	√	√	√	√	√	√
	Post-marketing surveillance	√	√	√	√	√	√	√
	Sample analysis	√	√	√	√	√	√	√
	Advertising control	X	√	√	X	√	√	X
	Price regulation	√	√	√	√	√	√	√
	GMP inspection		√	√	X	√	X	X
	Clinical trial authorisation	√	X	X	X	√	√	X

*Adopted from Al-Essa, 2011

The Gulf Central Committee for Drug Registration (GCC-DR) was formed in May 1999 and includes Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, and Yemen. The GCC Drug Registration Committee, composed of two members from each of the seven countries, advanced in three stages. In September 2005, an intra-GCC Free Trade Area Agreement, came into effect by which all GCC national products including pharmaceuticals were exempted from custom duties within the GCC and any single consignment of foreign goods were charged import duty only at the port of entry into the GCC area. The formation of effective networks among national regulatory authorities participating in various harmonisation initiatives has several advantages. It facilitates the sharing of limited resources; eliminates duplication of activities; saves capital expenditure for all; supports cooperation and collaboration and international understanding; facilitates the building of an efficient regulatory capacity; and enhances public trust in the regulatory efforts (Jamel, 1998). The first stage of this initiative was a two year period during which all pharmaceutical and research-based companies in the Gulf region were registered; in the second stage the GCC-DR systems were evaluated and generic medicines from local manufacturers registered and the third stage involved the appraisal and registration of all complementary pharmaceutical products such as cosmetics and herbal compounds.

The Ministers of Health in 1999 agreed the two-phase proposal submitted by the Executive Office of the GCC Ministers of Health for Central Registry and approved the registry regulations. During phase one (1999-2001) new pharmaceutical products were assigned to register with both the local authority and the new Central Registration authority and included the registration of pharmaceutical companies. This also applied to new chemical entities and biological products. Phase two of this process started in 2002, mainly targeted to assess the whole system of the registration process and the inspection of pharmaceutical manufacturing plants. In fact, it was recognised that if the knowledge and experience of different authorities are shared for a specific task or responsibility, the best practice from each system could be combined for the advantage of all member states.

Since the GCC States constitute one regional community in its religion, language, population, similarity in geography, values, history, traditions, economic resources, social and cultural circumstances, they had to unify their efforts in different fields of life to face the rapid changes and the overall development requirements. The procurement of safe and effective pharmaceutical

products, hospital sundries and equipment of high quality at appropriate prices are organised through a central group purchasing program. Furthermore, the mission of GCC-DR is to establish a unified Gulf Drug Registration System that ensures effectiveness, safety and quality of medications as well as good manufacturing practices (GMP) according to international standards and post marketing surveillance after registration. The GCC-DR also emphasizes the use of highly effective and safe medications to protect public health in the Gulf Countries. The government control over medicines has grown in the last hundred years and now pharmaceuticals are among the most-regulated products in the world. At present, about 20% of countries have fully operational medicines regulations, 30% have either none or very limited drug regulation and a few have regulations of varying capacity (WHO 2006). In reality, many developing countries cannot ensure the safety, efficacy and quality of medicines available in their markets because they are resource constrained in terms of staffing, standard systems and training (WHO, 2008). However, the globalisation of pharmaceutical markets and production has also increased the spread and prevalence of unsafe medicines.

Protection of public health is the primary aim of any drug regulatory authority and is the foundation of any country's national drug policy that ensures a viable pharmaceutical industry as well as a high standard drug approval process. However, regulation is perceived as an obstacle to the availability of medicines in national or regional markets and has placed a significant demand on regulators to accelerate reviews and evaluations to approve new medicines in the shortest possible time (Hill, 2004)

The study by Hashan (2005) emphasized the differences between authorities in the GCC States in the areas which include structures, procedures, available resources, measures of quality & performance, degree of harmonisation within and between processes and approval times. The study provided a comprehensive understanding of the medicine regulatory processes in the Gulf States. It also elaborated the need for greater standardisation in requirements, performance, procedures and guidelines in the Gulf and other Arab countries which may lead to one regulatory body in the Gulf region.

The study by Al-Essa (2011) demonstrated the added value of the a harmonised strategic planning process in the GCC region. This research explored the differences in the Gulf States

which included structures, procedures, resources, quality measures and strategic parameters which facilitate an effective drug approval process for pharmaceutical companies in the GCC region.

The quality of the review in the GCC

The regulatory review process consists of the scientific evaluation of all data generated during product development which are described in the registration dossier and when data are considered satisfactory a marketing approval is granted. The key advantage of the centralised system in the Gulf is the availability of external expertise to complement the internal evaluators. This enhances the quality of the reports and more information is focused on the registration to ensure that product evaluation is carried out according to the required standards. In this manner, the quality of the product registration is assured across the GCC States.

Apart from obtaining an improved scientific evaluation from more than one state following an evaluation of the application dossiers, the CP allows further scope for the exchange of knowledge, ideas and experiences among the National Drug Regulatory Authorities in the GCC. This results in better coordination and quality reviews within the GCC.

The scientific evidence developed by a pharmaceutical company is evaluated to ensure that the product can be made available for use or prescribed to patients. Regulators must balance between the speed of access of the medicine to patients and ensuring that its benefits outweigh any risks. According to Dureja *et al* (2010) a well-funded, consistent, robust and transparent regulatory review system is indispensable to protect the public health and build confidence in the marketed medicines. Gradual strengthening of the regulatory authorities in the GCC region is fundamental so that they have the expertise and tools for evaluating new medicines efficiently. Also it is very important to analyse and scrutinise the differences and uniformity among the regulatory review processes carried out in all the GCC authorities.

Mallia-Milanes *et al* (2010) reported on the influence of the type of assessment carried out by different authorities which may affect the regulatory approval times. The study pointed out the existence of three types of review process offered for pharmaceuticals in Singapore which includes full, abridged and verification reviews.

A full review relates to products that have not yet received approval elsewhere and takes around 270 working days in Singapore to be completed and supported by external reviewers. The abridged review usually takes 180 working days, which is used for applications that have been approved by a recognized regulatory authority, (eg. US FDA, EMA, TGA, etc), before submission in Singapore. The verification review can be effected if the medicine has been approved by at least two benchmark authorities and takes a minimum of 120 working days.

McAuslane and Walker (2007) reported in a study of ten agencies, that Argentina alone utilizes the verification review system for pharmaceuticals and biologicals while Mexico, Egypt, Saudi Arabia, Malaysia and Singapore make use of the abridged assessment for most of their applications. Walker *et al.*, (2005a, 2005b and 2005c) stressed the significance of the pattern of the review process carried out by the regulatory authorities for pharmaceuticals in a timely manner.

The primary issue to be addressed is the understanding of the type of model being used to carry out dossier assessment in each GCC country and to quantify the extent of the scientific review approved in each member state. Karlton et al (1997) pointed out the importance of the quality of the dossiers in the realisation of rapid regulatory reviews and approval of new applications. Mediocre documents complicate the review process and may impact negatively upon the confidence in quality of the medicinal product and its manufacturer (Zellerhoff, 2001). It is the duty of the manufacturing companies to submit high quality dossiers for improving the efficiency of the approval process. Valuable capacity development and an effective application tracking system, assessment and decision-making, appropriate use of information technology, effective working, accountability and transparency of the medicine registration related decisions finally result in the overall competence of a unified registration process.

Global drug development and its influence on the regulatory environment in the Gulf Region

The World Trade Organisation (WTO) established a global patent protection act named TRIPS (Trade-Related Aspects of Intellectual Property Rights) (WHO, 2003a) in regards to New Chemical Entities (NCEs) in 1994. Patents can relate directly to active ingredients, formulations,

pharmaceutical salts, isomers, polymorphs, combinations, manufacturing processes and also the patent holder has the complete freedom to set the price. The seven Gulf States, with the exception of Yemen, recognised the TRIPS agreements. However, the TRIPS agreement eventually results in a price increase for new medicinal products which is unaffordable to most people living in developing countries (WHO, 1999,2004).

The world pharmaceutical market in 2014 is estimated to be around one thousand billion US\$. The Middle East and North Africa (MENA) in 2007 comprise around 2% of the global pharmaceutical market, with an average annual growth of 10.4%, the Arab market (22 Arab countries) comprises 1.5%, valued at around US\$6.2 billion, of which the largest market is the Saudi Arabia, valued at around US\$1.2 billion (Veronica, 2011; Nixon et al, 2013). The increasing number of conferences and studies on the central drug registration process reflects the need for greater harmonisation in medicine regulation within the Middle East and it is with this background that this research was initiated.

AIM AND OBJECTIVES OF THE STUDY

Aim

The aim of this study is to evaluate the GCC centralised procedure and the approval times since its inception in 1999 to 2010.

Objectives

- Evaluate the regulatory review process in Oman and identify the milestones and timelines (2006-2010)
- Identify the strengths and weaknesses of the Oman regulatory review process and propose strategies for improvement.
- Determine the similarities and differences in the regulatory reviews in each of the seven GCC states together with the characteristics of the review process.
- Examine the trends in the submission, registration and the associated approval timelines for patients' access to medicines in the GCC states.
- Appraise the GCC central registration regulatory review process.
- Examine the views and experiences of the GCC states and the pharmaceutical companies with respect to the GCC registration procedure.
- Identify the strengths and weaknesses of the centralised review process and propose strategies for improvement
- Develop a new model for the GCC-DR based on the evaluation and outcome of the centralised procedure since its inception.

CHAPTER 2

Study Rationale and Methodological framework

RATIONALE OF THE STUDY

The decision to centralise Drug registration within the GCC was a political one. Many were skeptical as to whether such centralisation would improve the time line in registering new medicines and thus facilitate earlier availability of new drugs to the population. Furthermore, individual countries were experienced in registration processes and believed that they were efficient enough. A number of such officials indicated that the individual countries were being deprived of their sovereignty and equality, they were therefore skeptical about the success of such initiative. Pharmaceutical companies were also doubtful about the GCC-DR system as to whether it would improve the review process and the approval timelines in the GCC region.

Many countries had adopted joint drug registration procedures and it is assumed that the process works and delivers efficiency. As it is now more than 10 years (1999) since the centralised drug registration system was established in the GCC, it was timely for an assessment of the GCC-DR timelines and the number of registered products to be evaluated. In addition it was decided to conduct a comparative study between the GCC-DR and the national approval timelines to complete the picture for both the individual authorities and the pharmaceutical companies.

It is intended to conduct studies involving the major stakeholders in the registration process. Current officials responsible for registration in the respective country, pharmaceutical manufacturers and those within the GCC-DR secretariat will be requested to participate in these studies. The questionnaire technique will be used for data collection to determine the success and impediment to the intended progress of the GCC-DR.

In the light of the GCC Central Drug Registration system, the seven regulatory authorities have had a long experience in joining their efforts to centrally register pharmaceutical products in the Gulf region. They were apprehensive about the possibility of changing their entire procedures and practices.

These concerns led to the conceptualisation of this study in order to examine the views of the seven GCC authorities about the current status of the GCC-DR system and its impact on their individual processes. Also the current research has focused on evaluating the pharmaceutical

industry's views about the advantages and disadvantages of the GCC-DR system and how this has impacted the speed of marketing authorisation for their products in each Gulf State.

METHODOLOGICAL FRAMEWORK

Development of the Study design

The present study employs the principles of quantitative, exploratory and constructive research methodologies with the primary aim of evaluating the GCC central drug registration procedure.

Background and review of the Study design

The Quantitative data collection methods rely on random sampling and structured data collection instruments that fit diverse experiences into programmed response categories. These methods produce results that are easy to summarise, compare, and generalise. Depending on the research questions, participants may be randomly assigned to different treatments and data collected on participants relevant to the outcome being measured. (Kidder et al,1987).

A cross sectional design will be adopted for data collection to gather specific data pertaining to all the seven Gulf States at different phases of the study. There are several advantages of the cross-sectional design, such as requiring less resources and being able to collect a large volume of data in the shortest possible time. The questionnaires, as assessment tools are important aspects of any research of such nature and usually reflect the perception of individual members of the target population about a particular issue. Furthermore, questionnaires techniques are used in studies to elicit reports of facts, attitudes, and other subjective states. A questionnaire is usually composed of a set of questions, answered by potential clients or the target population. The results can be presented as a table or a graph. A well-structured study using questionnaire techniques includes a clear and comprehensive statement of the study goals, data requirements, and the analysis plan (Dillman & Don et al, 1978; Bradburn et al, 1982).

Several different types of studies are utilized depending on the approach used and the overall study objectives expected. A one-off data collection is selected for the present study which can

also impart the advantages of baseline and comparative assessment points (Salant et al, 1994; Anon, 2000; Passmore et al, 2002).

The major strengths and weaknesses of questionnaire techniques are as follows:

Strengths

1. Are particularly useful in describing the characteristics of a large population.
2. Can be self-administered making it feasible to recruit large samples.
3. Are flexible and the least costly method of data collection.
4. Results can be generalised.

Weaknesses

1. Often appear superficial in their coverage of complex topics.
2. There is no way of telling how much thought a respondent has put in to the responses.
3. There is no way to tell how truthful a respondent is being.
4. Lacks validity.
5. People may read differently into each question and therefore reply based on their own interpretation of the question.
6. Questionnaires also invite people to lie and answer the questions very vaguely which they would not do in an interview.

Data Collection

Development of Data Collection Techniques

In deciding an appropriate data collection technique for this study questionnaires were reviewed alongside interviews. The cardinal difference between the two is that the questionnaires can produce either quantitative or qualitative data whereas interviews produce qualitative data. The attributes and different types of the two techniques are presented here.

Questionnaires

Questionnaires are usually an inexpensive and efficient method where no special conditions or equipment are required. It can also be compiled anywhere and distributed easily and the information can be collected from a large group of people in a timely manner. In a questionnaire

everyone answers the same questions therefore it can be compared easily. Learning how to design and use structured interviews, questionnaires and observation instruments is an important skill for researchers. Interviews have certain advantages over self-completion questionnaires. The interviewer can explain questions that the respondent has not understood and can ask for further elaboration of replies. However, interviews are more time consuming and it may also be open to interviewer bias, where the interviewer influences the replies by revealing their own opinions. Such biases can be avoided by using self-completion questionnaires.

Interviews

The interview is a more flexible form than the questionnaire technique and, if wisely used, can generally be employed to gather information of greater depth and be more sensitive to contextual variations in meaning. Interviews, however, can be non-scheduled, though still partly standardised. This is sometimes called a *semi-structured interview*. Here, the interviewer works from a list of topics (checklist) that need to be covered with each respondent, but the order and exact wording of questions is not important. Generally, such interviews gather qualitative data, although this can be coded into categories to be made amenable to statistical analysis.

The main advantages of the interview technique include (McNamara, 1999; Bourque and Fielder, 2003a):

- The presence of an interviewer allows for complex questions to be explained, if necessary, to the interviewee.
- Interviews can generally be longer than when self-completion techniques are used as interviewees are less likely to be put off by the length or to give up halfway through.
- There is more scope to ask open questions since respondents do not have to write in their answer and the interviewer can pick up on non-verbal clues that indicate what is relevant to the interviewees and how they are responding to different questions.
- Visual aids can also be used in the face-to-face situation.

The major limitations of the face to face interview are discussed below.

The cost associated with face-to-face interviews can limit the size and geographical coverage of the study. Interviewers can introduce bias, which will affect the reliability of responses. Such bias might emerge from the way in which questions are asked, or in the personal characteristics

of the interviewer, or in respondents' wish to give socially desirable responses. For instance, there tends to be an over-reporting of voting activity and of participation in voluntary activities in data gathered through interviews.

The studies using self-completion questionnaires have some distinct advantages over face-to-face interviews:

They are inexpensive to administer. The only costs are those associated with printing or designing the questionnaires, their postage or electronic distribution.

They allow for a greater geographical coverage than face-to-face interviews without incurring the additional costs of time and travel. Thus, they are particularly useful when carrying out research with geographically dispersed populations. Using self-completion questionnaires reduces biasing error caused by the characteristics of the interviewer and the variability in interviewers' skills. The absence of an interviewer provides greater anonymity for the respondent. When the topic of the research is sensitive or personal it can increase the reliability of responses.

Telephone interviews

Telephone interviews using interview schedules are becoming increasingly efficient with sophisticated developments in computer technology. Computer assisted telephone interviewing (CATI) systems are available and these provide clear instructions for the interviewer, display the interview schedule and allow electronic recording of responses as they are given. This omits the data entry part of the research because responses are recorded directly onto the computer.

The major advantages associated with telephone interviews are as follows:

- The researcher does not have to travel; interviews can take place over a wider geographical area.
- There are fewer interviewer effects *ie.* The personal characteristics of the researcher will be less obvious than in face-to face situations and is therefore less intrusive.
- The physical safety of the interviewer is not an issue.
- Telephone interviews are subject to greater levels of monitoring because supervisors can unobtrusively listen in to interviews to ensure that they are carried out correctly

Different Types of Questionnaire Techniques Used in Data Collection

Several methods are available for collecting data using the questionnaire technique and also depend on many factors for selecting the most appropriate method. These include the type and size of population being studied, timelines, budget, resources and purpose of the study (Diem, 2002a).

Paper or electronic mail-delivered

This method utilizes minimum resources to prepare; enables privacy of responses and it is relatively inexpensive or free of charge, still it may take time and requires follow-up to obtain representative responses.

Group-administered

This approach involves gathering a group of responders together administering the questionnaires and asking the group to complete them individually.

The method ensures a high response rate from those who receive the questionnaire and enables a full explanation of the study with the opportunity for questioning. The disadvantages of this method are the limited time availability for the responders to formulate their answers and the slow turnaround time. (Trochim, 2006).

Telephone-administered

This method utilizes pre-arranged telephone calls with the study participants and by recording the calls; the investigator can generate a digital data base with the interview texts. The time zones and languages among respondents may be a hurdle of this method leading to no contacts (Diem, 2002a; Trochim, 2006). It may also be possible to utilize an automated system where the study participants record their responses via a touch-tone telephone to a computer-based interview system. Text messages, to remind the respondents, together with cell phone facility may be utilised in this method.

Web-based method

In this method, the questionnaires may be displayed and posted on a web site which is to be completed by respondents in a fixed time period remotely. Web-based methods enable a quick and easy response and are inexpensive (Diem, 2002b; Bourque et al, 2003a).

Data Source

Information will be sought from the seven regulatory authorities who are members of the Gulf Cooperation Council (GCC) States (Table 2.1).

Table 2.1 Data source for the seven Gulf authorities

<i>Position</i>	<i>Agency</i>	<i>Country</i>
Director, Pharmacy & Drug Control	Ministry of Health	Bahrain
Drug Registration and Release Superintendent	Drug and Food Control - Ministry of Health	Kuwait
Director General of Pharmaceutical Affairs & Drug Control	Directorate General of Pharmaceutical Affairs and Drug Control- Ministry of Health	Oman
Head of Drug Registration Section	Drug Control Department- Supreme Council of Health	Qatar
Executive Director of Licensing Department - Drug Sector	Saudi Food and Drug Authority	Kingdom of Saudi Arabia (KSA)
Head of Registration and Pricing Department	Drug Control Department - Ministry of Health	UAE
Member of the board council	Supreme board of drugs and medical appliances	Yemen

Inclusion Criteria

For the Oman study and the evaluation of the review process and timeline in the individual GCC countries, all products from local, Gulf, Arab non-Gulf and international manufacturers, which have been approved for human use between 2006 and 2010 and 2008-2010 respectively, will be included. This includes: New Active Substances (NASs) and Existing Active Substances (EASs). The products which have complete date information e.g. submission date, regulatory evaluation time, companies' response time to the regulatory queries and approval dates will be included in the total approval time. In the GCC Centralised Procedure and GCC States studies, all products from local, Gulf, Arab not-Gulf and international manufacturers approved for human use between 2008 and 2010 will be included.

The opinions and suggestions of all the seven GCC states from the respective regulatory authorities as well as the pharmaceutical companies on their experiences with GCC central registration procedure will be collected by means of questionnaires.

Exclusion Criteria

Products which have incomplete data such as missing submission date or approval date will be excluded from the final analysis.

Data Collection Procedure

Confidential procedures will be used for all parts of the study. All the collected data may be aggregated to avoid identification of individual responders. The electronic or interviewer delivered questionnaires will be used to collect data which may allow the confidentiality and/or anonymity of the procedure ((Crow and Wiles, 2008). A questionnaire is useful when there is a need to collect information from the study participants in a reasonable time period. It is a structured technique for collecting primary data in a study using a series of structured questions for which the respondent provides answers. (Diem, 2002b)

Data Collection Monitoring and Timeline

A face-to-face meeting will take place to follow-up the data to be obtained from the Oman drug authority and to closely observe the regulatory review processes and the approval timelines in Oman. In addition, a face-to-face meeting with all the Directors and General Directors of Regulatory Affairs in the Ministry of Health in the GCC States will take place during the GCC-DR committee meetings. All the participants will be asked to provide the registration data for products approved in 2008, 2009 and 2010 based on the milestones in each authority. Clarification (validation) regarding the data set will be obtained from the GCC authorities through telephonic conferences and electronic mails.

The comparisons of the Gulf States and pharmaceutical companies' perspective on the effectiveness of the GCC centralized procedure require telephone-interview and email delivered questionnaire in order to:

- Identify the similarities and differences between the experiences of regulatory authorities and pharmaceutical companies with the Gulf Centralised Procedures

- Provide recommendations to improve the Gulf Centralised Registration Procedure
- Propose the strategies to maximise the benefits of a centralised registration system
- Collect feedback about the GCC centralized procedure questionnaire from the GCC regulatory authorities and pharmaceutical companies. Attempts will be made to clarify areas of the questionnaire which maybe unclear to the participants

Development of Questionnaires

There are different types of self-completed questionnaires such as mail-delivered, web-based or email-delivered. The email-delivered and web-based questionnaires will be adopted for this study . Following a series of consultations with experts and key regulators, it will be possible to test the applicability of the questions to evaluate views and experiences of the Gulf States with respect to the Centralised Procedure by conducting a pilot study involving two randomly selected GCC authorities.

Another questionnaire will be developed to evaluate the experiences and views of pharmaceutical companies with respect to the central registration review process. A pilot study will be conducted involving five pharmaceutical companies (two innovative and three generic) to examine the practicality and applicability of the industry questionnaire.

Chapters three, four, five, six, seven and eight will aim to provide evidence to establish consensus opinions on topics that do not have adequate information currently available. The studies in these chapters will focus on the collection of both qualitative and quantitative information. In situations where there is a need to define levels of agreement on controversial subjects but there is no unanimity of opinion because little evidence exists or available evidence is contradictory, consensus methods can be used. These methods attempt to assess the extent of agreement (consensus measurement) and resolve disagreement (consensus development) (Jones et al., 2000).

The most commonly used consensus methods are the *Delphi process*, the *nominal group technique* (also known as the expert panel) and the consensus development conference. The aim

of consensus methods is to determine the extent to which experts agree about a given issue (Jones et al., 1995). The features of consensus methods are described in table 2.2.

Table 2.2 Features of Consensus Methods (Jones and Hunter, 1995)

<i>Anonymity</i>	To avoid dominance; achieved by use of a questionnaire in Delphi and private ranking in nominal group
<i>Iteration</i>	Processes occur in "rounds", allowing individuals to change their opinions
<i>Controlled feedback</i>	Showing the distribution of the group's response (indicating to each individual their own previous response in Delphi)
<i>Statistical group response</i>	Expressing judgement using summary measures of the full group response, giving more information than just a consensus statement

Consensus Development Conference (CDC) method

Consensus Development Conference is a formal method developed by the US National Institutes of Health in 1977, for gaining feedback facilitated through face-to-face contact. A key feature of this method is the appointment of a carefully selected panel of people thought to be without vested interest, to listen to the evidence presented at a CDC meeting and prepare a report on the topic under discussion with recommendations (Fink et al, 1984).

Nominal Group Technique

The nominal group technique (NGT) is a group problem solving process involving problem identification, solution generation and decision-making. The NGT is a structured method for group brainstorming that encourages contributions from everyone.

This approach was developed in the USA in the 1960s which includes a highly structured meeting organized to collect information from appropriate experts about a given topic or issue. It involves two rounds in which panelists rate, discuss and then re-rate a series of items or questions. This technique is most commonly used in healthcare to examine the appropriateness of clinical interventions and has some features in common with focus groups (Jones et al, 2000). This method focuses on a single goal, e.g. the definition of criteria to assess the appropriateness

of a gene therapy intervention, rather than eliciting a range of ideas and it will therefore not be appropriate for the studies considered for this thesis.

Delphi approach

It is a forecasting method based on the results of questionnaires sent to a panel of experts. Several rounds of questionnaires are sent out, and the anonymous responses are aggregated and shared with the group after each round. The experts are allowed to adjust their answers in subsequent rounds.

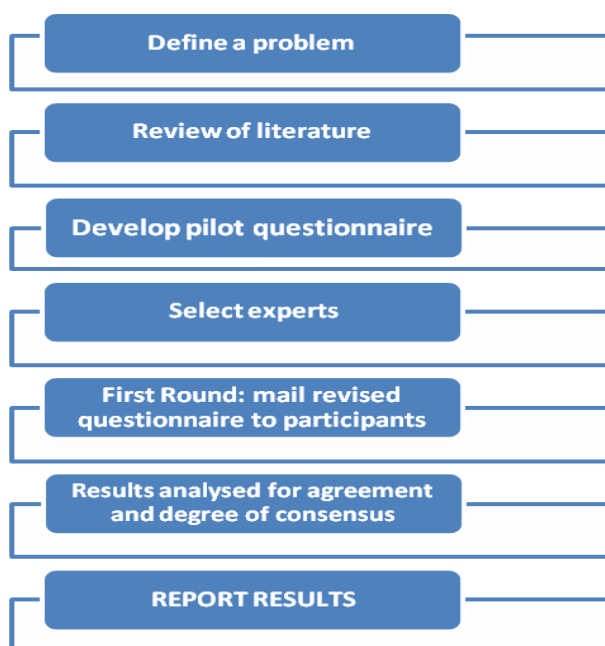
Because multiple rounds of questions are asked and each member of the panel is told what the group thinks as a whole, the Delphi Method seeks to reach the "correct" response through consensus. The Delphi technique was developed in the 1950s by RAND Corporation in Santa Monica, California (a non-profit institution that helps improve policy and decision-making through research and analysis) (Kaplan et al., 1950; Woudenberg, 1991). Since then the method has been adopted and interpreted widely in health services research (Mead et al, 2001) to obtain judgement from expert panels by systematically collecting and aggregating informed opinions from a group on specific issues.

The Delphi method seeks to aggregate opinions from a diverse set of experts, and can be done without having to bring everyone together for a physical meeting. This anonymity promotes a sense of freedom to express opinions without negative repercussion (Annells et al, 2003). The Panel members are encouraged to revise previous responses in subsequent iterations after reviewing new information submitted by other experts.

The Delphi approach can be a quick, inexpensive and a relatively efficient way of combining the knowledge and abilities of an expert group on a particular issue. It is viewed as a useful communication tool for generating debate as opposed to reaching conclusions. For the purpose of this study, the essence of the Delphi approach will be used to develop consensus of opinions in each of the previously defined topic areas as well as to collect information that can be used as scientific evidence (Figure 2.1). It is, therefore, imperative that detailed information be given about the proposed method of data collection and if questionnaires are used, their development should be described. Having defined the key problem in each of the research areas and identified

the appropriate individuals from regulatory authorities in the area, a pilot study will be conducted in the first round. Comments from the experts will then be incorporated and used to refine the questionnaire that will be mailed to all participants. Then the results from the questionnaire will be aggregated and analyzed before being reported back to participants.

Figure 2.1 Adoption of the Delphi Approach to be used in this study (Mead et al., 2001)



Development of the Study Plan

A comprehensive review and critical analysis of the literature reported in chapter one, demonstrated a significant gap in the area of the drug regulatory process for the Gulf countries (i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE and Yemen) and the GCC Centralised Procedure. In order to close this gap and improve the regulatory performance, it is vital to understand the regulatory review practices and evaluate the Gulf States and pharmaceutical companies' views and experiences with GCC Centralised Procedure to achieve an effective and improved Gulf Centralised regulatory system. Therefore, the following study plan was developed to capture data on the regulatory environment in the Gulf. These were then subjected to a significant scrutiny to fulfill the objectives of the study.

The research project will consist of six smaller studies each forming a thesis chapter that explores the core concepts of GCC drug regulatory field, namely,

- Evaluation of Oman Pharmaceutical Regulatory Review Process (*Chapter three*)
- Evaluation of the Regulatory Review Times in the GCC States (*Chapter four*)
- A comparative study of the centralised regulatory review processes in the seven GCC States. (*Chapter five*)
- An Evaluation of the Gulf States Views and Experiences with GCC Centralised Procedure. (*Chapter six*)
- An Evaluation of the Pharmaceutical Companies Experiences with the GCC Centralised Procedure. (*Chapter seven*)
- The Gulf Centralised Procedure- A Comparison between the Experiences of Regulatory Authorities and Pharmaceutical Companies (*Chapter eight*)

The outcomes of the research will be combined to derive the major areas that require further improvement to achieve a standardized and efficient regulatory review process for the GCC centralised system. The following methods will be employed to collect the required data:

1. To obtain a list of the key regulatory personnel in each drug regulatory authority in the GCC region.
2. A review of the literature and/publications on the subject of regulatory review process in the GCC States their centralised system.
3. To consult with regulatory experts and senior managers in the GCC regulatory authorities.
4. To develop two questionnaires with which to evaluate the Gulf States and pharmaceutical companies' views and experiences with GCC Centralised Procedure.
5. To produce two reports as a result of the assessment of the GCC centralised regulatory review process and the Comparison between the experiences of regulatory authorities and pharmaceutical companies with the GCC Centralised Procedure.
6. The reports will form the basis of the relevant chapters in this thesis.

Development of the Study Instruments

The sequence of events to be carried out to achieve the aim of the study will start with an evaluation of the regulatory approval timelines in Oman. This is a lengthy process which involves collecting data on the registration dates for 2006, 2007, 2008, 2009 and 2010 from the saved documents in the Oman MOH archives.

During the course of collecting data on the approval timelines in Oman, two questionnaires to examine the views and experiences of the Gulf Cooperation Council states and pharmaceutical companies, with respect to the Gulf central registration procedure will be prepared. The first questionnaire is planned to be distributed among the seven regulatory authorities in the GCC states and the second is intended for completion by pharmaceutical companies, already registered or yet to register their products through GCC centralised registration procedure. A pilot study is planned to be carried out by coordinating two GCC states and five pharmaceutical companies to assess the practicality, feasibility, applicability and relevance of the study instrument for assessing the Gulf Centralised Procedure.

The review times for New Active Substances (NASs) and Existing Active Substances (EASs) submitted to the GCC Centralised Registration will be obtained directly from the Executive Board of the Health Ministers Council for GCC States. Since the GCC registration office do not maintain a robust and complete electronic system of data capture, the data collection will have to be carried out manually.

Psychometric evaluation of the survey questionnaires

Evaluation process

Questionnaires should undergo evaluation of their psychometric properties before they are relied on for making decisions. Psychometric validation is used in various fields including education, psychology, and health research to define the properties of the scales which are included in such questionnaires. Psychometric principles such as applicability and acceptability, validity, reliability, consistency and responsiveness are considered in the present study (Mallia-Melanes, 2010).

Applicability and acceptability for use

Usually the applicability of a study instrument (Stewart, et al 1990) guarantees the appropriateness of its content to the purpose of the research being conducted. Furthermore, applicability describes the suitability of an instrument for its intended use in terms of wording, clarity and simplicity of language (Higginson and Carr, 2001). The willingness to respond to the questions by the study participants is another critical aspect in the acceptability of the study instrument. It also considers the time required from the participants to complete the questionnaire and whether the questions are clear, concise and easy to understand (McLeod et al, 2008).

Practicality

Practicality issues include the participant's comfort, cost and mode of administration of the study instrument (e.g. interviews or self-administered), convenience and ease of understanding of the questions (Ware *et al*, 1980a, 1981). The participants' lack of engagement can result in a low response rate, and high refusal rate, missing responses and longer administration time.

Validity

According to Kaiser and Smith (2001) validity is the most fundamental consideration in developing and evaluating tests. The most commonly used validity methods for assessing study instrument are content (face) validity and criterion validity. The concept refers to the degree to which evidence and theory support the interpretations of test scores demanded by proposed uses of tests". Ultimately the concept of validity measures what the method claims to measure and investigate sensitive issues of such method.

Content Validity

This method assesses the extent to which questions in a study serve to encompass the important facets of the notion the indicator is supposed to represent in a balanced way. The weighting of the results are also reviewed with the set of indicators (Anon, 2001).

Criterion Validity

The aim of the criterion validity is to correlate a new indicator with reference to a previously well established indicator (Anon, 2001) and assesses how the observed values of the indicator compare with another related measure. For example piloting the questionnaires by assessing

the practicality and applicability of questions will ensure that they are clear, feasible and unambiguous before using the final version for the main study participants

Construct Validity

Guyatt et al., (1993) describe this method as the most rigorous approach to establish validity. Construct validity examines the logical relationship that exists between a measure and the characteristics of the system being studied and also involves comparisons between the measures. Sub-types of construct validity include convergent validity (positive correlation with a related measure) and discriminate validity (low correlation coefficient) (Mallia-Milanes, 2010 ; Saw, 2001).

Reliability

The consistency and reproducibility of an instrument are the main parameters to be examined for testing its reliability (Pinar, 2002, McLeod et al., 2008). This quality of the instrument is always demonstrated by using internal consistency and test-retest reliability.

Sensitivity

The sensitivity of an instrument lies in its ability to detect small changes in parameters such as approval times, milestones, quality measures and strategic goals (Mallia-Milanes, 2010; Higginson and Carr, 2001 and McLeod et al, 2008).

DATA PROCESSING AND ANALYSIS

Data will be collected using electronic mail, postal mail, fax, interviewer delivered, computer assisted telephone interviews and semi-structured interviews. Irrespective of the delivery method, data will be entered into Microsoft Excel and developed specifically for each study. Data processing and analysis will be carried out using Microsoft excel and the Statistical Product and Service Solutions (SPSS). The sample mean will be used extensively for estimating the population means (the 'middle' value), as was the median (the value halfway through the ordered data set, below and above which there lies an equal number of data values). Where applicable ranges around the median and average will be shown to indicate the spread of the data. Scatter plot will be used to summarise data sets that are bivariate in order to give a good visual picture of the relationship between the two variables. Box and Whisker plot will be used on data sets measured on an interval scale to show the shape of the distribution, the central value

and variability. If the data is quantitative, descriptive statistics such as mean, median and range will be used and if the data is qualitative, content analysis will be employed to generate themes and sub-themes.

Quantitative Content

Hypothesis testing

Hypothesis testing refers to the process of choosing between competing hypotheses about a probability distribution, based on observed data from the distribution. There are two types of statistical hypotheses.

Null hypothesis: The null hypothesis, denoted by H_0 , is usually the hypothesis that sample observations result purely from chance.

Alternative hypothesis: The alternative hypothesis, denoted by H_1 or H_a , is the hypothesis that sample observations are influenced by some non-random cause.

To perform hypothesis testing a theory needs to be presented that is believed to be true or is to be used as a basis for an argument, but has not been proved. An example of a hypothesis could be the claim that a new drug is better than the current drug for treatment of the same symptoms (Easton and McColl. 2001). In each case two contrasting hypotheses are assessed: the null hypothesis, denoted by H_0 and alternative hypothesis denoted by H_1 . These two hypotheses are not treated on an equal basis as special consideration is given to the null hypothesis. This is due to the fact that the null hypothesis relates to the statement being tested, whereas alternative hypothesis relates to the statement to be accepted if or when the null hypothesis is rejected (Easton and McColl, 2001). Plausible arguments will be generated to test a series of hypotheses arising from the aims and objectives of the study.

Hypothesis testing will be used to:

- Evaluate the approval time in Oman
- Evaluate the approval time in the GCC Centralised Procedure.

Evidence will be generated to test a series of hypotheses for each of these studies.

Choice of Statistical testing procedures

A statistical test provides a mechanism for making quantitative decisions about a process or processes. The intent is to determine whether there is enough evidence to reject a conjecture or hypothesis about the process. Therefore, statistical inferences make use of information from a sample to draw conclusions (inferences) about the population from which the sample was taken (Easton et al., 2001). The sample mean will be used extensively for estimating the population means as will the median. Where applicable, ranges around the median and mean will be shown to indicate the spread of the data. Scatter plots will be used to summarise data sets that are bivariate (two variables) to give a good visual picture of the relationship between the two variables. Box and whisker plots will be used on data sets measured on an interval scale to show the shape of the distribution, the central value, and variability. The figure produced consists of the most extreme values in the data set (5th and 95th percentile values), the lower and upper quartiles (25th and 75th percentile values), and the median. Occasionally, pie charts will be used for sets of categorical data, each segment representing a particular category and the area of each segment being proportional to the number of cases in that category (Easton et al., 2001). Several statistical tests will be used in the present study, depending on the research question asked, the distribution of the data and the number and characteristics of the data set. For each analysis, the test used will be specified.

Regression

In statistics, regression analysis is a statistical technique for estimating the relationships among variables. It includes many techniques for modeling and analysing several variables, when the focus is on the relationship between a dependent variable and one or more independent variables. Regression analysis will be used to express the relationship between two (or more) variables algebraically. The regression equation indicates the nature of the relationship between two (or more) variables. In particular, it indicates the extent to which some variables can be predicted by knowing others, or the extent to which some are associated with others. A linear regression equation is usually written as $Y = a + bX + e$, where 'Y' is the dependent variable, 'a' is the intercept, 'b' is the slope or regression coefficient, 'X' is the independent variable (or covariate) and 'e' is the error term (Easton et al., 2001).

Correlation

Correlation analyses can be used to show the strength of a relationship between two variables. A correlation coefficient, statistically referred to as r , is a number between -1 and 1 which measures the degree to which two variables are linearly related. If there is a perfect linear relationship with a positive slope between the two variables, the correlation coefficient equals +1. There is a positive correlation whenever one variable has a high value and so does the other, or vice versa. If there is a perfect linear relationship with a negative slope between the two variables, the correlation coefficient equals -1. A correlation coefficient of 0 indicates that there is no linear relationship between the variables (Easton et al., 2001).

Mann-Whitney U-test

The Mann-Whitney U-test is a non-parametric test used to test the difference between the medians of two independent samples (Crichton, 2000a; Easton et al, 2001), for example males and females.

Wilcoxon Signed Rank test

The Wilcoxon Signed Rank test is a non-parametric test used to test the median difference in paired data (related samples). This test is the non-parametric equivalent of the paired t-test (Crichton, 2000b; Easton et al., 2001).

Kruskal-Wallis test

The Kruskal-Wallis one-way analysis of variance (ANOVA) is a nonparametric test used to compare three or more independent samples. It is used to test the null hypothesis that all populations have identical distribution functions against the alternative hypothesis that at least two of the samples differ only with respect to location. The outcome of this test is not conclusive as to which of the samples differ. The Kruskal-Wallis test is a logical extension of the Mann-Whitney U-Test (Easton et al, 2001).

Qualitative Content

The content analysis is a widely used qualitative research technique. Rather than being a single method, current applications of content analysis show three distinct approaches: conventional, directed, or summative. All three approaches are used to interpret meaning from the content of

text data and, hence, adhere to the naturalistic archetype. Content analysis does not proceed in a linear fashion and is more complex and difficult than quantitative analysis because it is less standardized and formulaic (Polit & Beck, 2004). Content analysis is a method of analysing written, verbal or visual communication messages (Cole, 1988). It is also known as a method of analysing documents allowing the researcher to test theoretical issues to enhance understanding of the data.

This method also serves for making replicable and valid inferences from data to their context, with the purpose of providing knowledge, new insights, a representation of facts and a practical guide to action (Krippendorff 1980; Sandelowski, 1995). Miles & Huberman (1994) presents the following three parallel flows of activity to explain the analysis.

- *Data Reduction*: the process of selecting, focusing, simplifying, abstracting and transforming the data. The purpose is to organize the data so that the final conclusion can be drawn and verified.
- *Data display*: taking the reduced data and displaying it in an organized compressed way so that the conclusions can be more easily drawn.
- *Conclusion drawing/verification*: deciding what things mean, noting regularities, patterns, explanations, possible configurations, causal flows, and propositions.

Miles and Huberman (1994) further describe pattern coding as a way to present data for a qualitative analysis, pattern coding is important since it reduces large amounts of data into a smaller number of analytic units. Codes are tags or labels for assigning units of meaning to the descriptive or inferential information compiled during a study. Codes are attached to “lumps” of varying size – words, phrases, sentences, or whole paragraphs, connected or unconnected to a specific setting’. This allows the researcher for a better focused analysis and helps to elaborate a cognitive map in order to understand local incidents and interactions. Codes are used to retrieve and organize the data which includes descriptive codes, interpretive codes, pattern code etc.

In this study, a set of steps is followed in order to analyze the generated data. The questionnaires prepared are decided to be piloted with two GCC regulatory authorities before the appropriateness of the final questionnaires is determined. Then they are e- mailed to the targeted

key regulators in the rest of the authorities for completion at pre-scheduled dates. The data present in the completed questionnaires will then be analysed and reduced where the required data is abstracted according to pre-set targeted information in individual GCC regulatory agency. Furthermore, the data will be displayed in a report format where the respondent's answers will be compared to one another in a clear organised manner. At the end the conclusions from the analyses will be drawn based on patterns of similarities and dissimilarities which are revealed in the data reduction and data display processes.

SUMMARY

- The chapter describes the rationale for carrying out the study to evaluate the GCC Centralised Procedure for the last ten years since its inception.
- The various methodologies, techniques and instruments that will be used in analysing the data obtained from the seven GCC regulatory authorities and the pharmaceutical companies have been described.
- A detailed description of the developmental technique of the two questionnaires was also provided and how the information obtained from these questionnaires are reduced, analysed and displayed in an organized manner.
- Methodological choices related to database management, data processing and data analyses were evaluated.
- The data to be collected from the GCC States revolve around three major areas, namely, the regulatory review processes and milestones, the registration timelines and the stakeholders views' and experiences with GCC Centralised Procedur

CHAPTER 3

Evaluation of the Pharmaceutical Regulatory Review Process in Oman

INTRODUCTION

The regulation of pharmaceuticals is mandated such that the government takes on responsibility as the gatekeeper of the public's health and safety and it does this by regulating the behaviour of the private sector for public purposes (Ratanawijitrasin 2002). Ensuring the safety, efficacy and quality of medicines available to the public is the main aim of drug regulation. If regulatory goals are to be achieved, appropriate structures must be established and the activities carried out to achieve the desired goals.

Ideally, a government should endeavour to have a drug regulatory authority that is created by comprehensive and up-to-date laws, is maintained as a unified but independent organisation, contains competent human resources, is free from political and commercial influence, is maintained by adequate and sustainable financial resources, is guided by transparent standards and procedures, is driven by outcome-oriented implementation and is monitored and evaluated systematically (Ratanawijitrasin 2002).

The time required by drug regulatory authorities to approve a new medicine may affect healthcare professionals and patients and unnecessarily long approval times delay access to new medicines that may improve the health status of patients (Rawson 2000). Oman had the advantage of being the last country in the GCC to start adopting the registration system and as a result the MOH review times decreased soon after the implementation of the new registration guideline (Ministerial Decision (86/2000)). Currently the registration decision must be within four months from the date of first submission of the registration file. However, many factors still affect the review process and delay product approvals e.g. lack of experts and resources.

This chapter evaluates the regulatory review process of new medicines in Oman and examines the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines that could have an impact on their availability to patients. It assesses the current regulatory situation in Oman in order to identify the key issues for improving review practices and patients' access to new medicines.

OBJECTIVES

The objectives of this study were to:

1. Evaluate the regulatory review process in Oman and identify the milestones.
2. Review the regulatory timelines for pharmaceutical products in Oman between January 2006 and December 2010
3. Identify the strengths and weaknesses of the Oman regulatory review process.
4. Propose strategies that can improve the regulatory review process

METHODS

Data source

Information on the total application numbers and approval dates from January 2006 to December 2010 were obtained directly from the Oman Ministry of Health. This includes New Active Substances (NASs), Existing Active Substances (EASs), biological products and vaccines. The data also includes the application submission date, the registration date and the overall review time. The products were classified into four groups (regions) according to the location of the manufacturing companies (GCC, non-GCC Arab, international and Asian). A questionnaire for studying the regulatory review process in the emerging markets was used in this research (McAuslane et al. 2009). This questionnaire consisted of four parts namely, a review of the regulatory review process, the requirements for submission of new drug applications, good review practices, and the timeline for the review process.

Hypotheses

This study examined the following hypotheses:

1. There was an increase in the number of pharmaceutical products approved in Oman between 2006 and 2010.
2. The largest number of products approved in Oman originated from international companies.
3. There was a significant increase in the total approval time in Oman between 2006 and 2010.
4. The time of approval for products from the Gulf pharmaceutical companies was shorter than for other companies.

5. There was a significant increase in New Active Substances (NASs) approval times in Oman between 2006 and 2010.
6. There is no difference in approval times between major therapeutic groups for NASs.

DATA PROCESSING AND ANALYSIS

The data were processed using Excel and SPSS for windows. The statistical analysis for Existing Active Substances (EASs) and New Active Substances (NASs) covered: the total number of registered products between 2006 and 2010; and regulatory approval time in Oman between 2006 and 2010 for different cohorts of pharmaceutical products (GCC, non-GCC Arab, international and Asian); different dosage forms (i.e. solids, semi-solids, liquids, injectables); and different therapeutic indications (i.e. Cardiovascular system (CVS), Central nervous system (CNS), Gastro-intestinal system, and Anti-Infectives). Non parametric tests were applied for the analysis of the data presented in this chapter.

RESULTS

For the purpose of clarity the results will be presented in three parts:

Part I: Review process map and milestones.

Part II: Products reviewed and their characteristics.

Part III: Good review practices in the assessment and registration process.

Part I: Review process map and milestones

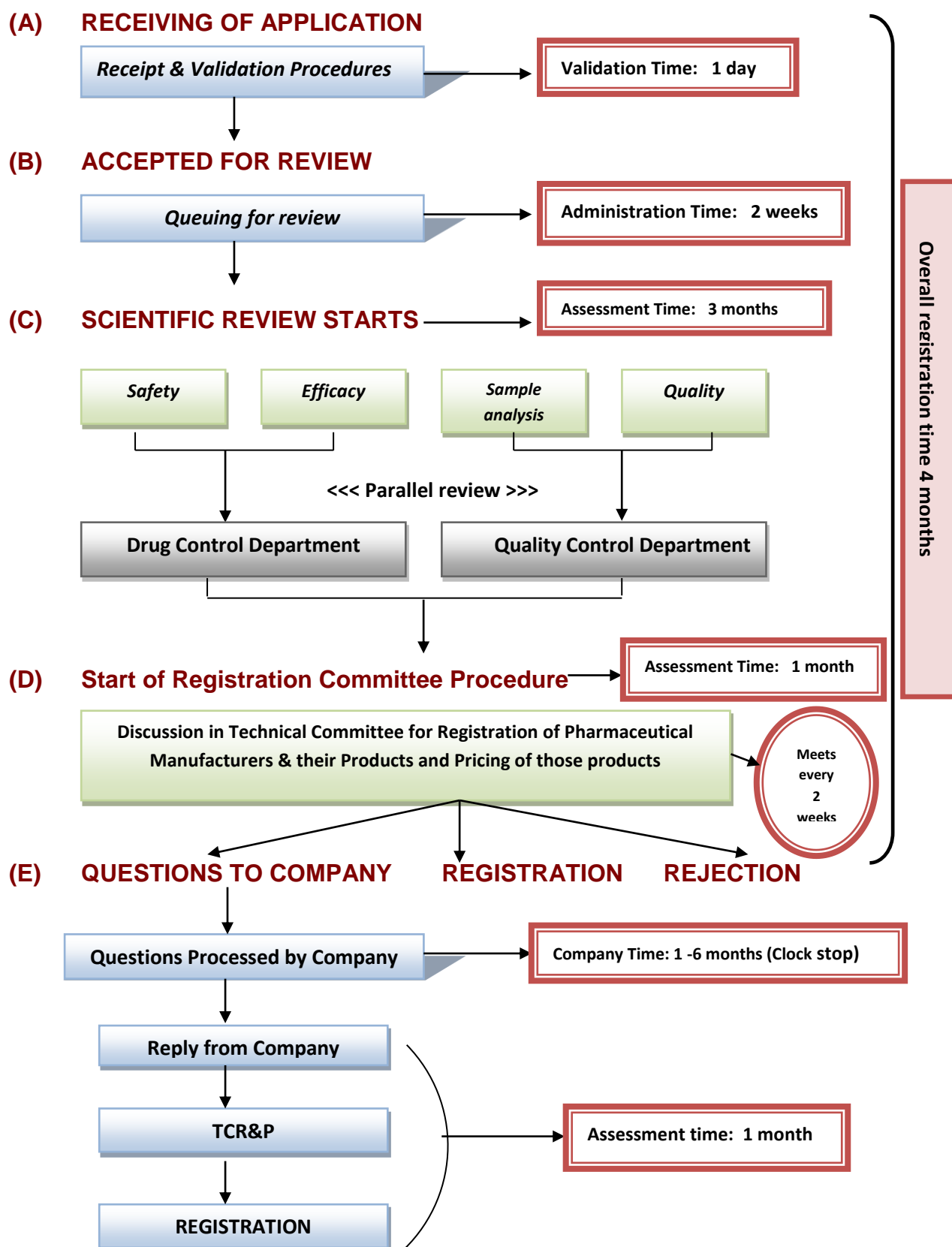
The review process map (figure 3.1) reflects the current situation of the Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&DC) and is a simplified representation of the main steps being followed for the review of New Active Substances (NASs) and Existing Active Substances (EASs). The map represents the review and authorisation of a product that is approved on the first cycle and does not include a second cycle for products approved subject to submission of additional data. The map also does not include the steps involved in the case of a refusal of an application (such as hearing, appeal etc.)

The Drug Control and Quality Control Laboratory Departments in DGPA&DC are responsible for reviewing the marketing authorisation applications. The two departments currently have a staff of 43 people, 22 of whom are involved in the process of review. There is no formal ‘fast

track' procedure, however, life saving medicines are not queued but are selected for review as a priority, although, the data requirements and review process are the same. The process map and milestones for Oman is shown in figure 3.1. The review process milestones in the review and approval are as follows;

- a) **The receipt and validation stage:** This includes administrative registration (reference number) and validation of legal requirements, the status of the company, details of the local agent and manufacturer as well as a 'checklist' validation of the application content (e.g. technical sections, CPP status). The product applications received are duly recorded electronically which then generate a unique tracking number. After receiving the product file, the company must pay the registration fee within one week. The file is rejected if the information is not complete and a new application must be made after completing the missing data. The time required for the receipt and validation procedures is only one day.
- b) **Queuing for review:** Once the file is accepted, it will be entered into a queue for review which takes around one week. The product dossier is divided into two parts; the safety and efficacy part which are reviewed by the Drug Control Department and quality by the Quality Control Laboratory. Administrative time is a measure of the 'backlog' time while valid applications queue for commencement of their review.
- c) **Scientific review:** Scientific review and analysis takes three months to complete for the Drug Control Department and Quality Control Laboratory, although both proceed in parallel. The start and finish of the scientific assessment is formally recorded. The QC laboratory sends the quality assessment report to the Drug Control Department where the reviewer, after completing a scientific product report form, submits the file to the Technical Committee for Registration of Pharmaceutical Manufacturers & Their Products & Pricing (TCR&P) for a decision.

Figure 3.1 PROCESS MAP FOR SULTANATE OF OMAN



- d) **Registration committee procedure:** The registration committee meets routinely every two weeks. The TCR&P, established by the Minister of Health, consists of members from two different directorates of the Ministry of Health, six members from DGPA&DC and two members from the Directorate General Medical Supplies. All of the members are Pharmacists and there are no external members. The company can meet with the internal directorate staff to discuss questions and queries that arise during the assessment, but they are only permitted to meet the Director and/or Section Heads. If the committee is satisfied with the safety profile of the product, it will be registered, otherwise rejected. If registered, a Product Registration Certificate signed by the Chairperson of TCR&P is issued within two weeks from the date of registration. In the case of a rejection, the company can appeal within two months from the date of receiving the Committee's rejection decision.
- e) **Questions to the companies:** In the case of any queries raised by the Committee, they will be conveyed by the Committee Secretary to the company to respond within a stipulated deadline which is normally given from 1 to 6 months. Once the response from the company is received within this stipulated deadline, it is discussed in TCR&P within one month from the date of its receipt and accordingly a final decision is taken. The issue of product authorisation also depends on the pricing agreement and discussion of pricing is separate from the technical review but does not delay the approval of products. The pricing negotiation starts after the end of the scientific review.

Models of regulatory review:

Many authorities apply different levels of data assessment to different applications, according to the type of product and/or its regulatory status with other authorities. Three basic types of review models for the scientific assessment have been identified as a result of discussions with regulatory authorities and workshop reports from CMR International Institute for Regulatory Science (McAuslane, 2006), namely,

1. Verification model (type I assessment)
2. Abridged model (type II assessment)
3. Full review model (type III assessment)

Verification model (type I assessment)

This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorized by two or more recognized reference agencies, elsewhere. The main responsibility of the authority in the importing country is to ‘verify’ that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorization(s).

Abridged model (type II assessment)

This model conserves resources, by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an ‘abridged’ independent review of the product in terms of its use under local conditions. This might include a review of the Chemical and Manufacturing Control (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition. Approval by a recognized agency elsewhere is a pre-requisite before the local authorization can be granted but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available.

Full review model (type III assessment)

In this model the authority has suitable resources, including access to appropriate internal and external experts, to carry out a ‘full’ review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. A Type III assessment could be carried out on a new application that has not been approved elsewhere but in practice legal requirements may dictate that the product must be authorized by a reference authority before the local authorization can be finalized. The model used by Oman in the assessment of all major application is an Abridged Assessment. Oman MOH is capable to conduct an independent review of product applications. However, Oman carries out a unique practice whereby the New Active Substances (NASs), being considered for approval, must be marketed in the product country of origin for at least 24 months before it can be registered in Oman. This requirement may be waived, depending on the product type, if evidence of registration in recognized

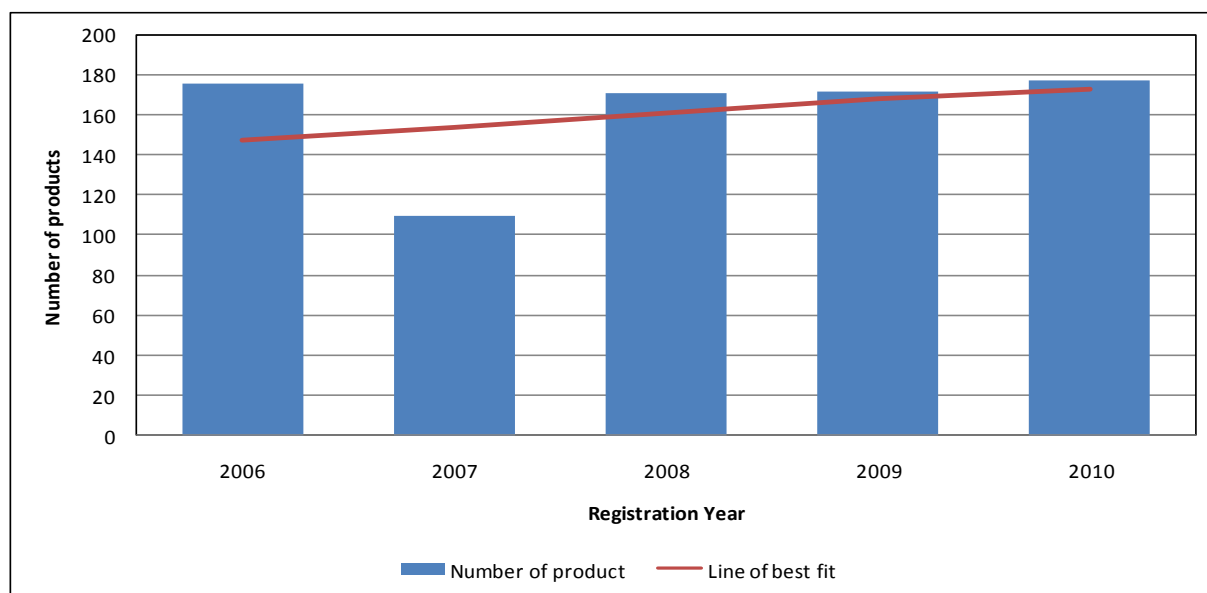
international reference agencies such United States Food and Drug Administration (US FDA), European Medicines Agency (EMA) and/or GCC Centralised Drug Registration (GCC-DR) System.

Part II: Products considered and their characteristics

Approval of all products in Oman (2006 - 2010)

A total of 807 pharmaceutical products for human use were successfully registered in Oman between 2006 and 2010 (Figure 3.2). This number included EASs and NASs with a similar portion for the years 2006, 2008, 2009 and 2010 (176; 22%; 171; 21%; 172; 21%; and 178; 22%, respectively), but there was dip in 2007 (110; 15%).

Figure 3.2: Total number of pharmaceutical products approved in Oman (2006-2010)



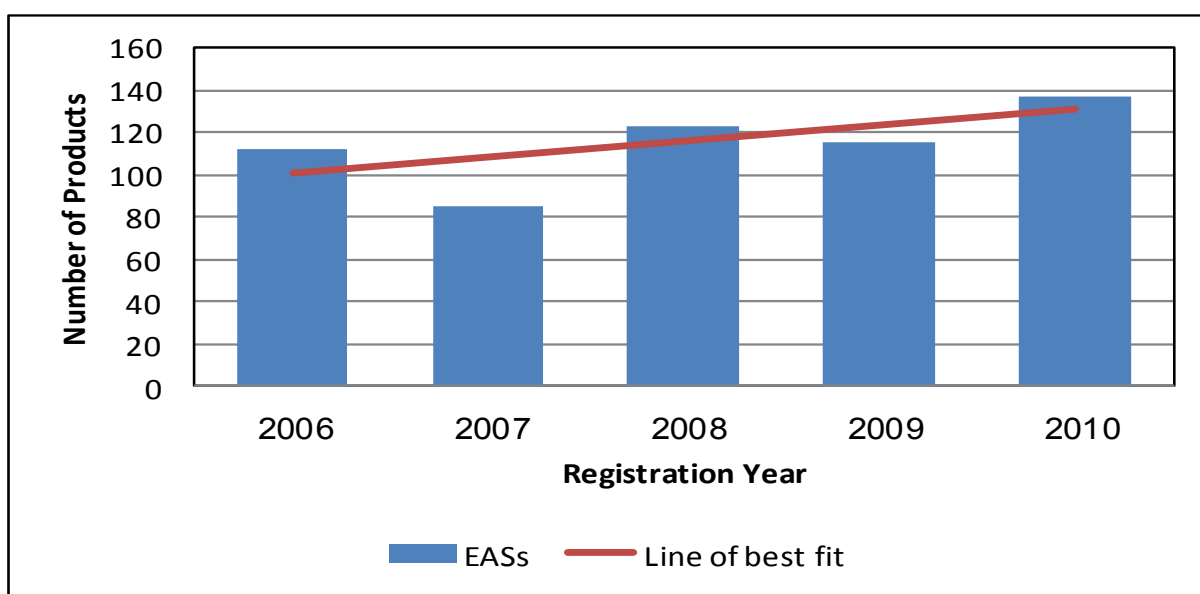
Statistical analysis of these data using a simple linear regression showed no significant increase in the total number of registered pharmaceutical products over the five year period ($p>0.05$).

This was possibly due to the development of new regulations for the approval of health products and alternative medicines. These new regulations resulted in an overload for the Quality Control Laboratory, increasing the analysis time required for pharmaceutical products. The results showed no significant increase ($p>0.05$) in the total number of registered pharmaceutical products from 2006 to 2010 (Figure 3.2).

Approval of Existing Active Substances (EASs) and New Active Substances (NASs) in Oman (2006 – 2010)

The total number of products registered in Oman between 2006 and 2010 was 807 and this included 573 EASs and 234 NASs. The highest number of EASs registered in Oman was seen in year 2010 (137) followed by year 2008 (123), year 2009 (116) year 2006 (112) and year 2007 (87) (Figure 3.3). Statistical analysis using a simple linear regression showed a significant increase in EASs registered over the five year period ($p<0.001$).

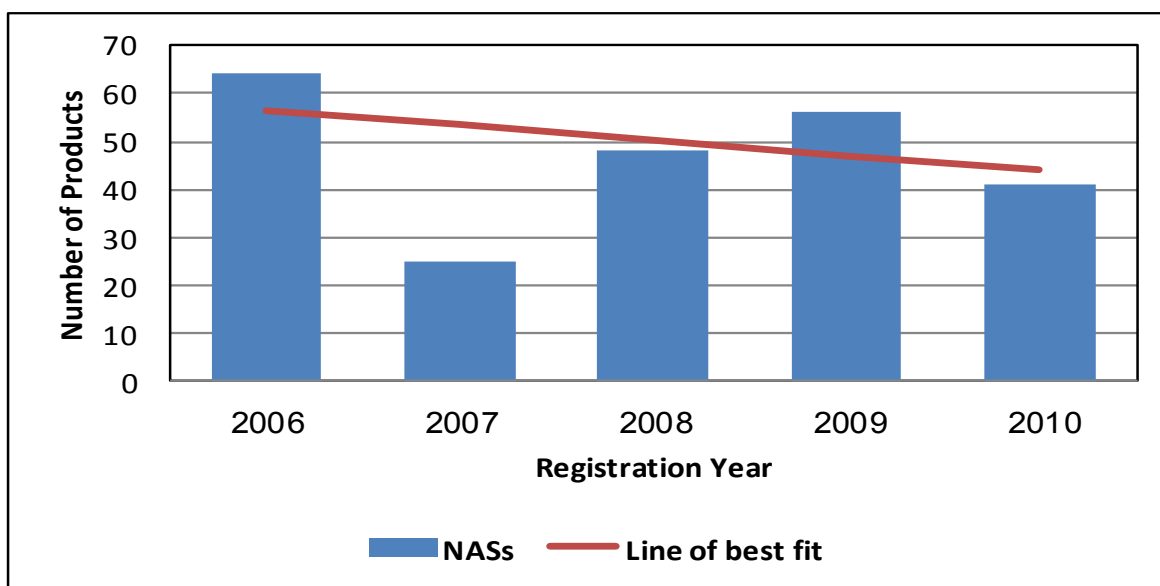
Figure 3.3: Number of EASs approved in Oman for the period (2006-2010)



Statistical analysis using a simple linear regression showed a significant increase in EASs registered over the five year period, ($p<0.001$).

The highest number of NASs was registered in 2006 (64; 36%), while the lowest number was in year 2007 (25; 23%) (Figure 3.4). From these 234 NASs, 226 (97%) were found to be from international companies. Statistical analysis using a simple linear regression showed a significant increase in the number of registered EASs with a significant decrease in the number of registered NASs ($p<0.001$).

Figure 3.4: Number of NASs approved in Oman for the period (2006-2010)



Statistical analysis using a simple linear regression showed a significant decrease in the number of registered NASs over the five year period ($p < 0.001$).

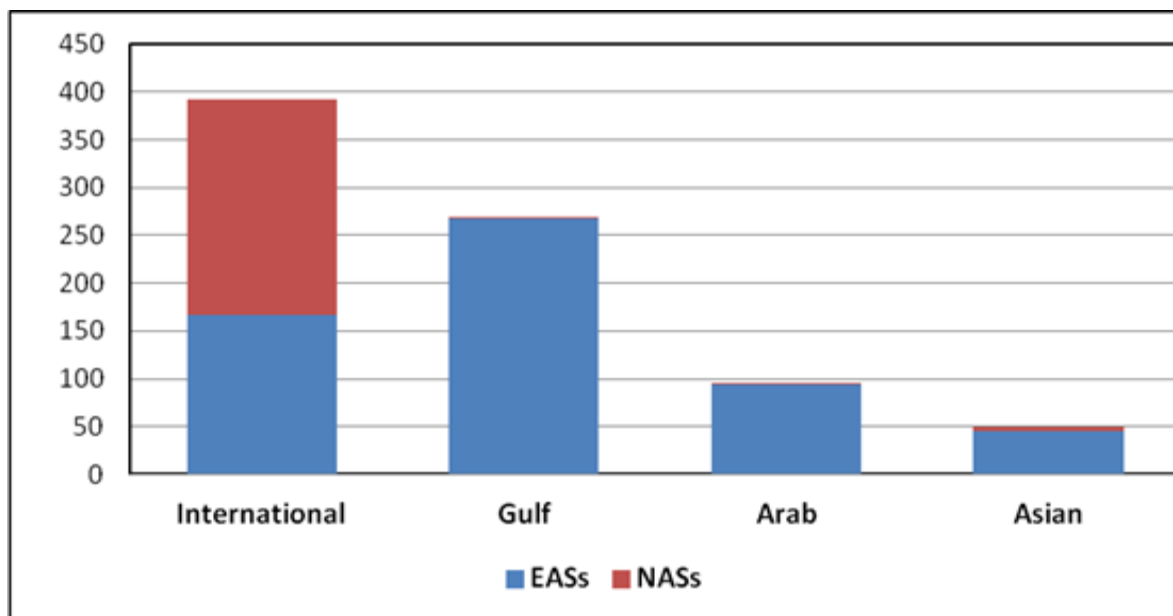
The number of pharmaceutical products registered for international, GCC, non-GCC Arab and Asian companies (2006-2010)

The number of products registered during the five years period varied for different cohorts of companies based on their geographical location, for example the highest number was for the international companies products (393; 49%), followed by the GCC Companies products (269; 33%), non-GCC Arab Companies products (95; 12%) and Asian Companies products (50; 6%) (Figure 3.5).

The Existing Active Substances (EASs) approved for GCC, international non-GCC Arab and Asian companies in Oman (2006-2010)

A total of 573 Existing Active Substances (EASs) were registered in Oman between 2006 and 2010. When examined by individual regions 267(47%) medicines were identified as being approved from GCC, 167(29%) from international companies, 94 (16%) from non-GCC Arab, and 45 (8%) from Asian companies. Statistical analysis of the data using Kruskal-Wallis Test (K-Test) over the five-year period showed that there was a significant increase in the number of registered Existing Active Substances (EASs) between 2006 and 2010 ($p < 0.001$).

Figure 3.5: Approved pharmaceutical products (EASs & NASs) for GCC, international, non-GCC Arab and Asian companies (2006-2010)



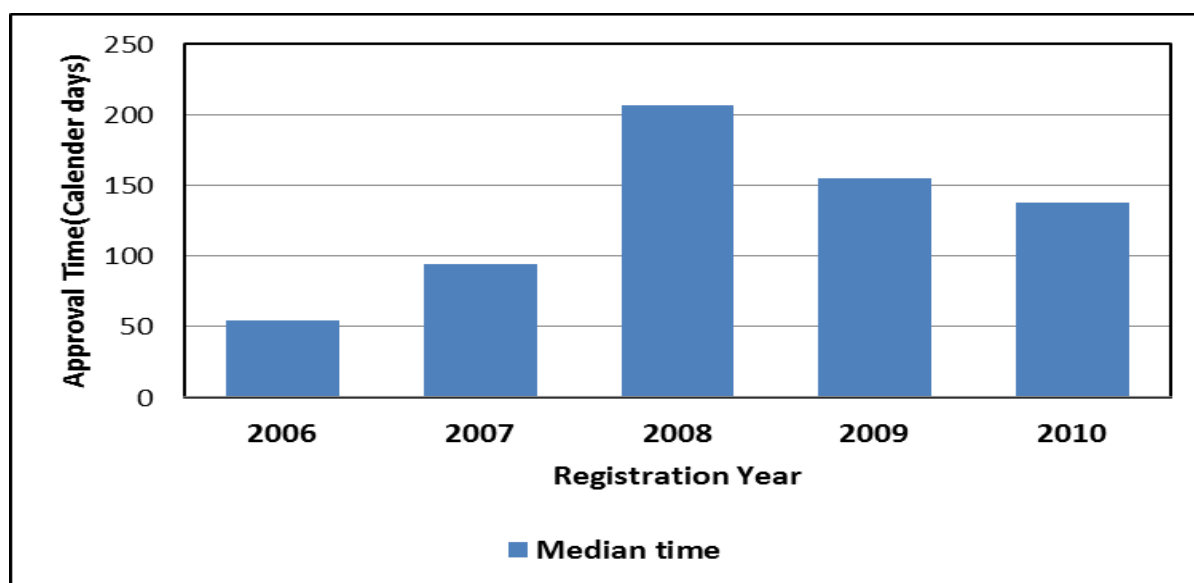
Approval times of all pharmaceutical products in Oman (2006 – 2010)

The total approval times for pharmaceutical products in Oman for the period of the study (2006 - 2010) was calculated for all of the 807 Existing Active Substances (EASs) and New Active Substances (NASs) from different pharmaceutical companies. The median approval time varied from 55 days in 2006 to 207 in 2008 while in 2010 it was 138 days showing a 33% decrease in the approval time (Figure 3.6). Statistical analysis using Kruskal-Wallis Test (K-Test) over the five-year period showed that there was a significant increase in approval times for pharmaceutical products from 2006 to 2010 ($p < 0.001$).

Approval time for Existing Active Substances (EASs) in Oman (2006 - 2010)

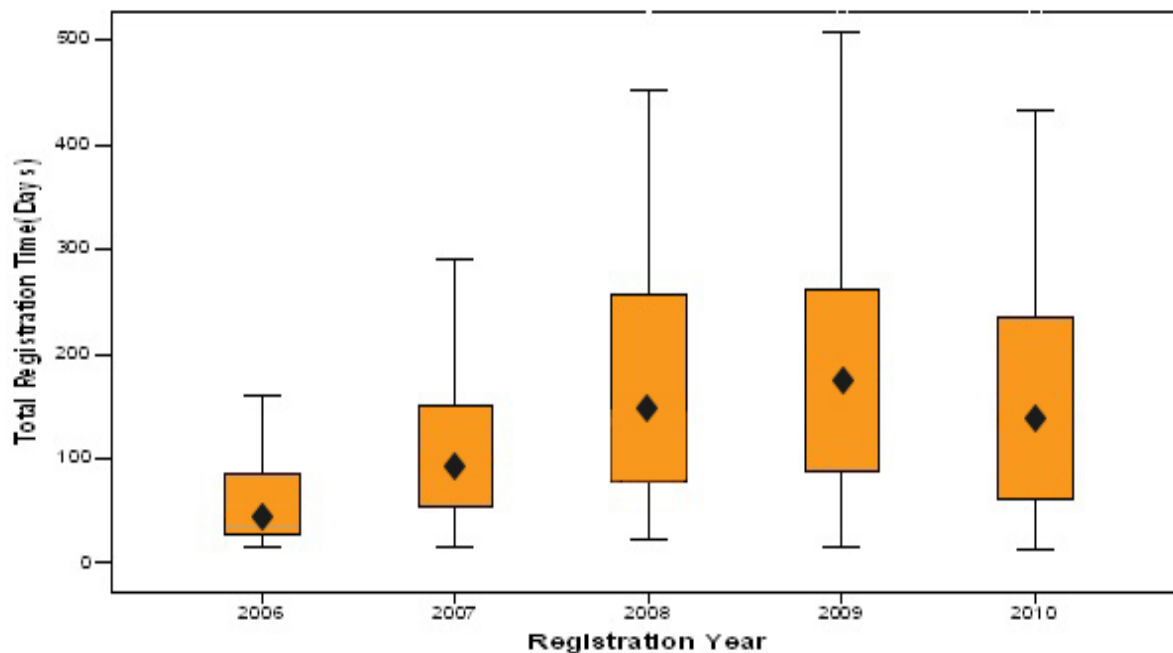
Approval time for 573 Existing Active Substances (EASs) registered in Oman varied over the period (2006-2010) (Figure 3.7). The lowest median in this period was seen for 2006 (39 days) and the highest median for 2009 (176 days). Statistical analysis using Kruskal-Wallis Test (K-Test) over the five-year period showed that there was a significant upward trend in the median approval time (39, 93, 149, 176 and 138 days respectively) for EASs between 2006 to 2010 ($p < 0.001$).

Figure 3.6: Median approval time for all pharmaceutical products in Oman (2006-2010)



Statistical analysis using Kruskal-Wallis Test (K-Test) showed that there was a significant increase in approval times for pharmaceutical products from 2006 to 2010 ($p < 0.001$).

Figure 3.7: Median approval time for Existing Active Substance (EASs) in Oman (2006-2010)

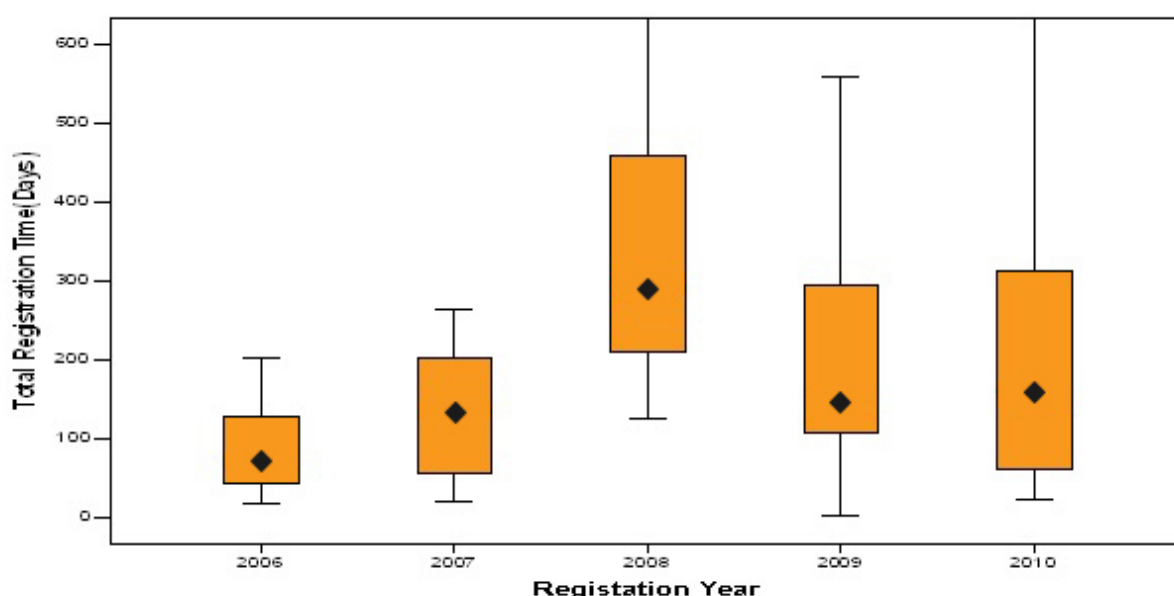


Statistical analysis of the data using non-parametric K- test shows a significant upward trend in the median approval time over the five year period ($P < 0.001$).

Approval time for New Active Substances (NASs) in Oman (2006 - 2010)

The highest number of products (64) was registered in the year 2006 with the median approval time of 72 days followed by 133 days for 25 products in 2007 and 292 days for 48 products in 2008. In year 2009, 56 products were registered with a median approval time of 147 days and 159 days for 41 products in 2010. The drop in the number of registered products in year 2007 was due to the development of the new regulations for approval of health and alternative products. These new regulations created an overload for the Quality Control Laboratory, increasing the time of analysis of pharmaceutical products. The results obtained from performing analysis of variance test showed that there was a significant upward trend in the median approval time for NASs products between 2006 and 2010 ($p < 0.05$). (Figure 3.8)

Figure 3.8: Median approval time for NASs in Oman (2006-2010)



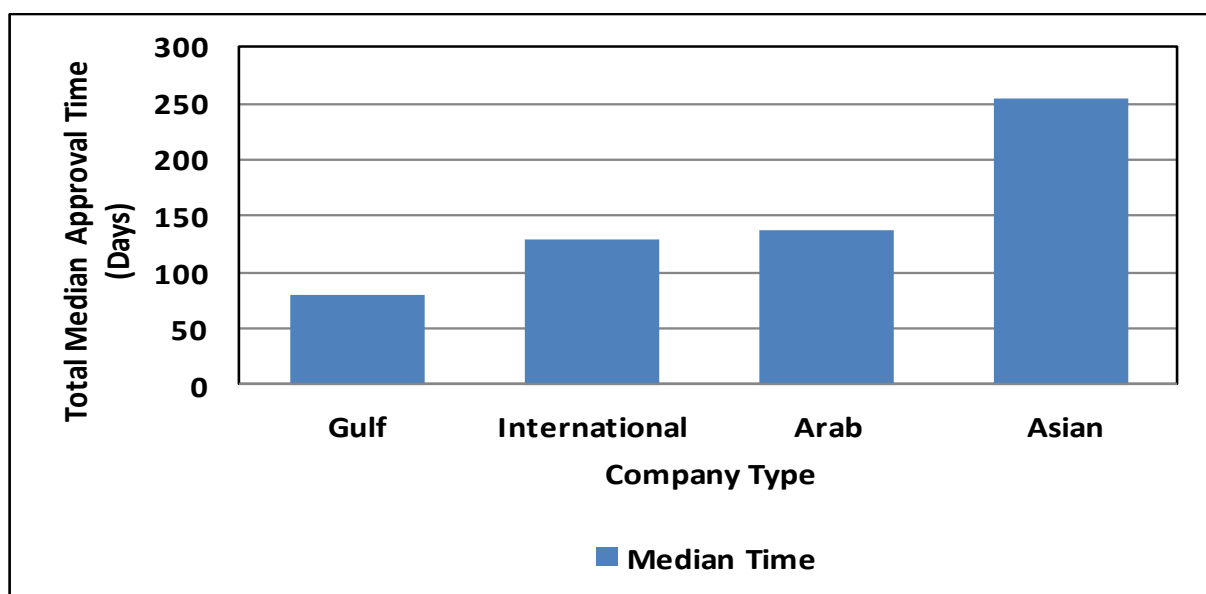
The results of variance test analysis showed that there was a significant upward trend in the median approval time between 2006 and 2010 ($p < 0.05$).

Approval time for Existing Active Substances (EASs) submitted by GCC, international, non-GCC Arab and Asian companies (2006-2010)

The median approval time for different cohorts of companies varied from 80 for the GCC companies to 254 for the Asian companies (Figures 3.9). The rapid approval time for the GCC States is due to their efforts; particularly Oman, Saudi Arabia, UAE, and Kuwait, to improve

their local manufacturing capabilities and the production capacity for the local population. EASs from Asian companies had the longest median approval time of 254 days. Statistical analysis of the data using non-parametric K- test showed that there was a significant difference in approval times between different cohorts of companies ($P<0.001$).

Figure 3.9: Median approval time for GCC, international, non-GCC Arab, and Asian companies Existing Active Substances (EASs) in Oman (2006-2010).

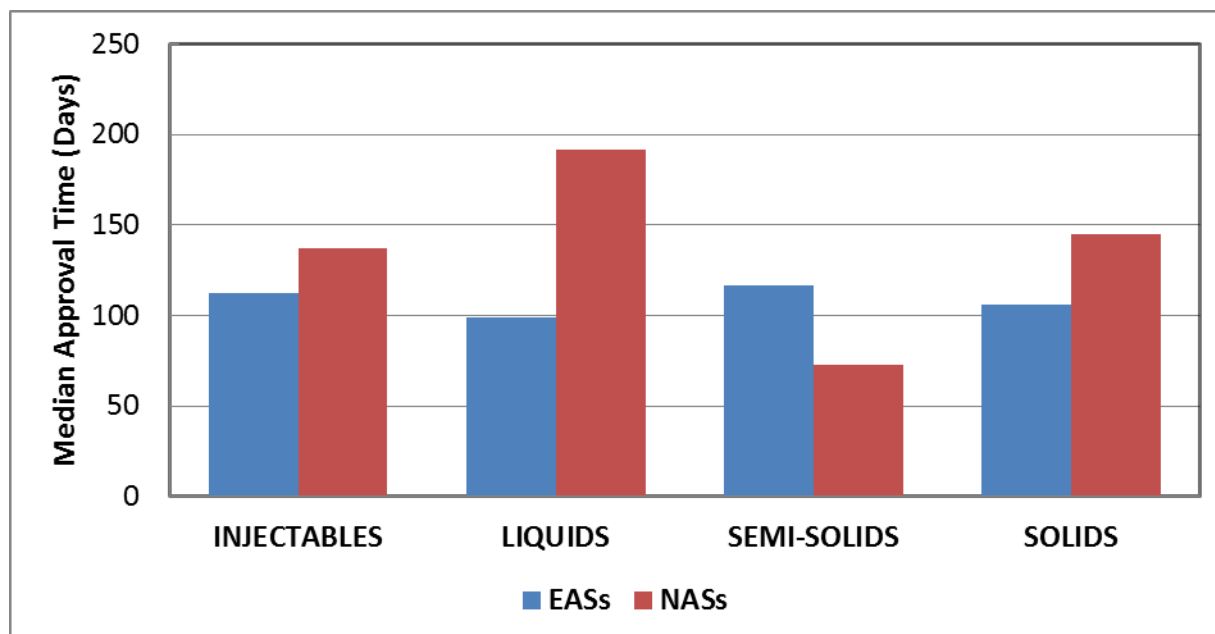


Statistical analysis of the data using non-parametric K- test showed a significant difference in approval time between different cohorts of companies ($P<0.001$).

Approval time for different dosage forms for all Existing Active Substances (EASs) and New Active Substances (NASs) in Oman, (2006-2010)

During the five years, 573 EASs were registered in Oman with the lowest number represented by the semi-solid dosage forms (48) followed by injectables, liquid dosage forms and the highest number was represented by solid dosage forms (364). Out of 234 NASs registered, the lowest number is represented by the semi-solid dosage forms (3) with a median approval times of 73 days and the highest by the solid dosage forms both in term of numbers (121) and median approval time (145 days) (Figure 3.10).

Figure 3.10 Median approval time for different dosage forms for EASs and NASs in Oman, (2006-2010)



Approval times for Existing Active Substances (EASs) and New Active Substances (NASs) by therapeutic class, (2006-2010)

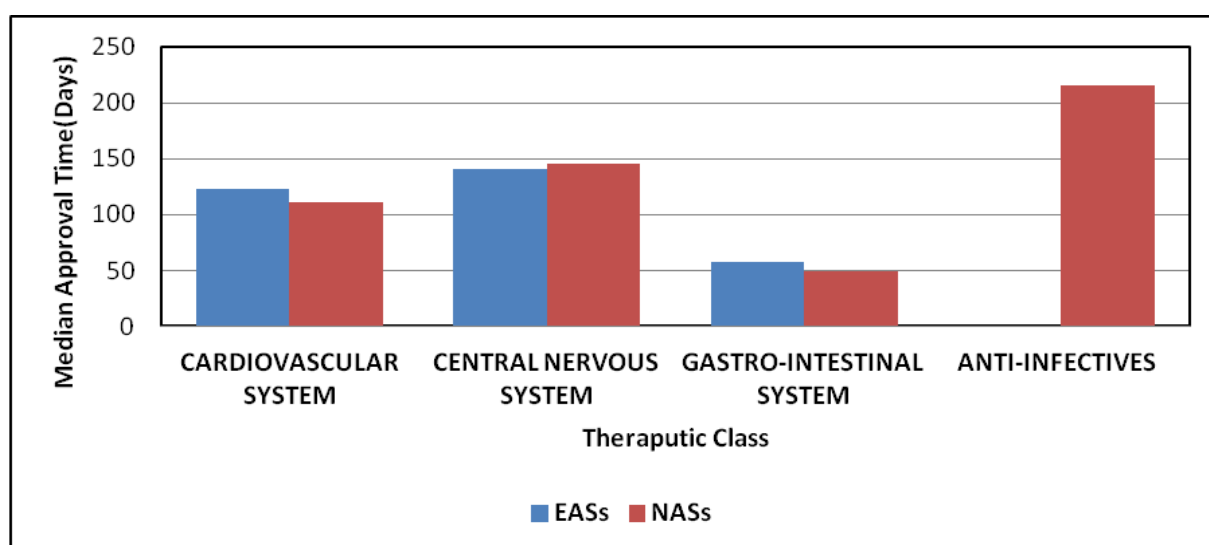
An examination of EASs by therapeutic class showed that the lowest number was represented by the immunological preparations (1 preparation) and the highest number by the injectables (117 preparations). The analysis of the approval time of EASs registered between 2006 and 2010 involved the four major therapeutic groups which dominate the pharmaceutical market in Oman, namely,

- The cardiovascular system (CVS)
- The central nervous system (CNS)
- The gastro-intestinal system
- Anti-Infectives

The range of median approval times for EASs analysed by therapeutic class varied from 141 calendar days for CNS products to 57 for gastro-intestinal products. The differing patterns of approval times for EASs from different therapeutic groups were attributed to the authority's assessment requirements which may or may not include the need for clinical and bioequivalent studies. This can be a lengthy process and has an impact on the overall approval timeline.

Another reason for such differences is the sponsor's response time to the authority's request and the level of communication between the two parties. During the period of study, 234 NASs were approved in Oman, with the lowest number represented by the ear, nose and oro-larynx preparations (1) and the highest number by cardiovascular preparations (40). Figure 3.11 shows the range of approval times for NASs analysed by therapeutic class and these varied from 216 days for anti-infectives to 49 for gastro-intestinal products.

Figure 3.11: Median approval times for different therapeutic classes for EASs and NASs in Oman (2006-2010)



There were several factors leading to the variation in approval times for different therapeutic groups. In some cases, consultations with different therapeutic committees within the Ministry of Health, for example Central Drug Committee (CDC) and National Antibiotic committee, which do not have regular meetings, may have caused delays in the approval time. Some medicines have longer pricing times due to a protracted period of negotiation with the companies.

Part III: Good review practice in the assessment and registration process

The ultimate measure of success in regulatory performance is the quality reviews and decisions, as well as the quality of the dossiers (Kendle, 2009; Karlton and Johnson, 1997 and McAuslane and Cone, 2006). The regulatory authority, industry and patients benefit from having a high quality review process that is well managed (Hynes et al., 2001 and Booz Allen Hamilton, 2008).

An efficient review allows the regulatory authorities to fulfill their public health mission to ensure that safe and effective medicines are made available to patients in a timely manner and allows for efficient use of resources. Patients benefit from the timely access to safe and effective therapies while pharmaceutical companies are able to market the product sooner and generate revenues (Booz Allen Hamilton, 2008). The regulatory challenge is to allow access to the safest and most effective pharmaceutical products in the shortest possible time with a highest degree of certainty (Alder, 2001). The results showed that the Oman regulatory authority, the Directorate General of Pharmaceutical Affairs & Drug Control (DGPA&DC), intends to implement a number of quality measures in the review and authorisation of medicinal products. It includes a well defined internal quality policy, good review practices, standard operating procedures, assessment templates and a peer review process.

General measures used to achieve quality

The DGPA&DC currently does not have an internal quality policy which defines the intentions and directions of the organisation related to quality as formally expressed by top management. But it is likely to be established in the near future. Similarly, good review practices are not formally documented at present but will be established soon. A well defined code about the process and documentation of review procedures would standardize and improve the overall documentation and ensure timeliness, predictability, consistency and high quality reviews.

Standard operating procedures were implemented in the DGPA&DC for certain procedures while for the remaining processes, SOPs will soon be established. Assessment templates would set out the content and format of written reports on scientific reviews however they are not in use currently but are likely to be established within the next few years. A peer review procedure is currently used for vaccines as there are two committees reviewing the vaccines marketing authorisation applications. Peer review, defined as an additional evaluation of the original assessment that is carried out by an independent person or committee, is unlikely to be established in the next few years.

Quality management

The three most important measures which the DGPA&DC identified for establishing quality measures were (1) to be most efficient, (2) to minimise errors and (3) to increase transparency.

To improve quality, the following activities were undertaken to bring about continuous improvement in the assessment and authorisation process:

- Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action.
- Carrying out internal quality audits (e.g. self assessments) and using the findings to improve the system.
- Having external quality audits by an accredited certification body to improve the system (e.g. WHO)

The DGPA&DC does not have a dedicated department for assessing and/or ensuring quality in the assessment and registration process for new medicines, however, there are plans to set up such a department in the future.

Quality in the review and assessment process

The guidelines issued under the Ministerial Decision No. 86/2000 serve as an official document to assist the industry in the registration of medicinal products in Oman. This Ministerial Decision is also available on the Ministry of Health website. Pre-application scientific advice is not available to applicants, but can be obtained during the file submission day. The applicants are allowed to make formal contacts with DGPA&DC staff to discuss an application during its review process.

There is a registration committee called “The Technical Committee for Registration of Pharmaceutical Companies and their Products and Pricing”. The committee consists of eight members and meets once every two weeks. New Active Substances (NASs) applications are reviewed by this committee while Major Line Extensions (MLE) are reviewed by the Drug Control Department in the DGPA&DC and not forwarded to the registration committee. The committee receives assessment reports from the Drug Control and Quality Control Laboratory staff that review the applications. Shared/Joint reviews are undertaken when products are submitted through the GCC Central Registration Procedure.

Training and continuing education

To maintain or improve the quality of the work, it is essential that reviewers follow training or refresher courses from time to time. These may concern general training about new developments in the regulatory science field or specialized training in carrying out a quality review process. The DGPA&DC does not currently have any formal training programmes for assessors. Training is mainly carried out through external courses, post-graduate degrees, participation in international workshops/conferences, placements and secondments in other regulatory agencies and inviting speakers to the authority. After training or attending a course, the reviewer should report and convey his/her experience or knowledge to colleagues and top managers and make proposals for any change of existing procedures or adoption of new practices to improve the overall performance of the reviewing staff.

Transparency of the review procedure

The DGPA&DC assigns a high priority to transparency of the review procedure. It has identified the following three top incentives for assigning resources to activities that enhance the openness of the regulatory system namely: political will, the need to increase confidence in the system and to provide assurances to the pharmaceutical industry. Information such as product approval and the price of medicines is routinely provided to the general public. The information can be accessed from the ministry's official website or provided on submission of a formal request. As far as transparency is concerned, the companies can follow up the progress of their application either through phone contact, email or meetings with the officials with prior appointment. There is an electronic system for registration and tracking of applications, which also can be used to:

- Track applications that are under review and identify the stage of the process
- Signal that target review dates have been exceeded
- Record the terms of the authorisation once granted
- Archive information on applications in a way that can be retrieved.

Drivers and barriers facing the review process in Oman

Understanding the drivers and barriers to achieving a quality regulatory review process can promote innovative and creative ideas and practices to help reviewers assess new products and underline the importance of monitoring the quality of the review process.

There are several motivating factors identified by DGPA&DC that contribute to accomplishing the desired effectiveness and efficiency of the authority's review procedures and decision-making for new applications, namely:

- Good tracking system
- Utilization of an assessment template.
- Good Management Plan
- Well qualified, trained and experienced reviewers

However, the DGPA&DC is facing several obstacles that are hindering its ability to ensure that new medicines are available in a timely manner, i.e:

- Shortage of experience personnel
- Lack of an independent budget
- Lack of an internal quality policy

DISCUSSION

This study has evaluated the pattern of total regulatory approval time in Oman between 2006 and 2010. It has also addressed the various factors which may have a positive or negative effect on the total approval time. It has been shown that the total number of registered Pharmaceutical Products in Oman (2006 - 2010) is 807 and this number includes Existing Active Substances (EASs) and New Active Substances (NASs).

Six hypotheses were generated for this study, as outlined previously and the findings are discussed below.

1) There was an increase in the number of pharmaceutical products approved in Oman between 2006 and 2010.

The largest number of registered medicines was found in 2006. In this year, there was no overload on the quality control laboratory since the actual approval of health products, using the recent guidelines and regulations (Circular 64/2005) did not start until 2005. However, the number of the registered medicines was similar in the years 2006, 2008 & 2009 with the exception of 2007 when there was a fall. This was largely due to the development of new regulations for approval of health products. These new regulations resulted in an overload on the

Quality Control Laboratory, increasing the time of analysis of pharmaceutical products. This hypothesis has therefore rejected.

2) The largest number of the products approved in Oman originated from international companies.

The number of products registered during the five year period (2006-2010) varied for different companies based on their geographical location. The largest number was for the international companies products, followed by the GCC companies, non-GCC Arab, and finally the Asian companies. International companies were the largest group registering products every year in Oman. This was due to the fact that the pharmaceutical companies must submit a full registration application when the manufacturing site has been changed for the same registered company. Thus, there was an increase in the number of changes in product manufacturing sources applications from the international companies during this five year period. Furthermore, international companies increased the number of their submissions to the Omani authority to obtain registration approval as evidence that would support their GCC-DR approval. The pricing process in Oman is the final step and price negotiations occur at the end of the scientific assessment. The Registration Committee makes the decision on the product registration and pricing. Oman has a robust pricing control system and this is one of the main reasons that pharmaceutical companies register their products in Oman prior to other GCC states. Using a price reference system, the pricing committee considers the manufacturer's wholesale and retail prices in the country of origin, export Cost-Insurance-Freight (CIF) prices to Oman as well as CIF prices in other GCC states. This hypothesis was accepted.

3) There was a significant increase in the total approval time for medicines in Oman between 2006 and 2010.

During the five years, the median approval time varied from 55 days in 2006 to 119 days in 2010. There was a significant increase in the median approval time between 2006 and 2008 which was due to the new regulations that were implemented by Oman MOH in 2006 for the registration of human health products. This was due to the increase in the number of local registration applications and the applications received from GCC-DR for Oman MOH evaluations. Registration for the pharmaceutical companies and their products must be renewed every five years as required by the Oman registration system. In 2006 Oman MOH requested

pharmaceutical companies to re-register their products. This re-registration was for the first time and led to an increase in the number of applications and an overload for the Drug Control Department and Quality Control Laboratory.

The WHO has clearly stated that the shortage of qualified personnel is the greatest problem faced by drug regulatory authorities (WHO, 2003a), and is one of the factors affecting patients' access to new medicines in Oman. All staff are paid according to established salary bands for the entire public service. Consequently, Oman MOH is unable to use salaries to attract and retain some of the skills that would strengthen the regulatory role. This hypothesis was therefore accepted.

4) The time of approval for products from Gulf pharmaceutical companies was shorter than other companies.

Median approval time varied for different companies from 80 to 254 days for GCC and Asian companies respectively. The rapid approval time is mainly due to the GCC States making efforts, particularly Oman, Saudi Arabia, UAE, and Kuwait, to improve their local manufacturing capabilities and the production capacity for the local population (Al-Essa, 2011). This led to a positive outcome in approval times, giving a median time of 80 days. There are other factors which have a positive effect on the approval time for local and Gulf companies but have a negative effect on the international, non-GCC Arab and Asian companies. For example, in decision-making, the geographical proximity of the company to the authority leads to an effective interaction and thus a faster response to any questions from the authority. Additionally, most locally manufactured products are EASs and do not need very much consultation during the scientific review compared to NASs. Furthermore, an understanding of the culture of the regulatory authority where there is no language barrier has a positive effect on the review process. However, a priority procedure is a common practice in many authorities, but often in relation to the importance of the medicine rather than geographic location. In Canada and Australia, pharmaceutical companies can apply to receive a priority review for their medicines and the regulatory authority then decides which medicines will be reviewed in this way. The FDA classifies all new medicine applications to receive either a priority or a standard review (Rawson et al., 2000a). In this study, it was found that the 31% of the products, which received priority approval, were manufactured by local companies or were for serious life-threatening

medical groups, e.g. cancer medicines. For the 5-year study period, products from Asian companies had the longest median approval time of 254 days. Oman requests limited clinical data in the form of bioequivalence studies to demonstrate that the EAS is bioequivalent to the original product. Bioequivalence presents the first challenge for the EAS registration because many manufacturers find it difficult and costly to perform high standard controlled trials that compare the proposed EAS with the original product. Meanwhile, for EAS's the laboratory sample analysis is carried out in parallel with the scientific review but the analytical step can be waived if the product is registered in Saudi Arabia, UAE, and/or Kuwait, which have recognized laboratories in the region. From these results this hypothesis has confirmed.

5) There was a significant increase in New Active Substances (NASs) approval time in Oman between 2006 and 2010.

The pricing process can markedly affect the registration time in Oman. The pricing time for NASs is longer than for EASs due to the period of negotiation. The registration committee sets the lowest possible price for the original brand product, which is usually the export price to the Saudi market. Saudi Arabia has much better negotiating power and hence the Omani agency wants to use this power to reduce the medicine prices. Pricing is the final step and no product will be issued a registration certificate before it is priced, but that proposed by the company is not necessarily agreed, although the company is given an opportunity to appeal before the final price is decided. Pricing negotiations start after the granting of registration approval of the medicine. This approach prevents the pricing step from being integrated into the review process and this delays the final approval time. Therefore, it would be preferable for the pricing process to be carried out in parallel with the review process rather than after granting registration approval. The analytical step is one of the approval requirements and takes up to almost 50% of the total approval time for all companies. Unlike Oman, none of the international authorities analyse the products pre-registration. Therefore, it is recommended that this step be carried out post-approval with product samples being selected from the market for analysis. This would reduce the registration time. Another inappropriate milestone is the submission of a Certificate of pharmaceutical Product and the price certificate which has to be legalized by the relevant authority and Oman embassy in the country of origin. Such regulations lead to registration delays and increase the burden for the companies and it is not a WHO requirement.

The findings from this study indicate that the company time for answering questions from the authority when companies submit analytical data are longer than the authority time for all cohorts of companies. No doubt this issue also causes a further delay in the registration of products, which affects patients' access to medicines submitted by international companies. Furthermore, the delay caused by companies leads to a waste of authority time and resources. In order to reduce the company time, it is recommended to implement an official clock-stop system by the Omani health authority while the company responds. This hypothesis was accepted.

6) There is no difference in approval time between major therapeutic groups for the NASs.

The results of this study shows that there are significant differences in the approval time between therapeutic groups, for example the approval time for the anti-infectives is three times longer than those for gastrointestinal products. There are several factors leading to these differences in approval times. In some cases, consultations with different therapeutic committees within the Ministry of Health for example the Central Drug Committee (CDC) and the National Antibiotic committee may cause delays in the approval time. In addition, the nature of the products evaluated, e.g. biological products may require a more detailed review than others. Some medicines have longer pricing time due to periods of protracted negotiations. Using a price reference system, the pricing committee considers the manufacturers wholesale and retail prices in the country of origin, export CIF (Cost, Insurance, and Freight) prices to Oman and CIF prices in other GCC states. These results do not support this hypothesis.

CONCLUSIONS

This study has assessed the trend in the regulatory approval times in Oman for the period 2006 to 2010. The findings show that although there is an increase in the approval time for all pharmaceutical company products, the median approval time for the five year period was 117 calendar days. This is within the time limit (4 months) which is fixed by the health authority for the overall registration time. It was found that products in the different cohorts of companies, which include local, GCC, non-GCC Arab and international companies have varying approval times which may be due to an internal unpublished policy of prioritization within the authority. However, there are many factors affecting the approval time, which include the quality of the

dossier, the geographical location of the company, communication within companies and various cultural factors. This study enabled the regulatory authority in Oman to be made aware of its own review time and the timing of each step within the process. Furthermore, since this study was based on regulatory authority data, a reliable and accurate source, it may enable pharmaceutical companies to better understand the factors that influence the review process and the overall review time. This, in turn, may help to accelerate the registration procedure and save time and resources by allowing a more rapid access to innovative medicines. The companies have the responsibility for most of the delay of their own product registration in Oman because they take a long time to respond to questions asked by the authority or to submit the analytical data.

SUMMARY

- The review time for the registration process during the period 2006 to 2010 is within the time limit fixed by the Oman health authority, but there has been an upward trend in regulatory approval times since 2006.
- The total approval time varies according to the geographical location of the company, and it was found that the shortest approval time was for products from local and Gulf companies.
- In addition to the factors already mentioned, the absence of separate sections for health products and herbal preparations in the Drug Control and Quality Control Laboratory Departments and the large number of samples to be analysed by the QCL from Directorate of medical supplies has a significant impact on total approval time.
- The pricing process for the NASs, the pre-registration analysis, lack of official clock-stop system and the delay in replying to regulatory queries, all have a delaying impact on approval time.
- The fees for the registration of the companies and their products are very low in Oman. This has led to a high number of applications and an increase in the median time of registration.

CHAPTER 4

Evaluation of Regulatory Review Times in the Gulf States

INTRODUCTION

Long regulatory approval timelines for new medicines delay their access to the market that may have the potential to improve patients' health status and of alleviating suffering. Variation in the availability of medicines in different countries has been studied since the early 1970s (Rawson, 2000), and some marked differences have been identified. Regulatory approval time is a key metric that is used to evaluate the performance of regulatory agencies (Hirako *et al.*, 2007). A study was previously made to evaluate the milestones and timelines involved in the regulatory review processes for different authorities (Hirako *et al.*, 2007). A specific study of the Gulf regulatory authorities (Hashan, 2005) highlighted important aspects of the drug approval procedures in each of the seven member states. However, the study provided limited information about the approval timelines and the duration of the milestones and stages involved in the review process because the authorities did not have electronic tracking systems to monitor such activities. This made it difficult, if not impossible, to allow cohorts of pharmaceutical products to be monitored retrospectively (Al-Essa, 2011).

Currently, within the GCC States, there are two registration systems, the national and the centralised procedure. In order to benchmark and make true comparisons between the different authorities, it is essential to identify first the common processes that occur during registration. However, there are no major differences in the legislation, regulations or requirements for marketing pharmaceutical products in the GCC States (Bahrain, Kuwait Oman, Qatar, Saudi Arabia, UAE and Yemen). All the national regulatory departments in the GCC States have regulations that govern and regulate most aspects of the pharmaceutical services by effective laws (Hashan, 1998). Apart from the registration process of medicinal products, some countries have price control also, in their remit.

It is recognized that individual authorities have different experiences and knowledge that could be of value to other member states through comparison of various systems and sharing of best practices to the benefit of all. To this effect, this study was conducted to explore the timelines of the approval processes in the GCC States. However, it is important to have a basic understanding of the regulatory review process in these countries in order to place the approval time in an appropriate context.

OBJECTIVES

The major objectives of this study are to:

1. Compare the number of registration applications submitted for pharmaceutical products over the three-year period from January 2008 to December 2010 in the GCC States.
2. Compare the regulatory approval times for registered products for Gulf, Arab non-Gulf, Asian and International pharmaceutical companies in the GCC States.
3. Assess the trends in approval times over the period 2008-2010.
4. Identify areas of the approval process in each of the seven Gulf States which might lead to delays in the registration of new medicines.
5. Provide possible solutions for addressing the delays in the registration timelines in the Gulf States.

METHODS

Participants

The participants were the authorities responsible for the regulation of pharmaceutical products in the GCC States (i.e. (Bahrain, Kuwait Oman, Qatar and Saudi Arabia) Yemen was excluded from this study because they could not provide data due to the unstable political situation in the country during the period of this study. The United Arab Emirates was also excluded from this study, as they are unable to furnish the full data due to changes in the drug regulatory organization that took place during the time this study was conducted. Additionally, they were also unable to extract some of the data as it was manually stored making retrieval of the required information very difficult.

Data collection

A face-to-face meeting with all the Directors and General Directors of Regulatory Affairs in the Ministry of Health in the GCC States took place during the GCC-DR meetings in 2011 and 2012. They provided the data on approval timelines as an Excel spreadsheet including the registration data for products approved in 2008, 2009 and 2010, based on the milestones in each authority. Clarification regarding the data set was obtained from the five authorities during 2012 through telephonic conferences and electronic mails.

The data consisting of all products from Gulf, Arab non-Gulf, Asian and International manufacturers, approved for human use in 2008, 2009 and 2010 in the GCC States, were included in this study. Products reviewed included both New Active Substances (NASs) and Existing Active Substances (EASs) and only those with a complete data set e.g. submission date and approval date were included in the analyses. In addition, relevant information regarding the regulatory review process of the five Gulf countries was collected by literature search. The overall data includes milestone and tables reflecting the specific characteristic of each system (Al-Essa et al, 2012).

Models of regulatory review:

Three GCC authorities utilize an abridged assessment (Bahrain, Oman and Qatar) as describe in chapter three. This is a critical practice to ensure the appropriateness of the product under local conditions. Bahrain uses a verification review for biological and biotech products because they have to be registered in other reference authorities to be accepted for review in Bahrain, and an abridged review for other major applications. Saudi Arabia is the only country that performs a full review on all types of applications, while Kuwait carry out a simple verification review on the registration dossiers.

DATA PROCESSING AND ANALYSIS

The Regulatory approval times were calculated as the time from submission of the product dossier to the regulatory authority until the final approval. The data sets processed include: the total number of registered products between 2008 and 2010 and regulatory approval time in GCC States between 2008 and 2010 for different groups of pharmaceutical products (GCC, non-GCC Arabs, International and Asian). Descriptive statistics including frequencies was used to present the results.

RESULTS

The results of this study are presented in two parts,

Part 1: Includes the process maps for the regulatory reviews in each of the five states together with characteristics of the review process.

Part 2: The results are presented under three headings:

- I: Total number of product approved in each Gulf states.
- II: Median approval times for the Gulf States by year 2008-2010
- III: Median approval times for the different pharmaceutical companies.

Part 1: The regulatory process maps for the Gulf States:

All the GCC authorities share similar goals and obligations to safeguard public health when assessing the safety, quality and efficacy of medicines before they are authorized for marketing. They also have a similar structure when reviewing pharmaceutical product dossiers, but the position of each milestone in the review process differs from one state to another.

The first study in the GCC was initiated by Hashan (2005) to assess the regulatory environment in the six GCC states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE) using comparative data on a country and regional level, in order to identify the key issues for improving regulatory practices and ensuring new medicines were available in an efficient and timely manner. The second study by Al-Essa (2011) was to map the key milestones and associated activities for each agency in the GCC region and to determine the quality measures employed by the agencies in their different procedures. Figures 4.1- 4.7 illustrate the process maps for each of the countries participating in this study as well as the characteristics of the process.

This part describes the comparison between the regulatory review processes in the seven GCC regulatory authorities.

Validation process

The validation process is the first contact between the sponsors and the regulatory authorities. Validation is an important checking point to ensure the correctness and completeness of the submitted data before entering the scientific assessment stage. The seven authorities record the date of receiving the registration dossier and carrying out a validation process to ensure that the documents submitted for registration are complete before they can be accepted for review. After examining the validation process, a considerable difference was observed in the time taken to validate the registration dossier from one country to another, with Oman performing the validation process immediately after submission while Bahrain takes 14 days to complete it.

Figure 4.1 PROCESS MAP FOR BAHRAIN

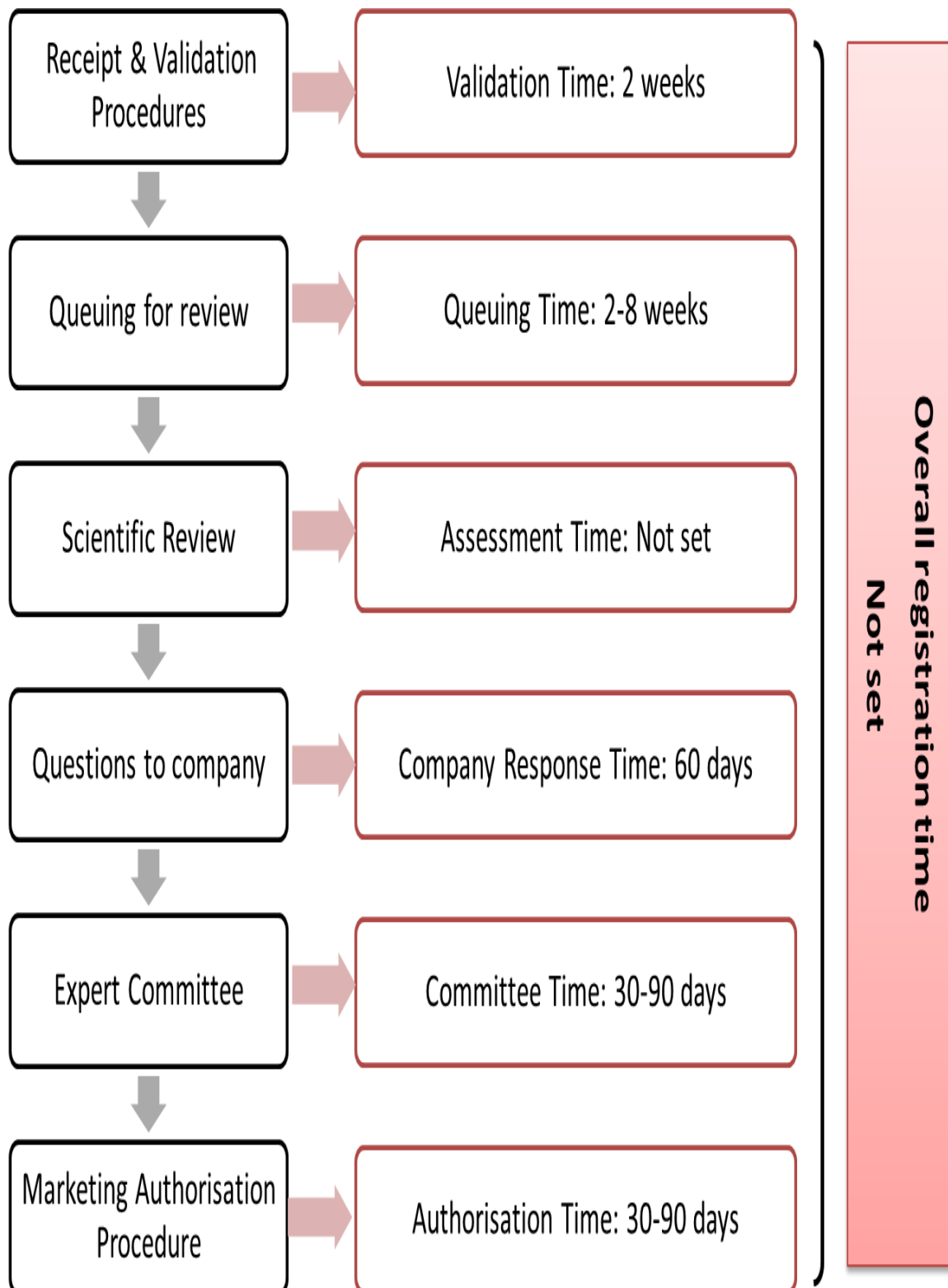


Figure 4.2 PROCESS MAP FOR KUWAIT

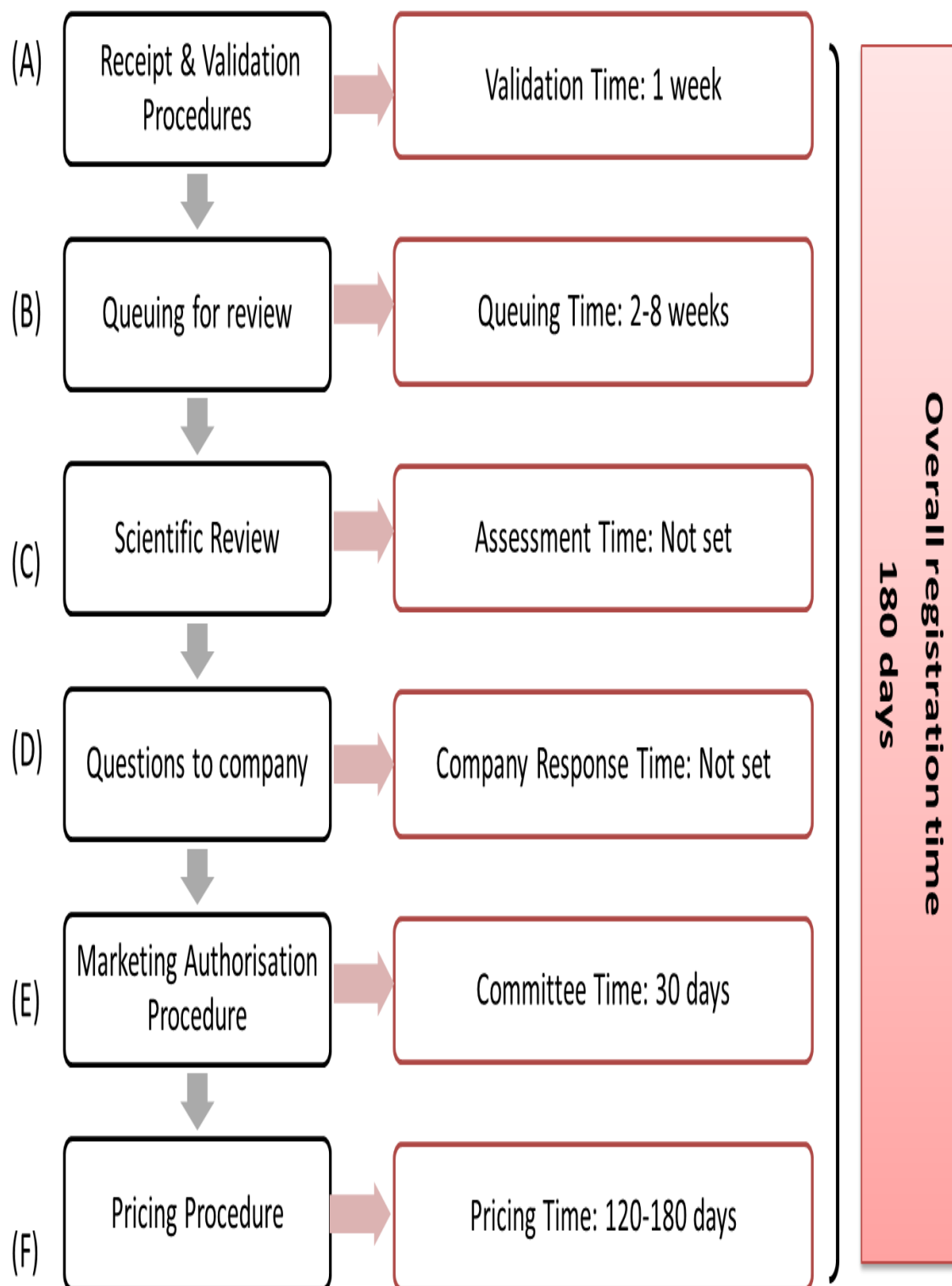


Figure 4.3 PROCESS MAP FOR OMAN

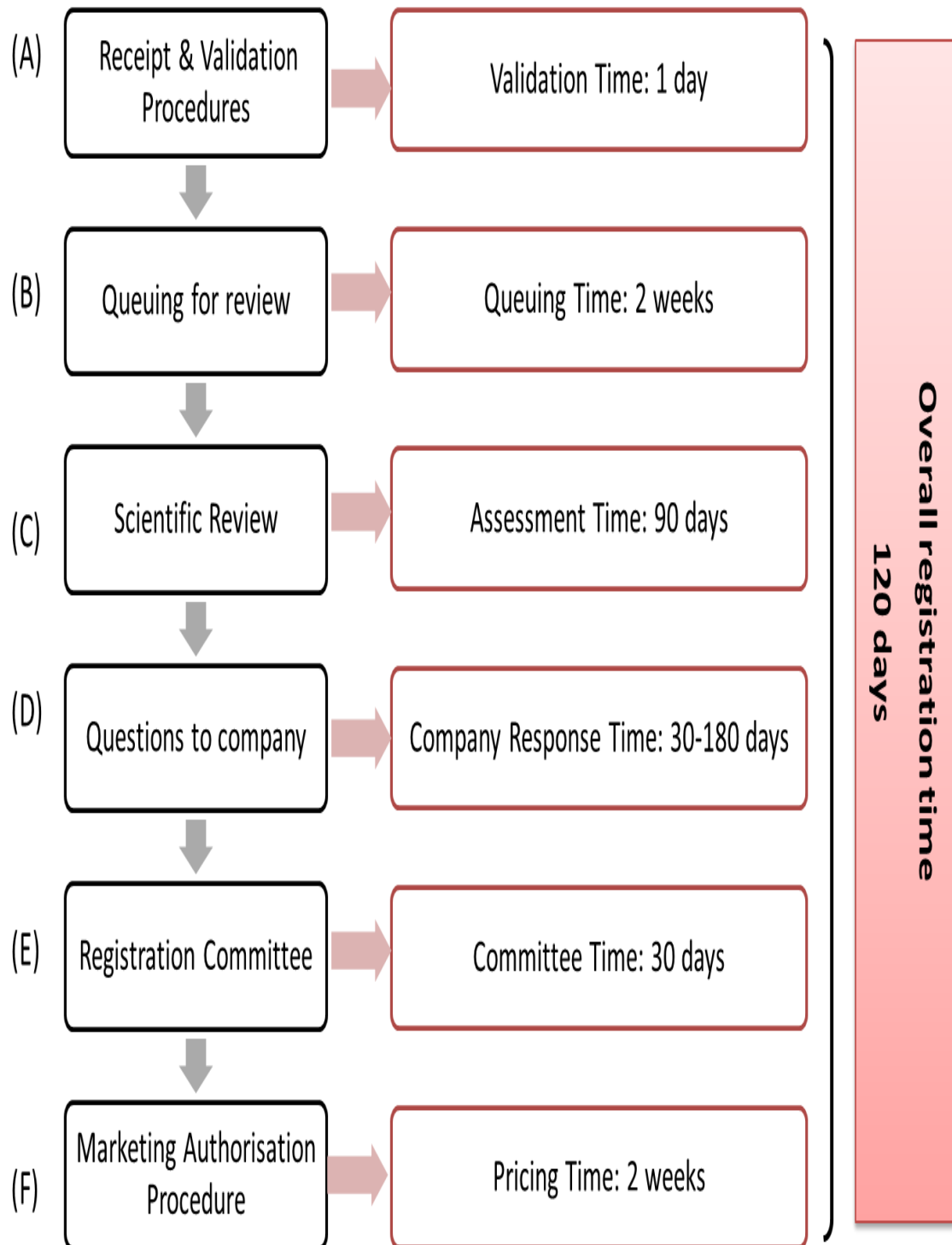


Figure 4.4 PROCESS MAP FOR QATAR

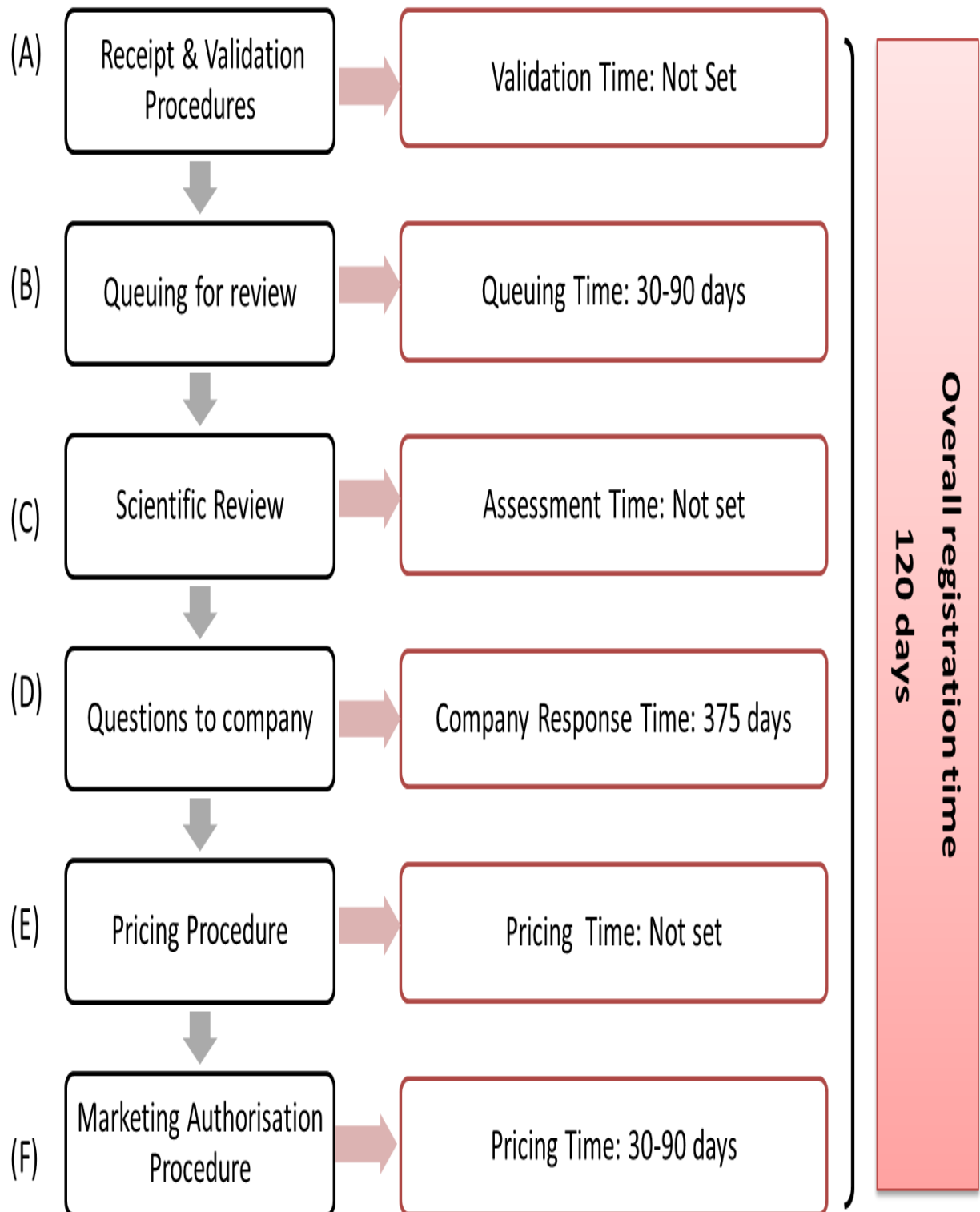


Figure 4.5 PROCESS MAP FOR KINGDOM OF SAUDI ARABIA

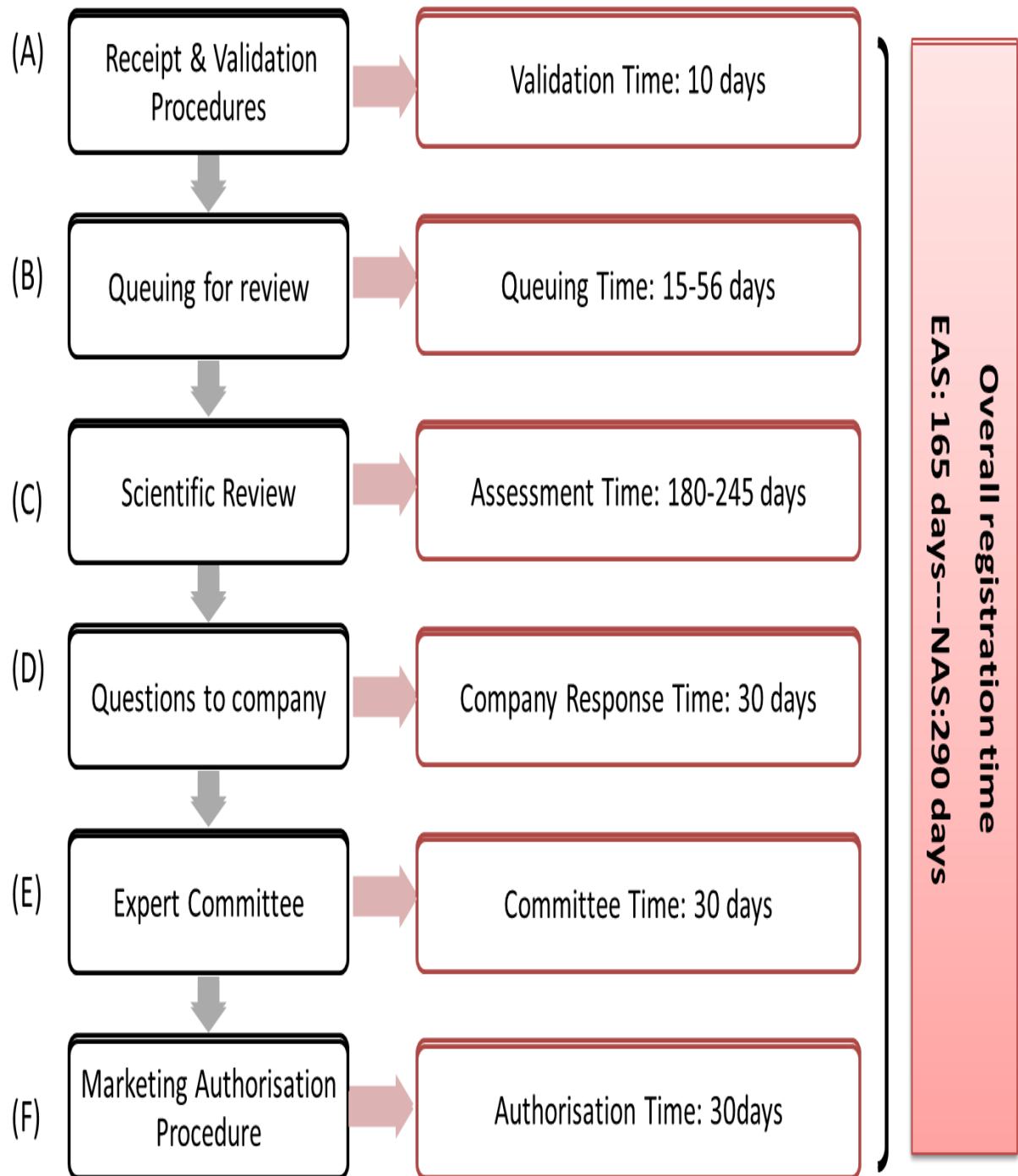


Figure 4.6 PROCESS MAP FOR UNITED ARAB EMIRATES

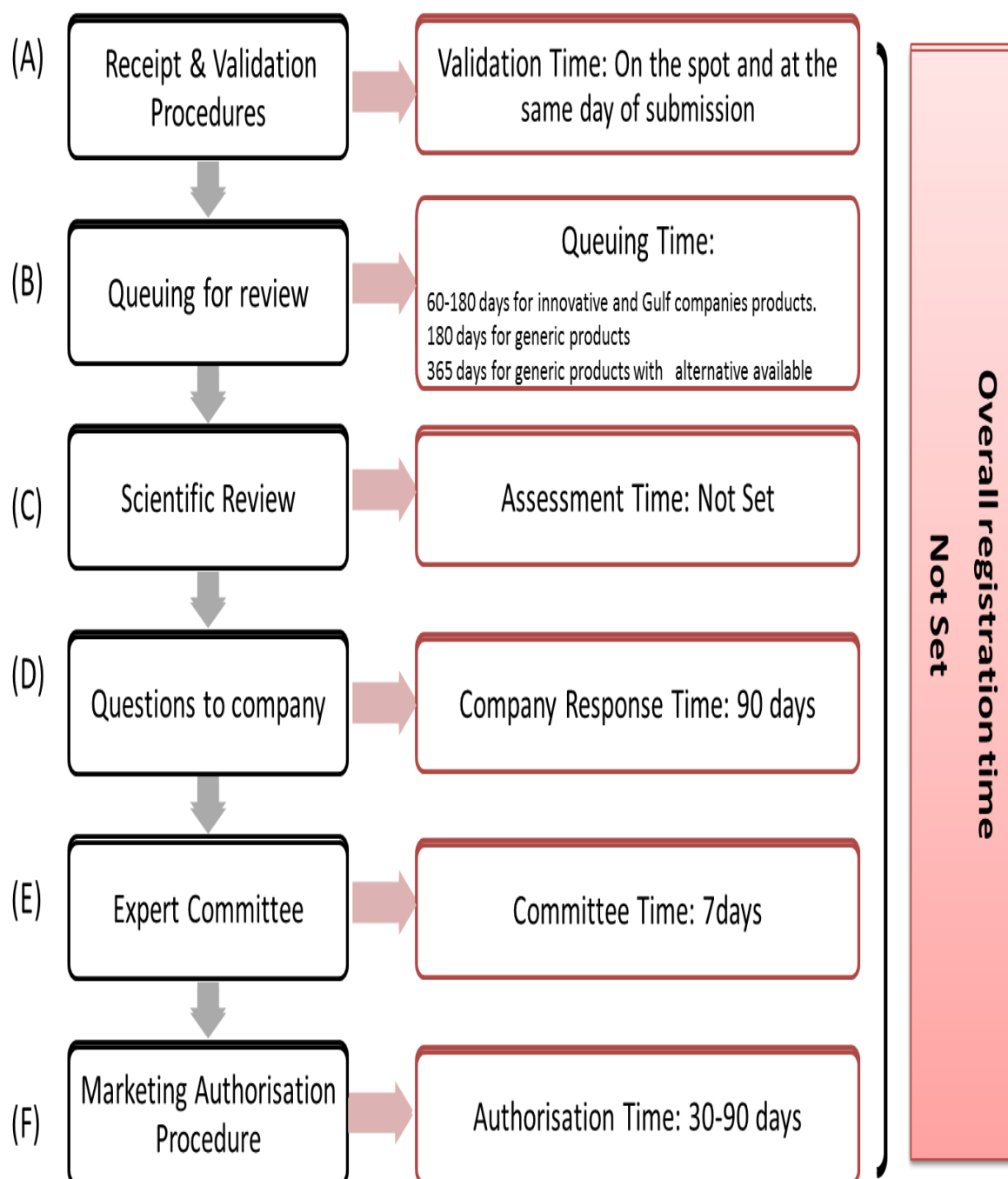


Figure 4.7 PROCESS MAP FOR YEMEN

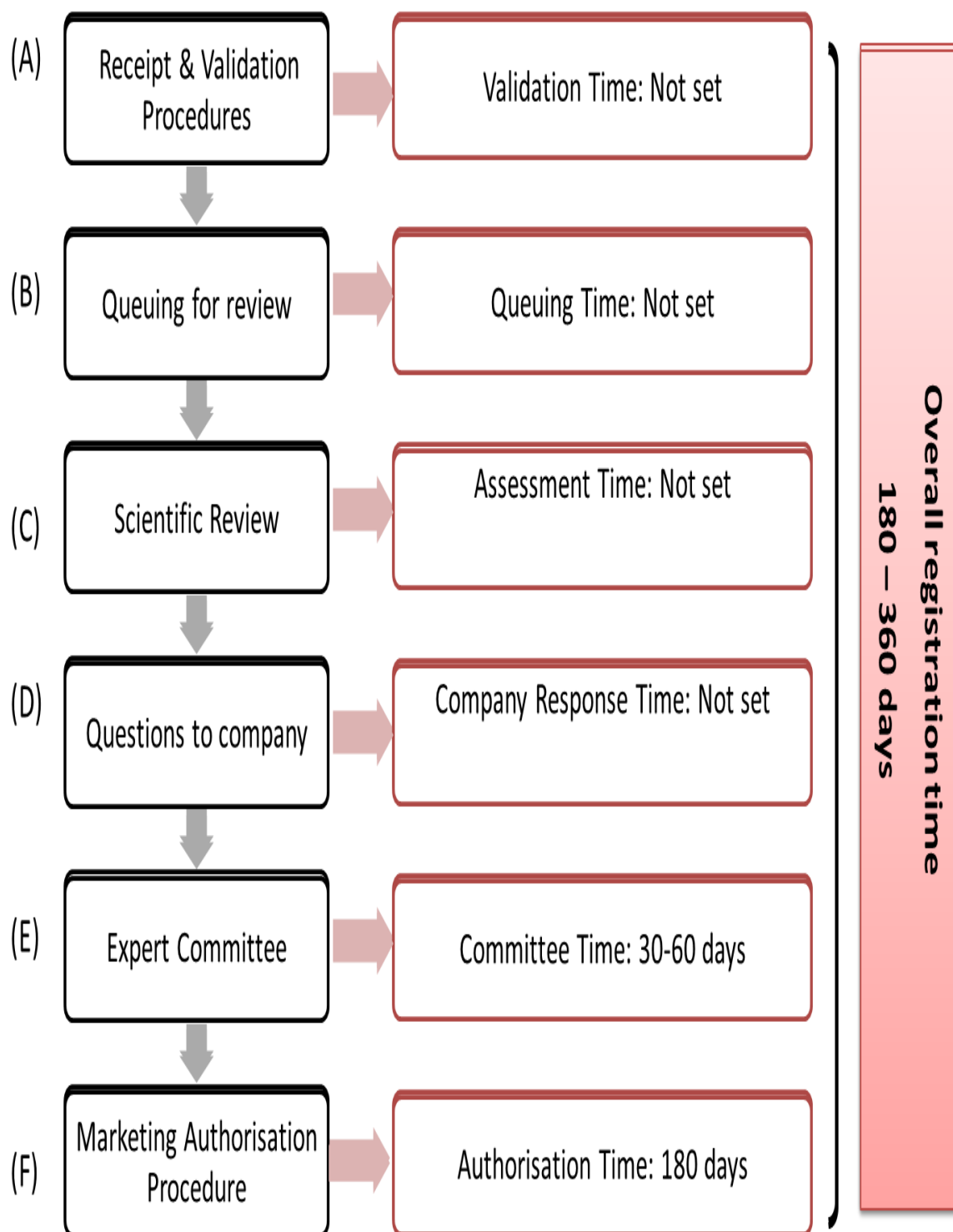


Table 4.1 Models of assessment and characteristics in the Gulf States

Type of review model	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Verification review	✓	✓	x	x	x	x	✓
Abridged review	✓	x	✓	✓	x	✓	x
Full review	x	x	x	x	✓	✓	x
Number of reviewers	7	15	22	3	40	12	10
Validation time (days)	14	7	1	NA	10	1	NA
Queuing time (calendar days)	14-56	14-56	14-56	60-90	NA	NAS: 60-180 EAS:180-365	NA
Scientific assessment (calendar days)	NA	NA	90	NA	180-245	NA	NA
Positive scientific opinion to final approval (calendar days)	30- 90	30	30	30 -90	30	30 to 90	180
Overall approval time (calendar days)	NA	180	120	NA	EAS: 165 NAS: 290	NA	180- 365

*NA= Not Applicable

Queuing stage

The queuing process is straightforward and allows appropriate handling of the received registration dossiers in an organized fashion. However, the lack of regular monitoring of queue time could lead to a backlog. The queuing time varies considerably across the Gulf region ranging from 14 days to over 365 days. For a medicine to remain in this stage for three months unjustifiably delays patients' access to medicines.

Scientific review Phase

The scientific assessment stage is the major part of the regulatory review process where the product quality, safety and efficacy dossiers are thoroughly evaluated. The starting date of the scientific assessment is generally recorded in most of the GCC States, except in UAE and Qatar, probably because the review process starts from the date of submission and ends at the date of granting the approval. Five regulatory authorities in the Gulf region have scientific committees as part of the scientific assessment process. Kuwait and Qatar do not have scientific committees and the quality of the review report depends on the assessors' experience and skills in evaluating

the registration dossier. The scientific assessment is not a target time in five GCC authorities while Oman and Saudi Arabia specified a time limit of 90 days and 180 to 245 days respectively.

Queries to companies

In this phase all the communications occur between the sponsor and the authority with regards to the registration of a new medicine in each GCC State. Questions and queries arising during the scientific assessment and quality control analysis stages are collected into a single batch to be sent to the sponsor by each of the seven GCC authorities. The sponsor's response time varies significantly between the seven GCC States with the shortest time limit being 30 days enforced by the Saudi Food and Drug Authority (SFDA) and the longest is approximately 365 days in Qatar. The clock-stop concept is perceived differently across the region. In Kuwait, for example, the authority does not enforce a limit for the sponsor's response time but if the sponsor fails to respond in two years, the authority ceases the registration process and returns the dossiers to the local agent and a new application is officially requested should the sponsor be still considering the product registration in Kuwait Bahrain and UAE, however, do not have a clock-stop system but they target a specified limit for the sponsors response time.

Overall target time for registration

While Bahrain Qatar and UAE were not setting a target approval time, the other four authorities have slight differences in their overall target approval times with the shortest one in Oman being 120 days.

Part 2: Total number of product approved in each Gulf states, median approval times for the Gulf States by year 2008-2010 and the median approval times for the different pharmaceutical companies

In this study, three major areas were examined, for the period 2008-2010 namely, (1) Trends in submission and registration of new pharmaceutical products; (2) Changes in the approval timelines; (3) Approval times for Gulf, Arab non-Gulf, Asian and International pharmaceutical products in the GCC States. The number of approved products in any regulatory authority is affected by many factors. For example, the number of dossiers submitted to the authority and the number of reviewers in the review section (Hashan, 2005). The GCC States are no exception and like many other authorities the number of approved products varies from year to year influenced by these and other factors.

Total number of products approved in each Gulf state

In general, the countries reviewed a similar number of products, but there was an increase in the number of approved products in 2010 in most GCC States compared to 2008 and 2009 with the exception of Saudi Arabia (Table 4.2). This may reflect an increased interest by the industry in the Gulf market or the authorities in the region were able to cope with an increased work load, translating into an increased number of products approved. The GCC regulatory authorities share common regulatory review practices that are critical in the establishment of a standardized review process for the GCC region. The differences identified in the five review processes were mainly due to the order of the steps carried out or the time spent in carrying out a certain procedure. As per Al-Essa (2011) the approval timelines in the GCC States depend on the type of products being registered, the quality of the submitted data and the level of interaction between the sponsor and the authority.

In 2010, Kuwait registered the highest number of products among all the GCC countries with a total of 210 products registered which is almost twice that of Saudi Arabia (92 products) (Table 4.2). Bahrain had the lowest number of products registered in total for 2008, 2009 and 2010 at 87, 149 and 174 products respectively. The analysis for each country is provided in the following paragraphs. Oman is the only country in the GCC with a more or less constant number of products registered between 2008 to 2010. Bahrain saw a steady rise in the number of registered medicines from 87 approved products in 2008, 149 in 2009 and 174 in 2010 (Figure 4.8). This steady increase in the registration of medicines in Bahrain was due to the decision from the Ministry of Health (MOH) in Bahrain to facilitate the procedures for the drug registration if the product is approved by advanced regulatory authorities such as EMA and USFDA or by one of the reference countries in the Gulf.

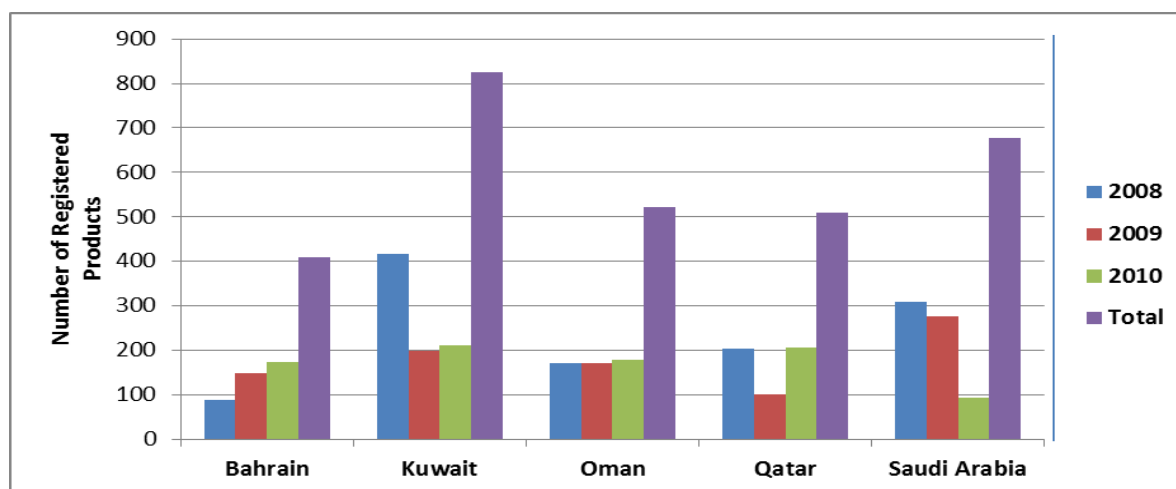
Kuwait, on the other hand, saw a decrease in the number of registered medicines in 2009 and 2010 of 198 and 210 respectively as compared to 416 in 2008. According to the Kuwait regulatory authority, the high number of approvals in 2008 was attributed to the pending files with minimum requirement which were finalised in 2008, Hence, an increase in total number of registered products in that year.

**Table 4.2 Number of approved products for Gulf Cooperation Council
(GCC) States in 2008, 2009 and 2010**

Countries	Type of company	2008	2009	2010
		Approved products	Approved products	Approved products
Bahrain	Gulf	5	5	51
	Arab non-gulf	25	37	42
	Asian	7	2	19
	International	50	105	62
	Total	87	149	174
Kuwait	Gulf	81	51	43
	Arab non-gulf	94	38	46
	Asian	17	3	5
	International	224	106	116
	Total	416	198	210
Oman	Gulf	52	37	56
	Arab non-gulf	15	25	29
	Asian	15	5	12
	International	89	105	81
	Total	171	172	178
Qatar	Gulf	56	57	134
	Arab non-gulf	39	13	11
	Asian	1	0	0
	International	107	30	62
	Total	203	100	207
Saudi Arabia	Gulf	150	91	16
	Arab non-gulf	25	52	19
	Asian	0	0	0
	International	134	132	57
	Total	309	275	92

In Saudi Arabia, the decrease in the number of registered medicines in 2010 as compared to 2008 and 2009 was attributed to the transfer of the tasks from the Ministry of Health to the Saudi Food and Drug Administration in July 2010. During the transition period, the ministry refrained from accepting new registrations until the transfer was completed, hence the decline in the number of products registered. In Qatar, the decrease in the number of registered medicines in 2009 as compared with 2008 and 2010 was attributed to the limited number of registration committee meetings in 2009. Since the number of meetings was reduced, the number of products registered was also affected.

**Figure 4.8 Number of approved products by the five regulatory authorities
(2008-2010)**

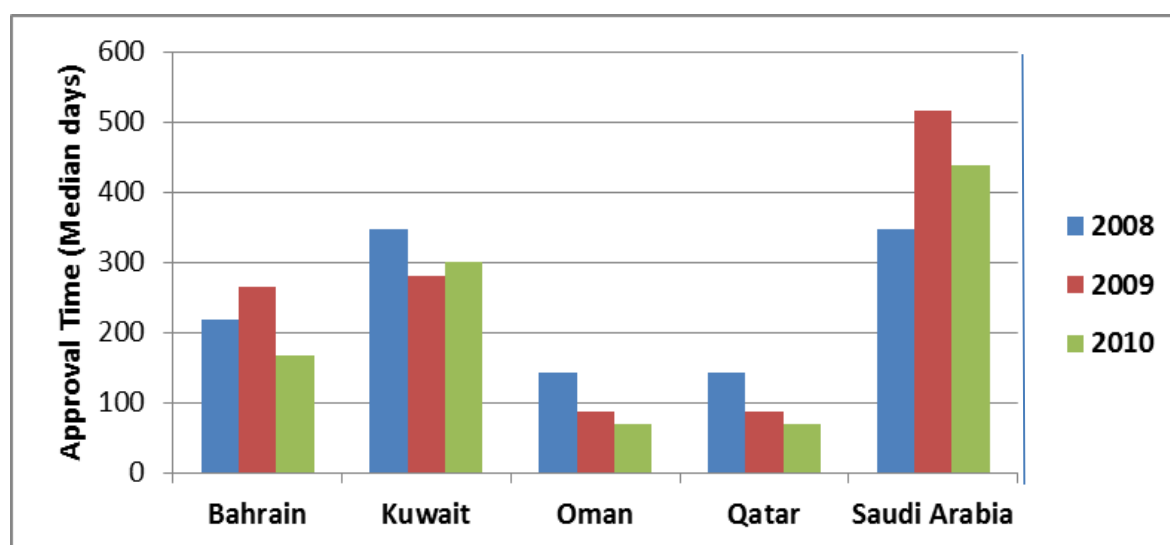


Approval times in Gulf States

There are differences in the milestones within the approval process among the GCC States. For example, the analysis step starts with the scientific assessment in Oman, Saudi Arabia, and Qatar (parallel procedure), but in Kuwait and Bahrain the analytical step comes after the scientific assessment (sequential procedure) and this could negatively impact the approval time. The GCC authorities also waive the analytical stage for products registered in Kuwait, Saudi Arabia, Oman, the GCC central drug registration (GCC-DR), and/or in countries with advanced regulatory systems such as the United States Food and Drug Administration or the European Medicines Agency (EMA).

The median approval time for all approved products in the GCC States ranged from 69 days in Oman and Qatar in 2010, to 587 days in Saudi Arabia in 2008 (Figure 4.9). The Saudi Arabia median approval time was two to three times the regulatory approval time in other GCC States. This may be attributable to some products remaining in the approval process for a longer time, or because some steps in the regulatory approval required more time to complete or because they carry out a full review. However, upon verification with the Saudi Arabia authority, the decrease in registration period for the three years (from 587 Day in 2008, 515 in 2009 and 439 day in 2010) was due mainly to the decrease in the number of registration applications received by the MOH. With fewer files, the evaluation process and decision-making were carried out in a timely manner.

Figure 4.9 Median approval times for all products (2008-2010)



Bahrain, recorded a decline in the registration period between 2008 and 2010. This decline in the registration period in the year 2010 (from 264 days in 2008 to 166 days in 2010) was attributed to the increase in the number of registration committee meetings and the increased number of reviewers. This expedited the approval process and reduced the registration process by 98 days.

Qatar also experienced a decrease in the registration period for the three years; 143 days in 2008, 87 Days in 2009 and 69 days in 2010. This was attributed to the increased number of reviewers, hence expediting the approval process. By taking into account products that had been approved by regulatory authorities in advanced countries such as the EMA and USFDA, the local approval process becomes more streamlined and shortened. Kuwait recorded a decline in the registration period for the same three years ranging from 346 days in 2008 to 300 days in 2010. Oman also recorded a decline in the median approval time from 143 days in 2008 to 69 in 2010. The increase in the approval time in 2008 was due to the development of the new regulations for approval of health and alternative products. These new regulations created an overload for the Quality Control Laboratory, increasing the time for the analysis of Pharmaceutical products.

Approval time for Gulf, Arab non-Gulf, Asian and International pharmaceutical products in the GCC States

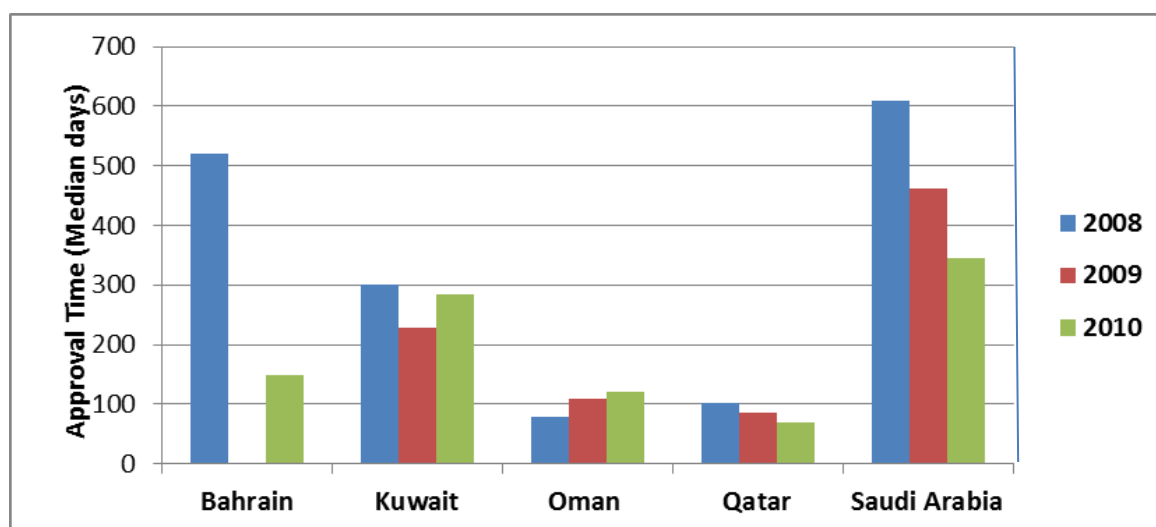
The approval times in the Gulf States varied based on the geographical location of the manufacturer. For local companies it is easier to contact the authority and faster to reply to

questions asked by the authority. International company products need a longer time for approval for many reasons, including priority given to local companies and cultural influences. Therefore, the following four figures examine the difference in the approval time for different types of companies in the GCC States.

Gulf companies products

The median approval time for the products from Gulf companies varied from about 70 days in Oman and Qatar in 2008, 2009, 2010 to more than 600 days in Saudi Arabia. The longest approval time was for Saudi Arabia at 609 days in 2008, as shown in (Figure 4.10). The regulatory review process for medicines in Saudi Arabia is carried out in the newly established autonomous “Saudi Food and Drug Authority” which commenced its activities in 2008. The review process in Saudi Arabia comprises thirteen steps which are critical to the whole process (Al-Essa, 2012). As a result, the approval time decreased significantly over the period of this study. The Saudi Arabia authority ascertained that the reduction in approval time was partly due to fewer product registration applications received in 2008, 2009 and 2010 from the GCC companies as well as the rapid responses from these companies regarding any clarifications. The improvement in the approval time in Oman and Qatar in 2010 was due to the positive effects of the Gulf Centralised Registration system. Qatar MOH for example requested the Gulf companies to register their products in the GCC Centralised system before they submit their products to the local procedure and this led to a reduction in the time needed to register the products. In Bahrain, the increase in the number of reviewers had a positive effect on approval times. But in Kuwait, the health authority thought the slight increase in approval times in 2008 and 2010 was mainly attributable to the delays in the companies’ response to the authority’s queries which affects the overall approval time. Bahrain, on the other hand, recorded an increase in the duration of medicine registration from Gulf pharmaceutical companies in 2008 (520 days), a decrease in duration recorded in 2010 and no registration of any products from Gulf companies in 2009. The decline in the registration period in 2010 was due to the increase in number of the registration committee meetings and in the number of reviewers. On verification, there were no specific reasons recorded as to why there was no registration for any products from Gulf pharmaceutical companies in 2009. One of the probable reasons might have been that the Bahraini market is very small in size and hence not attractive for companies to register their products locally.

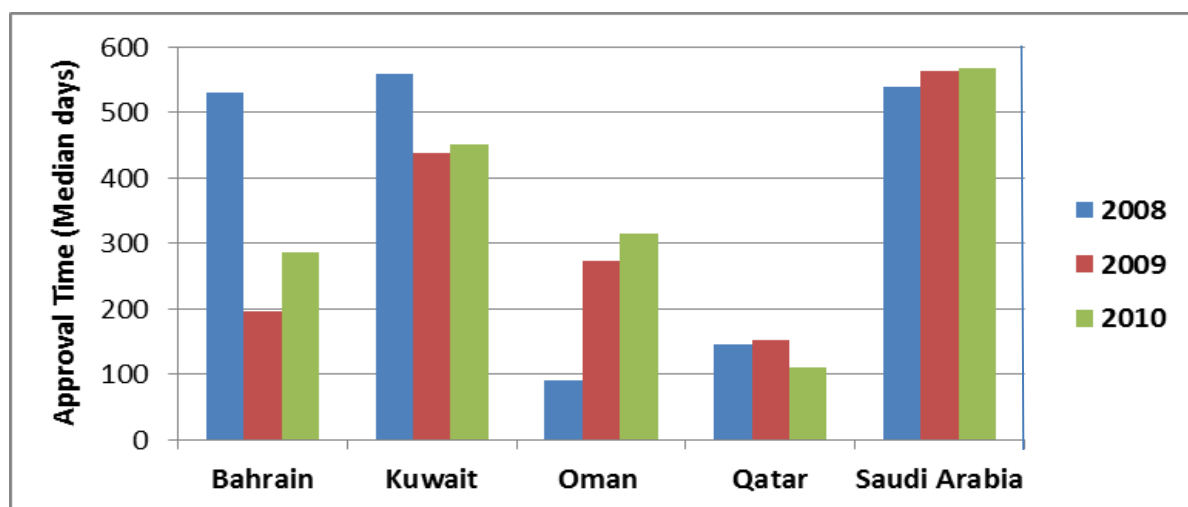
Figure 4.10 Median approval time for Gulf companies products (2008-2010)



Arab non-Gulf companies products

The median approval time varied from 91 days in Oman in 2008 to 567 days in Saudi Arabia in 2010. The approval time for Arab non-Gulf products in Saudi Arabia was four times that in the other GCC States (Figure 4.11). The increase in the median approval time to more than 560 days in 2009 and 2010, respectively, was due to an accumulated backlog for the registration applications during the transition period for the newly established authority SFDA. Furthermore, priority was also given to products from local and Gulf companies at the expense of Arab non-Gulf companies. Saudi Arabia also cited that the slow responses from Arab companies further delayed the approval process. In Kuwait, the median approval time was 559, 437 and 450 days in 2008, 2009 and 2010 respectively and the increase in 2008 was mainly due to lack of follow-up from the company to submit more documents or answer questions asked by the authority. The reduction by 90 days between 2008 and 2010 was mainly due to an increase in the number of reviewers in the registration section. The approval time in Bahrain, Oman and Qatar varied from 90 days to 531 (Figure 4.11). Qatar recorded a reduction in the duration of registration of medicines from Arab non-Gulf pharmaceutical companies and the median approval time is more constant over the 3 year period. This is attributed to an initiative by the Qatari MOH requesting the companies to register their products in the GCC Centralised system before they submit their products to the local system which led to the reduction in the approval time.

Figure 4.11 Median approval time for Arab non-Gulf companies products from (2008-2010)



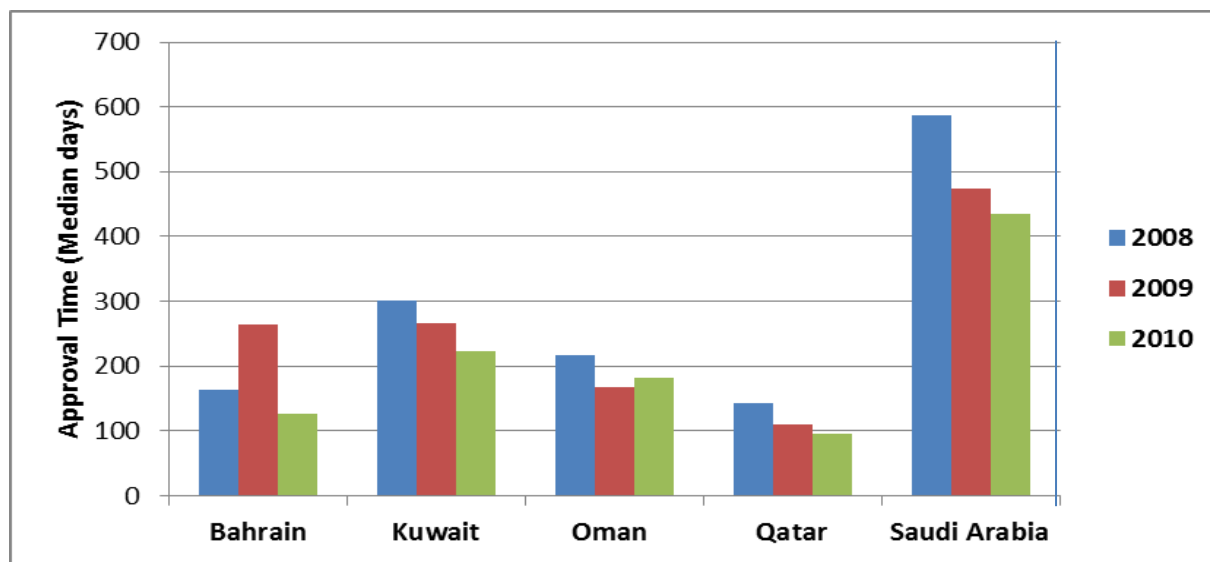
The increase in the approval time in Oman in 2009 and 2010 was mainly attributable to the delays of the company responses to the authority queries which affects the overall approval time. A significant drop in the registration timelines in Bahrain for the products from Arab non-Gulf companies was due to the decision from the Ministry of Health (MOH) to facilitate the procedures for drug registration for products approved by any reference authorities such as USFDA, EMA or SFDA.

International companies products

The median approval time in 2008 for products submitted by International companies varied from 143 days in Qatar to 587 days in Saudi Arabia (Figure 4.12). The approval time for Saudi Arabia is two to three times that of the other countries, with 587, 473 and 434 days in 2008, 2009 and 2010, respectively, which may reflect the fact that they carry out a full review. The mean fluctuated with an increase in 2008, mainly due to priority given to local and Gulf companies, which had a negative effect on the approval time for International company products. However, between 2009 and 2010, there was an increase in the median approval time, mainly due to products remaining in the approval process for a longer time. The median approval time for other GCC States varied from 70 days to 301 days, but it decreased with 143, 110 and 96 days in 2008, 2009 and 2010 in Qatar, due to the fact that the International companies submit complete dossiers. Furthermore, in Kuwait the reduced approval time was mainly because the NASs do not enter the quality control analysis stage as

long as the sponsor has provided complete pharmaceutical documents to ensure that this product is of the desired quality. EASs, however, are sent to the Quality Control laboratory for sample analysis and take the companies some time to follow up the queries.

Figure 4.12 Median approval time for International companies' products (2008-2010)



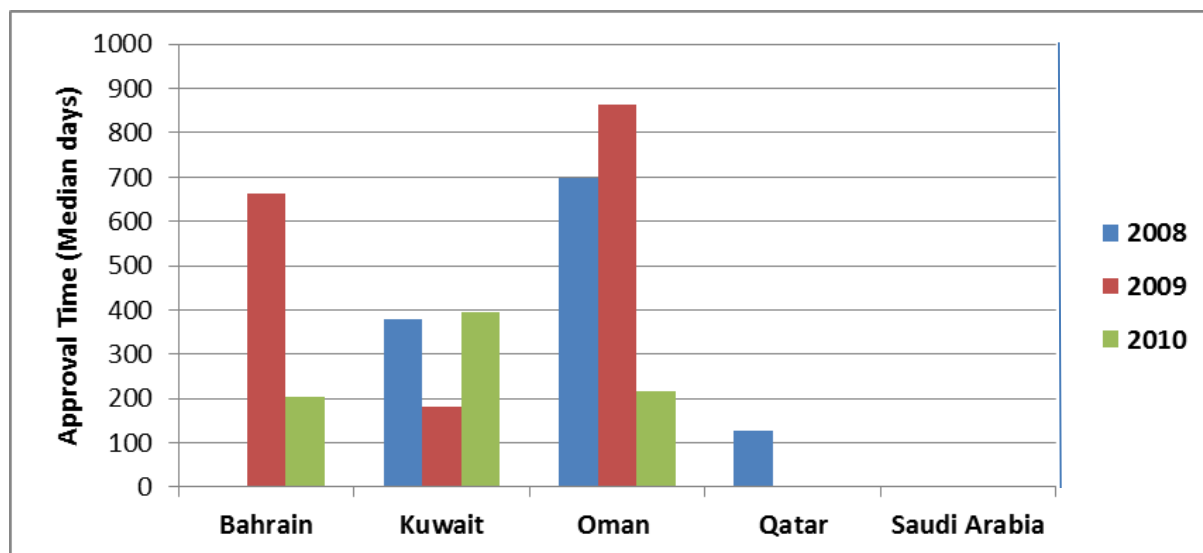
In Bahrain, there was an increase in the duration of the registration time for medicines from the Europe and the U.S. in the year 2009 (264 days) as compared to 164 days in 2008 and 127 days in 2010. The Bahraini authority stated that this was due to some changes in the administration process which led to a delay in drug registrations in 2009. In Oman, there was a decrease in the median approval time for products from International companies from 217 days in 2008 to 182 days in 2010. The reduction in approval time is due to the fact that more products from the International companies had been registered in GCC Centralised system which reduces the time needed to register the products locally.

Asian companies' products

The median approval time for products submitted in 2008 by Asian companies varied from 127 days in Qatar to 864 days in Oman (Figure 4.13). Saudi Arabia did not register any products from Asian companies during this period because these companies were unable to fulfill some of the registration requirements such as their product must first be registered with an advanced regulatory body such as EMA and USFDA. Similarly Qatar also did not

register any products from Asian companies in 2009 and 2010. Thus, only Oman, Kuwait and Bahrain registered products from Asian countries during these periods.

Figure 4.13 Median approval time for Asian companies' products (2008-2010)



Bahrain registered an increase in the timelines of registration for Asian pharmaceutical companies in 2009 (664 days) as compared to 203 days in 2010. The Bahraini authority stated that the increase was attributed to several reasons, for example the low demand for Asian pharmaceutical products in Bahrain, the products were not registered with reference authorities or the products did not fulfill all the registration requirements such as bio-equivalence studies.

The approval time for Oman was 697, 864 and 216 days in 2008, 2009 and 2010, respectively. The mean fluctuated with an increase in 2008 and 2009 mainly due to the development of new regulations for the approval of health products and alternative medicines and the delay in the company responses to the authority queries. While Oman and Bahrain registered an increased in the median approval time for Asian companies, Kuwait recorded a decline in 2009 from 380 days in 2008 to 181 days in 2009. The Kuwaiti authority stated that this was due to the increased number of reviewers. However, in 2010 the approval time had doubled from that in 2009.

DISCUSSION

The regulatory environment has changed in recent years, largely as a consequence of internal reviews designed to increase the efficiency and quality of the approval process. At the same time relationships have become more open both those between different national regulatory authorities and those between industry and the agencies perhaps due to the impact of restructuring and performance improvement initiatives.

In order to make a consistent, timely and high-quality review decision the drug registration agency has to acquire the following key components in their quality assurance system: 1. Standard operating procedures; 2. Guidelines for the reviewers'; 3. Review templates; 4. Training programs; and 5. Management review of individual files.

This study investigated the pattern of the total regulatory approval time in GCC States in 2008, 2009 and 2010 for pharmaceutical products from Gulf, Arab (non-Gulf), Asian and International companies. It revealed that the shortest median approval time was for the products from Gulf companies. In contrast, products submitted by Arab non-Gulf, Asian and International companies had the longest median approval times. The median regulatory approval time varied according to the geographical situation of the pharmaceutical companies. Several factors led to an improvement in the median regulatory approval time in the GCC States during the study period, such as the Gulf Central Registration which had a positive impact on submissions from the Gulf companies.

1. Trends in the overall approval times in the Gulf States

The study data showed a downward trend in the median approval time for most of the GCC States, during 2008 to 2010. However, the approval time for all approved products in the GCC States during this period varied from about 60 days in Qatar and Oman (2009 and 2010), and to about 609 days in Saudi Arabia (2008).

There are many factors which can affect and explain the differences in approval time in the GCC States. The main factor is the difference in the positions of milestones within the approval process, for example, the analytical step starts with the scientific assessment in Oman, Saudi Arabia, and Qatar (*parallel procedure*), but in Kuwait and Bahrain the analytical step comes after the scientific assessment (*sequential procedure*). The study

identified the negative influence of the sequential procedure on the products approval times. The speed and uniformity of the sample analysis can be achieved by fixing a time limit, which may improve the handling of the analytical procedure along with the required quality control tests in order to meet the target time. Furthermore, carrying out the quality control analysis in parallel with, rather than after the scientific assessment, would be a rational decision to avoid any impediment to patients' access to medicines.

Bahrain and Qatar do not specify target approval times as there are several factors involved in their decisions. The major influencing factors are, the types of products being registered (i.e. whether they are NASs, EASs, or therapeutically important or life saving products), the quality of the submitted dossiers and the level of follow-up and interaction between the pharmaceutical company and the authority. The other three authorities showed slight differences in their overall target approval times with the shortest one in Oman being 120 days. Regulatory approval times have also been influenced by the type of assessment carried out by different authorities. Bahrain and Kuwait conduct a verification reviews for all types of products registered in countries with competent authorities. Saudi Arabia performs a full review on all types of application while Oman and Qatar perform an abridged review for all products. It must be noted that all the GCC regulatory authorities require the submission of the Certificate of Pharmaceutical Product at one point during the registration process as this is the most important requirement for successful completion of the approval process in the five member states. The GCC states could take the Singapore system as an example to reduce the overall approval time by conducting verification review for all types of medicines which are previously authorized by at least two reference authorities, except for biological and biotechnology products.

GCC states should seek to increase the level of funding to bring about the required expertise and resources to conduct a more extensive review of important medicines, including biological and biotechnology products. A clock stop is another important approach which is not fully enforced in the GCC authorities to control the overall approval time. EMA is obliged by the regulation to reach a decision within 210 days, although the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data (EMA, 2009). In any case, the clock stop is an important practice that has several advantages for the review process, namely,

1. It controls the approval time

2. It keeps the sponsor alert to the time limit and the consequences of delays of their responses to the authority.
3. It improves the interaction and follow-up practices between the sponsor and the authority
4. It minimizes the backlog problem

2. The review times in the Gulf States

The review of new drug applications by regulatory agencies around the world is an immensely complex process and the factors influencing regulatory behaviour are numerous. According to the Centre for Drug Evaluation and Research (CDER) of FDA, the staffing and disease politics (media coverage of diseases) play an important role in the drug approval process. An appropriate number of staff has been the dominant influence on review times for New Active Substances. It is essential to have a target time for the scientific assessment and to monitor the assessment time in order to prevent delays that may impact the final approval time. In the US FDA reviewers are under constant pressure to meet time goals. They do not only review new drug applications (NDAs), but also other key documents submitted by sponsors, some of which also have time goals attached. At the same time, reviewers must provide advice to sponsors and stay abreast of the latest scientific advances in their fields. The results of a study on the US FDA's review process for NDAs, revealed that the allotted six months priority review and ten months standard reviews were found to be inadequate due to concerns of time pressure on the FDA reviewers which ultimately required the agency to hire close to an additional 300 employees within five years with funds from user fees (Rehnquist, 2003).

The main factors (Barrocliffes et al. 1994, Donnelly et al 1996) which may impact on review times are the harmonisation of technical requirements, increase in dialogue between industry and authorities, restructuring and reorganization of authorities, introduction by authorities of user fees and target review times. This suggests that differences in review times between competent authorities may be related to the way in which the review is managed. The time taken from reaching a positive opinion by the scientific committee to the final approval varies considerably across the region taking less than 30 days in Kuwait and Oman and less than 90 days in Bahrain, Qatar and Saudi Arabia. This is the time period to complete the final administrative procedures before granting the registration approval in each country. It is important for the authorities to consider improving their

internal bureaucratic procedures that cause unnecessary delays in the authorization time without any justifiable reason related to the quality of the submitted registration dossiers.

Most regulatory authorities have procedures for accelerated reviews like the fast track procedure in Europe, based solely on potential gain time from conditional licensing or from authorisation under exceptional circumstances. Hence the need for the product does not seem to be a determinant of the speed of the review. The utilisation of abridged reviews, mutual recognition and assessment review sharing among regulatory authorities may enhance the efficiency of scientific reviews. Initiatives such as increased dialogue, production of early guidelines and training of regulators may enable increased efficiency. The speed of review may depend on the need for the product, the quality of the dossier and the efficiency of the regulatory process. Still there is little evidence to show that the need for the product is a determinant of the review speed or the time to bring the product to the market. Accelerated reviews, fast track procedures and priority assessments constitute the efficiency of the regulatory agency (Lumley *et al* 1996). Facilities for accelerating the development of certain products for licensing under exceptional circumstances also are added measures in the regulatory process. Sometimes a fast track procedure means that under certain very specialized circumstances the regulatory authorities will assess a dossier ahead of time. The criteria should be solely those of a significant potential gain for public health. Adherence to strict time limits has been one of the quantitative measures for the success of a regulatory authority. This has been achieved partly through the introduction of a pre-submission phase and clear dialogue (sound scientific advice) with the applicant. Performance indicators like the Application Tracking Systems (ATS), monthly publication of decision tables, quality management systems, questionnaires, may accelerate the overall assessment and the drug registration process in the GCC states.

3. The influence of the type of Companies on approval times

Analysis of the 2008 data showed that, the approval time for the products of Gulf companies to be the shortest followed by Arab non-Gulf and International companies in most of the Gulf countries. The main reason for this is the priority given to local manufacturers in the Gulf States. In addition, the rapid responses from these companies also help to expedite the approval processes. The local manufacturers have an unwritten priority in all regulatory review processes, as a part of governmental support to encourage local industry. Such

priority treatment reflects positively on approval times. The approval time for products from the Gulf companies was the shortest, compared to other types of companies. The median approval time in some authorities in 2010 was similar e.g. in Qatar there was no significant difference between types of companies nevertheless the approval time for local products still showed continuous improvement during 2008, 2009 and 2010 at 102 days, 86 days and 69 days, respectively. The longest approval time was for products from Asian countries in Oman which was 864 days in 2009 and 395 days in Kuwait in 2010. An unwritten review priority has always been given not only to products from the Gulf companies but also to products indicated for serious, life-threatening conditions in the GCC states. This is in line with the Canadian priority review for medicines and medical device applications intended for the treatment, prevention or diagnosis of serious, life threatening or severely debilitating illnesses or conditions. Their priority review is specifically applicable where no product is currently marketed in Canada and/or where a new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall benefit-risk profile is better than that of existing therapies (Canadian Review process, 2006). The longer approval time for the products from local companies in Saudi Arabia, compared to other GCC States, may be due to the sequential approval process followed in Saudi Arabia. However, the median approval time for products from Gulf companies in 2010 in Oman was about 79 days and Qatar it was 70. These shorter approval times may be due to the parallel approval procedure used in Oman and Qatar. It is important to note that the scientific assessments in Saudi Arabia are carried out by independent specialist academic staff which could lead to more difficult questions and consequently require more time to respond on the part of pharmaceutical companies, while in the other GCC States, the scientific assessments are carried out by internal pharmacists.

In addition to the priority procedure, there are many other factors which affect the approval time of local companies positively, like the ease of establishing contact with key individuals in the authority and a rapid response to queries raised by the authority. Overall the median approval time is reduced radically for all products from all regions. The main reasons for this decrease in approval time between 2008 and 2010 in the Gulf States are due to the positive effect of the Gulf Central Registration, a rise in the number of reviewers in some GCC drug authorities and the parallel procedure used in the regulatory approval review process.

SUMMARY

- The findings from this study showed a downward trend in the median approval time for most of the GCC States between 2008 and 2010.
- The main reasons for the decrease in approval time in the Gulf States are due to the positive effect of the Gulf Central Registration, the rise in the number of reviewers in some GCC drug authorities and the parallel procedure used in the regulatory approval review process.
- Regulatory approval times in the GCC states have been influenced by the type of assessment carried out by different authorities.
- Clock stop is not fully enforced in the GCC authorities to control the overall approval time.
- The GCC states should seek to increase the level of funding to bring about the required expertise and resources to conduct a more extensive review of important medicines, biological and biotechnology products.
- Performance indicators such as Application Tracking Systems, monthly publication of decisions and quality management systems, may accelerate the overall assessment and drug registration process in the GCC states.

CHAPTER 5

An Evaluation of the GCC Centralised Regulatory Review Process

INTRODUCTION

The approval of medicines in different countries across the world has been and still is performed by regulatory agencies according to their national regulations, although, attempts to harmonise the regulations have been made for several years within the GCC region. The harmonisation of the regulatory review processes in the GCC States was initiated following the issuance of the GCC Health Ministers' Council Decree No. 8 in 1976 regarding the formation of a study group to report on how a centralised registration review system should be established to monitor the marketing of medicines and develop common guidelines for the participating authorities (Al-Essa, 2011).

This was followed by a series of GCC Ministerial Decrees relating to the establishment of a centralised registration system which was not approved until the Kingdom of Bahrain submitted a proposal for the formation of a "Central Committee for the Gulf States" to register pharmaceutical companies and their products. This committee ensures that the pharmaceutical companies apply satisfactory standards to guarantee manufacturing of high quality, safe and effective medicines and to standardise their regulations with regards to medicines importation practices in the Gulf States.

The Centralised Procedure for the registration of pharmaceutical companies and medicinal products has been established under the Executive Board of the Health Ministers Council for GCC States. The Executive Board is chaired by the Director General, who is responsible for supervising the work of the board and following up the resolutions and recommendations of the Health Ministers' Council, assisted by technical, administrative and financial departments.

The Gulf Centralised Committee for Drug Registration (GCC-DR) was formed in May 1999 and included Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates with Yemen (joining in 2003). The GCC-DR consists of two representatives from each member state. The main role of the committee is to register pharmaceutical companies and their products through the joint coordination of the safety, efficacy and quality of medicinal products.

In order to adopt the Central Registration System, the following two phases were proposed.

Phase 1: In the year 2000, pharmaceutical companies in the Gulf States had to register their products using the local national system while at the same time it was mandated that they also use the centralised system. During a period of two years the following was required:

- The registration of research companies by the GCC-DR in accordance with the centralised registration.
- The registration of new chemical entities, biological and new technology products.
- A priority was given to the Gulf States companies to register centrally.
- The registration of products which have not been through the centralised procedure but have been selected for the GCC international tender.

Phase II: The second phase took effect in 2002 following an evaluation of phase I and during this phase all the companies could submit their products through the GCC procedure.

During the eleven years (1999-2010) the GCC centralised system received 1,824 medicinal product applications and approved 1,165. This study has highlighted the different steps in the review process in the GCC-DR system and the way in which these influenced the overall timelines. Information was obtained to identify the practices that accelerate or delay the marketing authorisation. Therefore this study mapped the key milestones and associated activities and evaluated the quality measures employed by the GCC-DR process.

OBJECTIVES

The objectives of this study were to:

- Appraise the regulatory review process in the GCC Central Registration operation.
- Evaluate the review times for New Active Substances (NASs) and Existing Active Substances (EASs) submitted to the GCC Centralised Registration (January 2006 to December 2010).
- Identify the strengths and weaknesses of the centralised review process.
- Propose strategies that could help the GCC-DR enhance the drug review process leading to improved patient access.

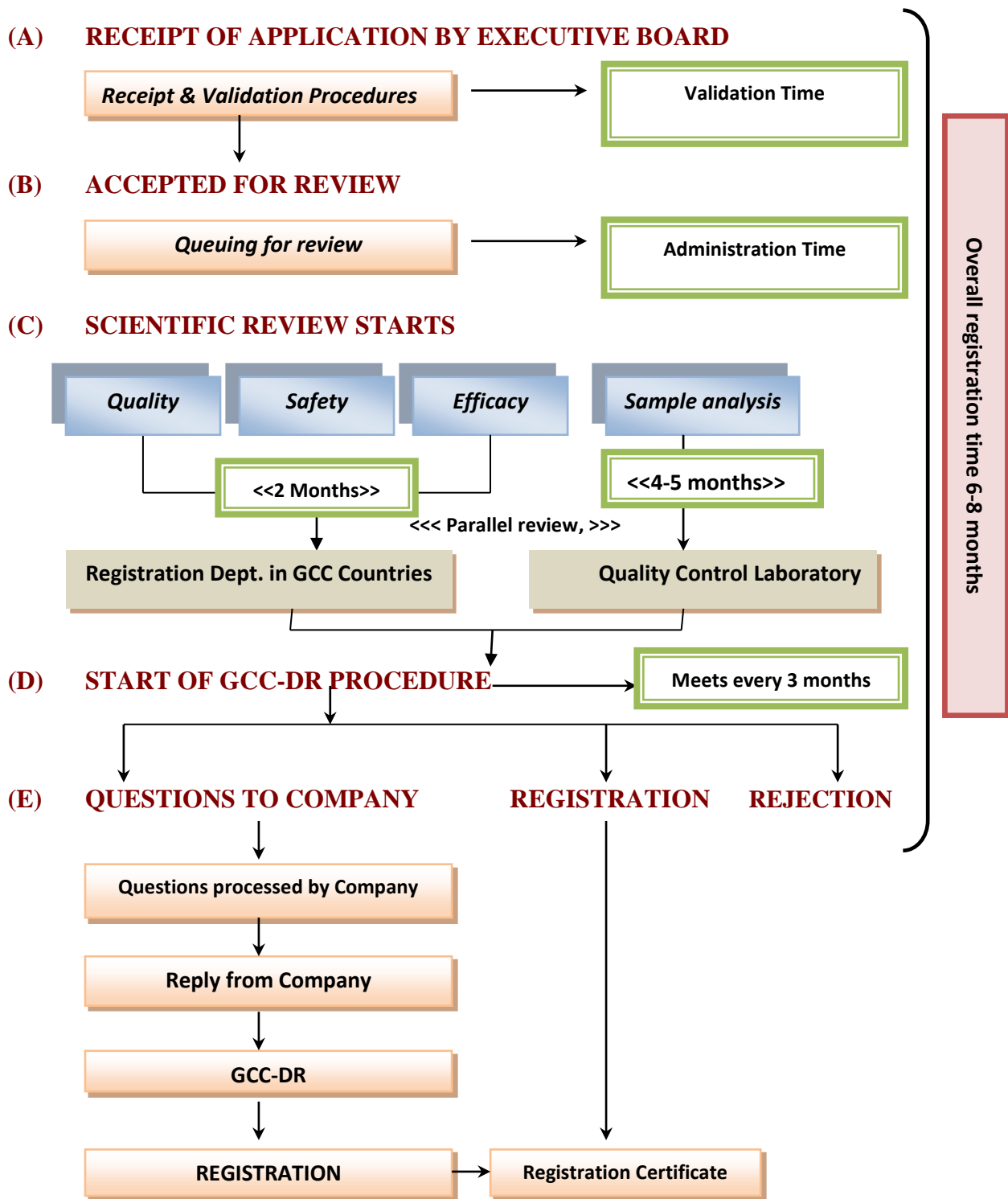
METHODS

Information on the total number of applications and approvals together with the timelines from January 2006 to December 2010 were obtained directly from the Executive Board of the Health Ministers Council for GCC States. The data included the application submission date, the registration date and the overall review time. The products were classified into four groups according to the location of the manufacturing companies (GCC, non-GCC Arab, international and Asian). The data also included information on different dosage forms (solids, semi-solids, liquids, injectables) and the therapeutic indications.

THE GULF CENTRALISED PROCEDURE REVIEW PROCESS MAP AND MILESTONES

Currently the Executive Board is responsible for receiving the registration files and the prescribed fee for the registration of pharmaceutical manufacturing companies and their products. After receiving the files, the Executive Board forwards the files to all the member states for their evaluation. Every member state should review the files and provide their recommendations to the GCC-DR. The registration of the company is decided based on the recommendation of the inspection team. If the company has been recommended to be registered, the GCC-DR issues the registration certificate; otherwise the company will be notified accordingly. The inspection team consists of three members from three different member States. The selection of members is carried out based on certain criteria where every member state would have an equal number of visits. Upon completion of the visit, the head of the inspection team will prepare a visit report and it is signed by other members of the team and then the report is submitted to the GCC-DR. Similarly, the GCC-DR forwards the registration files of the products to each individual Member State for evaluation. The samples are sent for analysis to one of the four laboratories (Saudi Arabia, UAE, Kuwait and Oman) which are accredited by GCC-DR. The registration of products is determined on the basis of the analysis reports. There are basically five steps for the regulatory authority in the Gulf Central Registration System. Some of these steps are critical and constitute a substantial part of the review process (Figure 5.1). The review process map indicates the main steps in the review and approval process and identifies the key milestones for monitoring and analysing timelines. Receipt and validation include administrative registration (reference number) and checks on legal requirements, the status of the company, manufacturer etc. as well as a ‘checklist’ validation of the application content (e.g. technical sections, CPP status). The pharmaceutical

Figure 5.1: PROCESS MAP FOR GCC CENTRALISED REGISTRATION



companies are required to submit 16 samples of their product in addition to eight copies of the product dossier and one original copy which would remain with the Gulf Central Registration Office. While two separate GCC States would be chosen through a computer program alphabetically according to the countries name, to act as rapporteurs, the other GCC States would keep the dossiers for documentation purposes. The rapporteurs are not chosen because of their expertise in a certain area of regulatory science, but to give equal opportunities to all the members states in a systematic manner of selection. Similarly, the reference laboratory chosen, to carry out the analysis, is based on the equity of the number of dossiers distributed between these laboratories and not on the ability of these laboratories to perform the analysis.

Hypotheses

This study examined the following hypotheses,

1. There was a significant increase in the number of products registered from 2006-2010.
2. The highest number of products approved by GCC-DR is linked to those originating from the companies in the GCC region.
3. There was a significant increase in the approval time between 2006-2010 in the GCC-DR.
4. The approval time for products from GCC pharmaceutical companies was shorter than for other companies.

RESULTS

Products considered and their characteristics

During the five year period (2006 - 2010), the number of pharmaceutical products for human use successfully registered through the GCC Centralised Registration procedure was 413. For the purpose of clarity the results will be presented in four parts as follows:

- Part I - Number of products approved in the Gulf Centralised Procedure.
- Part II - Approval time in the Gulf Centralised Procedure.
- Part III - Approval time for different dosage forms
- Part IV - Approval time for different therapeutic groups.

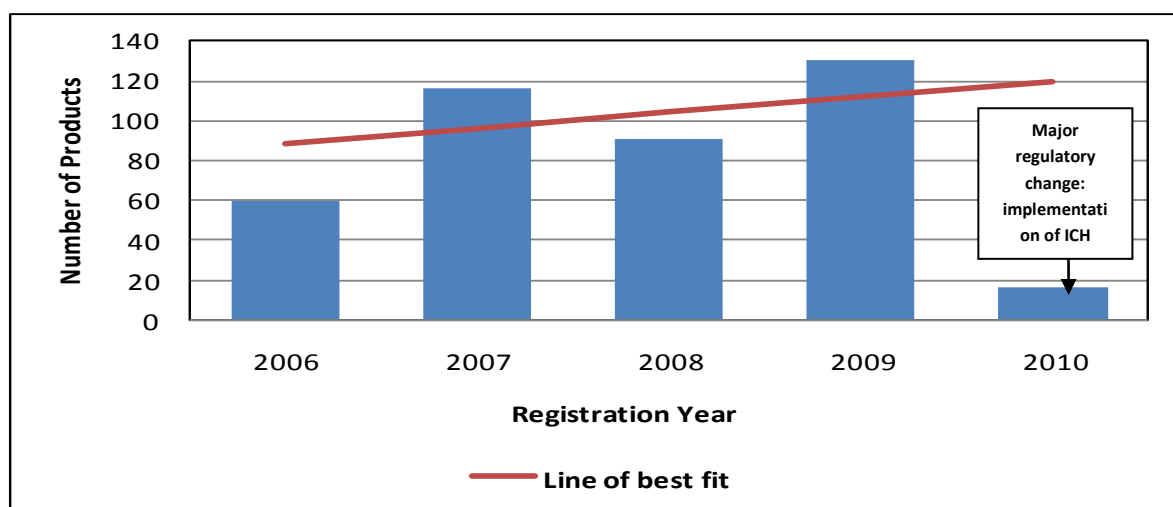
Part I: Number of products approved in the Gulf Centralised Procedure (2006 - 2010)

A total of 413 Pharmaceutical Products (EASs and NASs) were registered by GCC-DR during the time period 2006-2010. The highest number was found in the year 2009 (130; 32%) followed by the years 2007 (116; 28%), 2008 (91; 22%) and 2006 (60; 15%) (Figure 5.2). There was a substantial drop in the number of approved products in 2010 (16; 4%) which was due to the fact that the pharmaceutical companies failed to comply with the new GCC guidelines for the stability testing of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). The GCC countries come under climatic Zone III and IVa (hot and dry & hot and humid) the new guideline which was implemented in 2009 replaced the long-term testing condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ for climatic zone III and IV with $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$. The results showed an overall significant association ($p < 0.001$) between the total number of registered pharmaceutical products and registration years.

Approval of Existing Active Substances (EASs) and New Active Substances (NASs) in the Gulf Centralised Procedure (2006 – 2010)

Out of the total of 413 products approved in the Gulf Central Registration between 2006 and 2010, 317 products were EASs (Table 5.1) and 96 NASs (Table 5.2).

Figure 5.2: Total number of pharmaceutical products approved in the Gulf Centralised Procedure (2006-2010)



Statistical analysis of these data using a simple linear regression showed a significant association between the total number of registered pharmaceutical products and registration years ($p < 0.001$).

Table 5.1: Number of EASs Approved in the Gulf Centralised Procedure from various regions, dosage forms and therapeutic classes

Characteristics	Registration Year					
	2006	2007	2008	2009	2010	
Region	Number of EASs					Total
Arab	7	9	12	20	3	51
Asian	6	2	7	3	0	18
Gulf	38	64	46	46	12	206
International	5	10	11	16	0	42
Dosage Form						
Injectables	16	4	14	9	0	43
Liquids	6	18	15	22	3	64
Semi-Solids	9	15	13	6	1	44
Solids	25	48	34	48	11	166
Therapeutic Class						
Anaesthesia	2	0	0	1	0	3
Cardiovascular system	14	8	20	15	1	58
Central Nervous system	4	8	9	9	3	33
Ear, Nose and Oropharynx	0	1	0	0	0	1
Endocrine system	2	2	0	17	3	24
Eye	0	1	1	3	0	5
Gastrointestinal system	4	6	3	3	1	17
Immunological Products and Vaccines	0	0	0	0	0	0
Anti-infective	10	28	26	19	3	86
Musculoskeletal and Joint diseases	6	6	3	4	0	19
Malignant disease and immunosuppression	0	0	0	0	0	0
Nutrition and Blood	7	5	3	3	0	18
Obstetrics, Gynaecology and Urinary-tract disorders	0	0	0	1	2	3
Respiratory system	3	8	7	6	2	26
Skin	4	12	4	4	0	24
Total	56	85	76	85	15	

Table 5.2: Number of NASs Approved in the Gulf Centralised Procedure from various regions, dosage forms and therapeutic classes

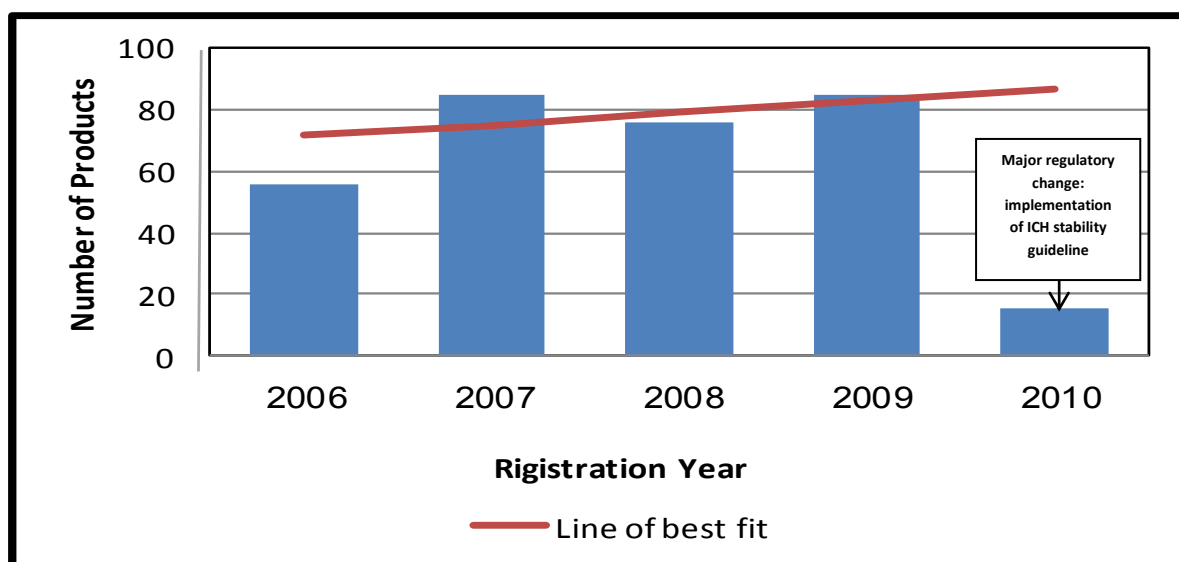
Characteristics	Registration Year					
	2006	2007	2008	2009	2010	
Region	Number of NASs					Total
Arab	0	0	0	0	0	0
Asian	0	0	0	1	0	1
Gulf	0	2	0	0	0	2
International	4	29	15	44	1	93
Dosage Form						
Injectables	2	21	9	26	1	59
Liquids	1	2	0	2	0	5
Semi-Solids	0	0	0	0	0	0
Solids	1	8	6	17	0	32
Therapeutic Class						
Anaesthesia	1	0	1	0	0	2
Cardiovascular system	0	6	7	11	0	24
Central Nervous system	0	1	2	2	0	5
Ear, Nose and Oropharynx	0	0	0	0	0	0
Endocrine system	1	3	0	10	0	14
Eye	0	1	0	0	0	1
Gastrointestinal system	0	1	1	0	0	2
Immunological Products and Vaccines	0	0	0	13	0	13
Anti-infective	0	0	0	2	0	2
Malignant disease and immunosuppression	0	2	3	0	0	5
Musculoskeletal and Joint diseases	0	0	0	1	0	1
Nutrition and Blood	2	17	1	4	0	24
Obstetrics, Gynaecology and Urinary-tract disorders	0	0	0	1	1	2
Respiratory system	0	0	0	1	0	1
Skin	0	0	0	0	0	0
Total	4	31	15	45	1	

There were a similar number of EASs approved centrally in 2007 and 2009 (85; 27%) followed by 2008 (76; 24%), 2006 (56; 18%) and 2010 (15; 5%) (Figure 5.3). Statistical analysis using a simple linear regression analysis showed that the increase in the number of registered EASs was statistically significant ($p < 0.001$).

The highest number of NASs was registered in 2009 (45), whilst the lowest was in 2010 (1) (Figure 5.4). Out of the 96 NASs, 93 products (97%) were found to be from international companies. Statistical analysis using a simple linear regression showed a significant increase in the number of registered NASs ($p < 0.001$).

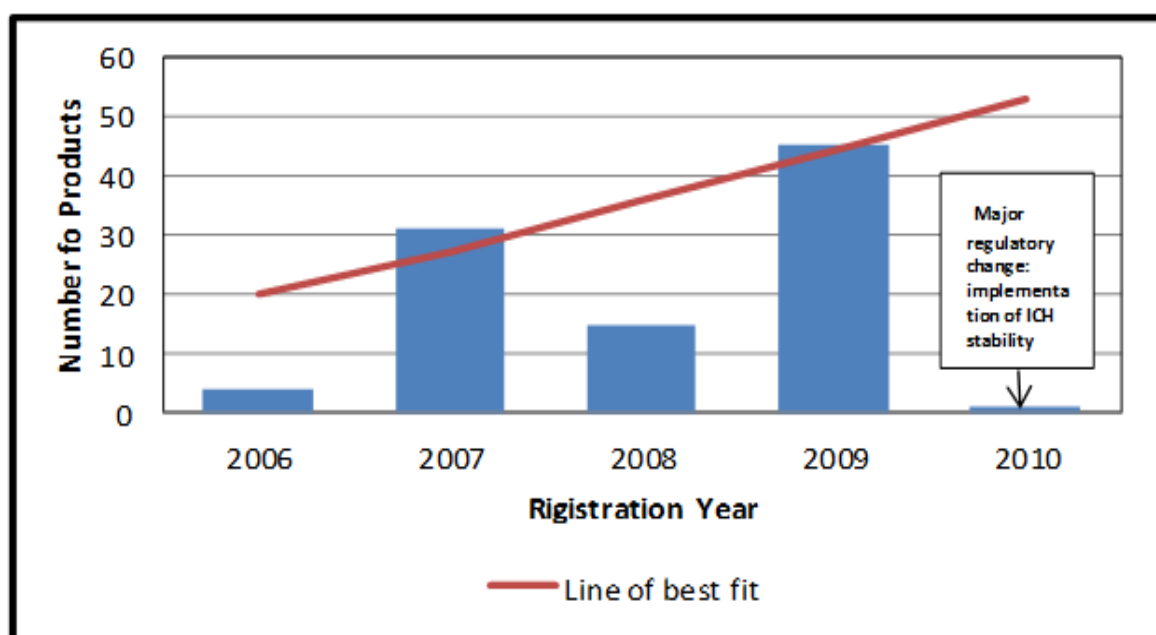
By individual regions, 208 (50%) medicines were identified as being approved from Gulf, 51 (12%) from Arab non-GCC, 19 (5%) from Asian and 135 (33%) from international companies (Figure 5.5). Out of the total of 317 EASs approved in the Gulf Central Registration between 2006 and 2010, by individual regions, 206 (65%) drugs were identified as being approved from Gulf, 51 (16%) from Arab non-GCC, 18 (6%) from Asian and 42 (13%) from international companies.

Figure 5.3: Number of EASs approved in the Gulf Centralised Procedure (2006-2010)



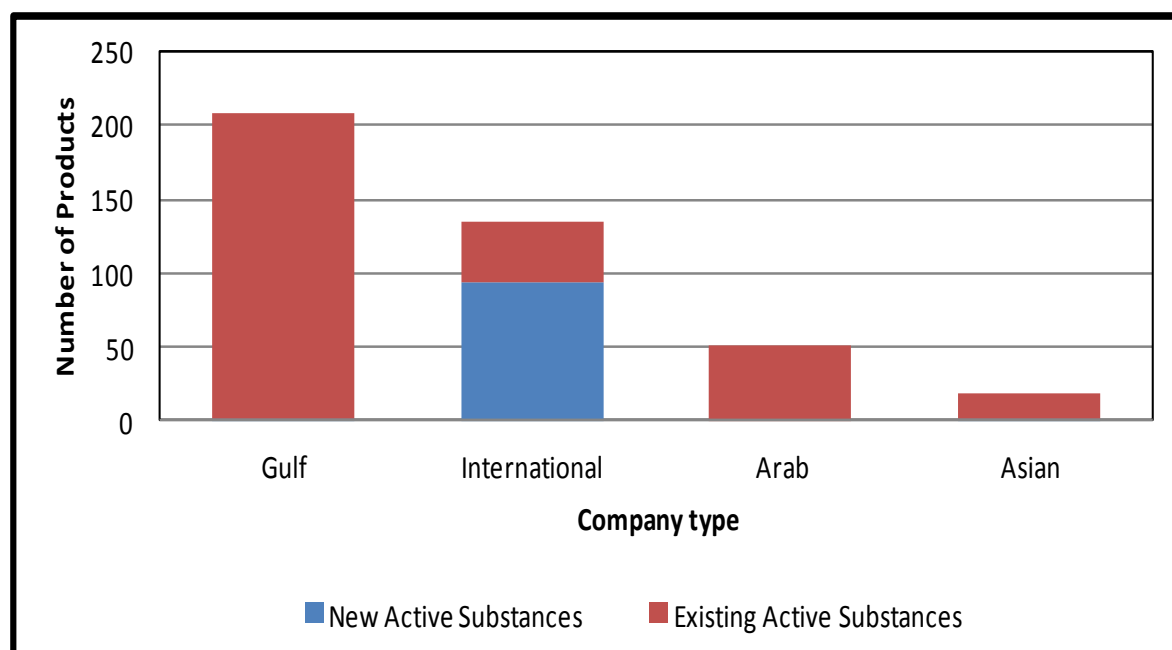
Statistical analysis using a simple linear regression showed a significant increase in the number of registered EASs ($p < 0.001$).

Figure 5.4: Number of NASs approved in the Gulf Centralised Procedure (2006-2010)



Statistical analysis using a simple linear regression showed a significant increase in the number of registered NASs ($p < 0.001$).

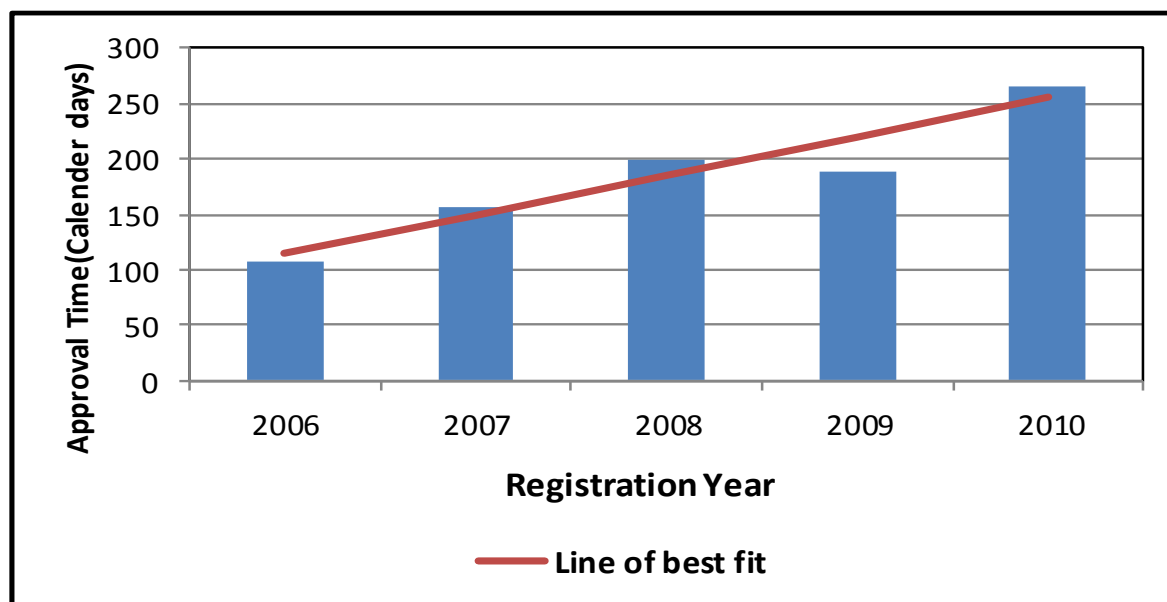
Figure 5.5: Approved pharmaceutical products (EASs & NASs) from GCC international, Arab non-GCC and Asian companies (2006-2010)



Part II: Approval times in the Gulf Centralised Procedure (2006 – 2010)

The total approval time for the period studied (2006 - 2010) includes all the 413 EASs and NASs from different companies. During the five years, the median approval time ranged from 107 days in 2006 to 265 days in 2010. There was a significant increase in the median approval time between 2006 and 2010 which was due to several factors. These included the limited number of meetings by the GCC-DR, although the seven member states met four to five times a year to discuss the product review reports, on the other hand there was a steady increase in the number of registration applications. Another reason for the delay in registration was the assessment review process where two authorities are selected alphabetically to review a registration dossier. There was also a lack of a standard evaluation template for product assessment which leads to an increase in the correspondence which is sent to the sponsor in several batches and at different times. Statistical analysis using the non parametric test (Kruskal-Wallis test) across the five-year period showed that there was a significant increase in the approval time for pharmaceutical products ($p < 0.001$) (Figure 5.6)

Figure 5.6: Median approval time for all pharmaceutical products in the Gulf Centralised Procedure (2006-2010)

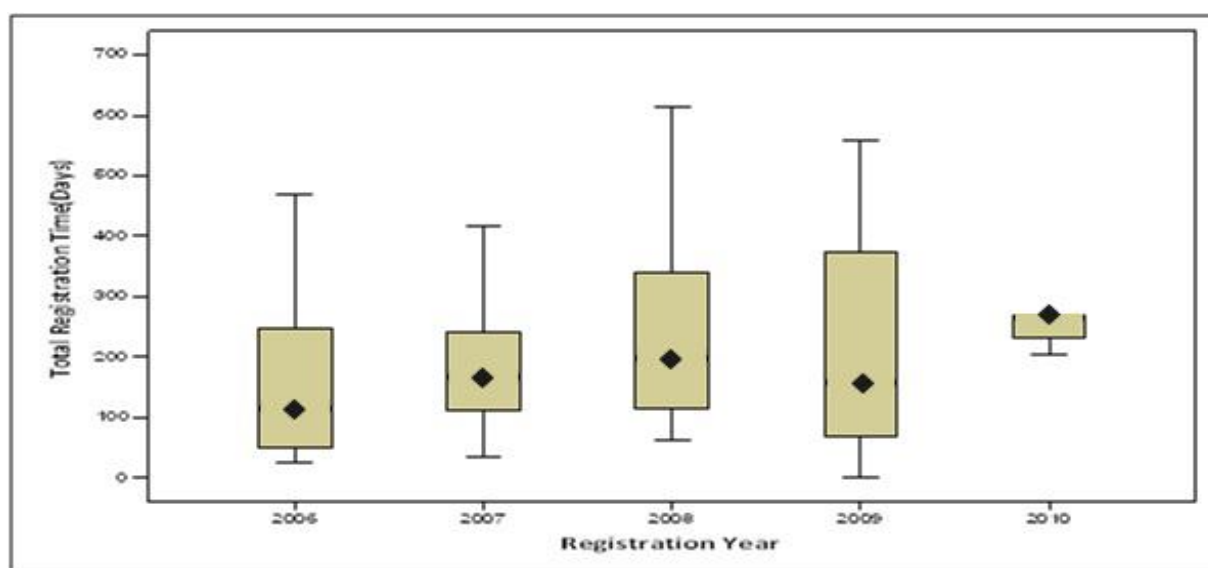


Statistical analysis using non parametric test (Kruskal-Wallis test) over the five-year period showed that there was a significant increase in the approval times for pharmaceutical products ($p < 0.001$).

Approval time of Existing Active Substances (EASs) in the Gulf Centralised Procedure (2006 - 2010)

Approval time for the 317 EASs approved in the Gulf Centralised Procedure between 2006 and 2010 varied from one year to the next. The lowest median approval time was for 2006 (114 days) and the highest median for 2010 (265 days) (Figure 5.7). Statistical analysis using the non parametric test (Kruskal-Wallis test) across the five-year period showed that there was a significant upward trend in the median approval time for EASs ($p < 0.05$). In general for the years 2006 to 2009 there is a wide range because in the centralised procedure there is no defined target time within which the company time is also not specified (no clock stop). However, in 2010 the range is significantly reduced because there were very few products approved as a result of the implementation of ICH stability guideline.

Figure 5.7: Median approval time for EASs in the Gulf Centralised Procedure (2006-2010)



Statistical analysis using the non parametric test (Kruskal-Wallis test) over the five-year period showed that there was a significant difference in the median approval time for EASs ($p < 0.05$)

Approval time for Existing Active Substances (EASs) by GCC, international, Arab non-GCC and Asian companies (2006-2010)

The median approval time for EASs varied for different cohorts of companies based on location, for example the shortest approval time was for Gulf company products (134 days) and the longest for those of international companies (346 days). The shortest approval time

for Gulf company products was due to the waiver of analysis requirements. A product is waived from analysis if it is registered in any one of the 4 GCC countries (Oman, Saudi Arabia, United Arab Emirates or Kuwait) where the Quality Control Laboratory for these States has the accreditation from the GCC. The median approval time for Arab companies was 227 and 332 calendar days for Asian companies. Statistical analysis using the non parametric test (Mann-Whitney U test) showed that there was a significant difference of approval time between international companies (median approval time=346 days) and Gulf companies (median approval time=134 days) ($p<0.001$).

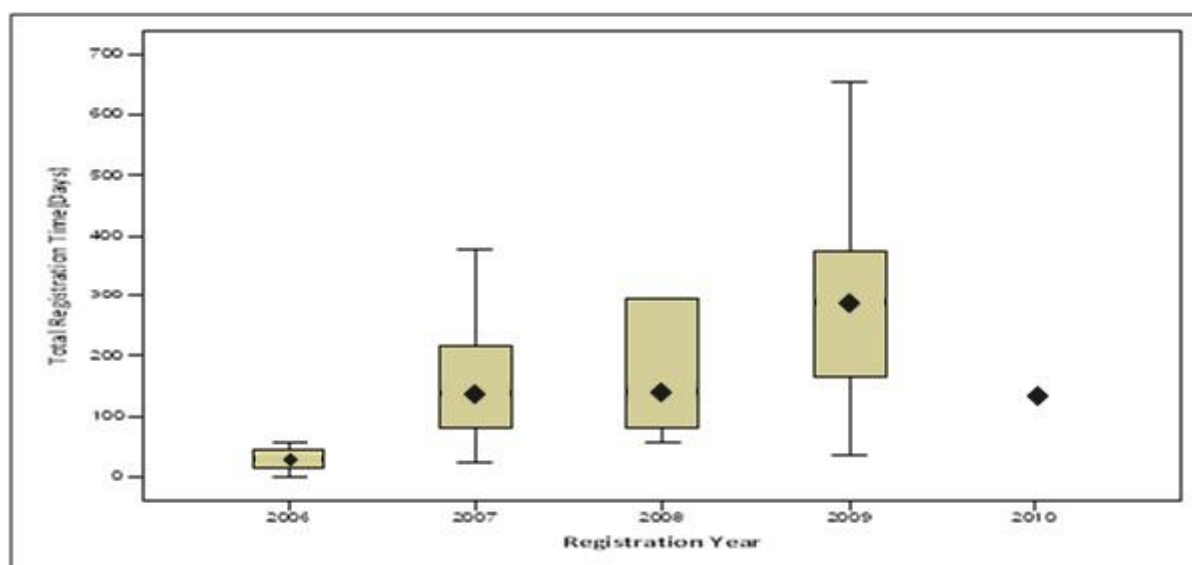
Approval time for New Active Substances (NASs) in the Gulf Centralised Procedure (2006 - 2010)

In the year 2009, the highest number of NASs was registered (45 products) with a median of 288 days. In 2006, only four products were registered with median of 31 days. In 2007, 31 NASs were registered with a median of 138 days. In 2008, 15 products were registered with median of 140 days. In 2010, the lowest number of products was registered (1 product only) with a registration time of 131 days. The results obtained from performing analysis of Kruskal-Wallis test showed that there was a highly significant upward trend in the median approval time for NASs products between 2006 and 2010 ($p<0.001$). This was due to several factors, including a limited number of meetings by the GCC-DR (only four to five times a year) and during this period there was a steady increase in the number of registration applications (Figure 5.8). The reason for the variation in approval times is similar to that expressed for EASs. This variation is not acceptable and could be mitigated by introducing target times.

Part III: Approval time for different dosage forms for all Existing Active Substances (EASs) and New Active Substances (NASs) in the Gulf Centralised Procedure (2006-2010)

From the 317 EASs registered with the Gulf Centralised Procedure between 2006-2010, the lowest number constituted the injectable forms (14%) followed by the semi-solid dosage forms (20%) with the highest represented by solid dosage forms (52%). Approval times

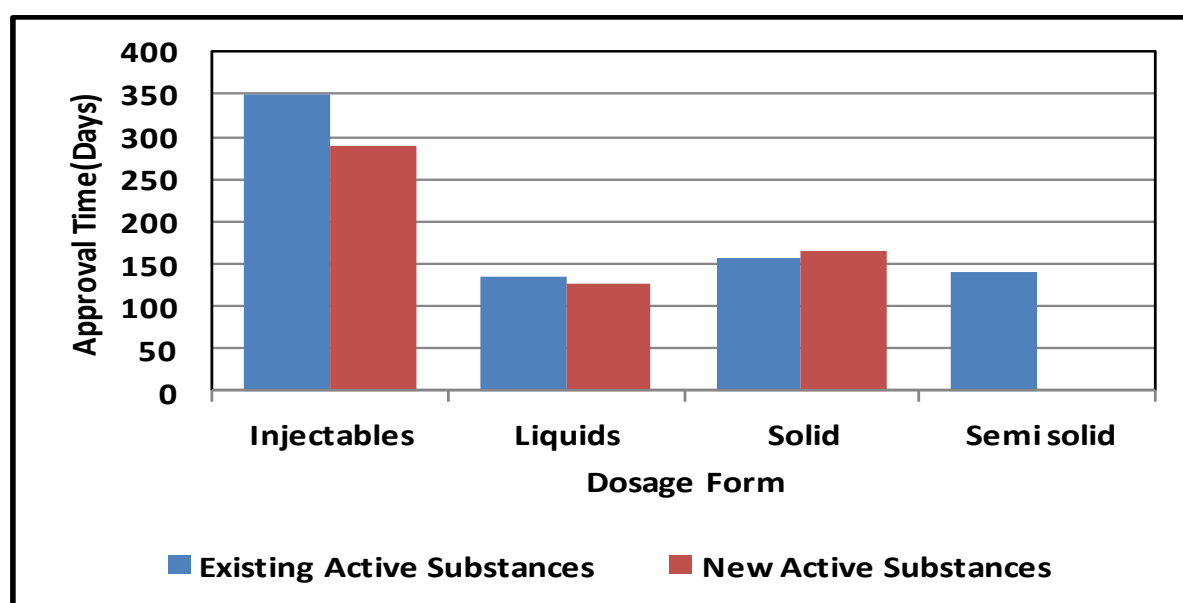
Figure 5.8: Median approval time for NASs in the Gulf Centralised Procedure (2006-2010)



Statistical analysis using the non parametric test (Kruskal-Wallis test) showed that there was a significant difference in the median approval time for NASs between 2006 and 2010 ($p < 0.001$).

ranged from 138 days for liquids to 350 days for injectables (Figure 5.9). In general, when the dosage form is more complex, additional time is needed to approve the product. Special studies and more steps are needed to analyse some products such as solutions for IV infusion which need additional tests such as sterility and pyrogen testing.

Figure 5.9: Median approval time for different dosage forms for EASs and NASs in the Gulf Centralised Procedure (2006-2010)



In terms of dosage forms, out of the 96 NASs registered in the Gulf Centralised Procedure (2006-2010), the lowest number registered was represented by the liquid dosage forms (5) with a median approval time 128 days. The highest number registered was represented by the injectable forms (59) with a median approval time 288 days.

Part IV: Approval times for Existing Active Substances (EASs) and New Active Substances (NASs) by therapeutic class, (2006-2010)

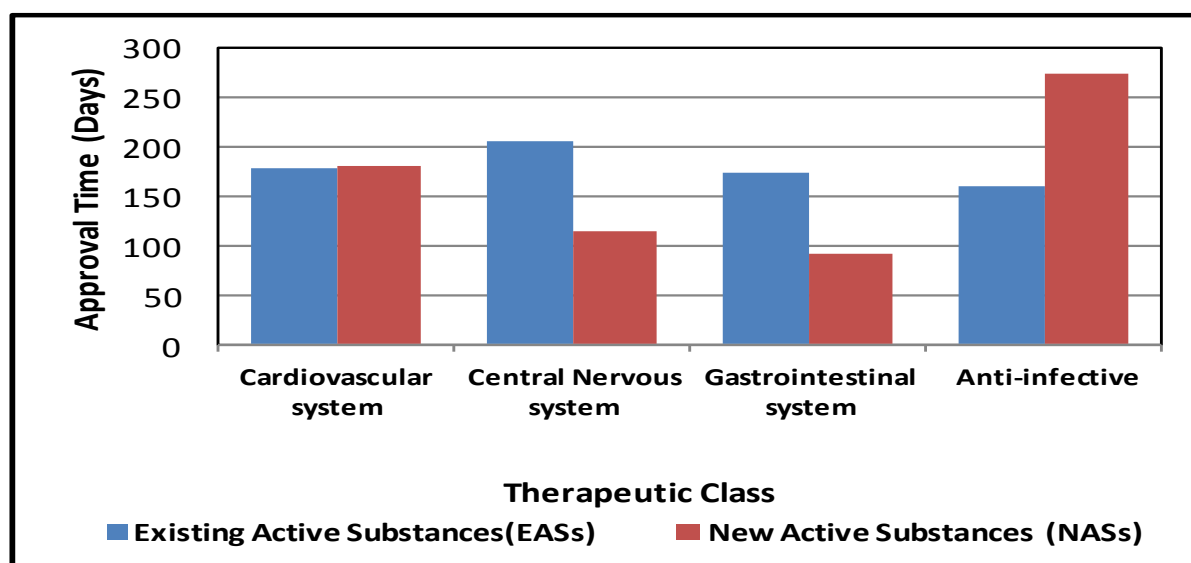
The therapeutic class of 314 EASs was assessed and the lowest number was represented by ear, nose and oropharynx preparations (1 preparation) and the highest number represented by anti-Infective (86 preparations). The analysis of the approval time of EASs registered between 2006 and 2010 involved the four largest therapeutic groups, namely,

- The cardiovascular system (CVS)
- The central nervous system (CNS)
- The gastro-intestinal system
- Anti-infective

The range of approval times for EASs analysed by therapeutic class varied from 206 days for central nervous system products to 162 for anti-infective products (Figure 5.10). The trend in approval times for EASs from different therapeutic groups was attributed to the GCC-DR assessment requirements depending on the nature of the products which may include the need for both clinical and bioequivalent studies and the prolongation of the analytical time.

Ninety-six NASs were approved between 2006-2010 and the lowest number was represented by the eye, musculoskeletal and joint disease and respiratory system preparations (one preparation) whereas, the highest number was represented by cardiovascular and nutrition and blood preparations (24 preparations). The median approval times for NASs analysed by the main therapeutic classes ranged from 274 days for anti-infective products to 92 for gastro-intestinal products. The main factor for the variation in the approval time for different therapeutic groups was the nature of the products evaluated.

Figure 5.10: Median approval time for different therapeutic class for EASs and NASs in the Gulf Centralised Procedure (2006-2010)



DISCUSSION

This study investigated the pattern of total regulatory approval times in the Gulf Centralised Procedure over the period from 2006 to 2010. It also addressed the various factors which may have a positive or negative effect on the total approval times. It showed that the total number approved in the Gulf Centralised Procedure was 413 including both Existing Active Substances (EASs) and New Active Substances (NASs). The outcomes revealed that the largest number of medicines submitted for review and approved by GCC-DR occurred in 2009. The study examined four hypotheses and their respective findings are discussed below.

Hypothesis 1: There was a significant increase in the number of products registered from 2006 to 2010.

The highest percentage of approved products was in the year 2009. There was a considerable decrease in the number of approved products in 2010. This was due to the fact that the pharmaceutical companies failed to comply with the new GCC guideline for stability testing of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). The new guideline was a major challenge to most of the pharmaceutical companies leading to the rejection of those which failed to meet the new stability study specifications. Other factors influencing the number of approved products in 2010 were that the Saudi FDA began to evaluate all the products in addition to the two rapporteurs from the Gulf States designated

to review the products. This resulted in a large number of queries raised from the Saudi Food and Drug administration (SFDA) which substantially delayed the review process and there was a significant decrease in the number of products approved in 2010. However, despite this change in 2010, this hypothesis was accepted.

Hypothesis 2: The highest number of products approved by GCC-DR is linked to those originating from the companies in the GCC region.

The number of products approved during the period of the study varied for different companies based on their geographical location. The highest percentage of products approved was from the Gulf companies, followed by Arab companies, international companies and finally the Asian companies. However, the highest number of products approved from GCC companies could be due to several factors including; that the GCC manufacturers increased their efforts to obtain the GCC-DR approval in order to facilitate entry into the international tender which is the common purchase route by GCC states. This has an impact on the number of submissions and approvals in GCC-DR. Other factors that might have also contributed to the increased number of products approved by GCC-DR from GCC companies was the decision to waive the requirement to submit full time stability studies during the first submission. The GCC manufacturers need to submit only one year full time stability data during the first submission. However, non-GCC manufacturing companies need to submit full time stability studies for the whole shelf life. This is because the GCC States are making efforts to support and improve their local manufacturing capabilities and the production capacity for the local population. The lower number of products approved by GCC-DR was from non-GCC manufacturing companies due to the strict GCC regulations that require evidence of registration in countries with developed regulatory systems. Therefore this hypothesis was accepted.

Hypothesis 3: There was a significant increase in the approval time between 2006-2010 in the GCC-DR.

During the five year period of the study (2006 – 2010), the median approval time significantly increased due to several factors which included the limited number of meetings by the GCC-DR and the increased number of applications for registration. Other factors that delayed the registration were the assessment review process where two authorities are

selected alphabetically to review the registration dossier. In addition, the lack of a standard evaluation template for product assessment leads to an increase in the correspondence which is sent to the sponsor in several batches and at different times. It is recommended to have one standard assessment template and rather than selecting the reviewing authorities alphabetically, the dossier should be sent to all countries and all assessments combined into one final report on which the final decision in the GCC-DR could be based. A clock-stop system is not enforced in the Gulf Centralised Procedure and this delays the company response to queries from the GCC Central registration committee. The implementation of a clock-stop will ensure the sponsor meets the deadline and would allow more time for the reviewers to complete the assessment of the submitted data. The sample analysis stage is an essential part of the review process that impacts on the overall approval time. It is completed after the scientific assessment as the outcome of the sample analysis affects the final approval decision. Carrying out the quality control analysis in parallel, rather than after the scientific assessment, would avoid the impact in the overall registration time. The queuing process is straightforward and allows appropriate handling of the registration dossiers in an organised manner. However, the lack of regular monitoring of queue time could lead to a backlog. Managing the priority review is another important issue that needs recognition by GCC-DR and should be dealt with according to set guidelines and SOPs that clearly specify the conditions under which products can be taken out of the queue for such review. Therefore, adequate resources and electronic handling of the queuing process should be provided to support accurate follow-up of the pending dossiers, priority reviews and fast-track products. On the basis of these findings this hypothesis has been accepted.

Hypothesis 4: The approval time for products from GCC pharmaceutical companies was shorter than for other companies.

The approval time for pharmaceutical products varied for different cohorts of companies based on their location, for example the shortest approval time was for the Gulf company products and the longest for international companies and this was due to the waiver of analysis requirement. The analysis is waived for a product if it is registered in any one of the four GCC countries (Oman Saudi Arabia, United Arab Emirates or Kuwait) where the Quality Control Laboratory has the accreditation from the GCC. There are other factors which have a positive effect on the approval time for Gulf companies but have a negative effect on the international, Arab non-GCC and Asian companies.

This includes the geographical proximity of the company to the authority which leads to an effective interaction and thus a faster response to any question asked by the authority. Additionally, most locally manufactured products are EASs and do not need very much consultation during the scientific review compared to NASs.

However, a priority procedure is a common practice in many authorities, the rapid approval time is also due to the GCC States making efforts; particularly (Oman, Saudi Arabia, UAE, and Kuwait) to improve their local manufacturing capabilities and the production capacity for the local population (Al-Essa, 2011). The data supported this hypothesis and therefore it was accepted.

For the first time this study has examined the centralised regulatory review process in the Gulf region and identified which steps within the process take the most time. In addition, it has highlighted the factors which may improve or delay the approval process resulting in accelerating patients' access to medicines. Furthermore these results may improve the registration process thereby saving time and resources.

SUMMARY

- There was a significant upward trend in the regulatory approval times in the Gulf Centralised Registration process between 2006 and 2010.
- The limited number of meetings per year led to a delay in the feedback for the submitted files to GCC-DR by the companies.
- Further correspondence after registration should be dealt with by individual local health authorities rather than centrally.
- The reference laboratory chosen to carry out the analysis is based on equity of the number of dossiers distributed between these laboratories, not on the ability of these laboratories to perform the analysis and that can lead to an increase in the analysis period.
- There was no clock-stop system and this delayed the company response to queries from the GCC Central registration committee.
- The re-registration (renewal) of pharmaceutical companies and their products led to a reduction in the number of new product applications reviewed by GCC-DR in 2010.

- The lack of a standard assessment template for product evaluation leads to a number of requests for additional data at different stages of registration. A standard template could possibly avoid such delays and lead to more consistent outcomes.
- Using information technology and e-mails could speed up the registration process rather than the manual exchange of the product registration files between the Executive Office and the member states.

CHAPTER 6

An Evaluation of the Gulf States Views and Experiences with GCC Centralised Procedure

INTRODUCTION

The historical implementation of the central registration system was subject to several criticisms with challenges from both the pharmaceutical industry as well as government. The GCC-DR received 1,824 medicinal product applications out of which 1,165 (64%) applications were approved during the eleven years from 1999 to 2010. The pharmaceutical industry was apprehensive about whether the GCC-DR system would be a hindrance to the timely approval of medicines in the region while the government officials were concerned about losing sovereignty to the centralised authority (Hashan, 2005). The collaborative efforts between the member countries however proved to be effective and substantiated the support of the GCC-DR system for each GCC country improving the regulatory approval processes and operation efficiencies at the national level.

Two members from each of the seven GCC countries represent the GCC Central Drug Registration (GCC-DR) Committee with the current procedure in force and two member countries are chosen to review a registration dossier. The selection of those countries is unbiased and purely based on alphabetical order and all the GCC countries are equally responsible for evaluating the quality, safety and efficacy of medicines. Thus, all seven GCC countries consisting of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE and Yemen are provided with copies of the product registration dossier for their individual assessments. The member countries meet four to five times a year to discuss the product review reports issued by the reviewers from each country and an approval decision is made by common agreement.

The only studies that have addressed the GCC region was the one reported by Hashan in 2005 and later by Al-Essa in 2011. They reported that there are three common phases in the GCC regulatory review process: submission, evaluation, and authorisation. The similarities and differences in the key milestones and activities in the GCC states made it possible to propose a new process, which could underpin the degree of standardisation required for a strong regulatory body that facilitates an effective drug approval process for the region (Al-Essa, 2011). These are the key components essential for the development of a strategic plan for strengthening drug regulations in the Gulf region. This chapter evaluates the experiences and opinions of all seven Gulf States regulatory authorities with the GCC Central Registration Process.

OBJECTIVES

The main objectives of this study were to:

- Evaluate the regulatory views and experiences of all seven Gulf States with respect to the Centralised Procedure.
- Appraise the barriers and opportunities to the full implementation of the Gulf Centralised Procedure.
- Make recommendations to improve the Gulf Centralised system as well as to identify its future strategy based on the views of the national regulatory authorities.

METHODS

There is a lack of information and research on the GCC Centralised Registration Procedure and therefore, with this limited information, there is a need to develop suitable measurement tools in order to obtain the relevant data required for this study. The development of the assessment instrument was carried out over 5 phases;

Phase 1 – Identify target population and item generation

Phase 2 – Development of themes and item reduction

Phase 3 – Development of the first version of the instrument, Gulf Assessment of Centralised Procedure (GACP)

Phase 4 – Pilot study

Phase 5 – Development of the final version of the GACP

This final version of the study instrument was sent to the seven Gulf States and followed up after one month.

RESULTS

This section presents the results from the development of the GACP and the views of the seven GCC regulatory authorities. For the purpose of clarity the results will be presented in two parts: Part I - The development of the study instrument (GACP); and Part II - The views of seven Gulf states about the Centralised Procedure.

Part I: The Development of the Study Instrument (GACP)

Phase 1 – Target population and item generation

An informal interaction and dialogue was held with the members of the GCC-DR which consist of two individuals (The head of the agency the head of the registration department) from each of the seven member states in the Gulf region. This allowed the generation of items for the development of the GACP. In addition, the relevant literature was also reviewed to inform this phase of the development.

Phase 2 – Development of themes and item reduction

There were a total of five themes emerging from the item generation phase based on the objectives of the study. The first version of the questionnaire comprised 5 sets of questions pertaining to the following headings;

Theme 1- Value of centralised procedure consisting of seventeen sub-themes.

Theme 2- Utilization of resources consisting of five sub-themes;

Theme 3- Regulatory expertise consisting of eight sub-themes;

Theme 4- Importance of CP consisting of five sub-themes;

Theme 5- General observations consisting of seven sub-themes.

Phase 3 – Development of the first version of the instrument: Gulf Assessment of Central Procedure (GACP)

Any item that was mentioned by only one individual was not included in the themes and sub-themes unless these were country or regulatory authority specific items. Having selected the themes and sub-themes, these were put in an appropriate structured questionnaire. These were then reviewed by an expert panel using four appropriate parameters; namely; language clarity, completeness of the statement, appropriate relevance and scaling. Account was also taken with regard to the length of the items and their readability.

Phase 4 - Pilot study

The purpose of the pilot study was to assess the practicality, feasibility, applicability and relevance of the study instrument to assessing the Gulf Centralised Procedure. Having developed a structured questionnaire it was sent to the head of agency in two GCC States;

namely Oman and the UAE. Feedback on the first version of the questionnaire was obtained from Oman and UAE Drug Control Authorities. The pilot study clearly indicated that such a study into the GCC Central Registration Procedure was essential to bring about standardisation and harmonisation of procedures. This would inevitably improve the registration processes for both the applicants as well as the approving authorities.

Based on the feedback from the pilot study, the following item was deleted.

Part 1 – Question 1.1.7: Do you think your agency has the necessary expertise for the Centralised Procedure and are you willing to contribute?

The following item was added in Part 1 of the questionnaire.

Part 1 – Question 1.1.8: Is your agency willing to contribute to the revision of these guidelines?

Finally at the end of the questionnaire, six simple questions were added to enable feedback and opinions about the questionnaire that was used to obtain the information from each of the Drug Regulatory Authorities in the GCC. This feedback was critical in order to design more effective assessment instruments for future studies (Figure 6.1).

Phase 5 – Development of the final version of the GACP

Following the pilot study and implementation of the changes suggested by the participating regulatory authorities, the development of GACP was completed. Thus, the final version of the instrument consists of 42 items grouped into five major categories. In addition it includes an introductory page collecting the respondents' personal details (Figure 6.2). The final version of the questionnaire was sent to all seven Gulf States with a clear guideline on the aims and objectives of the study and a confidentiality note that would ascertain the confidential procedure for the collection of data to prevent the identification of individual respondents. Generally the structure of the questionnaire did not differ from that used in the pilot study. Only minor adjustments and refinements were carried out to make the final questionnaire more user friendly and easily understood by the respondents.

Figure 6.1

**An Evaluation of the Gulf States views and experiences with
GCC Central Registration process**

Evaluation of the Experience with GCC Central Registrations



Practicality and Applicability

Your opinion about the questionnaire you have just completed is very important in its further refinement. Please take a few moments to give us your views by answering the following six questions:

	<u>Yes</u>	<u>No</u>
1. Did you find the questionnaire easy to complete?	<input type="checkbox"/>	<input type="checkbox"/>
2. Did you find the questionnaire easy to understand?	<input type="checkbox"/>	<input type="checkbox"/>
3. Did you find the questionnaire relevant?	<input type="checkbox"/>	<input type="checkbox"/>
4. Did you find the questionnaire clear?	<input type="checkbox"/>	<input type="checkbox"/>
5. How did you find the length of the questionnaire? about right <input type="checkbox"/> too short <input type="checkbox"/> too long <input type="checkbox"/>		
6. How long did it take you to complete the questionnaire? minutes		

Thank you for your help.

Figure 6.2

<div></div> <p>An Evaluation of the Gulf States views and Experiences with GCC Central Registration process</p> <p>SURVEY QUESTIONNAIRE</p> <p>Contact: Mohammed Al Rubaie alrubavee@hotmail.com</p> <p>FINAL VERSION April 2011</p>	<hr/> <p>An Evaluation of the Gulf States views and experiences with GCC Central Registration process</p> <hr/> <p>CONTENTS</p> <p>Introduction and Background 3</p> <p>Aims and Objectives..... 4</p> <p>Methodology.....4</p> <p>Pilot Study.....4</p> <p>Confidentiality..... 5</p> <p>Outcome..... 5</p> <p>Regulatory Authority & Personal Details6</p> <p>Part I – Value of Centralised Procedure (CP).....7</p> <p>Part II – Utilisation of resources.....9</p> <p>Part III – Regulatory expertise.....10</p> <p>Part IV – Importance of the Gulf Central Committee for Drug Registration...11</p> <p>Part V – General observations12</p> <hr/> <p>Page 2</p>
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Introduction and Background

The approval of drugs in different countries across the world has been and is still performed by regulatory agencies according to the national regulations. However attempts to harmonize the regulations between nations have been made for several years within the Gulf States. A Centralised Community Procedure for the registration of Pharmaceutical companies and medicinal products has been created under the Executive Board of the Health Ministers Council for GCC States. The Gulf Central Committee for Drug Registration (GCC-DR) was formed in May 1999 including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen (Yemen joined in 2003). There are two representatives from each member state. The main role of the committee is to register pharmaceutical companies and their products through joint coordination on evaluation of scientific safety, efficacy and quality of medicinal products.

The key aim of the Central Registration is to unify the systems and procedures in the process of registration of pharmaceutical companies as well as medicines and ensure that pharmaceutical companies are using the foundations of the pharmaceutical quality, as well as to ensure drug quality and safety after marketing by post-marketing surveillance.

From October 1999 to October 2009, the GCC Central Registration received 1688 medicinal products applications (innovator and generics). It approved 1128, but still there are so many challenges which lead to delays in medicines' access to GCC states such as the need to reregister products in individual countries after central registration and the long time taken to register the manufacturer prior to submitting the product file to Central Registration Office. This is in addition to the need to establish an effective method for sharing workload amongst the regulatory authorities in GCC states.

In this study, we aim to gather and evaluate the opinions and views of all the 7 GCC states from the regulatory authorities as well as the pharmaceutical companies on their experiences with GCC Central Registration Procedure. The study can be of value in formulating a baseline for any further change/improvement in the GCC Central registration system.

Aims and Objectives

The aims and objectives of this study are to:

- 1) Study the regulatory views and experiences from each individual GCC states towards the GCC Central Registration Procedures.
- 2) Survey the views and experiences of the pharmaceutical companies towards the GCC Central Registration Procedure
- 3) Make a comparison between the views and experiences expressed by each individual regulatory agencies from the GCC states and the pharmaceutical companies.
- 4) Identify the barriers to the implementation of the GCC Central Registration Procedures and to recommend measures to improve the system.

Methodology

In order to obtain the views and experiences of the regulatory agencies from GCC states and pharmaceutical companies, two different questionnaires have been prepared. The first questionnaire will be distributed to the regulatory authorities in 7 GCC states and the second one to 65 pharmaceutical companies who have registered their pharmaceutical products through the GCC Centralised Registration Procedure and to 20 companies who have not used the GCC Centralised procedure for registration of their products.

Pilot Study

Prior to sending these questionnaires to all the 7 GCC States and pharmaceutical companies, a pilot study has been made with 2 GCC states and 5 pharmaceutical companies. The pilot study involved the practicality and applicability of answering these questionnaires in terms of its relevance, clarity, length and even the time taken to complete them. All these factors have been taken into consideration while preparing these questionnaires, to ensure that the data being collected is valid, complete and reliable.

**An Evaluation of the Gulf States views and experiences with
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Confidentiality

Cardiff University in association with CMR International Institute for Regulatory Science has over 25 years experience in the handling of detailed, highly confidential information, and the continuing and growing support for its studies demonstrates the confidence which companies and regulators place in its integrity.

A confidential procedure will be used for the collection of data with identifying information being coded and aggregated upon receipt in order to prevent the identification of the individual study participants.

Outcome

A report will be prepared once the study has been completed and this report will be made available to all participants with a view to gaining a better understanding of the GCC Centralised procedure. It is also hoped the findings of this study will facilitate greater harmonization of the GCC countries regulatory review process leading to increased use of GCC centralized procedure by the pharmaceutical companies.

**An Evaluation of the Gulf States views and experiences with
GCC Central Registration process**

Regulatory Authority & Personal Details

Country													
Agency Name													
Company Name													
Address													
Name of person completing this questionnaire	<u>Name:</u> <u>Email:</u>												
Position													
Phone Number													
Email address													
Years of experience in pharmaceutical industry													
Qualifications	<table border="0"> <tr> <td></td> <td><u>Yes</u></td> <td><u>No</u></td> </tr> <tr> <td><u>Undergraduate</u></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td><u>Postgraduate</u></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td><u>Member of relevant professional body</u></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>		<u>Yes</u>	<u>No</u>	<u>Undergraduate</u>	<input type="checkbox"/>	<input type="checkbox"/>	<u>Postgraduate</u>	<input type="checkbox"/>	<input type="checkbox"/>	<u>Member of relevant professional body</u>	<input type="checkbox"/>	<input type="checkbox"/>
	<u>Yes</u>	<u>No</u>											
<u>Undergraduate</u>	<input type="checkbox"/>	<input type="checkbox"/>											
<u>Postgraduate</u>	<input type="checkbox"/>	<input type="checkbox"/>											
<u>Member of relevant professional body</u>	<input type="checkbox"/>	<input type="checkbox"/>											
Age years												
Gender	Male <input type="checkbox"/> Female <input type="checkbox"/>												

**An Evaluation of the Gulf States views and experiences with
GCC Central Registration process**

Part I - Value of Centralised Procedure (CP)

1.1 General

1.1.1	Do you consider the quality of decision-making of the CP to be? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
1.1.2	Do you consider that the CP should be extended to <input type="checkbox"/> Herbal Product <input type="checkbox"/> Health products <input type="checkbox"/> Medical devices <input type="checkbox"/> No other products
1.1.3	What do you believe should be the average time line for the approval of product in CP? <input type="checkbox"/> 1-3 months <input type="checkbox"/> 3-6 months <input type="checkbox"/> 6-12 months <input type="checkbox"/> more than 1 year
1.1.4	Do you think the time line for Centralised Procedure could be shortened? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, how?
1.1.5	Do you think certain aspects of the registration procedure could be simplified? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, how?
1.1.6	Do you think the Centralised Procedure has appropriate guidelines for the regulatory review in GCC-DR? <input type="checkbox"/> Yes <input type="checkbox"/> No
1.1.7	Do you think any current guidelines need to be revised or updated? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, which?
1.1.8	Is your agency willing to contribute to the revision of these guidelines? <input type="checkbox"/> Yes <input type="checkbox"/> No

**An Evaluation of the Gulf States views and experiences with
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1.1.9	Do you have any concerns about GMP inspections? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, is it related to - <input type="checkbox"/> expertise of inspection <input type="checkbox"/> quality of reports <input type="checkbox"/> other
1.1.10	Do you consider the organization and administration of the GCC-DR to be effective and efficient? <input type="checkbox"/> Yes <input type="checkbox"/> No If no, please give reason(s) by ticking all the relevant boxes <input type="checkbox"/> voting system <input type="checkbox"/> choosing the countries for conducting the evaluation <input type="checkbox"/> administrative <input type="checkbox"/> other issues (describe)
1.1.11	Do you consider that every agency makes an adequate and appropriate contribution to GCC-DR? <input type="checkbox"/> Yes <input type="checkbox"/> No

1.2 Assessment of Centralised Procedure (CP)

1.2.1	How do you rate the assessment procedure by the GCC-DR? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
1.2.2	How do you rate the implementation of the regulatory guidelines by the GCC-DR? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
1.2.3	How do you rate the scientific and technical expertise in the GCC-DR? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
1.2.4	How do you rate the quality of the Centralised Procedure decision making in comparison to your national system? <input type="checkbox"/> Better <input type="checkbox"/> Same <input type="checkbox"/> Worse

**An Evaluation of the Gulf States views and experiences with
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	<i>Safety data</i>	Internal experts _____
		External experts _____
	<i>Efficacy data</i>	Internal experts _____
		External experts _____
	<i>Pharmacovigilance data</i>	Internal experts _____
		External experts _____
	<i>Bioequivalence data</i>	Internal experts _____
		External experts _____
	<i>Biological / Biosimilar data</i>	Internal experts _____
		External experts _____
	<i>Vaccines data</i>	Internal experts _____
		External experts _____
	<i>GMP inspection</i>	Internal experts _____
		External experts _____
	<i>Others (if any) state</i>	Internal experts _____
		External experts _____
<i>Total number of Internal experts _____ External experts _____</i>		

**Part IV - Importance of the Gulf Central Committee for Drug
Registration (GCC-DR)**

What value does the GCC-DR system provide to your agency in terms of?:	
4.1	<i>Expertise</i> <input type="checkbox"/> High value <input type="checkbox"/> Moderate value <input type="checkbox"/> Little value <input type="checkbox"/> No value Please comment:
4.2	<i>Training</i> <input type="checkbox"/> High value <input type="checkbox"/> Moderate value <input type="checkbox"/> Little value <input type="checkbox"/> No value Please comment:

**An Evaluation of the Gulf States views and experiences with
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4.3	<i>Collaboration with other national agencies</i> <input type="checkbox"/> High value <input type="checkbox"/> Moderate value <input type="checkbox"/> Little value <input type="checkbox"/> No value Please comment:
4.4	<i>Sharing of pharmacovigilance data</i> <input type="checkbox"/> High value <input type="checkbox"/> Moderate value <input type="checkbox"/> Little value <input type="checkbox"/> No value Please comment:
4.5	<i>Guidelines harmonization</i> <input type="checkbox"/> High value <input type="checkbox"/> Moderate value <input type="checkbox"/> Little value <input type="checkbox"/> No value Please comment:

Part V - General observations

5.1	Do you believe the current centralised evaluation system provides a better scientific opinion than the national system? <input type="checkbox"/> Always <input type="checkbox"/> Frequently <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely
5.2	Do you consider the current system provides consistent evaluations in comparison with national evaluation? <input type="checkbox"/> Always <input type="checkbox"/> Frequently <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely
5.3	Do you support having a standard price for specific medicines throughout the GCC states? <input type="checkbox"/> Yes <input type="checkbox"/> No If NO, why?
5.4	Do you support the continuity of national registrations in parallel to CP? <input type="checkbox"/> Yes <input type="checkbox"/> No

**An Evaluation of the Gulf States views and experiences with
GCC Central Registration process**

In order to provide a summary of your views, can you please complete the following questions?	
5.5	<p>In your opinion, what are the 3 major advantages of CP system compared to the national system? (Please state in order of importance).</p> <p>1.....</p> <p>2.....</p> <p>3.....</p>
5.6	<p>In your opinion, what are the 3 major disadvantages of CP system compared to the national system? (Please state in order of importance).</p> <p>1.....</p> <p>2.....</p> <p>3.....</p>
5.7	<p>What are your three main recommendations to improve the CP system?</p> <p>1.....</p> <p>2.....</p> <p>3.....</p>
5.8	<p>Additional comments, if any:</p> <p>.....</p> <p>.....</p>

The final version of the questionnaire was well received by all the Drug Regulatory Authorities in the region. They successfully completed the questionnaire and submitted the completed documents in good time. Their full co-operation was significant for the success of this study.

Part II: The views of seven Gulf States about the Centralised Procedure

The regulatory authorities who are responsible for the regulation of pharmaceutical products in the seven Gulf States participated in the survey and a 100% response rating was achieved. (Table 6.1).

Table 6.1 - List of the seven participating authorities in the Gulf Cooperation Council (GCC) States

Position	Agency	Country
Director, Pharmacy & Drug Control	Ministry of Health	Bahrain
Drug Registration and Release Superintendent	Drug and Food Control - Ministry of Health	Kuwait
Director General of Pharmaceutical Affairs & Drug Control	Directorate General of Pharmaceutical Affairs and Drug Control- Ministry of Health	Oman
Head of Drug Registration Section	Drug Control Department- Supreme Council of Health	Qatar
Executive Director of Licensing Department - Drug Sector	Saudi Food and Drug Authority	Kingdom of Saudi Arabia (KSA)
Head of Registration and Pricing Department	Drug Control Department - Ministry of Health	UAE
Member of the board council	Supreme board of drugs and medical appliances	Yemen

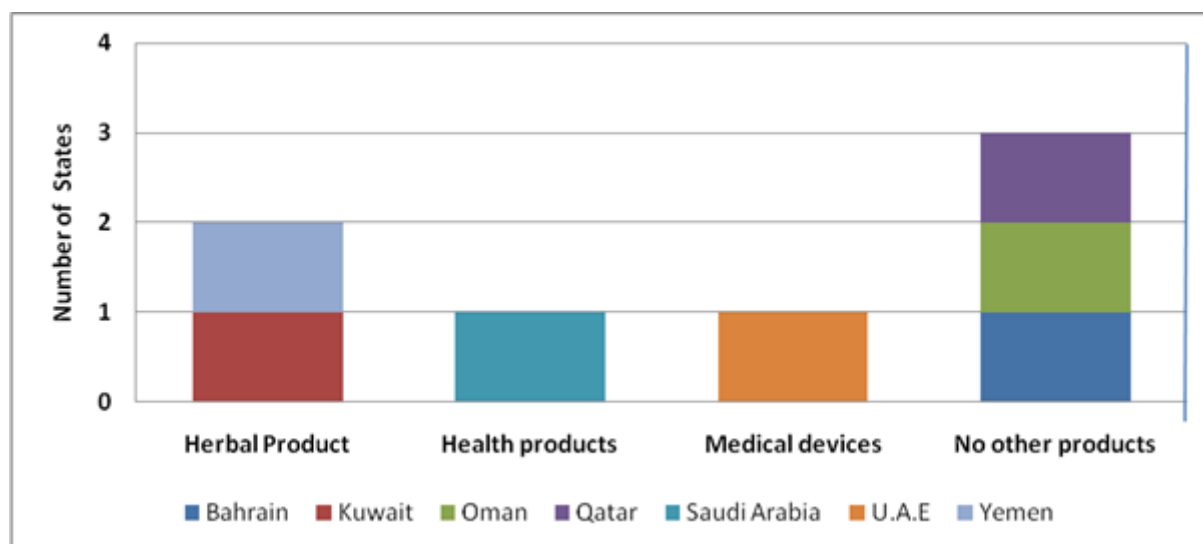
Section 1 - Value of the Centralised Procedure (CP)

The complete responses from all GCC member states indicated that the Centralised Procedure (CP) had indeed contributed to an effective system for authorising medicinal products for the GCC. This was ascertained from their views that the GCC-DR achieved its main objective, by providing the best possible scientific opinion for the CP. They also agreed that the CP has appropriate guidelines for regulatory review in the GCC-DR and that the

quality of the CP decision-making is satisfactory to good as compared to the national system. The CP which has been put in place since 1999 is clearly still functioning well as six of the member countries indicated that the quality of the CP Decision-Making process is good. Only Saudi Arabia rated the quality of processes as satisfactory.

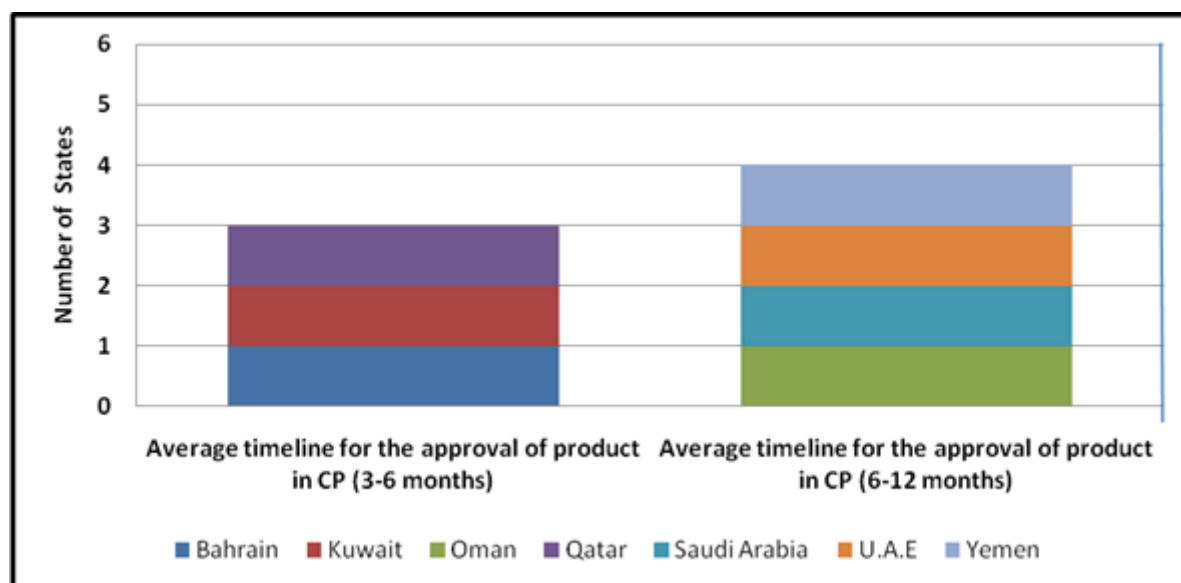
This signifies that all GCC member countries support the centralised procedure in registering pharmaceutical products. With the strong support for the CP, four member countries (Kuwait, Saudi Arabia, UAE and Yemen) indicated that the CP should be extended to other products to include herbal products, health products and medical devices while Bahrain, Oman, and Qatar reported that CP procedure should not be extended to other products (Figure 6.3).

Figure 6.3 The products which could potentially be registered under the Centralised Procedure



The suggested range for the approval timeline for products reviewed in the Centralised Procedure should be between 6-12 months as indicated by four of the member countries (Oman, Saudi Arabia, UAE, and Yemen) while Bahrain, Kuwait and Qatar indicated that it should be 3-6 months (Figure 6.4). The latest data available (2010) indicated that the median approval time for the Centralised Procedure was nine months (chapter 5).

Figure 6.4 Proposed approval timeline for products in Centralised procedure

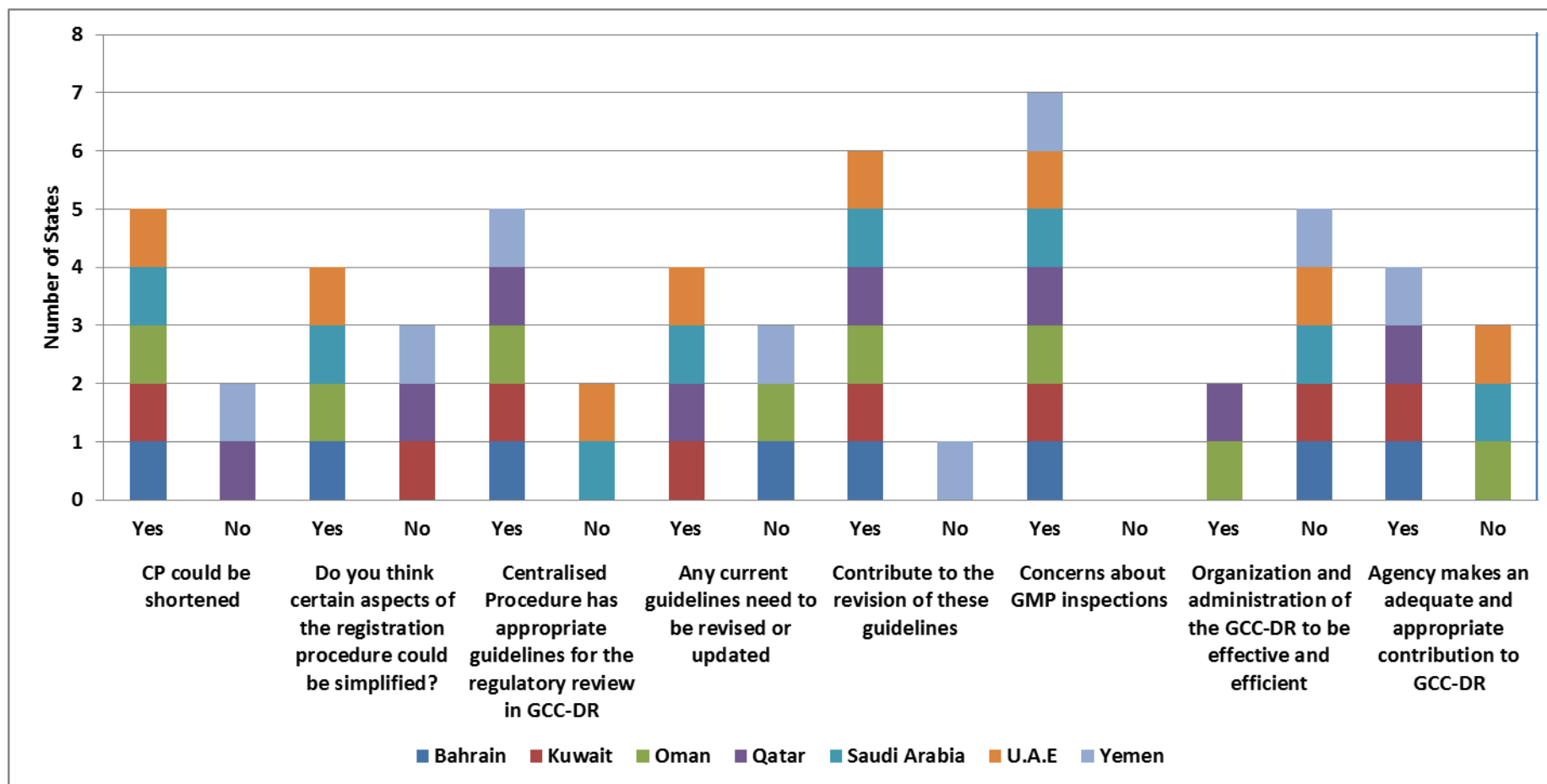


Responses for GCC authorities with regard to improving the CP

Registration process and timelines

The long approval time could be the main obstacle in advocating the CP as the main route for registration of products in the region. As a result, five of the member countries (Bahrain, Kuwait, Oman, Saudi Arabia and UAE) agreed that the CP process could be shortened, although two (Yemen and Qatar) indicated otherwise (Figure 6.5). Bahrain and UAE indicated that the CP approval time can be reduced by following the exact rules and regulations in the guidelines by all sectors. In addition, if the verifications were carried out at the time when the applications were submitted, the time line could be reduced. UAE also added that another way would be for the reviewing country to send the applications with preliminary assessment before the committee meets for their discussion as the committee sees the assessment for the first time at their meeting. To reduce the timeline further, Oman stated that the member states should not demand more requirements in order to avoid delaying the whole process; but they should encourage the sponsors to respond expeditiously to any such requests and by increasing the number of meetings. Kuwait stated that adopting mutual recognition from mature regulatory authorities would shorten the approval time. Saudi Arabia, on the other hand, advocated parallel national approvals in the Gulf could also expedite the process.

Figure 6.5 – Responses for the GCC authorities with regard to improving the GCC Centralised Procedure



Bahrain, Oman, Saudi Arabia and UAE, agreed that certain aspects of the registration procedure could be simplified to reduce the duration of the CP process. Bahrain stated that this could be done by developing a written policy for fast track registration, while Saudi Arabia and UAE advocated the implementation of electronic communication along with an online submission. Oman stated that the countries must consolidate all the requests for additional information to be sent to the sponsors as one single batch instead of in several batches and at different times.

Centralised Procedure guidelines

Bahrain, Kuwait, Oman, Qatar, and Yemen agreed that the CP has appropriate guidelines for the regulatory review in GCC-DR while UAE and Saudi Arabia report that currently the guidelines are not adequate. Bahrain, Kuwait, Qatar, Saudi Arabia, and UAE, indicated that some current guidelines need to be revised or updated. The areas recommended include GMP inspections, generics registration, contract manufacturing and biological / biosimilar registration. These guidelines should also be revised on a regular basis according to international requirements. All the member countries with the exception of Yemen indicated that they would be willing to contribute to the revisions of CP guidelines.

GMP Inspections

All member countries indicated their concerns about GMP inspections. Six of the member countries reported on the quality of expertise for GMP inspectors as well as the quality of the reports. UAE cited other causes which included the inconsistency of the inspections and decision-making with regard to classification of defects and time given for corrective actions and their follow-up.

The effectiveness and efficiency of the GCC-DR

Only Qatar and Oman indicated that the organisation and administration of the GCC-DR are effective and efficient. Bahrain, Kuwait, Saudi Arabia, UAE, and Yemen reported that the organisation and administration of the GCC-DR is not effective and efficient. Bahrain, Saudi Arabia, UAE and Yemen cited the voting system as the contributing factor to the ineffectiveness which in turn affects the efficiency of the GCC-DR system. Kuwait cited that choosing the countries to conduct the evaluation affected the effectiveness and

efficiency. In addition, Kuwait indicated that there is political pressure in some Gulf States for special consideration to be given to local manufacturers. Bahrain also added that the SOP for the voting system, which requires total agreement between all member states, should be written into the policy document.

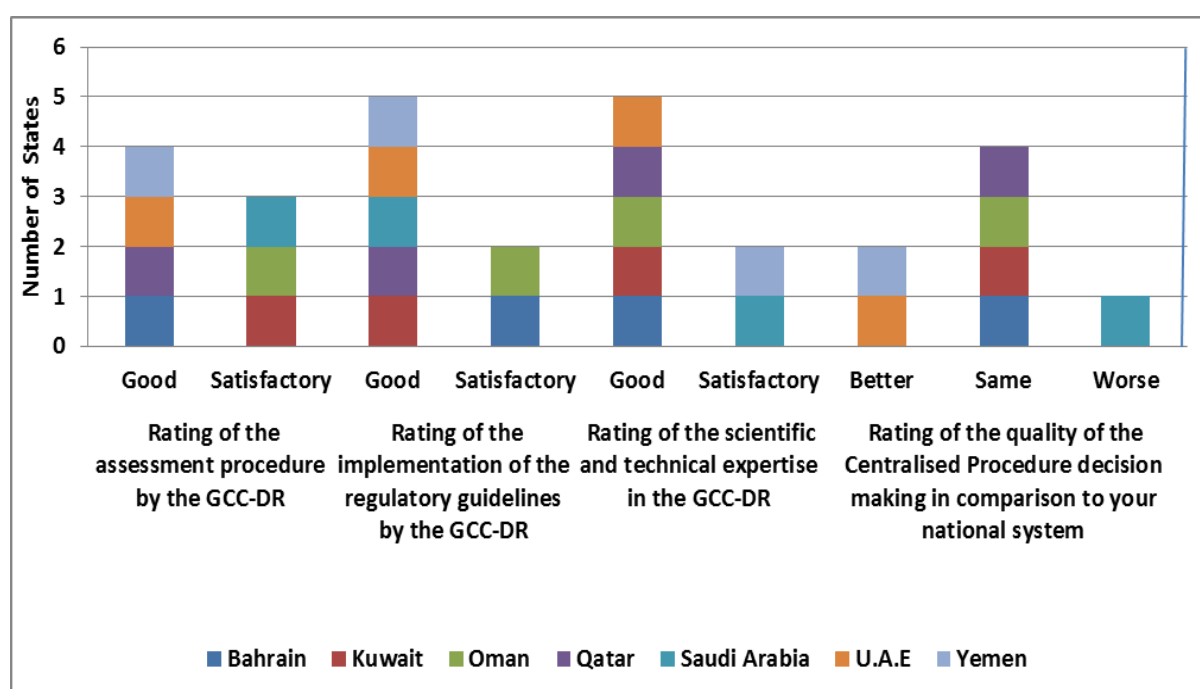
Contribution to GCC-DR

Four member states (Bahrain, Kuwait, Qatar and Yemen) considered that every agency made an adequate and appropriate contribution to GCC-DR while the remaining three member states (Oman, Saudi Arabia and UAE) believe that all agencies did not make an adequate contribution.

Assessment of Centralised Procedure

In general the GCC Drug Regulatory Authorities are satisfied with the GCC-DR assessment procedure, implementation of the regulatory guidelines and the availability of the scientific and technical expertise as is shown in Figure 6.6.

Figure 6.6 – Member states assessment of the Centralised Procedure



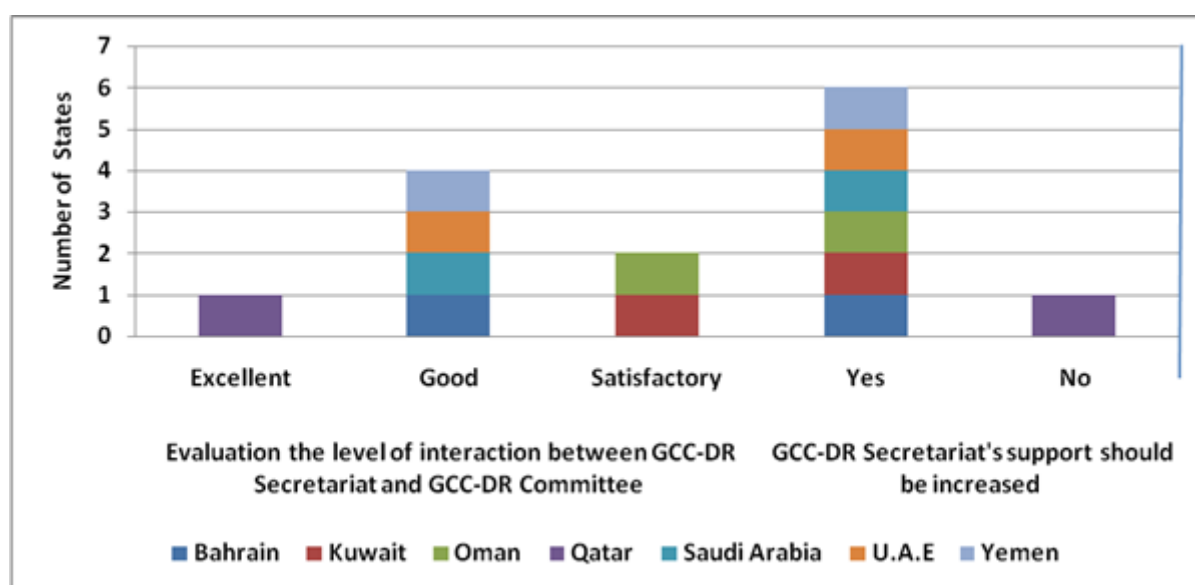
However, only two member countries (UAE and Yemen) stated that the quality of the CP decision-making is better that of their national system (Figure 6.6) while four members (Bahrain, Kuwait, Oman and Qatar) indicated that it is about the same as their national system. On the other hand, Saudi Arabia indicated that the quality of the CP decision-making

is worse than that of their national system and this is certainly a cause of concern that needs to be further investigated.

GCC-DR Secretariat activities

The GCC-DR secretariat activities were also evaluated to ascertain the quality and deficiency, if any, within the organisation. Five member countries (Bahrain, Kuwait, Oman, Qatar and UAE) indicated that the level of interactions between the GCC-DR Secretariat and the GCC-DR Committee was good to excellent. Only two member countries (Saudi Arabia and Yemen) stated that it was only satisfactory. However, all member states, with the exception of Qatar, indicated that the GCC-DR Secretariat's support to the GCC-DR Committee should be increased (Figure 6.7).

Figure 6.7– Level of interaction between GCC-DR Secretariat and the Committee



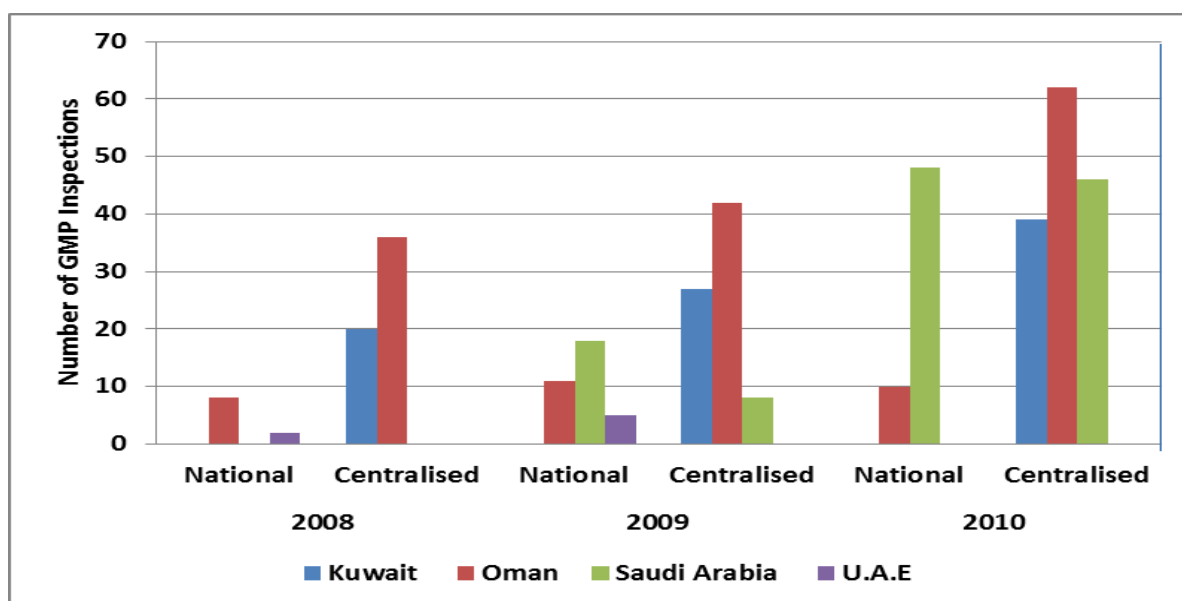
The member states added that the Secretariat's support could be enhanced by increasing the number of staff and improving the follow up system between the members. They also recommended that there should be expert pharmacists at the Secretariat's office to validate the submitted files and this would ensure that the approval process is streamlined. This view was also reiterated by another member country who stated that the Secretariat needed to include one or two pharmacists who have enough experience in drug registration and GMP inspections. Furthermore, since it is an administrative issue, more scientific staff are needed to organise the dossiers distribution, follow up the status of the companies, and communicate with other GCC countries members.

Section 2 – Utilization of Resources

The key issues explored here centred on the allocation of resources to various activities carried out at the national or centralised level. All member states indicated that limited resources did pose moderate problems for their agency in relation to their activities with the Centralised Procedure. However, only Kuwait, Qatar, Saudi Arabia and UAE indicated that they did not lack the expertise required for the assessment of the Centralised Procedure applications. Bahrain, Oman and Yemen stated that they did lack the necessary expertise and that they would be able to overcome this issue by increasing their budget and engaging the resources required.

Further information was gathered on how the GCC States evaluated their allocation of resources depending on the various CP activities. Only Oman, Saudi Arabia and UAE conducted GMP inspections at both national and centralised level (Figure 6.8). Generally there is an increasing trend for the conduct of GMP inspections at a centralised level.

Figure 6.8 – Number of GMP Inspections conducted by GCC (2008 - 2010)

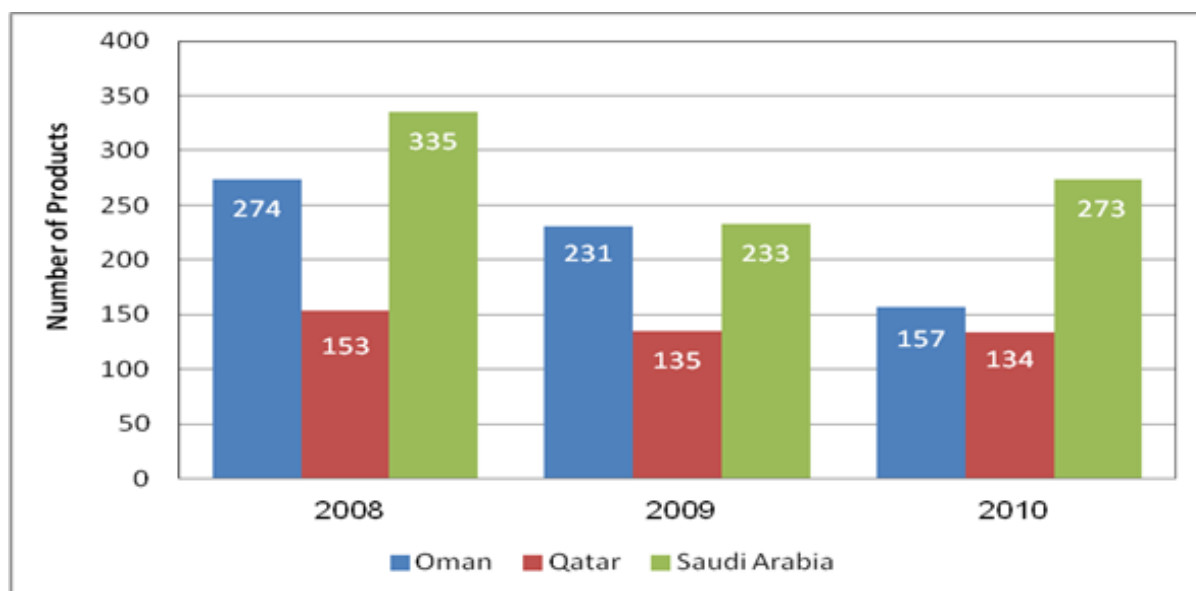


Based on the data collected from Oman, Qatar and Saudi Arabia (Figure 6.9), it could be ascertained that the number of product evaluations at a national level is more than those carried out under the CP. This indicates that most pharmaceutical companies prefer to receive approval at a national level rather than through the CP. This is further reinforced by the fact that half of the states indicated that the current CP evaluation system would not be sustainable due to the lack of resources, together with the current expertise and the heavy

national workload. There are a total of 250 internal and external reviewers available in the GCC. However, this number varied from state to state with Saudi Arabia having the largest number (121) while Yemen has the lowest number (11). With an increasing number of products to be evaluated, the number of reviewers within the GCC may not be sufficient to process the number of new products, thus resulting in the long delay experienced by the pharmaceutical companies.

From the data collected via the questionnaire (Figure 6.8). UAE conducted a total of seven GMP inspections at a national level for 2008 and 2009. Oman conducted a total of 29 GMP inspections at a national level between 2008 and 2010 whereas Saudi Arabia conducted 66 such inspections for 2009 and 2010. It is obvious that there is an increasing trend in the conduct of GMP inspections at a national level over the three year period (2008 to 2010). More GMP inspections were carried out centrally in which the total inspections completed by Kuwait, Oman, Saudi Arabia and UAE for the three year period was 280. There is also an increasing trend towards central GMP inspections conducted by the four GCC countries from 56 in 2009 to 147 in 2010 which is an increase of more than 100%.

Figure 6.9 – Number of Products evaluated by Oman, Qatar and Saudi Arabia (2008 - 2010)



Product evaluations in Oman, Saudi Arabia, Qatar and at national and central registration reached a total of 1957 for the period 2008, 2009 and 2010 (Figure 6.9). The highest number of product evaluations was carried out in the year 2008 with a total of 762 or about 40% of the total number. Saudi Arabia has the highest total number of products evaluated (841),

followed by Oman (662) and Qatar (422). This survey also indicated that four member states did not provide the data for products evaluated by them between 2008 to 2010 for the central registration. The data for Saudi Arabia was combined with that of the national data as it was not differentiated when the data was first collected. There is no data available from Bahrain, Kuwait, UAE and Yemen for centralised product evaluation. In general, it could be ascertained that the number of products evaluated at a national level is more than those conducted within the Centralised proceed.

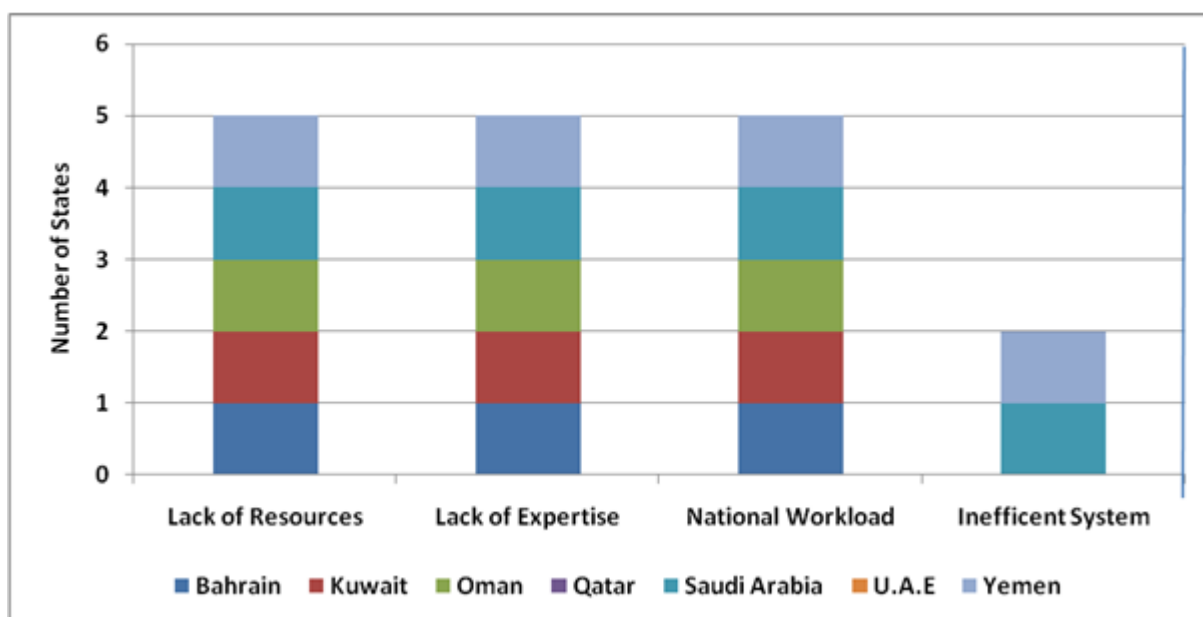
Limitation of resources for product evaluation

All member countries indicated that limited resources posed moderate problems for their agency in relation to the activities within the Centralised Procedure. However, Kuwait, Qatar, Saudi Arabia and UAE indicated that they did not lack the expertise required for the assessment of the Centralised Procedure submissions although Bahrain, Oman and Yemen indicated that they did lack the necessary expertise. The member states which indicated that the lack of expertise would be a problem in the future stated that they would seek additional budget and utilise external reviewers. All member states also indicated that they have a unit or person within their authority that coordinates CP activities. The entity varies from state to state depending on the size of the organisation and the related activities. Bahrain, Kuwait, Oman and Yemen indicated that the current system is not sustainable while the remaining Qatar, Saudi Arabia and UAE indicated that it is. The countries which indicated that the current system is not sustainable cited the lack of resources as the main factor. The lack of expertise is another key concern as well as the national workload as the third factor (Figure 6.10).

Part III: Regulatory Expertise

This section of the report examines the regulatory expertise residing within the national agencies that would enable the evaluation of different parts of the registration applications. Table 6.2 provides a summary of all the data pertaining to the internal and external expertise available in each agency.

Figure 6.10 – Factors that affect the sustainability of the Centralised Procedure



Generally local internal specialised reviewers are available within each agency and these account for almost three times the number of external experts. The highest number of internal experts are involved with the quality data review (30%) while the lowest number is involved in the review of the biological data (4%) (Table 6.2). Saudi Arabia has the largest number of internal reviewers totalling 77 while Yemen has the lowest number (11). Oman, UAE and Yemen rely entirely on internal reviewers. However, there is a direct correlation between the number of experts, the number of products evaluated and GMP inspections carried out by these member states (Table 6.3).

Saudi Arabia reported the highest number of evaluators totaling 121 (internal and external) and they managed to complete 841 product evaluations at national and central levels (2008, 2009 & 2010) as shown in Table 6.3. With their reviewers, Saudi Arabia was able to carry out 65% of the total GMP inspections carried out at national level. Product evaluations in Oman, Qatar and Saudi Arabia at national and central registration reached a total of 1,957 for the period 2008, 2009 and 2010.

Table 6.2 – Number of internal and external personnel in different areas of expertise within the Gulf States

Gulf States	Quality data		Safety data		Efficacy data		Pharmacovigilance data		Bioequivalence data		Biological/Biosimilar data		Vaccines data		GMP inspection		Others (if any) state		Total	
	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext	Int	Ext
Bahrain	8	5	0	0	0	0	1	0	6	1	0	0	0	0	9	0	0	0	24	6
Kuwait	8	0	4	0	10	0	0	0	4	0	2	0	0	special committee	2	0	0	0	30	
Oman	9	0	2	0	2	0	2	0	1	0	1	0	2	0	5	0	0	0	24	0
Qatar	3	1	3	1	3	1	1	1	0	0	1	0	1	0	0	0			12	4
Saudi Arabia	25	2	9	1	9	1	6	13	1	3	2	0	2	0	17	15	6	9	77	44
U.A.E	3	0	2	0	2	0	1	0	2	0	2	0	3	0	1	0	2	0	18	0
Yemen	3	0	0	0	0	0	0	0	1	0	0	0	0	0	7	0	0	0	11	0
Total	59	8	20	2	26	2	11	14	15	4	8	0	8	0	41	15	8	9	196	54
% of Reviewers	30	15	10	4	13	4	6	26	8	7	4	0	4	0	21	28	4	17	100	100

* Int = Internal

* Ext = External

**Table 6.3 – Relationships between capacity and workload for each Gulf State
(2008, 2009 & 2010)**

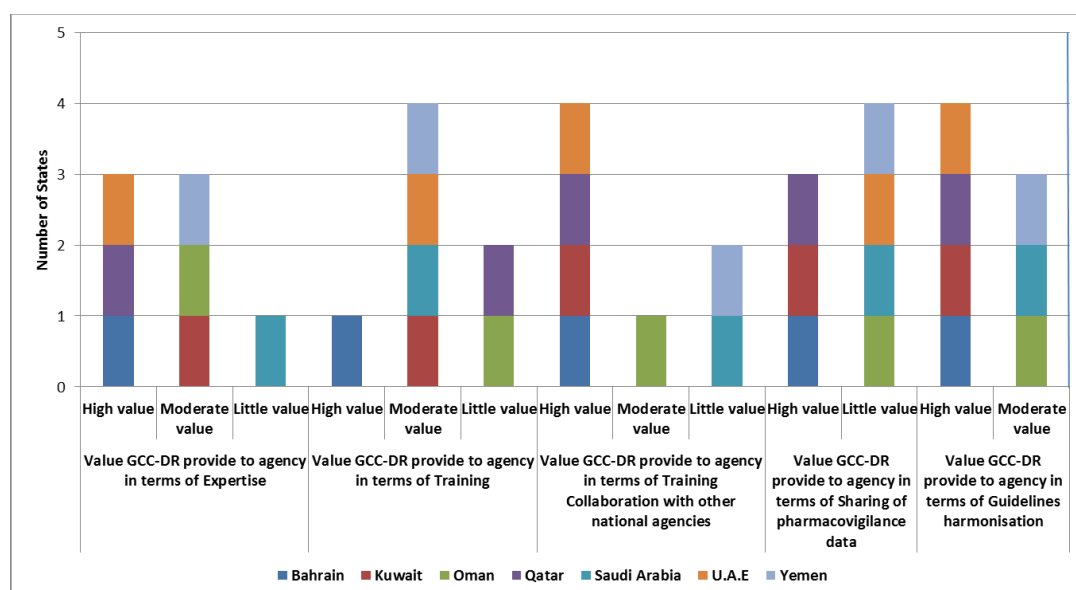
Gulf States	Internal evaluators	External evaluators	Total	Percentage %	Total Product Evaluation at National & CP Level	Percentage %	Total GMP Inspections done at National Level	Percentage %
Bahrain	24	6	30	12	NA	NA	NA	NA
Kuwait	30	NA	30	12	NA	NA	NA	NA
Oman	24	0	24	10	662	34	29	28
Qatar	12	4	16	6	422	22	NA	NA
Saudi Arabia	77	44	121	48	841	44	66	65
U.A.E	18	0	18	7	NA	NA	7	7
Yemen	11	0	11	4	N A	NA	NA	NA
Total	196	54	250	100	1925	100	102	100

NA – Not Available

Section 4 – Importance of GCC-DR

Despite the large number of products being evaluated at a national level, the GCC member states agreed that the GCC-DR system provides salient advantages to them in terms of the availability of specialised expertise, training, sharing of pharmacovigilance data and harmonisation of guidelines. The most valued service is the collaboration with other national agencies and the provision of guidelines for harmonisation of the central and national processes. (Figure 6.11).

Figure 6.11 – The value of professional functions to the GCC-DR system by the Gulf States



Generally, Bahrain, Qatar and UAE indicated that all the services rendered by the GCC-DR system are of high value to their respective agencies while Kuwait, Oman and Yemen indicated that they are of moderate value. Only Saudi Arabia indicated that the services provided by the GCC-DR system are of little value. The most valued service is the collaboration with other national agencies and the harmonisation of the guidelines.

Expertise

In addition, the member states added that by continuously engaging with the GCC-DR evaluators through discussions and debates, national evaluators would be challenged to acquire more information and knowledge about the subject of debate and in so doing expand their experience. These active intellectual exchanges are essential since those applications which would be evaluated and registered centrally would be then registered automatically by the individual GCC States.

Training

With regards to training, the respondents stated that such training could be of higher value if the frequency for shared workshops is increased and becomes an essential part of each GCC-DR committee meeting attended by reviewers, evaluators and committee members. Many shared workshops at a GCC level enriched the expertise of the evaluators who attended. In addition, through such workshops there is a great potential for the companies to participate at GCC level and opens up the opportunity to share knowledge and expertise for all participants. To facilitate the training efforts, it was suggested that training plans be prepared periodically at GCC-DR level.

Collaborations with other agencies

The member states indicated that the exchange of information, experience and plans should be initiated between all national agencies in the region on a regular basis. This is clearly beneficial and natural when the committee members are meeting on a regular basis and have the opportunity to share information. Networking among member states becomes easier with better established teamwork and this facilitates communication and enhances further collaborations.

Sharing of Pharmacovigilance Data

The member states indicated that the sharing of pharmacovigilance data is most important because at least three member states do not have reviewers in this area. They added that the potential benefit of the GCC-CP is not fully exploited. If it was, then the CP will be of very high value to all member countries. It needs more resources and a specialised unit at the central level equipped with the right software and supported by unified systems at the country levels. In addition, the respondents suggested that there should be a system for sharing scientific data between all national agencies

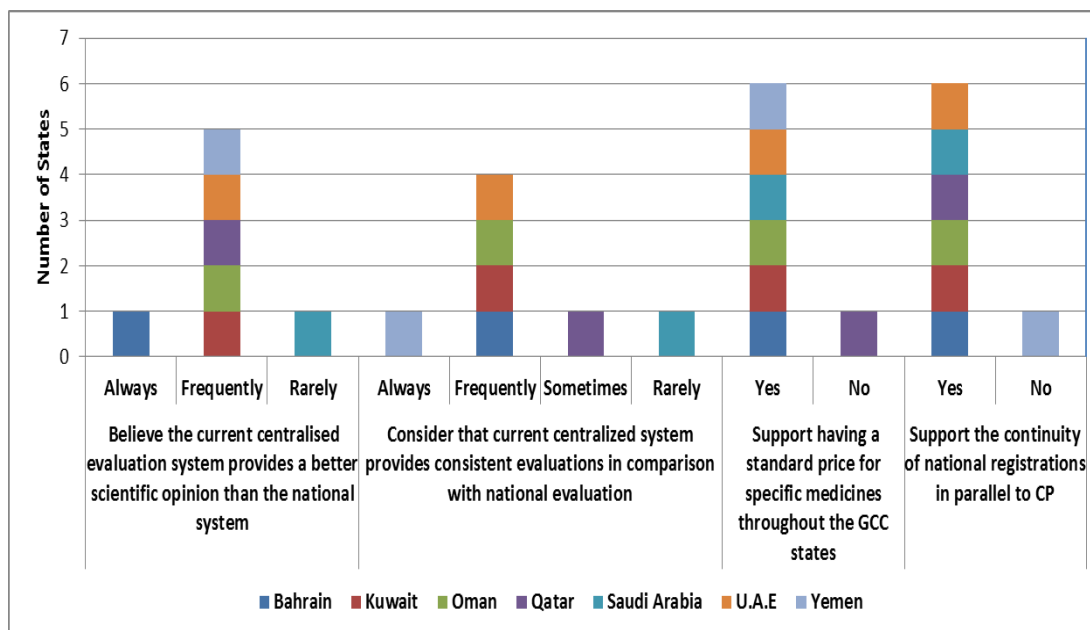
Guidelines Harmonisation

The member states indicated that the GCC-CP is a great opportunity to harmonise guidelines and requirements. The GCC States recognised the importance of expediting these guidelines as eventually the GCC registered products will have the option to be marketed in their country. If guidelines are not harmonised this would mean inconsistency in the product quality and the guidelines would also avoid duplication of effort. All members reiterated that similar registration requirements and circumstances permit the adoption of guideline harmonisation. In addition, they stated that the regular updating of guidelines is essential.

Section 5 – General Observations

All the national agencies in the GCC indicated that the integrity of the evaluation results and better scientific opinion are the key to the success of the centralised evaluation system (Figure 6.12). Hence, it can be ascertained that the CP has achieved its mandate to provide a better and efficient registration system in comparison to the national system. The GCC agencies provided details of the main advantages and disadvantages of the CP system in comparison to the national system. Their recommendations to improve the CP system included streamlining and harmonising the approval process.

Figure 6.12 – A comparison between the centralised and the national systems



Kuwait, Oman, Qatar, UAE and Yemen indicated that the centralised evaluation system mostly provided a better scientific opinion than the national system. Bahrain, on the other hand indicated that the centralised evaluation system always provides a better scientific opinion than the national system while Saudi Arabia indicated that it was rarely better (Figure 6.12).

All the GCC States with the exception of Saudi Arabia indicated that the current centralised system mainly provides consistent evaluations in comparison with national evaluation. Hence, this is clear evidence that the integrity of the evaluation results and better scientific opinions are the key to the success of the centralised evaluation system.

All GCC member countries agreed on having a standard price for specific medicines throughout the GCC States as shown. However, Qatar was against this, citing the reason that there would be differences in the proportions of sales and consumption of medicines between the states and this leads to different profit margins. All GCC member countries agreed to support the continuity of national registration in parallel to the centralised procedure while Yemen did not agree to support such a motion due to limited financial capabilities in comparison to other six member states and for this reason the Centralised Procedure is a cost-effective option for Yemen.

Major advantages of the CP system compared to the national system

The major advantages of the centralised procedure as compared with the national system are shown in table 6.4. Generally, respondents agreed that the first key advantage of the CP system is the availability of external expertise to complement the internal reviewers. This enhances the quality of the report and more information is focused on the registration to ensure that product evaluation is carried out according to the standards. In this manner, the quality of the product registration is assured across the GCC States.

Major disadvantages of the CP system compared to the national system

The main disadvantage of the system is the long approval process together with the differences in recommendations between the national and the centralised procedure. The inflexibility of the system and the limited number of meetings per year further delays the whole process thus making the CP system not as attractive as national registration for companies (Table 6.5).

Practicality and Applicability of the GACP

An evaluation of the GCC states experiences in participating and completing the questionnaire for this study was carried out. Generally all the participating states found the questionnaire easy to complete and understand and they found the questionnaire relevant and clear. Six states found the length of the questionnaire about right while only Kuwait indicated it was too long. Three states (Oman, Qatar and Yemen) indicated that they took 30 minutes to complete the questionnaire, Bahrain took only 20 minutes while Kuwait and UAE took about 120 minutes. Saudi Arabia could not ascertain the amount of time taken to complete the questionnaires.

Table 6.4 – Summary of the major advantages

- | |
|--|
| <ol style="list-style-type: none">1. Better quality scientific evaluation since more than one state is studying the file2. More scope for exchange of knowledge, ideas and experiences3. Drug regulatory coordination4. The burden and workload is divided5. Better GMP Inspections6. Guidelines consensus and harmonisation7. Exchange of Pharmacovigilance reports |
|--|

Table 6.5 – Summary of the major disadvantages

- | |
|---|
| <ol style="list-style-type: none">1. The delay in registration process in comparison to the national system2. Conflict of some of the recommendations and/or designs with national system3. The lack of ability to contact the applicant directly to verify or clarify issues4. The inability to track the full history of the application as the process of review and follow up is fragmented5. Lack of a standardised assessment template6. The limited number of meetings7. Increase in the number of applications lead to rushed evaluation by the countries8. Difficulty in activating some of the recommendations |
|---|

DISCUSSION

This study was carried out to examine the regulatory views and experiences of all seven Gulf States with respect to the Central Registration Procedure as well as identifying the barriers and opportunities to improve the CP. Several challenges face the GCC health authorities to successfully operate the GCC-DR system. The seven states identified the need for regulatory reforms during the last 12 years, and this has enabled the improvement of their national system which has enhanced patients' access to high quality medicines throughout the region. The central registration system has faced several criticisms both from the pharmaceutical industry who were apprehensive about whether the GCC-DR system would be an obstacle to the timely approval of medicines in the region as well as government officials who were concerned about losing sovereignty to the centralised authority (Hashan, 2005). However, the effective collaborative efforts between the member states substantiated the support of the GCC-DR system from each GCC authority with an improvement to regulatory approval processes and operational efficiencies at the national level.

The most significant finding from this study is that the National Drug Regulatory Authorities in the GCC believe that the Centralised Procedure (CP) has contributed to an effective system for authorising medicinal products in the GCC. This is ascertained from their views that the GCC-DR CP achieved its main objective of providing the best possible scientific opinion for the CP. They also agreed that the CP has appropriate guidelines for the regulatory review in the GCC-DR and that the quality of the CP decision-making is satisfactory to good as compared to the national systems. Apart from obtaining better quality scientific evaluations, since more than

one state is studying the application dossiers, the CP allows more scope for the exchange of knowledge, ideas and experiences among the National Drug Regulatory Authorities in the GCC. This results in better drug regulatory coordination within the GCC. As a result of this study it could be ascertained that product evaluation at a national level is more frequently carried out than at the CP as most pharmaceutical companies prefer to have their products reviewed at a national level. As an outcome of this more than three of the states indicated that the current CP evaluation system would not be sustainable due to the lack of resources and the heavy national workload.

This lack of resources presents moderate problems for the GCC States in relation to their activities within the Centralised Procedure. The GCC States recognise the importance of resources, both human and financial, for the development of strong regulatory systems. However, the lack of resources can be compensated to some extent by effective collaboration among countries and information sharing (WHO, 2008). Furthermore, the GCC authorities are able to allocate financial resources due to their strong economic status, but the availability of human resources and expertise remains a challenge for the development of a robust drug regulatory system.

There are a total of 250 internal and external professional evaluators available in the GCC. However, this number of evaluators varied from country to country with Saudi Arabia having the largest number (121) and Yemen having the lowest with only 11. With the increasing number of products to be evaluated, the number of specialised experts within the GCC may not be sufficient to process product registration, which will result in further delays for pharmaceutical companies. Increasing the number of external experts in the GCC States may be the best solution for this problem to reduce the workload on the internal reviewers but this may have a possible impact on the quality of the review.

Pharmaceutical companies have mixed feelings about whether they can gain faster marketing authorisation through the national regulatory systems or the regional centralised system. The goal of any pharmaceutical company is to complete the registration requirements and gain access to the national GCC markets in the shortest possible time. In the end, two approval routes, national and centralised exist side-by-side in the GCC region. For the centralised system to dominate, member states should seek ways to increase their collaborative efforts to bring their systems closer towards

standardisation that would facilitate the regional registration process and maintain patients' access to safe and effective medicines within a reasonable time frame. The long approval timeline in the CP approval process is a major obstacle to advocating a central approval procedure. The majority of GCC States agreed that the CP process should be shortened and they indicated that the timeline for the Centralised Procedure could be reduced by:

- All member states following the GCC guidelines.
- The verifications of the registration documents being carried out at the time of submission.
- The reviewing agency sending the applications with preliminary remarks/deficiencies before the committee meets for their discussions.
- The member states not demanding additional data to avoid delaying the whole process.
- Increasing the number of GCC-DR meetings.
- Taking in to account the prior approval by mature regulatory authorities.

One way forward is to consider the verification model for the assessment of a new registration dossier. This model can be used for applications for products that are registered in a reference country with established mature regulatory authorities (McAuslane et al., 2009). If not, a more specialised review can be considered for products which are not registered elsewhere. Singapore, for example, conducts a verification review for all types of medicines which are previously authorized by at least two reference authorities, except for biological and biotechnology products.

The member States also agreed that certain aspects of the registration procedure could be simplified to reduce the duration of the CP process, these aspects are to:

- Implement electronic communication together with online submissions.
- Send all the requests for further information or clarification questions to the companies at one time instead of in several batches.
- Have a written policy for fast track registration such as life-saving anti-cancer and anti-HIV drugs.

Despite the large number of products being evaluated at a national level, the GCC member states agreed that the GCC-DR system provides significant advantages in terms of the availability of specialised expertise, training, sharing of pharmacovigilance data and harmonisation of guidelines. The most valued service is the collaboration with other national agencies and the provision of guidelines for harmonisation of the central and national processes.

The GCC agencies agreed that the key advantage of the CP system is the exchange of knowledge and information between the member States. This enhances the quality of the report and more attention is focused on the registration to ensure that the product evaluation is carried out according to set standards and thus the quality of the product registration is assured across the GCC States. In addition, the inflexibility of the system and the limited number of meetings per year further delays the whole process thus making the CP system less attractive for companies to obtain their product approval.

SUMMARY

- This study has demonstrated that the GCC-DR Centralised Procedure achieved its main objective by providing the best possible scientific opinion. Appropriate guidelines for the regulatory review in GCC-DR was of considerable value while the quality of the CP decision-making ranged from satisfactory to good as compared to the national system.
- All member countries indicated that limited resources did present moderate problems for their agency in relation to their activities with the Centralised Procedure.
- There are more products being registered at a national level than at the CP. Despite the preference to evaluate products at a national level, these agencies agreed that the Centralised Procedure (CP) had indeed contributed to an effective system of authorising medicinal products for the GCC by providing the best possible scientific opinion for the quality of the CP decision-making as compared to the national system.

- The main disadvantage of the system is the long process to obtain the approval. The inflexibility of the system and the limited number of meetings per year further delays the whole process thus, making the CP system less attractive for companies.
- The member countries recommended that the GCC-DR streamlines and harmonises the CP approval process with national systems in order to improve the effectiveness and efficiency of the Centralised Procedure.

CHAPTER 7

An Evaluation of the Pharmaceutical Companies Experiences with the GCC Centralised Procedure

INTRODUCTION

The primary aim of drug regulation is the protection of public health. Hill (2004) suggested that for some the balance between controlling pharmaceuticals in the interests of ensuring public health and encouraging the development of pharmaceutical products has shifted in favour of the innovative industry. However, others perceive regulation as an obstacle to the availability of medicines in national or regional markets and this has placed a significant demand on regulators to expedite reviews and evaluations to approve medicines (Hill, 2004). Nevertheless, medicines regulation is the foundation of any country's national drug policy that ensures a viable pharmaceutical industry as well as a high standard drug approval process.

The establishment of the International Conference on Harmonization (ICH) between the United States, Europe and Japan in 1990 reflected a need felt by the research based industry and certain governments to streamline the approval process for the registration of new medicines (Mallia-Milanes, 2010). The term harmonisation refers to the standardisation of technical requirements for medicines regulation, of which the requirements relate to quality, safety and efficacy of medicines and this can differ from one country to the other. Since its inception, ICH has evolved, through its Global Cooperation Group (GCG) to respond to the increasingly global phase of drug development. The GCG was originally formed as a subcommittee in 1999, in response to the growing interest in ICH guidelines beyond the ICH regions and one such harmonisation was that of GCC, the Gulf cooperation council. This collaborative mechanism ensures ensure a more transparent and streamlined process for the marketing authorization of pharmaceutical products in the GCC region.

The Gulf centralised registration process is facing several challenges which lead to delays in patients' access to medicines with the need to re-register products in individual countries after central registration. In addition there is a requirement to register the manufacturer prior to submitting the product file to the Central Registration Office. Currently there is the need to establish effective methods for sharing the workload amongst the regulatory authorities in the GCC states. A paucity of studies at the GCC level, probing into the views and experiences of individual pharmaceutical companies with the GCC central registration system, has made its improvement a constant challenge. Hence, this study is envisaged to explore the importance of the system and identify challenges and critical success factors to

enhance the effectiveness and efficiency of the central registration procedure. Patients benefit from the timely access to safe and effective therapies while pharmaceutical companies are able to market the product sooner and generate revenues for further research and development.

OBJECTIVES

The objectives of this research were to:

- Evaluate the experiences and views of pharmaceutical companies with respect to the central registration review process.
- Appraise the barriers and opportunities to the implementation of the Gulf Centralised Procedure.
- Make recommendations to improve the Gulf Centralised system as well as to identify its future strategy based on the views of the pharmaceutical companies.

METHODS

With limited information and the lack of data on the GCC Central Registration Procedure, there is a need to develop suitable measurement tools in order to obtain the relevant information required in this study. In Chapter 6, an assessment tool for the evaluation of the Centralised Procedure by the Drug Authorities in the GCC was developed and the findings reported. In this Chapter, the emphasis will be on the pharmaceutical companies and evaluating their experiences in obtaining approval for their products. The development of the assessment instrument was completed over 5 phases;

Phase 1 – Identify target population and item generation

Phase 2 – Development of themes and item reduction

Phase 3 – Development of the first version of the instrument, Companies Assessment of Centralised Procedure (CACP)

Phase 4 – Pilot study

Phase 5 – Development of the final version of the CACP

This final version of the study instrument was sent to 100 pharmaceutical companies (50 generic and 50 innovative) and followed up after one month.

RESULTS

This section presents the results from the development of the CACP and the views of pharmaceutical companies. For the purpose of clarity the results will be presented in two parts: Part I - The development of the study instrument (CACP); and Part II - The views of the pharmaceutical companies about the Centralised Procedure

Part I: The Development of the Study Instrument (CACP)

Phase 1 – Target population and item generation

An informal interaction and dialogue was held with a number of pharmaceutical companies at a consultation meeting organised by the GCC-DR in the spring of 2010. This allowed the generation of items for the development of the CACP. In addition these items were cross-referenced with the Gulf States instrument in order to ensure that relevant items were also retained for the CACP.

Phase 2 – Development of themes and item reduction

There were total of five themes emerging from the item generation phase based on the objectives of the study. The first version of the questionnaire comprised five sets of questions pertaining to the following headings;

Theme 1- General Introduction consisting of eight sub-themes;

Theme 2- Centralised Registration Procedure consisting of eight sub-themes;

Theme 3- Interaction with GCC-DR consisting of six sub-themes;

Theme 4- Scientific Opinion consisting of nine sub-themes;

Theme 5- General observations consisting of eight sub-themes.

The General Information included their preference for using the system, national vs. centralised, data on the number of products submitted and registered through the centralised procedure, along with their experience and opinion of the system itself. Theme 2 deals with the guidelines, quality of scientific opinions, appeal procedure, implementation of the common technical document submission format and harmonisation of the procedure. Interaction of the company with GCC-DR with respect to the quality and timing of information received, their relationship with individual member countries, influence of the pharmaceutical companies on the

GCC–DR formed Theme 3 Scientific opinion in terms of regulatory expertise was included in Theme 4, and Theme 5 contains general observations from pricing to recommendations to improve the procedure, their views on the present system and future strategies.

Phase 3 – Development of the first version of the instrument, Companies

Assessment of Central Procedure (CACP)

The selected themes and sub-themes were put into an appropriate structured questionnaire. These were then reviewed by a social science expert using four appropriate parameters; namely; language clarity, completeness of the statement, appropriate relevance and scaling. Account was also taken with regard to the length of the items and their readability.

Phase 4 – Pilot study

The purpose of the pilot study was to assess the practicality, feasibility, applicability and relevance of the study instrument to assessing the Gulf Centralised Procedure from the companies' perspective. The structured questionnaire was sent to five targeted companies (two innovative and three generic).

Feedback from the first questionnaire was obtained from these companies. This pilot study clearly indicated that such a project into GCC Central Registration Procedure from the pharmaceutical companies' perspective was essential to bring about standardisation and harmonisation of the approval process. This would inevitably improve the registration system for both the applicants as well as the approving authorities. Based on the respondents feedback minor changes were made to the questionnaire. These changes included adding refinement to questions 2.1 and 2.2 in Part 2 and repositioning questions 3.3 and 3.4 in Part 3 of the questionnaire. Finally, six simple questions were added to the questionnaire to obtain the views of the respondents about the practicability, applicability and relevance of the CACP. This feedback was critical in order to design a more effective assessment instrument for future studies (Figure 7.1).

Figure 7.1

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Evaluation of the Experience with GCC Central Registrations

Practicality and Applicability

Your opinion about the questionnaire you have just completed is very important in its further refinement. Please take a few moments to give us your views by answering the following six questions:

	<u>Yes</u>	<u>No</u>
1. Did you find the questionnaire easy to complete?	<input type="checkbox"/>	<input type="checkbox"/>
2. Did you find the questionnaire easy to understand?	<input type="checkbox"/>	<input type="checkbox"/>
3. Did you find the questionnaire relevant?	<input type="checkbox"/>	<input type="checkbox"/>
4. Did you find the questionnaire clear?	<input type="checkbox"/>	<input type="checkbox"/>
5. How did you find the length of the questionnaire? about right <input type="checkbox"/> too short <input type="checkbox"/> too long <input type="checkbox"/>		
6. How long did it take you to complete the questionnaire? minutes		

Thank you for your help.

Phase 5 – Development of the final version of the CACP

Following the pilot study and implementation of the changes suggested by the participating companies the development of CACP was completed. Thus, the final version of the instrument consists of 39 items grouped into five major categories. In addition it includes an introductory page collecting the respondents' personal details (Figure 7.2). The final version of the questionnaire was sent to 100 companies who had registered their products through the either centralised registration procedure and/or national registration systems. The questionnaire was sent with a clear guideline regarding the aims and objectives of the study with a statement assuring them of the confidentiality of the study.

Part II: The views of the pharmaceutical companies about the Centralised Procedure



An analysis of the target audience was carried out by listing all pharmaceutical companies who had interactions with the national registration system and/or the CP in the GCC region. This list of the companies registered with the CP was obtained from the GCC-DR office in Saudi Arabia. The profile of each company was analysed to ascertain their suitability and their willingness to provide information for the study. Fifty generic and 50 innovative companies were selected for the study from the list of registered companies, half of them with experience registering their products through the CP while the other half had the experience of registering their products through the national system.

Characteristics of the study participants:

The CACP was distributed to 100 pharmaceutical companies out of which 30 responses were received (30%) (Appendix 1). The remaining, who did not respond, could be categorised into four groups:

- 1- Unwilling to participate
- 2- Lack of experience
- 3- Lack of response, and
- 4- Sensitivity of the information required

Figure 7.2

<div data-bbox="512 386 665 513">  </div> <div data-bbox="844 386 994 513">  </div> <div data-bbox="510 601 999 662"> <p>An Evaluation of the Pharmaceutical Companies experiences with the GCC Central Registration</p> </div> <div data-bbox="600 788 907 818"> <p>SURVEY QUESTIONNAIRE</p> </div> <div data-bbox="672 847 835 906"> <p>Contact: Mohammed Al Rubaie alrubayee@hotmail.com</p> </div> <div data-bbox="694 1059 810 1099"> <p>FINAL VERSION April 2011</p> </div>	<div data-bbox="1216 280 1832 328"> <p>An Evaluation of the Pharmaceutical Companies experiences with the GCC Central Registration</p> </div> <hr/> <div data-bbox="1456 437 1590 464"> <p>CONTENTS</p> </div> <div data-bbox="1216 569 1800 983"> <p>Introduction and Background 3</p> <p>Aims and Objectives..... 4</p> <p>Methodology..... 4</p> <p>Pilot Study4</p> <p>Confidentiality..... 5</p> <p>Outcome..... 5</p> <p>Company and Personal details..... 6</p> <p>Part I – General 7</p> <p>Part II – Centralized Registration Procedure 8</p> <p>Part III – Interaction with Gulf Central Committee for Drug Registration..... 10</p> <p>Part IV – Scientific opinion 11</p> <p>Part V – General observations 11</p> </div> <hr/> <div data-bbox="1487 1181 1554 1204"> <p>Page 2</p> </div>
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An Evaluation of the Pharmaceutical Companies experiences with the GCC Central Registration

Introduction and Background

The approval of drugs in different countries across the world has been and is still performed by regulatory agencies according to the national regulations. However attempts to harmonize regulations between nations have been made for several years within the Gulf States. A Centralized Community Procedure for the registration of Pharmaceutical companies and medicinal products has been created under the Executive Board of the Health Ministers Council for GCC States. The Gulf Central Committee for Drug Registration (GCC-DR) was formed in May 1999 including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen (Yemen joined in 2003). There are two representatives from each member state. The main role of the committee is to register pharmaceutical companies and their products through joint coordination on evaluation of scientific safety, efficacy and quality of medicinal products.

The key aim of the Central Registration is to unify the systems and procedures in the process of registration of pharmaceutical companies as well as medicines and ensure that pharmaceutical companies are using the foundations of the pharmaceutical quality, as well as to ensure drug quality and safety after marketing by post-marketing surveillance.

From October 1999 to October 2009, the GCC Central Registration received 1688 medicinal products applications (innovator and generics). It approved 1128, but still there are so many challenges which lead to delays in medicines access to GCC state such as the need to reregister products in individual countries after central registration and the long time taken to register the manufacturer prior to submitting the product file to Central Registration Office. This is in addition to the need to establish an effective method for sharing workload amongst the regulatory authorities in GCC states.

In this study, we aim to gather and evaluate the opinions and views of all the 7 GCC states from the regulatory authorities as well as the pharmaceutical companies on their experiences with GCC Central Registration Procedure. The study can be of value in formulating a baseline for any further change/improvement in the GCC Central registration system.

An Evaluation of the Pharmaceutical Companies experiences with the GCC Central Registration

Aims and Objectives

The aims and objectives of this study are to:

- 1) Study the regulatory views and experiences from each individual GCC states towards the GCC Central Registration Procedures.
- 2) Survey the views and experiences of the pharmaceutical companies towards the GCC Central Registration Procedure
- 3) Make a comparison between the views and experiences expressed by each individual regulatory agencies from the GCC states and the pharmaceutical companies.
- 4) Identify the barriers to the implementation of the GCC Central Registration Procedures and to recommend measures to improve the system.

Methodology

In order to obtain the views and experiences of the regulatory agencies from GCC states and pharmaceutical companies, two different questionnaires have been prepared. The first questionnaire will be distributed to the regulatory authorities in 7 GCC states and the second one to 65 pharmaceutical companies who have registered their pharmaceutical products through the GCC Centralized Registration Procedure and to 20 companies who have not used the GCC Centralized procedure for registration of their products.

Pilot Study

Prior to sending these questionnaires to all the 7 GCC States and pharmaceutical companies, a pilot study has been made with 2 GCC states and 5 pharmaceutical companies. The pilot study involved the practicality and applicability of answering these questionnaires in terms of its relevance, clarity, length and even the time taken to complete them. All these factors have been taken into consideration while preparing these questionnaires, to ensure that the data being collected is valid, complete and reliable.

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Confidentiality

Cardiff University in association with CMR International Institute for Regulatory Science has over 25 years experience in the handling of detailed, highly confidential information, and the continuing and growing support for its studies demonstrates the confidence which companies and regulators place in its integrity.

A confidential procedure will be used for the collection of data with identifying information being coded and aggregated upon receipt in order to prevent the identification of the individual participants.

Outcome

A report will be prepared once the study has been completed and this report will be made available to all participants with a view to gaining a better understanding of the GCC Centralised procedure. It is also hoped the findings of this study will facilitate greater harmonization of the GCC countries regulatory review process leading to increased use of GCC centralized procedure by the pharmaceutical companies.

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Company and Personal Details

Company Name		
Address		
Name of person completing this questionnaire	Name: Email:	
Position		
Phone Number		
Email address		
Years of experience in pharmaceutical industry		
Qualifications	Yes	No
Undergraduate	<input type="checkbox"/>	<input type="checkbox"/>
Postgraduate	<input type="checkbox"/>	<input type="checkbox"/>
Member of relevant professional body	<input type="checkbox"/>	<input type="checkbox"/>
Age years	
Gender	Male <input type="checkbox"/> Female <input type="checkbox"/>	

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Part I – General

1.1	Which system do you prefer to use for the registration of your pharmaceutical products? <input type="checkbox"/> National system <input type="checkbox"/> Centralized system																		
1.2	Have you ever submitted any of your pharmaceutical products through GCC-Centralised Procedure ? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, please give reason(s) by ticking all the relevant boxes <input type="checkbox"/> Convenience <input type="checkbox"/> Timeline of registration <input type="checkbox"/> Cost / resources required <input type="checkbox"/> Requirement to GCC tender <input type="checkbox"/> Ease of subsequent CPP registration <input type="checkbox"/> Other factors (please describe) If NO, please give reason(s) by ticking all the relevant boxes: <input type="checkbox"/> Company strategy regarding registration in selected GCC states <input type="checkbox"/> Timeline of registration <input type="checkbox"/> Cost / resources required <input type="checkbox"/> Experience with national system <input type="checkbox"/> Subsequent pricing of products <input type="checkbox"/> Concern over possible rejection by GCC-DR <input type="checkbox"/> Other factors (please describe)																		
1.3	How many products did you submit and were registered through the Centralised Procedure in the last 5 years? <table border="1"> <tr> <td>Years:</td> <td>2006</td> <td>2007</td> <td>2008</td> <td>2009</td> <td>2010</td> </tr> <tr> <td>No of products submitted</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No. of products registered</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>	Years:	2006	2007	2008	2009	2010	No of products submitted						No. of products registered					
Years:	2006	2007	2008	2009	2010														
No of products submitted																			
No. of products registered																			

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

1.4	Do you consider the quality of decision-making of the Centralised Procedure is? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
1.5	Do you think that the Centralised Procedure takes more time for registering your products than the individual local registration in GCC states? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, at what stage do you think the Centralised Procedure take more time?
1.6	Do you think the timelines for registration in the Centralised Procedure could be shortened? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, how?
1.7	Do you think certain aspects of the registration procedure could be simplified? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, how?
1.8	Do you think that the registration fee for Centralised Procedure is? <input type="checkbox"/> Reasonable <input type="checkbox"/> Too low <input type="checkbox"/> Too high

Part II - Centralized Registration Procedure

2.1	Do you consider the Centralised Procedure guidelines are? <input type="checkbox"/> Easy to understand <input type="checkbox"/> Not always clear <input type="checkbox"/> Generally unclear If the answer is 'Not always clear', please specify:
2.2	How do you rate the quality of the GCC-DR scientific opinions? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

2.3	Do you consider the current appeal procedure to be sufficient in the case of negative opinion issued by GCC-DR? <input type="checkbox"/> Yes <input type="checkbox"/> No If NO, please comment.....
2.4	Do you consider implementation of the common technical document format will be a barrier to your company submitting to the Centralised Procedure ? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, please comment.....
2.5	How do you rate the efficiency and effectiveness of the GCC centralized pharmacovigilance procedures? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor Why (please comment).....
2.6	In general, do you consider the transparency of Centralised Procedure to be: <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor Why (please comment).....
2.7	Do you think the Centralised Procedure should be made compulsory for certain range of products? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, for which class of products.....
2.8	Do you think the Centralised Procedure has contributed to be harmonization of the legislation throughout GCC? <input type="checkbox"/> Yes <input type="checkbox"/> No

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Part III – Interaction with Gulf Central Committee for Drug Registration (GCC-DR)

3.1	From your experience, how do you rate the interaction of your company with GCC-DR in terms of ?																																																
3.1.1	Quality of information received: <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor <input type="checkbox"/> No experience																																																
3.1.2	Timing of the registration procedure: <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor <input type="checkbox"/> No experience																																																
3.2	How do you rate your company's relationship with the Registration Department of the GCC-DR? <input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor <input type="checkbox"/> No experience																																																
3.3	Do you consider that the relationship between the GCC-DR and Pharmaceutical Companies could be improved? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, how.....																																																
3.4	How do you rate your relationship with GCC national Regulatory Authorities? (Please tick mark in the relevant column)																																																
	<table border="1"> <thead> <tr> <th>Gulf State</th> <th>Excellent</th> <th>Good</th> <th>Satisfactory</th> <th>Poor</th> <th>No Experience</th> </tr> </thead> <tbody> <tr><td>Bahrain</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>Kuwait</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>Oman</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>Qatar</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>Saudi Arabia</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>UAE</td><td></td><td></td><td></td><td></td><td></td></tr> <tr><td>Yemen</td><td></td><td></td><td></td><td></td><td></td></tr> </tbody> </table>	Gulf State	Excellent	Good	Satisfactory	Poor	No Experience	Bahrain						Kuwait						Oman						Qatar						Saudi Arabia						UAE						Yemen					
Gulf State	Excellent	Good	Satisfactory	Poor	No Experience																																												
Bahrain																																																	
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Oman																																																	
Qatar																																																	
Saudi Arabia																																																	
UAE																																																	
Yemen																																																	
3.5	Do you believe that the pharmaceutical industry can influence the GCC-DR procedure? <input type="checkbox"/> Yes <input type="checkbox"/> No Please comment:																																																

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

Part IV - Scientific opinion

4.1	Do you think that GCC-DR has access to the best possible experts in terms of:			
	Regulatory expertise	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	Scientific opinions expertise	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
4.2	Please rate your opinion with regard to regulatory expertise within the GCC DR for assessment of: (Please tick mark against your rating):			
	Description	Excellent	Good	Satisfactory
	Quality data			
	Safety data			
	Efficacy data			
	Pharmacovigilance data			
	Bioequivalence studies			
	Biological/biosimilar			
	Vaccines data			
	GMP inspections			
	Others (if any, please specify).....			
			

Part V - General observations

5.1	Do you believe the current centralized evaluation system provides a better scientific opinion/outcome than the national system?
	<input type="checkbox"/> Always <input type="checkbox"/> Frequently <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely <input type="checkbox"/> No difference
5.2	Do you consider that current centralized system provides consistent evaluations in comparison with national evaluation?
	<input type="checkbox"/> Always <input type="checkbox"/> Frequently <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely
5.3	Do you support having a standard price for specific medicines throughout the GCC states?

**An Evaluation of the Pharmaceutical Companies experiences with the
GCC Central Registration**

	<input type="checkbox"/> Yes <input type="checkbox"/> No
	If NO, why?
5.4	Do you support the continuity of national registration in parallel to Centralised Procedure ?
	<input type="checkbox"/> Yes <input type="checkbox"/> No
In order to provide a summary of your views, can you please complete the following questions?	
5.5	In your opinion, what are the 3 major advantages of Centralised Procedure compared to the national system? (Please state in order of importance).
	1.....
	2.....
	3.....
5.6	In your opinion, what are the 3 major disadvantages of Centralised Procedure compared to the national system? (Please state in order of importance).
	1.....
	2.....
	3.....
5.7	What are your three main recommendations to improve the Centralised Procedure ?
	1.....
	2.....
	3.....
5.8	What would be the company's future strategy in regard to Centralised Procedure?

5.9	Additional comments, if any:

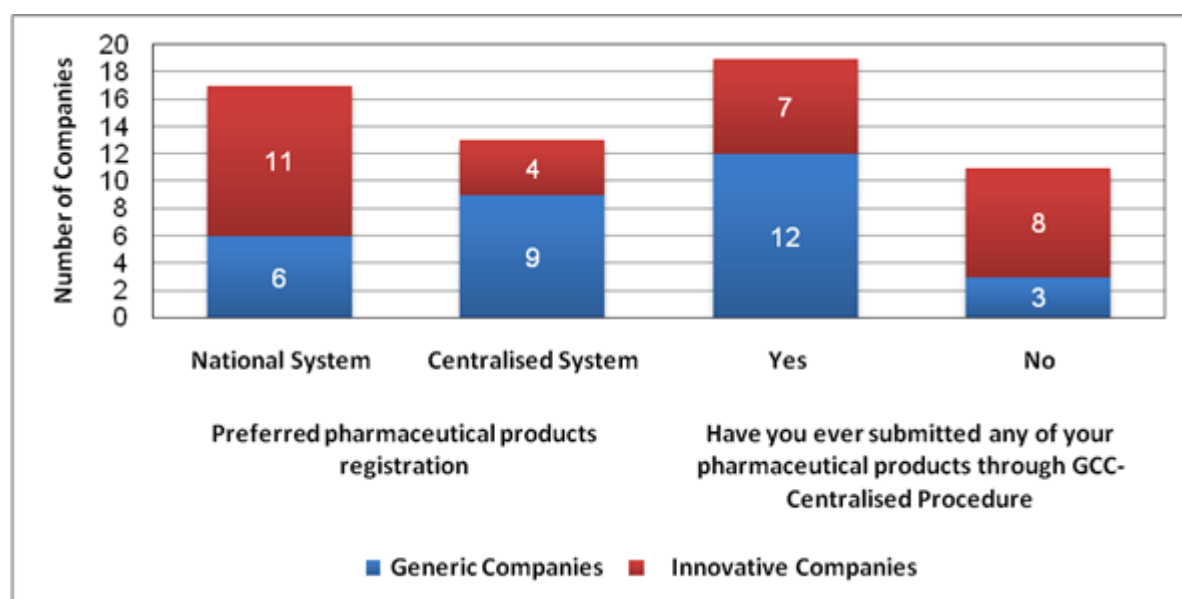
The CACP scores:

In order to answer the main evaluation questions covering the experience of these companies with GCC-DR Central Registration Procedure the results are presented under five sections.

Section 1 – Companies general views about the Centralised procedure

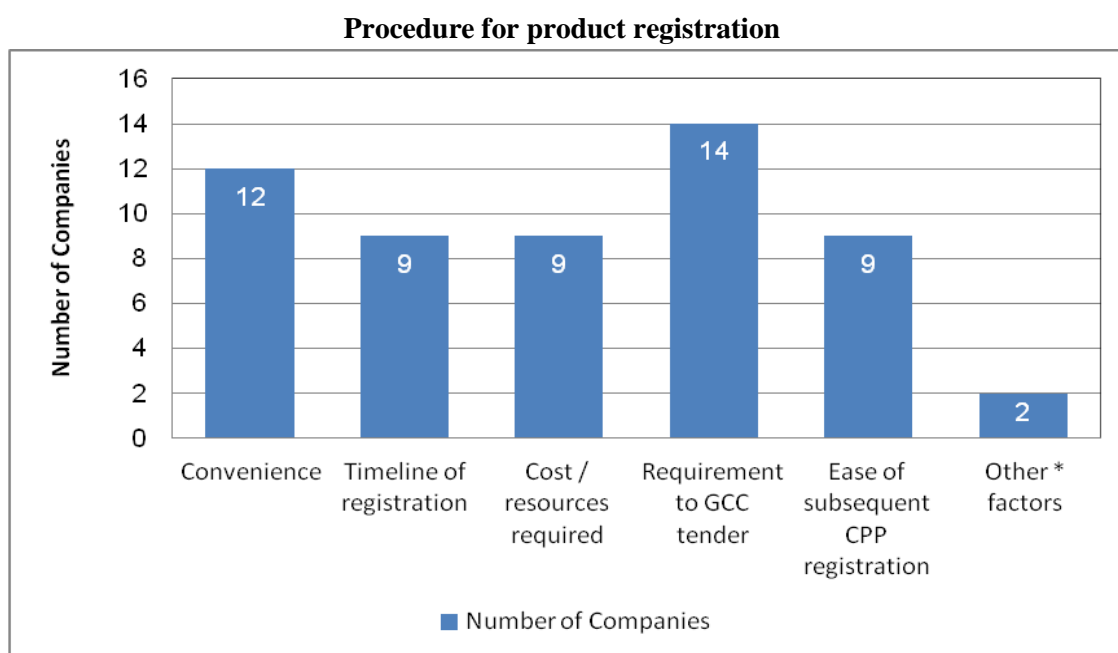
In this section, the companies' experiences in registering their products through the Centralised Procedure were examined. Their preference for using this system, national versus centralised was determined. Data on the number of products submitted and registered through the centralised procedure, along with their experience and opinion of the system itself were also recorded. Generally, more than half of the companies who responded preferred the national registration procedure to the Centralised Procedure (Figure 7.3) The majority of the pharmaceutical companies preferred to register their products through the national system than the centralised system. Eleven innovative companies preferred the national system rather than the CP while six generic companies choose the national system instead of the CP. Nineteen companies had submitted their products for registration under the centralised system, while more generic companies (12) had submitted their products to the CP than the innovative companies (Figure 7.3).

Figure 7.3 – Number of companies and their preferred pharmaceutical registration system



Only the 19 companies who had the experience of registering their products through the CP were able to provide critical information on the strengths and weaknesses of the CP registration system. The main reasons for choosing the centralised registration system over the national system are illustrated in Figure 7.4. This shows that 14 pharmaceutical companies were able to meet the requirements to GCC tender specification, convenience (12 companies) and timeliness of registration, cost/resources required and ease of subsequent CP registration. One of the respondents indicated that the central registration team is more accessible, easier to communicate with, flexible and understanding about the companies' issues. It is also faster in approval than the national authority. Another respondent indicated their choice of product registration system would be dependent on their company's strategy and the nature of the product.

Figure 7.4 – Reasons for companies preference in using the Centralised



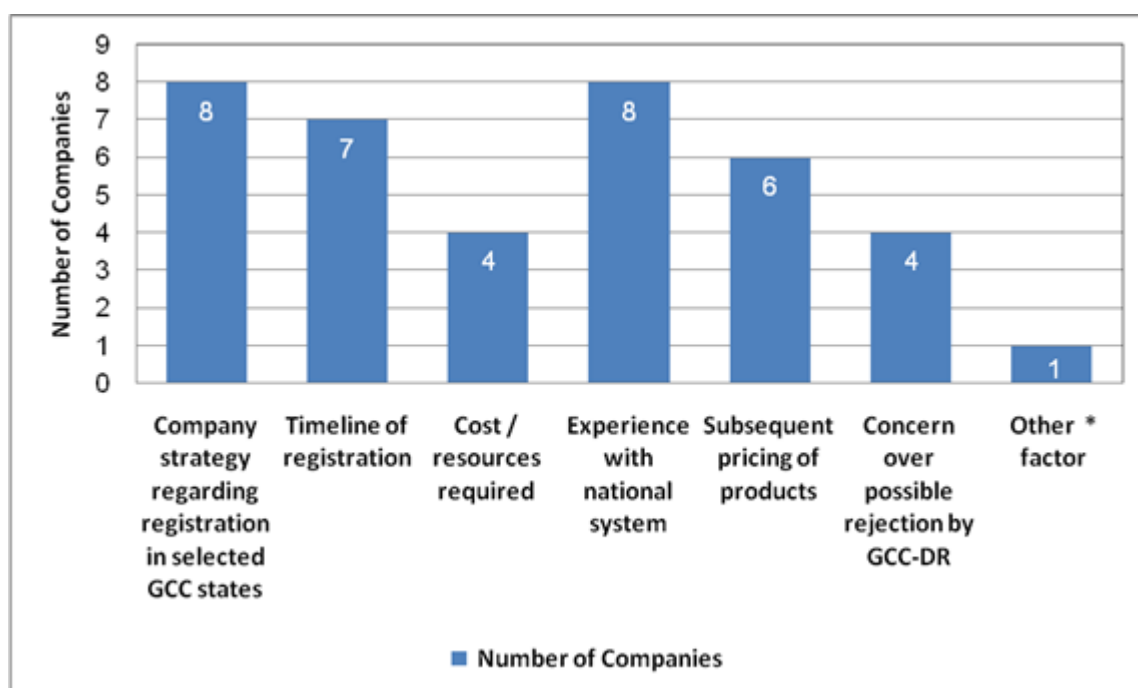
***Other Factors**

1. *Central registration team more accessible, easier to communicate with flexible and understanding about the companies' issues. Faster in approval than the national and is a respectable authority.*
2. *Depending on the company strategy and the nature of the product*

Figure 7.5 shows the reasons why pharmaceutical companies did not prefer the centralised system. Eight of the companies stated that their product strategy was aligned to the registration in selected GCC states, hence the preference for national registration. The timeline for registration and the experience with the national systems registrations resulted in a total of seven responses. The rest cited the cost and resource

requirement and subsequent pricing of products as well as a concern over possible rejection by GCC-DR. One of the companies highlighted that for highly specialised, orphan, and important products, they preferred to go via the national procedures, since they found it more transparent and easier to communicate with the regulatory authorities. The CP is a strategic option, but due to a limited number of GCC-DR annual meetings, the companies cannot take the risk for important products that are required to be available in the countries faster, since CP may take a longer time compared with national registration.

Figure 7.5 – Reasons why companies did not prefer the Centralised Procedure



**Other Factor*

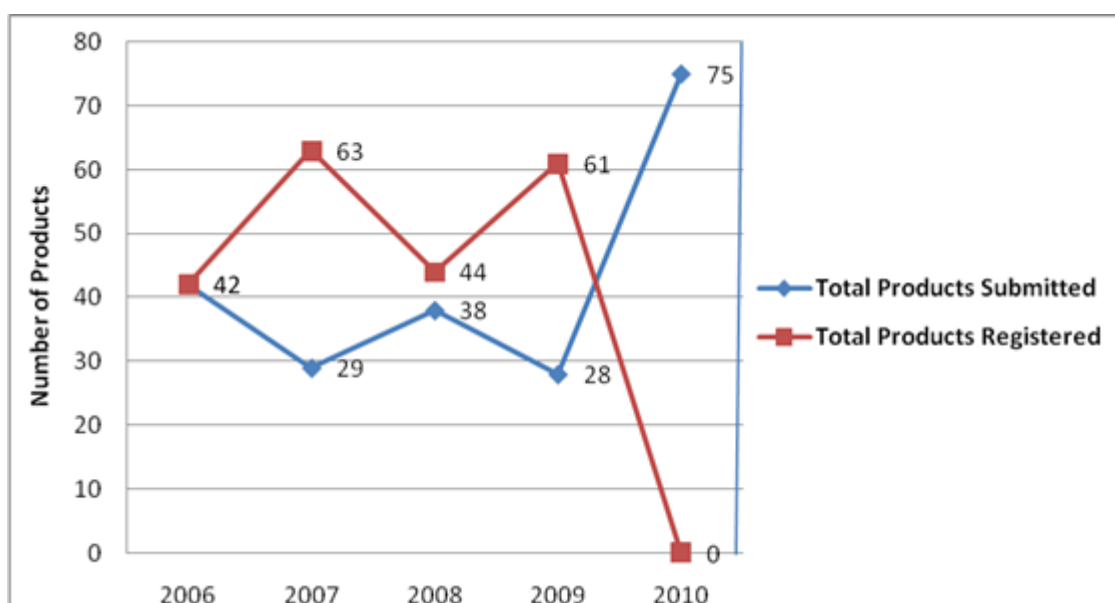
Due to the limited number of GCC-DR annual committee meetings, the company cannot take the risk for important products registration that must be made available in the countries quickly, since it may take a long time to receive GCC-DR comments.

The number of products submitted for approval to the Centralised Procedure by 13 companies varied between 29 to 75 submissions annually (Figure 7.6). The year 2010 saw a substantial increase in the number of applications by almost 3 times as compared to the previous year (2009). This could be an indication that the companies realised the benefits of obtaining an approval from the GCC-DR to market their products to the seven member states seamlessly. The total number of products submitted from 2006 to 2010 was 212 while the total products registered were 210 for

the four years (2006 to 2009). An upward trend can be seen in product submissions and product registrations under the CP system. This clearly indicates that though there were challenges in processing the products for approval at GCC-DR level, it certainly is gaining recognition as a viable option. Twenty companies believed the quality of decision-making of the Centralised Procedure to be good or excellent while seven companies stated that it was only satisfactory.

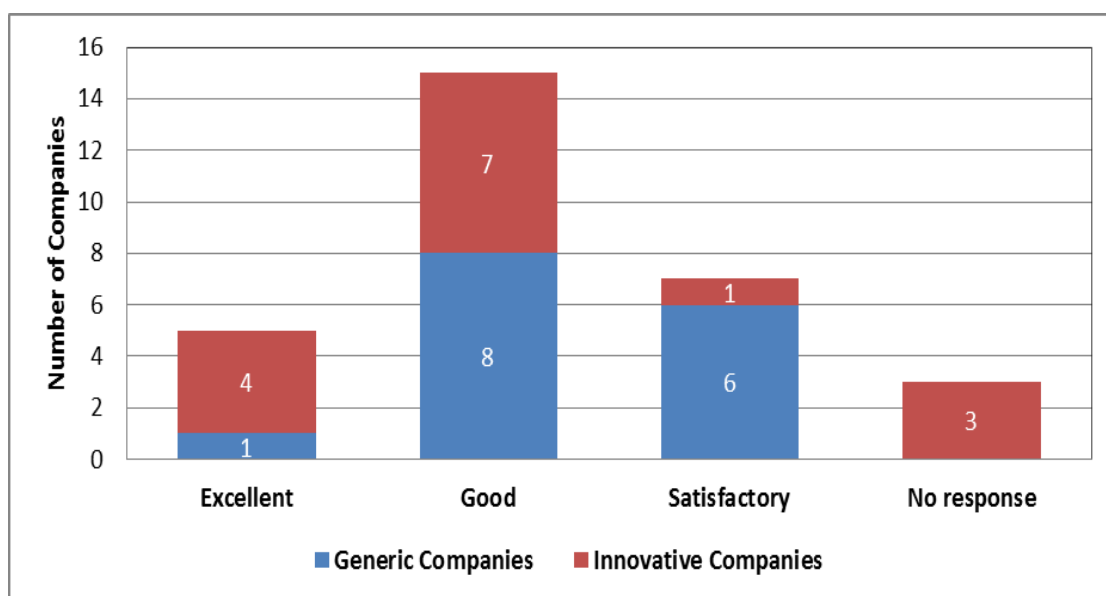
This is an indication that although there are issues with the centralised registration system, the quality of its decision-making is still satisfactory for most companies (Figure 7.7). Although some companies had no experience of registering their products through the CP they were still able to provide their opinion about this system.

Figure 7.6 – Number of products submitted and approved through the Centralised Procedure



Twenty companies stated that it took them more time to register their products through the centralised system. The pharmaceutical companies also stated that the limited number of meetings by the Central Committee was one of the main causes of the delay in product registration; thus their preference for national registration. The delay in product registration is also attributed to the fact that the submission of the documents for review and approval by the Committee has to be done earlier before the summer hiatus if the companies wish to complete the procedure in good time.

Figure 7.7 –The quality of decision-making of the Centralised Procedure



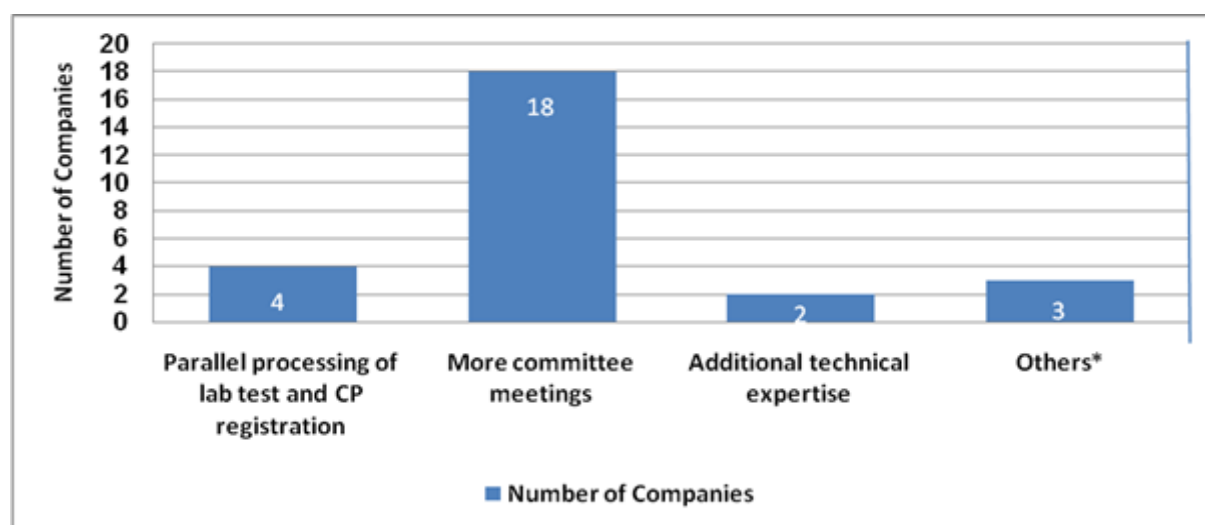
However, unlike the national registration procedure in which both the product and the pricing registration could be done concurrently, the company has then to wait for the product approval centrally before proceeding with the pricing approval locally.

Further delays in product approval and registration in the CP were caused by long technical documents evaluation, distribution of the files for the reference countries for evaluation and analysis feedback and a long queue for submission and review by the committee. The issue of sequentially processing for national registration after the Centralised Procedure added a further delay to the approval process and it could take between 1.5 to 2.5 years for approval to be attained for each product. Furthermore, with so many issues to be discussed in the CP Committee meetings coupled with the limited number of meetings per year meant approval and registration issues would take a longer time to be resolved, hence lengthening the approval process. More delays are caused when evaluators waited until after the CP meetings to pass their comments and requests for additional information instead of asking for this immediately on reviewing at the first stage.

Twenty-seven companies indicated that the timelines for registration in the Centralised Procedure could be shortened and twenty of these companies also stated that by having more GCC-DR meetings this could be achieved. Others believed that having additional technical expertise and conducting parallel processing of the laboratory tests and the CP registration could also shorten the process however,

Parallel processing was induced in 2011. Figure 7.8 summarises how certain aspects of the registration procedure could be simplified. Twenty of the companies also indicated that certain aspects of the registration procedure could be simplified. The majority of these respondents believed that electronic submissions and automation of some of the processes could assist in simplifying the Centralised Procedure as a whole and hence shorten the whole process. Others indicated that the technical evaluation could be simplified by relying on documents submitted to GCC since these were the same documents already submitted and approved in the US/UK and other reference countries. Finally, 16 of the companies indicated that the current registration fee for the Centralised Procedure is reasonable while 11 of the companies stated that it is too high. Hence, the cost factor from the registration perspective is not the key reason why companies preferred the national registration system to the Centralised Procedure to obtain approval for their products.

Figure 7.8– Companies’ suggestions on how certain aspects of the registration procedure could be simplified



*Others

1. The pricing procedure in the individual GCC states should be in parallel with the CP Registration.
2. The communication with the companies could be via email or other means of electronic transmission.
3. Stop the site inspection if the site was in a reference country and has the appropriate GMP and manufacturing license (same as the national registration).
4. Have one registration certificate for all GCC states from GCC-DR (once registered, no need to submit again per each country to gain approval).

Section 2 - Centralised Registration Procedure

The companies experiences in submitting and registering products under the CP is reviewed in this section. Generally the companies were satisfied with the quality of the guidelines and scientific advice as well as their opinions on the implementation of the Common Technical documents, pharmacovigilance procedures, and transparency of the Centralised Procedure. In addition, the majority of the companies also agreed that the CP led to the harmonisation of national procedures in the GCC legislation. Half of the companies indicated that the Centralised Procedure guidelines were easy to understand (eight generic and seven innovative companies), 10 companies (six innovative and four generic companies) stated that the guidelines were not always clear and another three companies indicated that they were generally unclear (Figure 7.9). Those who stated that the guidelines were not always clear further provided their explanation for their choice. They pointed out that there were no guidelines for all registration requirements (e.g. available guidelines are for Stability Studies and Bioequivalence study only). Variations to the guidelines were also not available. The biotechnology products registration guidelines were very short and ambiguous and many of the requirements, that the committee asked for, were not included. In addition, they commented that the committee sometimes went outside the guidelines and asked for additional requirements found in other international guidelines (oscillating between EU and FDA, especially with stability and Bioequivalence). They also stated that the patient information leaflets (PIL) requirements were not clear and many times the committee asked for amendments for the PIL that was internationally recognized. Hence, they were not provided with clear criteria in this matter. Finally, they added that the registration certificates for manufacturing sites were not harmonized with regards to the nomenclature of the production lines which created confusion when required to register a product from such a site later.

Quality of GCC-DR Scientific Opinions

The majority of the companies indicated that the quality of the GCC-DR scientific opinions ranged between good to excellent while five companies stated that it was only satisfactory (Figure 7.10). It can be concluded that the pharmaceutical companies in general were satisfied with the quality of the GCC-DR scientific opinions despite the hassle and the issues faced in getting their products registered through the Centralised Procedure.

Figure 7.9 – Companies’ view on the Centralised Procedure guidelines

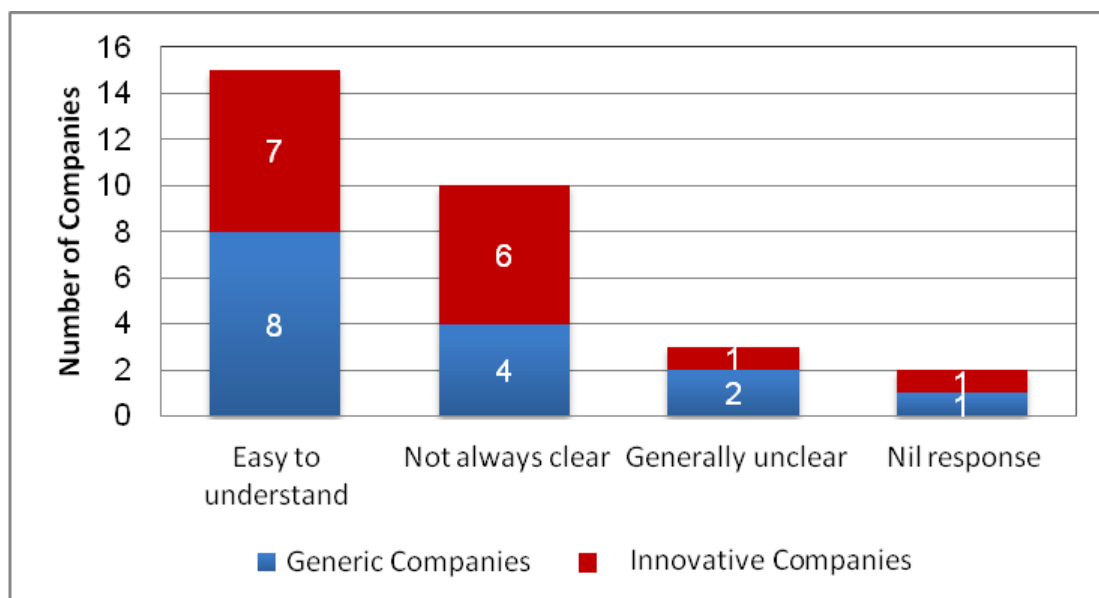
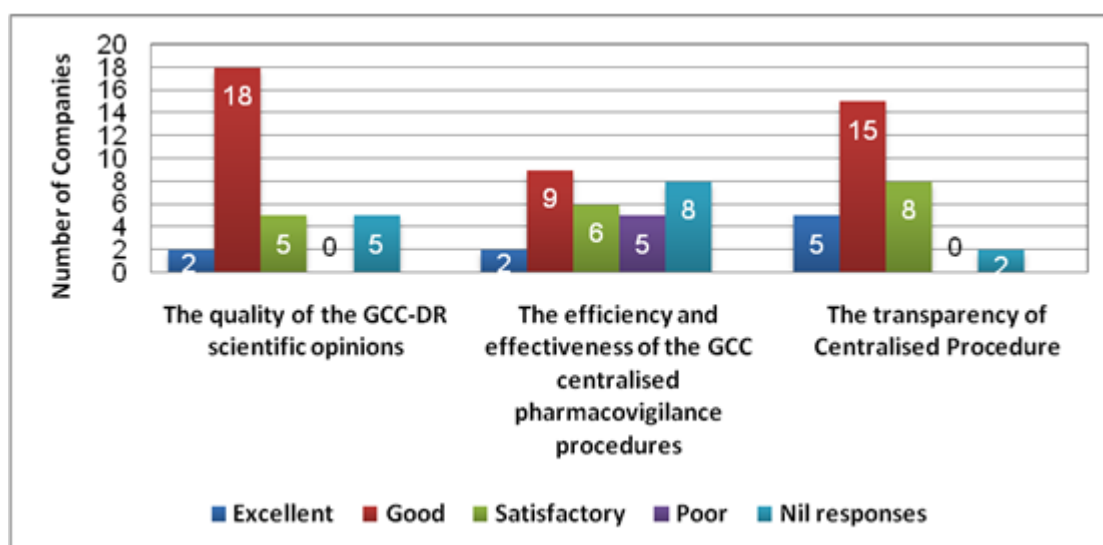


Figure 7.10 – Companies’ views on the quality of the GCC-DR scientific advice, efficiency and effectiveness of the centralised pharmacovigilance procedures and the transparency of the Centralised Procedure



Similarly, the majority of the companies also stated that the current appeal procedure was sufficient in the case of a negative opinion issued by the GCC-DR, although, 10 companies felt otherwise. They further added that there should be meetings between the GCC-DR and the companies so that these companies could explain the reasons for the appeal which may not have been understood by the committee previously. Therefore, these views should be considered by the member states. Also, the GCC needs to take in to account the registration certificates issued from the mature

regulatory authorities such as FDA and EMA. Other respondents also stated that the GCC-DR had no experience in dealing with appeal cases and hence there was neither any clear timelines nor clear answers provided to the companies as justification for the rejection. This made it very difficult for the companies to convince all the members of the committee of their positive opinion or challenge the rejection decision. There were also no response received by the companies in case of a negative opinion by the GCC and the submission of their appeal document.

Seven companies indicated that the implementation of the common technical document format would be a barrier to their company's submission of product registrations through the Centralised Procedure. Nevertheless, they also stated that to work in the same CTD format for all the GCC countries individually in addition to GCC-CP, would encourage many manufacturing companies in the region to obtain the approvals from GCC-CP. However, the resources, specialised personnel and hands-on training are not enough. At present, not all the member states are at the same level for receiving and processing CTD applications. Most medium size and Arab companies did not have any idea about such a format and they would need a considerable time before they could fulfil these requirements. This would be very difficult for these companies and would be costly to submit the same documentation but in a "different" ICH format. Moreover, such a requirement has been applied without prior notice or time allowance. As a result, it may take a much longer time to get the final approval. Some form of flexibility should be accepted as there are old and rare products which do not have a CTD dossier. This new requirement would also mean that there would be additions in the required documents. Some of these documents and tests may require more time to be prepared, thus, this would delay the process of registration.

The efficiency and effectiveness of the GCC centralised pharmacovigilance procedures

The majority of the companies who responded were satisfied with the efficiency and effectiveness of the GCC centralised pharmacovigilance procedures as the GCC-DR had continued to be vigilant and monitor Adverse Drug Reactions (ADR) of medicines speedily. In addition, currently the companies believe that the current GCC guidelines for pharmacovigilance are not clear, even though the Saudi FDA guidelines are well recognised. However five companies (Figure 7.10) indicated that although the efficiency and effectiveness of the GCC centralised pharmacovigilance procedures

were poor, they were not aware of any pharmacovigilance systems in the region being implemented. However, the five companies had strict internal systems related to safety, PV and Risk Management Plans (RMP).

The transparency of Centralised Procedure

Five companies indicated that the transparency of the Centralised Procedure was excellent because the GCC-DR was open in their communications; it was easy to meet the central organization team member who was willing to simplify the issues and had great understanding with a high level of transparency. On the other hand half of the companies stated that although the CP transparency was good as there were clear guidelines, refinement was needed in the follow-up of the application process. Overall, 70% of the companies disagreed that the Centralised Procedure should be made compulsory for certain range of products. However, six companies agreed that the Centralised Procedure should be made compulsory for the following range of products:

- Prescription only Medicine
- Narcotics and controlled drugs
- Medicinal, Herbal and Health products
- Biotechnology products especially coming from non stringent countries.
- Vaccines
- Life saving medicines and products that are crucially required in these markets

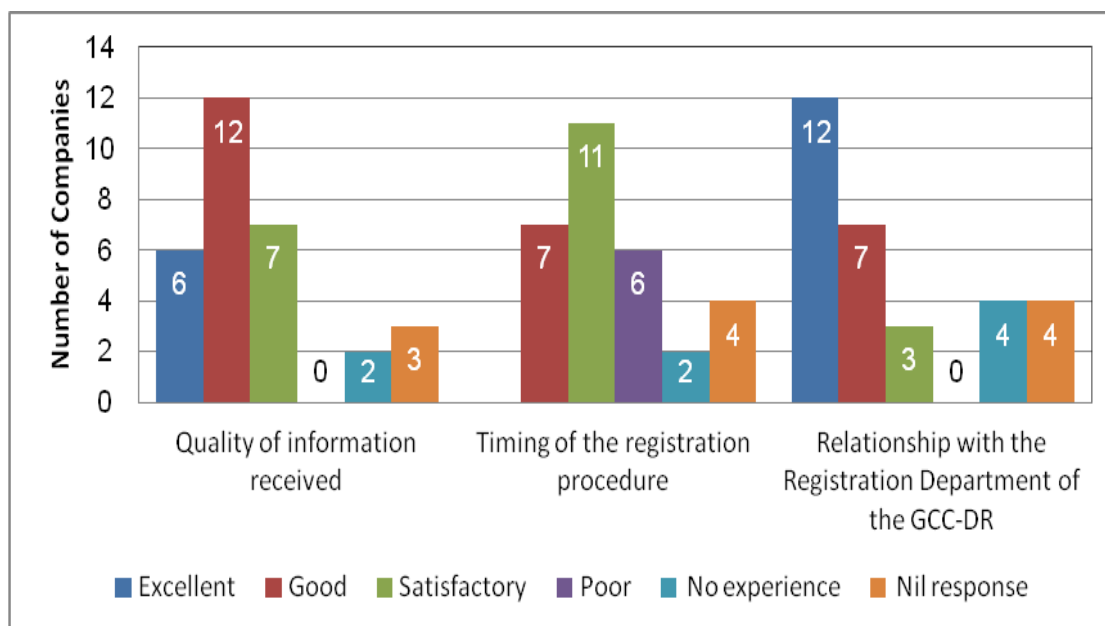
Finally, 18 companies agreed that the Centralised Procedure has contributed to the harmonisation of the legislation throughout the GCC while eight of the respondents did not agree.

Section 3 - Interaction with Gulf Central Committee for Drug Registration (GCC-DR)

Generally, the companies were satisfied with the level of interaction with the GCC-DR in terms of the quality of the information received and the relationship between the authorities. The majority of them also agreed that the pharmaceutical industry can influence the GCC-DR Centralised Procedure through sharing of knowledge and experiences and promoting closer collaboration.

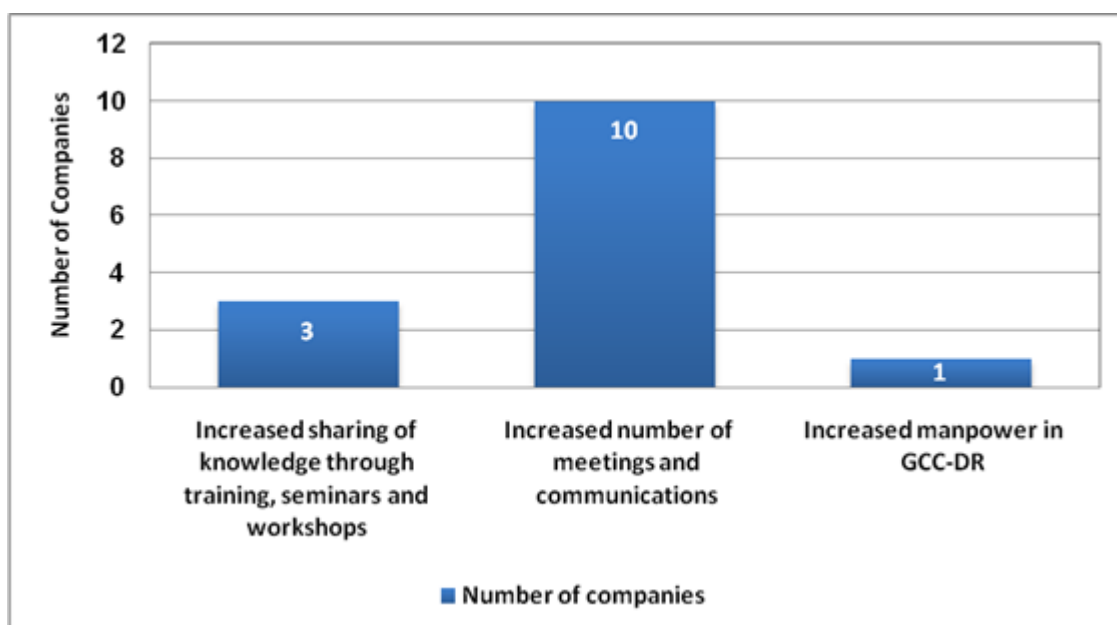
Based on the same data, more than 15 companies were satisfied with the timing of the registration procedure at GCC-DR while six companies indicated that the timing of the registration was poor. Nineteen companies indicated that their relationship with the Registration Department of the GCC-DR was good or excellent and 22 companies indicated that they were satisfied with the relationship (Figure 7.11).

Figure 7.11 – Companies’ view of the level of interaction on the quality of information received, timing of the registration procedure and their relationship with the Registration Department of the GCC-DR



Although many companies refrained from commenting on their relationship with the GCC-DR because of its sensitivity, however they indicated that the relationship could be improved. Some of the ways in which this could be improved are summarised in Figure 7.12. Three companies suggested that the increased sharing of knowledge through training, seminars and workshops would promote more interactions between the companies and the GCC-DR especially in discussing changes to regulations and procedures. This would significantly improve the relationship between companies and the GCC-DR and could contribute to providing healthcare benefits to GCC states.

Figure 7.12 – Companies’ views on some of the ways to improve the relationship between the companies and the GCC-DR



Ten companies suggested that there should be an increased number of meetings as well as improved communication between the GCC-DR and the pharmaceutical companies. Through openness and regular communication with the companies and having open dialogue and meetings to determine companies needs, the relationship between the two organizations would be improved. This would also promote consistency in decision-making and provide transparency and clear justifications should there be any rejections in the future.

One of the companies indicated that the number of GCC-DR staff is low as compared to the considerable amount of work they have to carry out; therefore the quality of the relationship is adversely affected. Hence, increasing the number of GCC-DR staff is essential to ease the workload and improve their relationship with the companies. Others suggested that the GCC-DR must work as the centre for all GCC Pharmaceutical companies. They should promote regular activities such as running conferences and training courses in different fields of pharmaceutical manufacturing, case-studies, training on registration guidelines in GCC and in other regulated markets. Also, it should include distributing statistics on GCC pharmaceutical companies and medicines, improving knowledge on pharmaceutical technology among pharmaceutical companies and linking with other international conferences on medicines and related issues. In addition, they suggested that by providing electronic online services, the companies would be able to track the progress of their product's

registration status and comments, anytime, anywhere. This would greatly facilitate communication with the GCC-DR and expedite information requests. Twenty companies agreed that the pharmaceutical industry can influence the GCC-DR procedure and that it could be done in the following manner;

- Through sharing of knowledge, experiences and interaction, the pharmaceutical companies could provide support at any level through their worldwide experience with authorities and regulators. As an important partner in the registration process, the companies would be able to provide the GCC-DR with effective and efficient services and quality products.
- The pharmaceutical companies could contribute to drafting and refining the guidelines and GMP inspection systems to make them more effective and efficient.
- They could assist the GCC-DR in streamlining the procedure in order to improve and expedite the registration process.
- They also added that private accredited laboratories could be engaged to help facilitate the procedure and by giving priority to the registration of new products from local industries.

Section 4 - Scientific Opinion

Twenty companies indicated that the scientific opinions from the CP were relevant with respect to their regulatory expertise. Generally, they were satisfied with the quality and safety data, bioequivalence studies and vaccines data provided by the GCC-DR experts for the pharmaceutical products registration and approval process. Generally, half of the companies indicated that the quality of the assessment provided by CP experts for safety, efficacy, pharmacovigilance, bioequivalence studies, biological/biosimilar, vaccines data and GMP inspections were good or excellent (Table 7.1) with only six companies indicating that the assessment for efficacy data, pharmacovigilance data, biological/biosimilar and GMP inspections were poor. There was also a high percentage of companies (36%) who did not provide their responses for this question which probably indicated that they may not have had the appropriate experience in these areas.

Table 7.1 – Companies’ opinion regarding regulatory expertise within the GCC-DR

Review Expertise	Excellent	Good	Satisfactory	Poor	Total
Quality data	5	16	3	0	24
Safety data	5	13	5	0	23
Efficacy data	5	14	3	1	23
Pharmacovigilance data	2	6	8	3	19
Bioequivalence studies	6	7	6	0	19
Biological/biosimilar	2	8	1	1	12
Vaccines data	3	7	1	0	11
GMP inspections	9	10	1	1	21

Section 5 - General observations

The majority of the companies believe that the CP has a more efficient registration system as compared to the national system and indicated the main advantages and disadvantages of the CP system based on their experiences. Three companies indicated that the current centralised evaluation system always provides a better scientific opinion/outcome than the national system, while five companies stated that this occurs frequently. Nine companies indicated that the GCC-DR sometimes provided better scientific opinion/outcome than the national system while three companies stated that this happened rarely. However, more than half of the companies agreed that the current centralised evaluation system did provide better scientific opinion/outcome than the national system (Figure 7.13).

Nine companies agreed that the current centralised system provided consistent evaluations in comparison with the national evaluation while ten companies indicated that this happened sometimes and only six companies stated that this happened rarely (Figure 7.13). Clearly, attaining a standard consistency of the evaluation reports continuously is critical to the quality and efficacy of the centralised GCC-DR procedure. Half of the companies did not agree with the idea of having a standard price for specific medicines throughout the GCC states and the reasons for their disagreement are shown (Figure 7.14). The most critical aspect, as cited by 14 companies, is the difference in economic aspects of the various GCC states as differences in the cost of living and demographics would impact the volume of the products, hence the price of the medicines.

Figure 7.13 – A comparison of the companies' views of the national versus the centralised system with respect to scientific opinion and consistency of evaluations

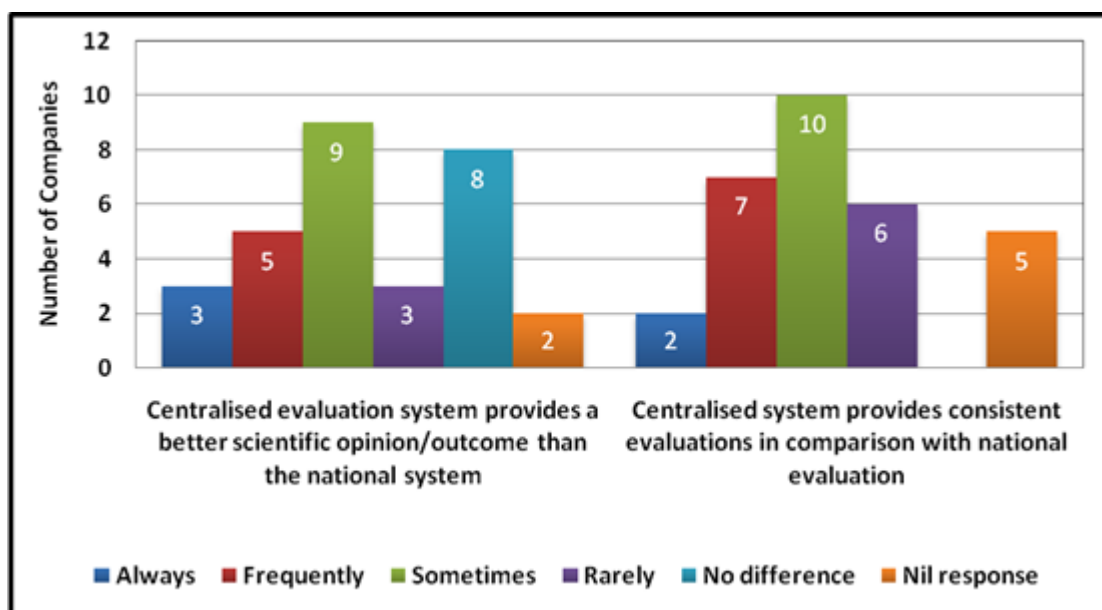
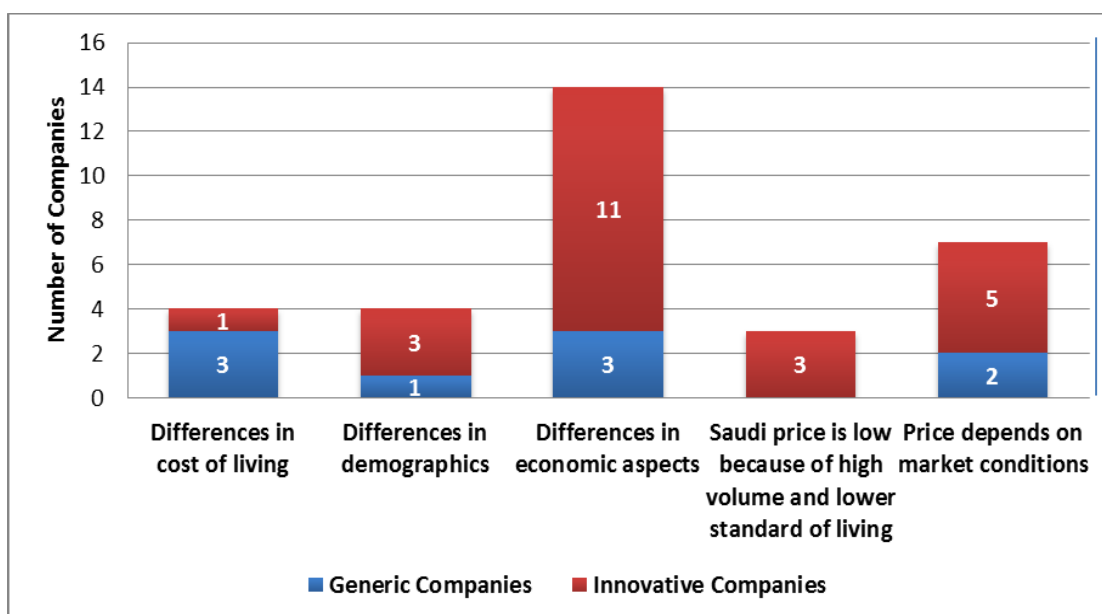


Figure 7.14 – Companies' views as to why a standardised pricing is not appropriate



It is therefore a complex task to set a standard price for specific medicines throughout the GCC states. Finally, 80% of the companies stated that they would support the continuity of a national registration in parallel to the Centralised Procedure while 20% of the companies would not.

Advantages of the Centralised Procedure compared to the National System

Fourteen companies who responded to the survey clearly indicated that one decision from the GCC-DR has a considerable advantage as the product could be promoted faster, easier and is highly recognisable in the seven GCC states. The advantages of the Centralised Procedure as compared to the national system are as follows;

a. Harmonisation of procedures

One approval procedure, one set of documents for the entire approval process and one file with the same format for one submission. The procedure is much simpler and less complicated. This would save time and effort and promote transparency.

b. One decision for all seven countries

In this way medicinal products can be available to all GCC States at the same time once they have been approved by GCC-DR. This facilitates the registration of manufacturing sites in one step. Hence, it would reduce the burden on internal company resources to prepare “dossiers” for additional registration.

c. Others

- Collective and diversified opinions from the different GCC states add more value to the CP decision.
- Products registered at the GCC level will add value to the company and it will open new markets for its products,
- The implementation of CTD format in the central and national levels.
- Proceed with other countries with less documentation.
- If there are no major objections from the committee, then the approval is faster

Disadvantages of the Centralised Procedure compared to the National System

The major disadvantage of the CP as compared to the national system is that it is a time consuming and costly process, followed by the inconsistency of the process and the insufficient number of meetings. The companies also stated that the need to re-submit product files at a national level after approval at the Centralised Procedure is another disadvantage. Sometimes more details are required in terms of the assessment of products by the national system compared to the Centralised Procedure. The companies are also concerned about the possible rejection by GCC-DR that would affect other GCC countries national registration. They stated that although the products are acknowledged by national authorities as final approval in one or more of the member states, they still need to go through the full CP process. By not using communication such as electronic mail, the GCC-DR further delays any correspondence with the companies which could facilitate the registration processes. In addition, the companies also indicated that inter-committee politics may affect certain decision-making outcomes which are not standardised.

The three major disadvantages of the Centralised Procedure as compared to the national system are as follows;

Time consuming procedure and costly process - The procedure of registration involves a very lengthy period both at the quality control laboratory for analysis as well as at the committee level. Feedback is not clear and there is no direct communication with principal companies. Coupled with the high registration fee, the long registration process is the key disadvantage of the Centralised Procedure.

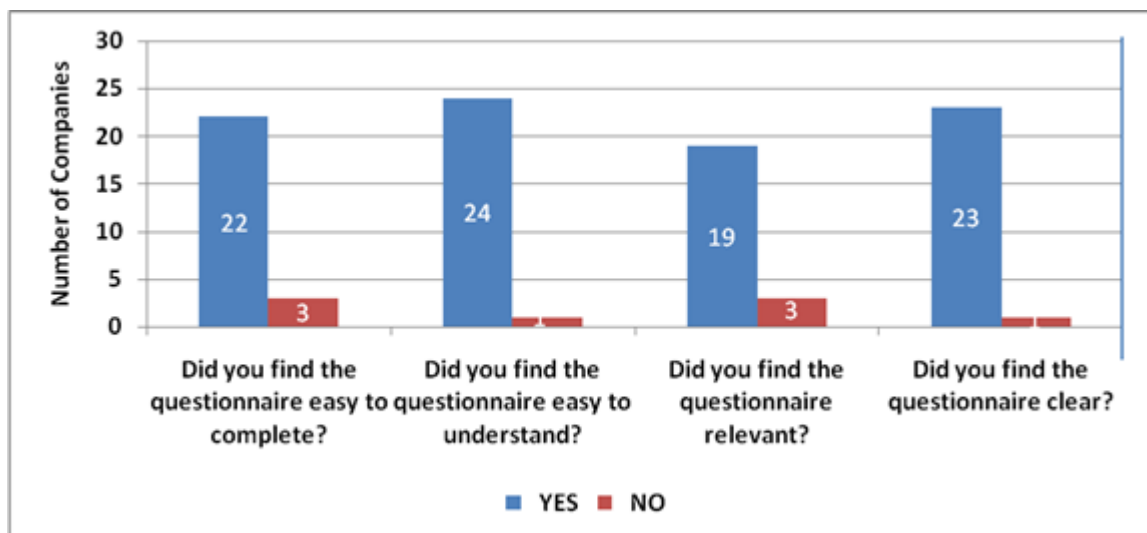
Inconsistency of the process – The absence of guidelines leads to inconsistency in the opinions and some radical differences occur at national level. Many of the documents submitted to the GCC are requested again at a national level after GCC approval. Some states do not accept registration without prior GCC-DR approval. National authorities do not approve the product for distribution even after attaining GCC-DR registration through the CP system.

Quarterly meetings - Once a quarter committee meetings is not sufficient to process the application. Hence, the long delay in the approval process.

Practicality and Applicability of the CACP

An evaluation of the companies' experiences in participating and completing the questionnaire for this study was carried out. Twenty-two companies (88%) found the questionnaire easy to complete while 12% of the companies found it difficult (Figure 7.15). Twenty-four (96%) of the respondents found the questionnaire easy to understand while only one company found it difficult to understand. Nineteen (76%) of the respondents found the questionnaire relevant while only 3 companies (12%) found the questionnaire not relevant. One of the companies stated that the questionnaire was not always relevant. Twenty-three (95%) of the respondents found the questionnaire clear while only one company stated that the questionnaire was not clear. Twenty-one 83% of the companies participating in this study found the length of the questionnaires about right. Only 17% of the companies indicated that the questionnaire was too long. Nine (30 %) of the companies took about 30 minutes to complete the questionnaire while 35% took more than 30 minutes and the remaining 35% took less than 30 minutes. Thirteen percent of the companies took only 10 minutes to complete the questionnaire which was the shortest time while 5 (21%) of the companies took more than an hour and the longest time taken was 120 minutes.

Figure 7.15 Summary of responses on the questionnaire



DISCUSSION

An efficient review allows the regulatory authorities to fulfill their public health mission to ensure that safe and effective medicines are made available to patients in a timely manner and allows for the efficient use of resources. Patients benefit from the timely access to safe and effective therapies while pharmaceutical companies are able to market their products sooner and generate revenues (Booz Allen Hamilton, 2008). The regulatory challenge is to allow access to the safest and most effective pharmaceutical products in the shortest possible time with the highest degree of certainty (Alder, 2001). In the GCC states, pharmaceutical companies can choose whether to register new products via each regulatory authority individually or via the central registration system and the length of the expected review time will influence this decision. Therefore, evaluating the pharmaceutical industry's views about the advantages and disadvantages of the GCC-DR system and how this has impacted the speed of the marketing authorisation time of their products in each Gulf State was essential.

Pharmaceutical companies were able to provide critical information on the strengths and weaknesses of the CP registration system. Based on this experience, only 13 companies surveyed preferred the CP registration system, of which nine were generic companies. The main reasons for choosing the centralised registration system over the national system include:

- The ability of the pharmaceutical companies to meet the requirement of GCC tender specification.
- The convenience of the system,
- An improvement of patients' access to safe and effective medicines in the GCC region.
- The central registration team is more accessible and easier in communication,
- The companies' strategy and economic-related factors.

The pharmaceutical companies which preferred the national system stated that their product strategy was aligned to the registration in selected GCC states for the following reasons and hence their preference:

- Timeline of registration.
- Experience with national system.
- Concern over possible rejection by GCC-DR.
- More transparent and communication easier with local national regulatory authorities.
- Limited number of GCC-DR annual meetings.

However, despite the majority of the companies' preferences for a national registration, the companies indicated that the CP has a better and efficient registration system as compared to the national system. The companies agreed that the CP provides better scientific opinion/outcome than the national system and that the CP provides consistent evaluations as compared to the national system. The companies indicated that through harmonisation of the processes, which would entail one approval procedure, one set of documents for the entire approval process and one file with the same format for one submission, the procedure is much simpler and less complicated.

This saves time and effort and promotes transparency. Furthermore, a medicinal product can be available to all GCC states at the same time once it has been approved centrally. This also facilitates the registration of manufacturing sites in one step and hence, reduces the burden on internal company resources. However, the time consuming procedure and costly process coupled with unclear feedback and lack of direct communication between the GCC-DR and the companies are some of the major issues that hampered the CP registration system. The absence of guidelines leads to inconsistency and therefore some radical differences occur at national levels. Many of the documents submitted for the GCC-CP are requested again at a national level and some GCC countries do not approve the product for distribution even after attaining GCC-DR registration. Moreover, committee meetings held only four times a year is insufficient to address all the product registration issues which results in further delays.

Although more than 60% of pharmaceutical companies stated that it took more time to register their products through the centralised system, they still felt that the GCC-DR Centralised Procedure is the way forward for several reasons:

- By registering their products at GCC level they would have gained access to seven markets in the GCC states.
- The CP leads to the harmonisation of the procedures at the national level and better quality scientific opinions.
- The current centralised system provides consistent evaluations in comparison with national evaluation.

The majority of these respondents indicated that electronic submission and automation of some of the processes could assist in simplifying the Centralised Procedure and hence shorten the whole process. Others indicated that the technical evaluation could be simplified by relying on documents submitted to the GCC since these were the same documents already submitted and approved in the US/UK and other reference countries.

Pharmaceutical companies in general were satisfied with the quality of the GCC-DR scientific opinions despite the hassle and the issues faced in getting their products registered through the Centralised Procedure. In addition, the pharmaceutical companies were satisfied with the efficiency and effectiveness of the GCC centralised pharmacovigilance procedures as the GCC-DR, through this procedure, has monitored Adverse Drug Reactions (ADR) of medicines rapidly.

All the companies indicated they were satisfied with the level of transparency of the Centralised Procedure. They cited that the GCC-DR were open in their communication, and it was easy to meet the central organization team member. They were willing to simplify the issues, had great understanding and there was a high level of transparency in the GCC executive office. However, there is still room for improvement in the follow-up of the application process. Generally, the majority of the companies indicated that they were satisfied with the relationship that they had established with the Registration Department of the GCC-DR. They suggested that increasing the sharing of knowledge through training, seminars and workshops could promote more interactions between the companies and the GCC-DR authority especially in discussing changes to regulations and procedures. This will significantly improve the relationship between companies and GCC-DR authorities and can contribute more in providing healthcare benefits to GCC States. The companies also

suggested that there should be an increase in the number of meetings and communications between the GCC-DR committee and the pharmaceutical companies. Through openness and regular communication with the companies and having open meetings to define companies needs, the relationship between the two organisations would be improved. This would also promote consistency in decision-making and provide transparency and a clear justification should there be any rejections in the future. In addition, they suggested that providing electronic online services would greatly facilitate communications with the GCC-DR and expedite information requests. Pharmaceutical companies also agreed that the pharmaceutical industry can influence the GCC-DR procedure through knowledge sharing, interactions and collaboration as a partnership basis. Through such activities, the pharmaceutical companies could provide support at any level through their worldwide experience with authorities and regulators. The pharmaceutical companies could contribute in drafting and refining guidelines and the GMP inspection system to make them more effective and efficient. They could also assist the GCC-DR in streamlining the procedure in order to improve and expedite the registration process.

Finally, the GCC authorities are facing an increasing number of pharmaceutical companies who are demanding more efficient, effective and transparent regulatory services. This places a significant pressure on the Gulf States to improve the quality of the regulatory review process as well as to expedite the marketing authorization of pharmaceutical products without affecting the quality of the new medicines. The GCC-DR challenge in the beginning was to convince companies to consider submitting their dossiers to the centralised procedure. The submission process is voluntary as GCC-DR cannot implement a compulsory system until the required level of standardization in the regulatory review systems has been reached. However, pharmaceutical companies still have mixed feelings about whether they can gain faster marketing authorization through the national regulatory systems or the regional centralised system (Al Essa, 2011). After all, the goal of any pharmaceutical company is to complete the registration requirements and gain access to the national GCC markets in the shortest possible time. In the end, two approval routes, national and centralised, are permitted to exist side-by-side in the GCC region. But for the centralised system to dominate, member states should seek ways to increase their collaborative efforts to bring their systems closer towards standardization that would facilitate the regional registration process and maintain patients' access to safe and effective medicines within a reasonable time frame.

SUMMARY

- The pharmaceutical companies who responded to the survey were able to provide critical information on the strengths and weaknesses of the CP registration system.
- In general pharmaceutical companies were satisfied with the quality of the GCC-DR scientific opinions despite the difficulties and the issues faced in getting their products registered through the CP.
- The participant companies were satisfied with the efficiency and effectiveness of the GCC centralised pharmacovigilance procedures as the GCC-DR, through this procedure, rapidly monitors adverse drug reactions.
- All the companies indicated they were satisfied with the level of transparency of the CP as the GCC-DR were open in their communication, it was easy to meet the central organisation team member, they were willing to simplify the issues and had great understanding.
- The GCC-DR has a significant advantage as the product could be promoted faster, easier and is highly recognisable in the seven GCC States.
- The major disadvantage of the CP as compared to the national system is the time and the expense involved in the process, followed by the inconsistency of the process and the insufficient number of meetings. The companies also stated that the need to re-submit product files at a national level after approval at the Centralised Procedure is a further disadvantage.
- The study confirmed that although more than half of the 30 pharmaceutical companies preferred the national registration system as compared to the GCC-DR Centralised Procedure, they agreed that the CP is the way forward for the future as it will bring about harmonisation of the registration process, quality scientific opinions and faster access to the GCC market.

CHAPTER 8

The Gulf Centralised Procedure- A Comparison between the Experiences of Regulatory Authorities and Pharmaceutical Companies: a Proposed new model

INTRODUCTION

The Centralised Procedure was designed to improve the operation of the ‘Single Market’ for medicinal products, the avoidance of duplication of scientific evaluation and the reduction of the administrative burden. Apart from these, product safety enhancement and harmonisation are also important for this region. However, the situation in the Gulf Centralised Registration procedure is complex because each state has its own government, constitution, legislation, regulatory requirements and healthcare systems, as well as differences in history and medical practices.

Today regulatory authorities are thinking in terms of Global and Regional themes, for example the European Medicines Agency (EMA), the African Regulatory Harmonization Initiative (AMRH), and the International Conference on Harmonisation (ICH) for Europe, Japan and USA. However, such efforts are not risk-free due to the influence of regional groups in pursuing harmonisation of drug registration. In addition, more stringent registration requirements may displace substandard medicines from the market.

The Ministers of Health in most of the Gulf States have expressed their doubts about the ability to secure the expertise required for registration while at the same time there is the fear of losing their sovereignty to the centralised authority (A. Rahman, 2005). The successful development and registration of a medicinal product requires effective dialogue between the pharmaceutical industry and the health authorities. For the pharmaceutical industry, good communication with the health authorities is essential during the entire lifecycle of a medicinal product, which include the registration procedure and the subsequent maintenance phase (Heidenreich, 2004). The main goal of both the pharmaceutical industry and the health authorities is to establish a positive benefit/risk ratio and an appropriate benefit/risk management system for medicinal products. Pharmaceutical companies should contact the health authorities at an early stage in the development in order to achieve this goal. Early and frequent dialogue between these two stakeholders can build a good relationship between the future assessors of the marketing authorisation applications and the responsible managers of the company. This may rule out problems and issues with the development of the product and thus reduce the risk of an application been rejected.

The result will be more rapid access to essential priority medicines, including important new treatment options such as generic fixed-dose combinations of assured quality and affordable prices by the communities and patients in Gulf States. National drug regulatory authorities need to be better equipped to register medicines in a cost effective and timely manner and this will lead to increased efficiencies across GCC Countries. Capacity building will enhance the quality of the registration decision, whilst streamlined processes and improved information management lead to effective medicines control. As a result drug regulatory authorities may enjoy substantial savings and increased patient reach with generic equivalents (in the context of high volume and high value essential medicines. Beyond this, Governments could enjoy additional economies of scale via pooled procurement which is only possible when the same medicine is registered across all participating countries.

OBJECTIVES

The main objectives of this comparison were to:

- Identify the similarities and differences between the experiences of regulatory authorities and pharmaceutical companies with the Gulf Centralised Procedure.
- Develop a new model for the GCC-DR based on evaluation and the outcome of the centralized procedure.
- Propose a business plan which would enable the implementation of the new model

METHODS

An assessment of the Centralised Procedure was carried out with two groups of stakeholders in the GCC. The first study Gulf Assessment of Centralised Procedure (GACP) evaluated the experience and opinions of all seven Gulf regulatory authorities with the GCC Centralised Registration. The second study Companies Assessment of Central Procedure (CACP) evaluated the experiences and views of pharmaceutical companies with respect to the centralised registration review process. In this chapter, a comparative analysis between the GACP and the CACP is presented to highlight the

issues and challenges faced by these stakeholders as a prelude to the recommendations to be made to the GCC-DR. Information from chapter 5, 6 and 7 was used to develop the new GCC-CP model and proposed business plan which would help to implement the new model.

RESULTS AND DISCUSSION

The results of this comparison will be presented in three parts:

Part I: The Similarities and Differences between the Experiences of the Drug Regulatory Authorities and the Pharmaceutical Companies.

Part II: The proposed model for GCC-CP.

Part III: The proposed business plan which would help to implement the new GCC-CP model.

Part I - The Similarities and Differences between the Experiences of the Drug Regulatory Authorities and the Pharmaceutical Companies

At the introduction of the GCC-DR system in 1999, government officials were concerned about losing sovereignty to the centralised authority (Hashan, 2005). The central registration system has faced criticism for some aspects and approval for others from both the member states of the centralised authority and the pharmaceutical companies dealing with the system. An interesting development which contributed to the improvement of the GCC-CP was the appointment of “Cameron McKenna and Andersen Consulting” to audit the EMA's centralised and decentralised drug registration procedures. An EMA audit survey mandated a review of that agency's activity within six years of its inception.

The report of this survey namely the Evaluation of Community Producers for the Authorisation of Medicinal Products was published in October 2000. It was based on interviews with and/or questionnaire responses from trade associations, national drug registration authorities, professional and patient associations, national ministries with interests in drug approval and pharmaceutical companies. The audit report contained the following summary of survey responses:

- 1) The centralised and decentralised procedures are both perceived to have contributed to the creation of a harmonised community market for medicinal products.
- 2) There is some criticism of particular aspects of both systems. However, in general, the two systems provide a strong foundation for future progress to a harmonised and efficient regulatory environment. Because of their different attributes, there is a strong desire on the part of both applicants for marketing authorisations and the competent regulatory authorities to maintain the parallel systems.

The survey examined many aspects of both the centralised and mutual recognition procedures. The auditors did not limit their research to the EMA's activities, but they investigated member states' response to EMA decisions. This audit survey examined the level of satisfaction with the Centralised Procedure. Of the 32 companies that had obtained marketing authorizations by this route, 88% were satisfied with the system and 3% was very satisfied. These results are identical to the outcomes of this study. The member states regulatory authorities of EMA were more enthusiastic about the Centralised Procedure with 73% being satisfied while 20% were very satisfied with its operation. These results from Europe also mirrored the outcomes of this study in the Gulf States.

A well coordinated, reliable centralised regulatory framework effectively reduces the administrative burden and duplication of scientific evaluations by participating member states. The companies believe that if this procedure was streamlined, was faster and transparent it could be the system of choice. As the documents for a medicinal product are submitted as a common single registration, this results in cost saving and an efficient follow up opportunity in all the seven Gulf States. At the beginning of 2014, the GCC-DR will initiate the CTD electronic submission (as NeeS [Non-eCTD electronic Submissions] format), which is currently implemented by internationally recognised agencies and as from January 2015 only the eCTD format will be accepted. This approach is useful in that it assists the pharmaceutical companies in understanding the rules of the submission process and thus helps both the industry and the authority to make better decisions (TGA, 2009). The findings from this study highlight the ten years achievement of the Centralised procedure and

its future potential as identified by the health authorities as well as the pharmaceutical companies. The pharmaceutical companies shed some light on the advantages and disadvantages of the centralised system which were similar to the views of the national regulatory authorities of the member states, although in some ways they were different. Both the regulatory authorities and the pharmaceutical companies agreed that the centralised procedure is an effective system for authorizing the marketing of medicinal products in all of the GCC countries in one procedure and is the way forward, but there is room for improvement in the procedure and the follow ups.

With regard to submission preference the majority of the pharmaceutical companies, which took part in this study, preferred the review at a national level mainly due to their experience with the national regulatory authorities, therefore making it easier to gain market authorization. The long duration of the CP process contributes to the preference for the national submission as well as the fear of rejection by a centralised authority. The preference of the pharmaceutical companies to apply to national authorities is confirmed by the responses of the national regulatory authorities which stated that the number of national applications was greater than those submitted to the centralised authority adding to the workload of the national regulatory authorities in addition to their CP workload.

Despite the preference of the pharmaceutical companies for national submissions, they find the registration at the CP to be better and more efficient. Ease of communication has been reported for both the national procedure and CP although there is no direct access to CP by the pharmaceutical companies. Most of the national regulatory authorities of the member states concur with the fact that the duration of the process to obtain market authorisation through the centralised procedure should be shorter to make it more appealing to applicants. The duration of the centralised procedure could be shortened by several means which include increasing the number of CP committee meetings per year which has been clearly recognized by both the pharmaceutical companies and the national regulatory authorities. The lack of resources, mainly human expertise on the side of national regulatory authorities, contributes as well to the delays even though there is effective collaboration and sharing of information between the national regulatory authorities. Recruiting external experts can aid the national regulatory authorities with the shortage of human expertise but there is a fear that this will impact the quality of the review. The demand

for additional requirements by different national regulatory authorities adds to the delay and length of the process. The most effective way is to optimise the process of evaluation by the centralised authority by finding a more appropriate model. According to the regulatory authorities' views, standardisation of the system would also be a means to improve and facilitate the regional registration process and maintain the supply of safe and effective medicines within a reasonable time frame. The national regulatory authorities in the Gulf have found the shared experience, ideas and knowledge at the centralised meetings to have enriched their own experience and knowledge which is reflected in their performance at the national level. The clear outcome of this collaboration and joint effort between the national regulatory authorities produces an improved scientific opinion and a higher quality of decision-making. Pharmaceutical companies have also indicated their agreement with this where they found consistent evaluation of submission and a better scientific opinion received from the centralised authority than from the national regulatory authorities leading to a more efficient system.

One major aspect of CP approval reported by both the pharmaceutical companies and the member states is the centralised pharmacovigilance procedures and reporting system which are efficient and effective. In addition, member states of the centralised authority find the GCC guidelines to be sufficient and appropriate for their intended purpose. On the other hand, pharmaceutical companies, submitting to the centralised authority, struggle due to the absence of appropriate guidelines leading to inconsistency. Also there are differences when accessing the market at a national level such as re-requesting documents already submitted for the CP or not even approving the product for distribution after attaining GCC-DR registration.

Certain aspects of the registration procedure can be modified in order to move forward and improve the quality of the experience. Both the national regulatory authorities of the member states and the pharmaceutical companies have agreed that the use of electronic on-line submissions to the centralised authority, as well as electronic communication between the member states, is one way to expedite the process. This is the current method implemented in the recognised established authorities worldwide such as EMA and FDA. Further, a recognition of the assessment by established mature regulatory authorities through implementation of the verification procedure is a means of improving the process and easing the burden

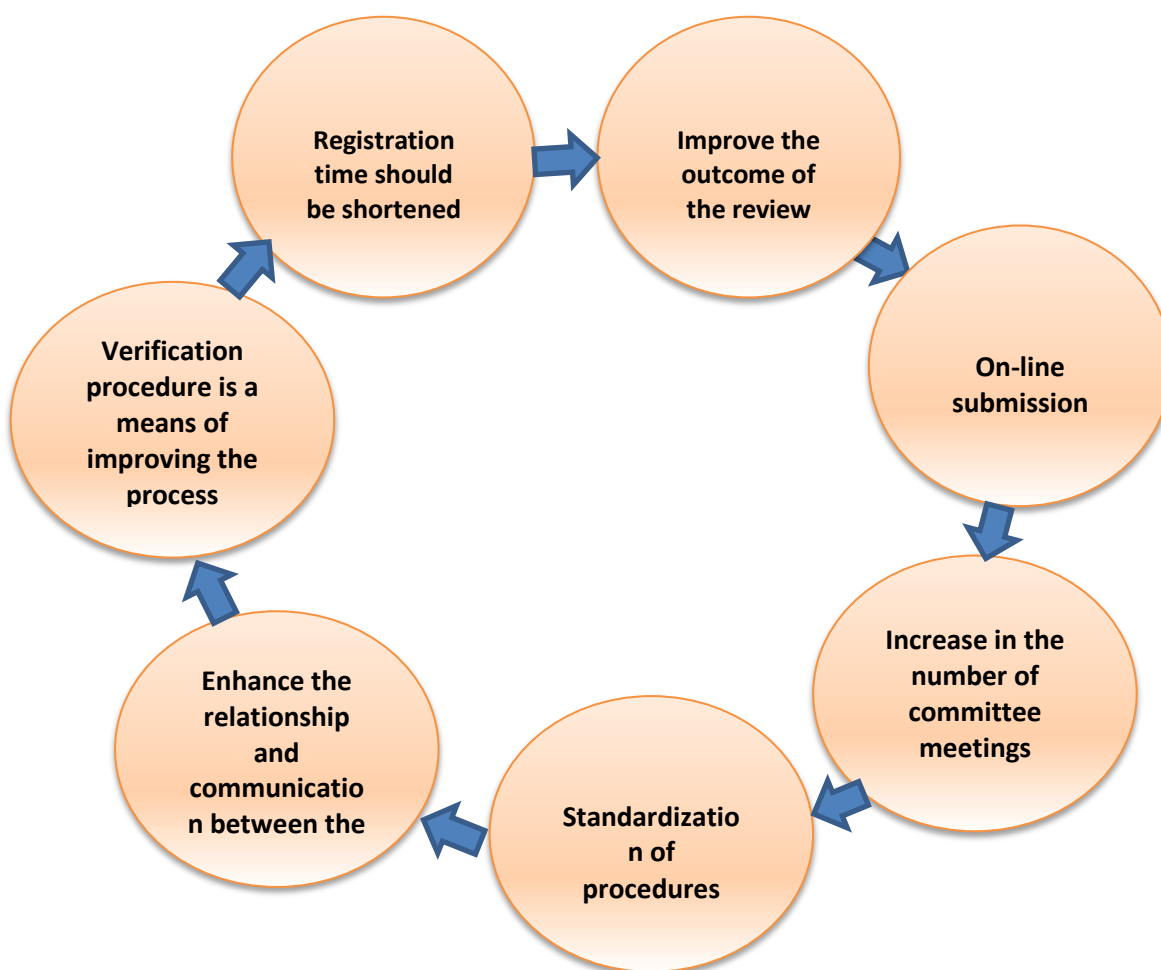
of the high workload on the national regulatory authorities and for the pharmaceutical companies as well. Harmonisation of requests and clarifications sent to the pharmaceutical companies is yet another way agreed by both the pharmaceutical companies and the national regulatory authorities. The national regulatory authorities identified the need for training, seminars and workshops to improve the experience of their expert staff. Pharmaceutical companies have suggested the same where the additional interactions between pharmaceutical companies and the national regulatory authorities would improve the overall knowledge of the national regulatory authorities especially as the pharmaceutical companies have worldwide experience. Also it would further enhance the relationship and communication between them. The pharmaceutical companies even suggested helping to draft, improve and refine guidelines including GMP. One of the key concerns, as highlighted by the companies, is the limited number of committee meetings per year. The quarterly meetings to validate the pharmaceutical products are clearly insufficient to meet the increasing demands for product registration and approval. The companies recommended that the frequency of the GCC – DR committee meetings needs to be at least 8 per year or every 45 days. In addition, sub-committees could be formed with more frequent meetings to handle specialised matters such the registration of life saving products.

The companies recommended that the comments and opinions of the countries, where the products have been registered nationally, should be considered when products are being evaluated by the GCC-DR. In this way, the approval process would be expedited and this would facilitate faster approvals at a national level after the products have been approved by the GCC-DR. Over half of the companies supported the GCC-DR procedure while five companies out of thirty preferred the national registration system. The main reason companies move toward local registration is because of the delay and queuing at CP. Nevertheless, the companies agreed that if the GCC-CP improves it will increase its acceptability of the marketing authorisation issued centrally in other markets. They also suggested the use of University laboratories to speed up ‘product testing’ against additional fees.

The only way to improve support for the GCC registration is to give some advantages over the national registration for companies who choose this route. It is very important to note that most companies are seeking to establish a single registration system, either national or centralised, for their products. Dealing with two registration

systems in the same region is impractical. For all these reasons, companies usually adopt the most economically viable registration system that meets their corporate objectives. In conclusion, figure 8.1 summarises the key issues to be consider in the new proposed GCC model.

Figure 8.1: Key issues to be consider in the new proposed GCC model



Part II - The proposed model for GCC-CP

The time taken to register a pharmaceutical product differs from country to country and from product to product. However, it is possible to complete the review process within a reasonable time frame if the data are available and adequate. Many countries have legislative maximum times allowed for the review of a dossier. For example, the target time-frame for completing the review process in the EU centralized system is 210 days, although the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data (EMA, 2009). This compares to the median of 304

days taken by the US FDA (CIRS, 2013). Several challenges faced the GCC health authorities to successfully operate the centralised system. Therefore, they encountered the need for regulatory reforms during the last 12 years, in order to improve their individual systems and to unify their procedures to expedited improved patients' access to high quality medicines throughout the region. The GCC-DR challenge in the beginning was to convince companies to consider submitting their dossiers via this procedure. The pharmaceutical companies still have mixed feelings about whether they can gain faster marketing authorization through the national regulatory systems or the regional centralized system. After all, the goal of any pharmaceutical company is to complete the registration requirements and gain access to the national GCC markets in the shortest possible time.

It is crucial for the GCC states to identify the most prevalent driving forces for improving the centralised procedure and to attract the pharmaceutical companies to use this system. From the results of this study and the information in chapter 5, 6 and 7 a model can be proposed based on the current GCC-DR centralised procedure (Figure 8.2) and taking account of the comments in part I of this chapter. The model's main features are as follows:

- Maintain the main structure of GCC-DR centralised procedure.
- Amend the parts that are time consuming in the current GCC-DR centralised procedure.
- Allow all member states to participate in the review process and the conclusions reached in a timely manner.
- Adopt an electronic system of review for the proposed model to overcome infrequency of meetings and the possibility of all member states participating in the review process in a remote manner.
- Adopt electronic communication with applicants for deficiencies for improved review process.
- Adopt a clock-stop timing for the review process based on the automation of the review process.

This model (Figure 8.3) is based on the current GCC review process. It maintains the main features of the approval process namely receipt & validation, management of the overall dossier review cycle, registration approval by heads of authorities and upholding the independence and sovereignty of member states within the approval process.

However, the proposed model eliminates the steps in the approval process which are time consuming and present redundancy in the process. The main step to be eliminated relates to the questions raised by member states following the review. Clearly this step raises the question as to why member states would raise questions that are not highlighted by the two reviewing authorities. This at best produces doubts regarding the review capabilities of certain member states while at worst raises doubts about the GCC review process in general. On one hand each member state must be allowed the possibility to state their views regarding the application, while on the other hand there is a need to achieve review time efficiency. To realize such a target the model proposed is as follows:

- A. **Receipt phase:** Receipt of the application is carried out in accordance to the published GCC guidelines for NAS's and EAS's. The applicant should request a submission date for the application which would be provided by the GCC office. It is of importance that the applicant would provide a statement that the application being submitted has observed all the relevant GCC guidelines. This statement has a functional effect on the clock-stop as it is quite frequently observed that applicants submit partially completed dossiers, especially the local industry, making promises to bring missing or complete data at a later date. The applicant must be held accountable in such cases and this can only be done according to local laws if such documents are provided, otherwise the receiving officer will usually be held responsible. Furthermore, the statement will serve as time zero for the "clock-stop". The receipt process should be conducted at the GCC Executive Office and performed by GCC staff. This phase is actually maintained as the current practice of application receipt at the GCC office.
- B. **Validation phase:** The validation phase may be critical for agencies like Health Canada, US FDA or EMA, when many dossiers are submitted by the applicant whereby the submission is screened to ensure that the data are complete and of suitable quality for review. In this phase for the GCC-CP the requirements are checked against the requested formal requirements. This should include the administrative registration (reference number) and checks on legal requirements, the status of the company, manufacturer etc. as well as a 'checklist' validation of the application content (e.g. technical sections, CPP status).

Figure 8.2 The current GCC-CP registration system

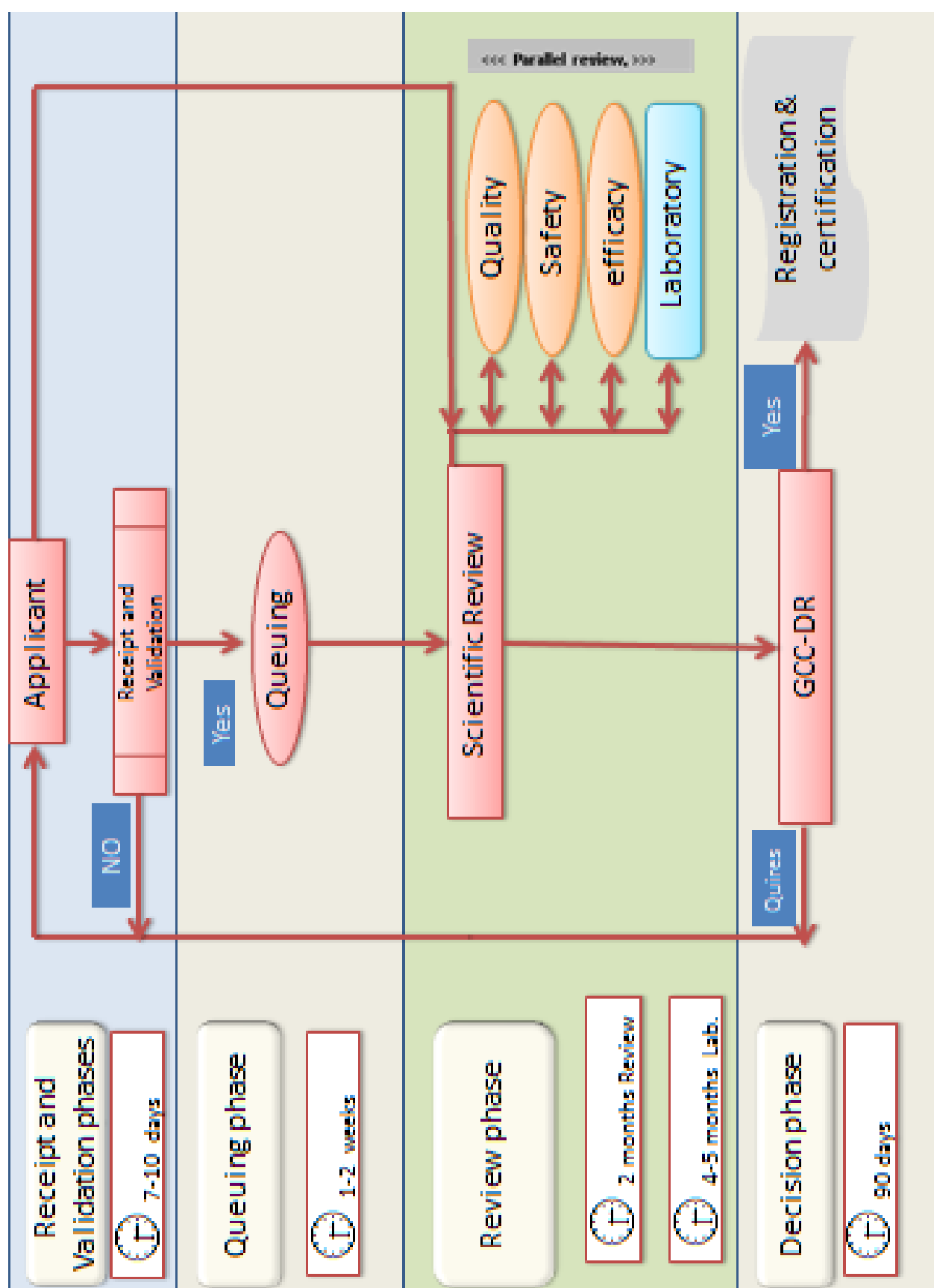
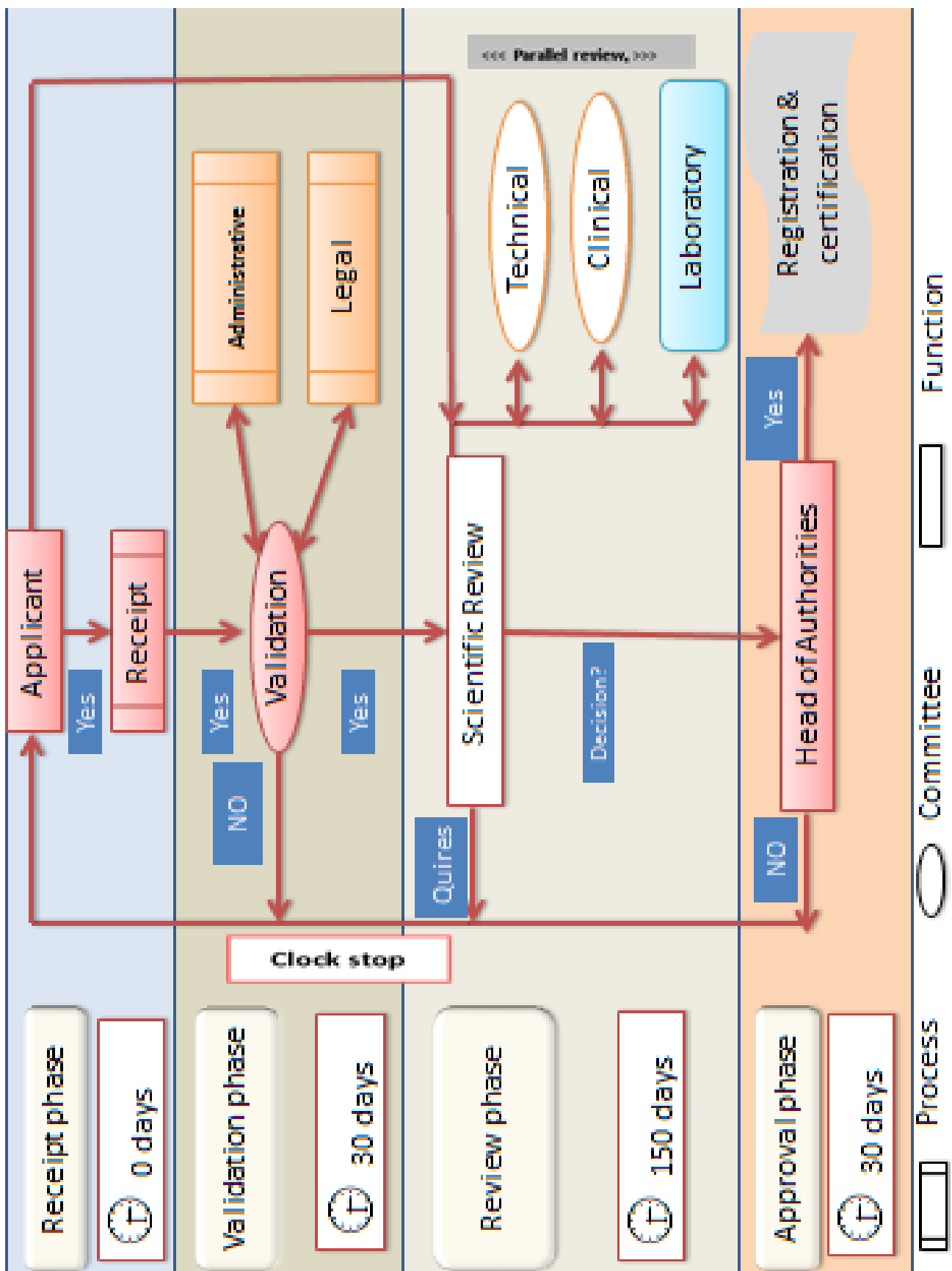


Figure 8.3 The proposed model for GCC-CP



Further checks on patent compliance are necessary and any contractual arrangements such as contract manufacturing or licensing agreements are also checked. The allocated clock-stop time for both processes of administrative and legal formalities should be 30 days. The validation processes are carried out at the GCC office. In effect the validation process should make sure that the submitted application is in compliance with the formal requirements as stated in module 1 of the CTD specifications together with further checks that all the required technical data is provided. This phase is maintained as the current practice of application validation by the GCC office.

C. **Review phase:** The scientific assessment stage is the major part of the review process and requires considerable amount of evaluation of data relevant to the safety, efficacy and quality of the pharmaceutical product. Therefore, it is essential to focus the attention on providing the appropriate skill sets and the facilities as well as establishing guidelines, SOPs, training and continuing education programmes and the electronic handling of the review process to implement the desired good review practices (GRPs). In the new proposed model the scientific review should be overhauled to allow all member states to participate in the review process in a one-step approach. This necessarily means that steps (C), (D) and most of (E) of the current GCC model of practice are merged into one step in the proposed model. In this phase, two committees are established from all member states. Therefore each member state is represented in each of the two committees to ensure the active participation of all states. The two committees are as follows:

- a. **Clinical committee:** this committee should consist of experts from the member states and should be responsible for reviewing the clinical requirements for both NAS's and EAS's dossiers. In effect this committee is concerned with safety and efficacy/modules 4 and 5 of the approved GCC CTD standard.
- b. **Technical committee:** this committee should consist of experts from the member states and should be responsible for reviewing and approving API's and excipients in the formula as well as the finished product. This committee is very similar to the EDQM committee in the EU in addition

to the technical review committee in respective EU member states. This committee would focused on module 3 of the GCC CTD standard.

The clinical and technical committees cover all aspects with regard to the safety, efficacy and quality of the product while any legal aspect that may relate to the product would have already been checked during the application validation process. The clinical and technical committees approach to the product's review compared to the two step approach of the current model would lead to considerable time saving and review process efficiency and transparency. Each member state would be able to state their approval or concerns during the review process in that particular committee. A letter of deficiency relating to that committee would be issued to the applicant with a time limit for the applicant to respond. The committee's meeting time can be organised in a manner to allow for the review of new applications while keeping about 30% of the meeting time for replies to issued letters of deficiencies. The committees should meet at least once a month to keep the process efficient and timely. The allocated clock-stop time for both committees concurrently is 150 days. The tasks performed in the committees are done primarily by members of staff from health authorities of the member states and not from the GCC office staff.

- c. **Laboratory analysis:** the required laboratory tests should be performed concurrently with the application review process of both clinical and technical committees. The allocated clock-stop time for the laboratory to complete the required tasks is 120 days which is well within the 150 days clock-stop time allocated for both clinical and technical committees. This should be the default and implies that the work of both clinical and technical committees and the laboratory is harmonized and synchronized to complete the work within the 150 days time limit.

- D. **Approval phase:** Once the two committees grant approval for their part as well as the laboratory decision to approve the product, their respective decisions are transferred to the head of authorities meeting to give the approval to issue the registration certificate. If, for any reason, the heads of the authorities are concerned regarding any aspect of the application they will issue a letter of concern to the appropriate organisation which might be the GCC management

staff, specified committee(s), the laboratory or the applicant. Once the concern is answered then an instruction to issue the registration certificate is mandated. The heads of authority's approval is to check that the approval process steps and an adequate review is observed. This may represent a quality assurance task performance to guarantee good review practices at the GCC office. The allocated clock-stop time for this phase should be 30 days and the tasks are entrusted to the heads of health authorities of the GCC member states. The heads of authorities in this case should be considered as the approval council (head of agencies) and they should meet, every month. The allocated clock-stop time for this committee is 30 days. This takes into account the meeting frequency of this committee making sure that once the applications passes all requested formal and substantive requirements the application's final approval by the heads of authorities shall be compliant with the clock-stop. Once the approval is granted by the approval council then the GCC office should issue the registration certificate for the product under application.

In order for the above proposed model to function the following are required:

- a. Clear guidelines for the review process are laid down by the council of heads of authorities. Good review practices should be mandated in such guidelines. The GCC should elect one authority to host a training academy for all aspects related to the sciences and skills needed by the GCC and member states staff involved in the review process.
- b. Electronic management (Computerisation) of the whole process of the review including an electronic review system which allows committees to hold meetings, while each committee member is in their office, utilising modern computer software and communication tools and devices. Using modern meeting techniques will result in cost savings, process efficiency and significant review time saving. Further electronic process management will enable external experts to participate in meetings of the various committees if required without the need to make travel arrangements giving expert support to the work of the GCC reviewing process.

This new model would allow the GCC to adopt a clock-stop approach to the review process. The GCC's main bottle neck is the "questions to the applicants" raised by non-reviewing member states. This proposed model eliminates such a bottle neck through the participation of all member states in the reviewing committees. The time saving should allow GCC to promise 210 calendar days for NAS's and of course fewer days for EAS's is expected, but at worst would be the 210 days.

However, adopting the clock-stop dictates that the applicant's expected response time and date is indicated to the applicant. Failing to meet the response date by the applicant should allow the GCC to remove the application from the review process after warning, in order to reduce the review pipeline. Clear guidelines for the clock-stop concept and the use of such a concept should be clearly documented and announced.

The laboratory analysis requirement should be performed in a manner that eliminates delays in the analysis process. This is based on member states laboratories declaring their readiness to meet the clock-stop requirement and availability of time for analysis. Even though each of Kuwait, Oman, UAE and KSA Quality Control (QC) laboratories are well equipped for conducting analysis of pharmaceutical products, member states should agree on accreditation criteria for QC laboratories in order to officially identify that these laboratories are able to meet these accreditation criteria.

In addition, each member state with the ability to meet the accreditation criteria should also be able to accommodate 120 days clock-stop to complete the assigned task. Analysis tasks are assigned to laboratories that declare their ability to meet the clock-stop requirements and tasks are given to member states laboratories in order to give analysis tasks to member states laboratories in a fair manner. This would allow all participating laboratories equal opportunities to contribute to the process of product approval in the GCC system. In this way, laboratory tasks, assigned in this model, would eliminate the long analysis time and undue waiting experienced currently.

Part III - A proposed business plan underpinning the implementation of the new GCC-CP model

Quality management practices are an integral part of several established drug regulatory authorities (eg. EMA, FDA) including governance configuration and its business processes. These practices help to ensure that the agency operates to consistently high levels of quality, efficiency and cost-effectiveness. In terms of financial resources, it is worth investigating the impact of different budget structures on performance across authorities (Anderson, 2007).

The agency charges a fee for processing applications from companies that want to bring a medicine to the market. It also charges fees for services related to the marketing of medicines in the EU in areas such as scientific advice, inspections, renewals and variations and the establishment of maximum residue limits. The total budget of EMA was 194.4 M€ in 2009 (EMA, 2010) and it is expected to be 239.1M€ in 2013. The budget process allows the EMA to cover its needs, mainly by fee revenue which is subject to fluctuation.

The pharmaceutical industry considers EMA fees fair and appropriate ‘to the services provided’. On the other hand the US FDA's federal budget request for fiscal year (FY) 2012 totalled \$4.36 billion (El Boghdady et al, 2012). About \$2 billion of this budget is generated by user fees and pharmaceutical firms pay the majority of these fees, which are used to expedite drug reviews. Even though the procedures and classifications differ considerably between EMA and FDA, the majority of stakeholders consider both agencies provide high quality evaluations for their products. It is noteworthy that the European pharmaceutical market size is 2/3 of the US pharmaceutical sector.

The EMA fee structure (EMA, 2010) appears complex in comparison with the FDA fee structure; there are specific cases for three different types of variations, such as type Ia, Ib, and II, beyond extension, additional fees for specific strengths or presentations, as well as referral fees. Several fee waivers favouring generics, biosimilars, orphan and paediatric products, small and medium sized enterprises exist in the EMA structure.

On the other hand, the FDA levies establishment fees (US\$, 457,200) every year from the authorised drug manufacturers. In a similar fashion, FDA also gives fee waivers like EMA, in special cases. Spending on medicines will reach nearly \$1,100Bn in 2015 (IMS, 2012). The U.S. share of global spending will decline from 41% in 2005 to 31% in 2015, while the share of spending from the top five European countries (Germany, France, UK, Italy and Spain) will decline from 20% to 13% over the same period. In contrast to EMA, the FDA fee requirements include application fees for previously filed applications or supplements , fees for designated orphan drugs or indications (both for prescription products or for a supplement) .

The FDA user fee programmes support the safe and effective review for human and animal medicines, biological products, medical devices and the review of other FDA-regulated products. User fees also allow FDA programs to achieve enhanced premarket review performance. Other FDA user fees support the regulation of tobacco products, the inspection of mammography facilities, the certification of color additives and the certification of FDA-regulated products exported from the United States. New user fees enacted by the FDA Food Safety Modernization Act support essential food safety activities. The budget includes inflationary increases for FDA user fee programmes, as authorized by law.

The Prescription Drug User Fee Act (PDUFA), enacted in 1992, authorizes FDA to collect fees from companies that produce certain human drugs and biological products. Since the establishment of PDUFA, user fees have played an important role in expediting the drug approval process. On July 9, 2012, the President sanctioned the Food and Drug Administration Safety and Innovation Act (FDASIA), which includes the reauthorization of PDUFA through to September 2017. PDUFA V will provide for the continued timely review of new medicines and biologic license applications in the US. The new law ensures that FDA will continue to receive a source of stable and consistent funding during fiscal years 2013-2017 and allow the agency to fulfill its mission to protect and promote public health by helping to bring to market critical new medicines for patients.

Government support in the form of a budget is the method of financing employed in most of the GCC States, however, only Saudi Arabia and Yemen are self-financed by fees. Governments are committed to support the GCC authorities financially and prioritise funding of the regulatory review process. In any case, arrangements should be made so that the financial sustainability is maintained for continuous and effective implementation of the various drug regulatory functions (Ratanawijitrasin, 2002).

The quality of the review process, the technological and scientific skills improvements remain a limiting factor without Governmental support (Hashan, 2006). The range of fees, however, varies significantly from country to country according to the funding structure and the services provided by each authority. The relatively high registration fees charged by the Saudi Food and Drug Authority (SFDA), compared to the other GCC authorities, are related to the autonomous support of the SFDA for its own practices, facilities and services through the direct access to the fees, rather than being collected by the central government revenue as in the other GCC States which may or may not be returned to the authority undertaking the work (Hill and Johnson, 2004).

The Yemen regulatory authority is an autonomous authority as well and therefore the registration fees are slightly higher than those charged by the rest of the GCC States, but considerably lower than SFDA probably to attract pharmaceutical companies to the local market in Yemen. It is agreed by all the GCC authorities that in order to improve the regulatory review process, the authorities need to increase their resources such as the number of experts, developing the information technology structure and establishing training and continuous education programmes.

Without appropriate funding, the authorities will always face difficulties in improving their regulatory systems. It can clearly be seen (Table 8.1) the parity among member states' fees ranging from no fees in Qatar to as high as USD 25,341 in Saudi Arabia. This wide difference in the range of the requested fees at national level from each member state will cause those with higher national fees to resist the GCC Centralised Procedure.

Table 8.1: Registration fees in the GCC States

	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen	GCC-CP	Proposed GCC-CP fees
Company Registration	5 BD = USD 13.3	250 KD = USD 887.2	100 OR = USD 259.7	NO FEE	(ONLY INSPECTION FEE)	1000 DH = USD 272.3	3000 USD	10000 SR = USD 2,667.5	(ONLY INSPECTION FEE)
Products NASs	5 BD = USD 13.3	100 KD = USD 354.9	75 OR = USD 194.8	NO FEE	95,000 SR = USD 25,340.8	1000 DH = USD 272.3	1500 USD	10000 SR = USD 2,667.5	USD 30,444*
Products EASs	5 BD = USD 13.3	100 KD = USD 354.9	75 OR = USD 194.8	NO FEE	40,000 SR = USD 10,669.8	1000 DH = USD 272.3	1500 USD	10000 SR = USD 2,667.5	USD 14,305*

*The proposed fees structure calculated according to the ratio of current national fees to the total fees for all member states in addition to 10% as administration fees. (The basic fees in EMA for a single strength= 274,400 Euro) (FDA New Drug Application (With Clinical Data) fees for 2014 fiscal year (FY) = \$2,169,100).

It is recommended that if the proposed model is implanted then each member state should decline their national fees in favour of GCC-CP fees and that the GCC-CP fees should be shared amongst member states where each share is calculated according to the ratio of current national fees to the total fees for all member states in addition to 10% as administration fees. For this model to be feasible in the future, the overall fees of the GCC-CP must be increased. The increased fees would allow member health authorities to benefit from these application fees and for tasks they perform during the application approval process. Further to the above, the fees for analysis should be awarded to the assigned QC laboratory of the member state performing the analysis task. Training is a key element for capacity building for the success of the proposed model. Training should be carried out to achieve higher performance with improved efficiency for member states for the review of GCC-CP applications. The training fees should be awarded to the member state hosting the training activity. The comparison of the views from pharmaceutical companies and regulatory authorities has identified the most important outcome as the desire for improving the GCC centralised procedure model.

SUMMARY

- Agencies and companies agreed that the centralised procedure had contributed to an effective system for authorising medicinal products in the GCC by providing the best possible scientific opinion for the quality of CP decision-making as compared to the national system.
- Enhancing sufficient resources like qualified and trained experts together with technical facilities would improve the quality of the GCC regulatory performance.
- It is crucial for GCC states to identify the most prevalent driving forces for improvement to the GCC centralised procedure such as on-line submissions and an increase in the number of committee meetings in order to attract pharmaceutical companies to use this system.
- Quality management practices are an integral part of several established drug regulatory authorities and its business processes. These practices help to ensure that an Agency operates to consistently high levels of quality, efficiency and cost-effectiveness.
- The overall fees of the GCC-CP should be increased in order to allow member health authorities to benefit from application fees and for tasks they perform during the application approval process.
- The comparison of the views from pharmaceutical companies and regulatory authorities has identified the most important outcome as the desire for improving the GCC centralised procedure model.

CHAPTER 9

General Discussion

A systematic examination of pharmaceutical regulation and its environment across countries can help shed light on a country situation, provide a new perspective on the constraints facing it and suggest options for improvement. A comparative approach is used in this study, on the grounds that countries can benefit from learning from one another. There are three basic reasons for conducting systematic comparisons between countries (Booz Allen Hamilton, 2006).

- **Strategy development:** comparing different ways of managing similar problems can provide both positive and negative lessons, i.e. guidance on what to do and what not to do. Comparing cross-country experiences is a useful way of developing policy instruments for problem-solving in a particular country.
- **Understanding:** comparing public policies can help improve understanding of how government institutions operate within their environment and suggest possibilities for improvement.
- **Interdependence:** the interdependence of nations as reflected in international agreements, regional political-economic groupings, bilateral treaties and collaboration is constantly increasing. Accordingly, problems that occur in one country can spill over into other countries more easily and rapidly today than at any other time in history. Similarly, policies adopted in one country often have important implications for others. In other words, knowledge about what has occurred in other countries can help a country prepare for new challenges of its own.

Making a positive decision about a pharmaceutical product requires careful weighing up of the potential benefits and harms and the scientific complexity of such decision-making should not be underestimated (Hill, 2004). From the authority's perspective, success is the licensing of quality medicines to enable patients to have access in a reasonable time frame without compromising safety and/or efficacy (Hashan, 2005). Therefore, a thorough review is carried out by the assessors with particular emphasis on the quality, safety and efficacy studies. The use of ineffective, harmful, poor quality medicines can result in therapeutic failure, deterioration of the disease being treated, resistance to medicines and sometimes death. It also undermines confidence

in the health review system, health professionals, pharmaceutical manufacturers and distributors (Rago and Santoso, 2008). The complexity and challenges of the drug registration system should not be overlooked. It is simplistic to believe that speeding up the registration process will improve patients' access to quality, safe and effective medicines. This is the industry's argument but neglects to take into account important issues such as the quality of the review. Given the pressures that arise from the legitimate business interests of the multinational pharmaceutical manufacturers, there needs to be support for regional activities designed to ensure the quality in the registration systems. This includes ensuring that there is adequate capacity to cover the required resources and appropriate guidelines at a country level to assess and control the quality of medicines.

Information sharing and harmonisation reduces workload and improves overall regulatory performance. Harmonization is the value added that directs expert knowledge and resources to functions that improve public and personal health and facilitates access to essential medicines. Formation of effective networks among national regulatory authorities participating in various harmonization initiatives facilitates sharing of scarce resources; eliminates duplication of activities; saves money for all; supports cooperation, collaboration and international understanding; facilitates in building regulatory capacity and enhances public trust in regulatory efforts.

The Gulf States faced significant challenges in dealing with their established regulatory bodies who were reluctant to give up their independence to the newly established GCC Central Drug Registration (GCC-DR) system (Al-Essa, 2011). The idea of implementing a central registration system came originally from the industrialised world, especially from the success stories of the European Medicine Agency which encouraged gulf regulatory organisations to structure the central registration system. The centralised process of the European Union drug regulatory agencies under one roof resulted in the development of EMA which has attained improved trust, transparency, communication and mutual recognition through the unification process. The European approach to national and central procedures differs greatly from that adopted in the GCC. The difference is conceptual and structural which is reflected in the procedural aspects and furthered the outcome of the

European approach. The missing link in the comparison between the European approach and the GCC approach is the following:

1. The European system was initiated based on the need for mutual recognition between some member states. This led to the mutual recognition procedure between some member states such as UK, France, Germany, etc. The system was further refined to the centralised procedure covering all member states. In this evolution the European approach presented a coherent system for review of medicinal products with standards acceptable to all member states. The system has inherent flexibilities for applicants to choose the national route for submission or the centralised procedure. Furthermore, the system allowed applicants to switch from the centralised procedure to the decentralised procedure. On the other hand, the GCC system evolved from the need for communal procurement of medicinal products not from mutual recognition needs. The foundation of the system is based on the GCC tendering procedure rather than communal review system. The review standards and consequently review quality leads to a non-harmonized system between member states. It is this non-harmonized system that led to the difficulties expressed clearly by GCC member state staff. In order to overcome this difficulty most member states are advocating national harmonization with GCC-DR.
2. The European system of review and approval leads a formal grant of marketing authorization for applicants without the need for follow up submission by member states. In this regard the centralised procedure in Europe represents a viable alternative to submission in multi-states in the EU while the GCC-DR does not offer the same opportunity and applicants need to go through the national procedure as well as following the central procedure approval.
3. For a review system to be effective all elements of the review system must be clearly defined through guidelines and procedure. One of the most important elements in any review system is the pricing guideline and procedure. The GCC-DR does not include the pricing element which is of course emanating from the intended purpose of the GCC-DR being the unified route for tendering in the GCC procurement of medicinal products.

4. The European Medicines Agency (EMA) has established systems of training its own staff and extends it to the training of scientific experts. Training takes into account entry level of review staff up to the continuous training of senior reviewers. Even non-employed personnel have their own training (EMA, 2011). The main purpose of the training is to ensure the review process is measured from different aspects namely effectiveness, efficiency, long-term effectiveness on EU citizens, impact on EU internal market and on different stakeholders (EMA, 2010). Training is the main tool to ensure a quality review and the absence of a GCC-DR training system directly affects the quality of the review procedure and consequently impacts all other features of the GCC-DR system.

From the above it becomes evident that a comparison between EMA and GCC-DR is not an objective assessment. Certain elements will look common between both central procedures by virtue of them being central procedures e.g. the participation of reviewers from all member states. However, for the EMA the criteria for a reviewer appointment is based on review skills attested by EMA for any national member state, while in the GCC-DR it is a formal procedure based on member state's discretion. The anomalies between GCC-DR and EMA could render the comparison misleading.

The quality of the review process is a comprehensive and multifaceted concept (Brown *et al.*, 2002). Previous studies have concluded that it is not sufficient to measure regulatory performance in terms of the speed of the approval process alone. Maxwell (2004) indicated that: "Concern about quality of care must be as old as medicine. But honest concern about quality, however genuine, is not the same as methodical assessment based on reliable evidence". Maxwell also identified six key dimensions of the quality, and these are (1) Accessibility (is the service accessible in terms of distance, time, and social barriers?) (2) Effectiveness (does the service produce the desired outcome?) (3) Efficiency (does the service produce the desired outcome with the least waste/at low cost?) (4) Equity (indicating the quality of access to services) (5) Relevance to need (is the service appropriate to the needs of its users?) (6) Acceptability (what is provided and the manner in which it is provided) (Moss, 2004). The quality of the regulatory review process, from the construction of the dossier to the final regulatory decision must also be examined (McAuslane and Cone,

2006). The importance of implementing and maintaining Good Review Practices (GRPs) are critical measures that need to be considered by the Gulf States to provide consistency and to improve efficiency, clarity, and transparency of the review process. It is important to adopt GRPs as standard processes through formal training of the review staff (US FDA, 2009).

The GCC authorities were found to be carrying out a number of activities to bring about continuous improvement in their regulatory review process. Various reasons were stated for introducing quality measures into their activities but the most common ones were to ensure consistency and efficiency and to minimize errors in the system (Al-Essa, 2011). Therefore, quality systems should be regularly reviewed to ensure that they are working effectively (Mallia-Milanes, 2010).

The purpose of this research has been to evaluate the regulatory review process in the GCC central registration and its impact on patients' access to medicines in the GCC States. The focus of chapter three was on evaluating the regulatory review process in Oman in order to identify areas of improvements in the system. Chapter four analysed the approval time over the period 2008-2010 in the GCC States. The evaluation of the review times for New Active Substances (NASs) and Existing Active Substances (EASs) in the GCC Centralised Registration system (January 2006 to December 2010) was the focus of chapter five while chapters six and seven assessed the views and experiences of the GCC regulatory authorities and pharmaceutical companies in order to identify the strengths and weakness of the current GCC centralised procedure. Finally, the similarities and differences between the experiences of regulatory authorities and pharmaceutical companies with the Gulf Centralised Procedure and a proposed new model for the GCC-DR was the focus of chapter eight.

The research began by thoroughly assessing the trend in the regulatory approval times in Oman for the period 2006 to 2010. The findings showed that although there is an increase in the approval time for all pharmaceutical company products, the median approval time for the five year period was 117 days. This is within the time limit (4 months) which is fixed by the health authority for the overall registration time. Oman is facing significant challenges reflecting the rapid advancement of regulatory services with limited resources possibly influencing patients' timely access to medicines. These challenges gave the regulatory agency no choice but to review and update its regulatory practices. The ability to regulate medicines effectively is

determined by a number of factors including the availability of guidelines, good written procedures and the provision of the appropriate resources to fulfill the regulatory needs. The lack of resources can be compensated to some extent by effective collaboration among countries and information sharing (WHO, 2008). The Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&DC) budget is not separated from the MOH, so development is minimized, due to priority within the government system. Increase in the registration fee and its use to develop the authority could help to improve the quality of the review.

Another important aspect that needs to be highlighted in Omani regulatory practices is the use of the verification model for the assessment of a new registration dossier. This model is acceptable for the majority of applications if they are registered in countries with recognized regulatory authorities. If not, it is critical to consider a thorough and more specialized review for products which are not registered elsewhere and for biotechnology and biological products. Singapore, for example, conducts a verification review for all types of medicines which are previously authorized by at least two reference authorities (e.g FDA, EMA), except for biological and biotechnology products (Health Science Authority (HAS, 2011).

In a further study a downward trend was demonstrated in the median approval time for most of the GCC States during 2008 to 2010. However, the approval time for all approved products in the GCC States during this period varied from about 60 days in Qatar and Oman (2009 and 2010), and to about 609 days in Saudi Arabia (2008). There are many factors which can affect and explain the differences in approval time in the GCC States. The main factor is the difference in the positions of milestones within the approval process, for example, the analytical step starts with the scientific assessment in Oman, Saudi Arabia, and Qatar (*parallel procedure*), but in Kuwait and Bahrain the analytical step comes after the scientific assessment (*sequential procedure*).

Regulatory approval times have also been influenced by the type of assessment carried out by different authorities. Bahrain and Kuwait uses a verification review for all types of products registered in countries with competent authorities. Saudi Arabia performs a full review on all types of application while Oman and Qatar perform an

abridged review for all products. The GCC states should seek to increase the level of funding to bring about the required expertise and resources to conduct a more extensive review of important medicines, including biological and biotechnology products. A clock stop is another important approach which is not fully enforced in the GCC authorities to control the overall approval time. The EMA is obliged by the regulation to reach a decision within 210 days, although the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data (EMA, 2009).

Furthermore, this research project investigated the pattern of total regulatory approval times in the Gulf Centralised Procedure over the period from 2006 to 2010. It also addressed the various factors which may have a positive or negative effect on total approval times. During the five year period of the study (2006 – 2010), the median approval time significantly increased due to several factors which included the limited number of meetings by the GCC-DR and increased number of applications for registration. Other factors that delayed the registration were the assessment review process where two authorities are selected alphabetically to review the registration dossier. In addition, the lack of a standard evaluation template for product assessment leads to an increase in the correspondence which is sent to the sponsor in several batches and at different times. It is recommended to have one standard assessment template and rather than selecting the reviewing authorities alphabetically, the dossier should be sent to all countries and all assessments combined into one final report on which the final decision in the GCC-DR could be based. Other factors that could speed up the registration process is an increase in the number of the committee meetings and using information technology and e-mails in the communication between the Executive Office and the companies.

The findings from this study also highlight the ten years achievement of the Centralised procedure and its future potential as identified by the health authorities as well as the pharmaceutical companies. Although, both the regulatory authorities and the pharmaceutical companies agreed that the centralised procedure is an effective system for authorizing the marketing of medicinal products, the pharmaceutical companies still have mixed feelings about whether they can gain faster marketing authorization through the national regulatory systems or the regional centralized system. After all, the goal of

any pharmaceutical company is to complete the registration requirements and gain access to the national GCC markets in the shortest possible time (AL-Essa, 2011).

In the end, two approval routes, national and centralized, are permitted to exist side-by-side in the GCC region. But for the centralized system to dominate, member states should seek ways to increase their collaborative efforts to bring their systems closer towards standardization that would facilitate the regional registration process and maintain patients' access to safe and effective medicines within a reasonable time frame. It is recommended that the comments and opinions of the countries, where the products have been registered nationally, should be considered when products are being evaluated at GCC-DR. In this way, the approval process would be expedited and this would facilitate faster approvals at a national level after the products have been approved by the GCC-DR. The only way to improve support for the GCC registration is to give some advantages over the national registration for companies who choose this route. It is very important to note that most companies require a single registration system, either national or centralised, for their products. Dealing with two registration systems in the same region is thought by some to be inefficient.

The GCC as a conceptual framework for harmonization among the member states has been extended to areas like pharmaceutical procurement. In this regard the centralised procedure was established as a step in the overall harmonization efforts of member states. The GCC-DR is gaining momentum and importance for the private sector as reflected in the responses of companies. Furthermore, the GCC-DR is contributing in a positive way, especially in smaller member states although efficiency needs to be improved. Efficiency can be clearly linked to the quality of decision-making during the review process and all member states considered the GCC-DR review to be of the same quality as the national review or better except for Saudi Arabia who considered the review quality as worse than national review. Member states sought to find a solution to improve the review process by utilising a standardised review template. This would avoid efficiency issues due to requests for additional data. In addition raising the scientific and review skills of participating staff from member states in the central procedure and by adopting clear SOPs for the review process would be of benefit. Furthermore, harmonization of national review guidelines and procedures within the GCC-DR would be an advantage as well. Needless to say the positive influence of such harmonization will result in efficiency at both national and central procedure level. For all these reasons, companies usually adopt the most economically viable registration system that meets their corporate objectives.

The GCC-DR system can be better executed by the formulation of policies and guidelines that are practical, concise and clear. A healthy interaction between regulatory agencies and pharmaceutical companies at an early planning stage may boost the overall central drug registration process. A competent registration process which is rooted in transparency of procedures and unbiased scientific opinions would lead to a smooth drug registration process among the GCC States.

Limitations of the study

As with any research there were a number of limitations including the following:

- For the evaluation of regulatory review times in the Gulf States it was not possible to obtain information of the review system or timelines for UAE or Yemen. This was despite several e-mails and follow-up phone calls. Although for the sake of completion it would have been ideal to have received data from both these States, it did not have a detrimental effect on the overall conclusions.
- The evaluation of the GCC Centralised regulatory review process only focused on approved products. It would have been an advantage in reviewing the timelines to have access to those products that were rejected, however, these were not available in an electronic form and so would have necessitated identifying these manually. Again, this would not have influenced the evaluation of the efficiency and overall performance of the GCC-DR.
- The evaluation of the pharmaceutical companies experiences with the GCC Centralised Procedure was limited by the response rate of 30%. This was despite an extensive follow-up of the companies who did not respond or who had limited experience with the centralised system. In such circumstances, the problem is not so much ending up with a low number, but rather the differences between responders and non- responders.

Recommendations

As a result of this research there are a number of recommendations that can be made. There is defiantly scope for improvement whether at national level or at the GCC-DR. Although many, if not most, of the desired improvements are a common to all member states some of them are specific to each member state. Common recommendations for all member states include the following:

- **Adoption of harmonized regulations**

Member states in the GCC-DR have collaborated to produce regulations that govern the approval process at the GCC-DR. The regulations are in effect the result of a common acceptance of the required standard for marketing authorization of pharmaceutical products. It is logical for each member state to adopt, at a national level, such regulations which would be the basis for greater harmonization within the GCC-DR and among member states should mutual recognition be contemplated between two or more states.

- **Training programmes**

Common training programmes are needed for reviewers in all member states. Such training programmes should provide the required knowledge and skills for reviewers. In order for such programmes to be effective, acceptable criteria for the attainment of training objectives must be agreed as well. This could be at a national, inter-state or common for all GCC states. Only qualified trainees should be allowed to progress to be official reviewers. Almost all developed health authorities have similar programmes for training employees to be reviewers and this is an essential element for any health authority.

- **Electronic process management**

The adoption of computer based systems for task management is often absent in most Gulf States despite the fact that they have adopted electronic governance in their countries. Computerization is seen in almost all aspects of life in the Gulf States and it is surprising that computer systems are not yet used in many Gulf States for the regulatory review process. Computerizations

of process management remain one of the most challenging tasks for most, if not all, GCC states. This task is assisted in that all member states and the GCC-DR have adopted the CTD (Common Technical Document) standard for dossier submission. Furthermore, the eCTD (electronic Common Technical Document) standard is already published by ICH and should allow the Gulf States to manage the computerization of the review process in an enlightened manner.

- **Qualifying programs for Quality Control Laboratories (QCL)**

In order to harmonize the standards for analytical procedures in each member state, common standards must be agreed by member states for each state QCL. This should be followed by appropriate training for all QCL staff and adopting of common accreditation criteria.

- **Batch analysis**

Like all Arab states, the GCC states perform release analysis for all submitted products for approval. Further, the QCL performs release analysis for every batch marketed. This places a burden on QCL in any country and prevents the QCL from performing their main task of assuring the product's quality in the market place. The GCC states need therefor to agree on the required function of the QCL in member states which should be similar to the European approach to QCL in European regulatory authorities.

Further recommendations are also suggested for the GCC-DR.

- **Adopt a new model for the regulatory review**

As already outlined a new model is proposed for the GCC-DR. Irrespective of whether the proposed model is acceptable or not, a new process model is needed to improve the performance of the GCC-DR. Any model must take into account the effectiveness and efficiency needs of the GCC-DR.

- **Proceed to full approval with pricing**

For the GCC-DR to operate effectively the mandate foundation of GCC-DR needs to be revised. The new mandate should state that the GCC-DR is the way forward for approvals within the GCC states for medicine and health products and this should include pricing of submitted products for approval.

- **Validation of authorized products in member states**

To minimize the work load, the GCC-DR should adopt and validate approved products already authorised in member states. In this regard the GCC-DR should develop guidelines for such validation and seek member states approval. The validation process should be a quality assurance process and ensure that this is within an acceptable standard for member state.

There are also a number of recommendations for individual member state,

- **Harmonize regulations with GCC-DR**

GCC-DR regulations should be adopted by each member state and this should be a formality within the state legal framework.

- **Adopt mutual recognition**

Member states should adopt mutual recognition with other member states with a similar review system. This would allow the development of the GCC-DR as an organisation similar to that of the European Medicines Agency.

- **Mutual recognition of QCL batch certificates**

Member states should adopt mutual recognition procedure for QCL batch certificates in order to reduce the work load and avoid unnecessary repetition in samples analysis.

- **Exchange programmes for reviewers**

Member states should adopt a programme of exchange for reviewers to allow experience to be shared between member states.

- **Electronic processes**

Member states should adopt the electronic management of processes and documents. This will relieve the bottle necks in work performance including the review procedures. Commercially available work flow systems, document management system and electronic review systems are readily available and in use by many health authorities worldwide but especially in Europe this has been an established practice. Most European authorities including the European Medicines Agency use validated software which is well accepted and commercially available.

Future work

- It would be of value to continue the evaluation of the Oman pharmaceutical review process and analysis of the timelines for NAS's and EAS's for the period 2011-2014. In addition it would be helpful to understand if there have been any improvements in good review practice.
- It would be advantageous to continue the evaluation of regulatory review times in the Gulf States for the period 2011-2014 and to make sure that responses are obtained from all states including UAE and Yemen.
- As an evaluation of the GCC centralised procedure is fundamental to any future model that might be implemented, it would be essential to update the timeline data for products that have been reviewed between 2011-2014.
- It would also be of value to repeat the evaluation of the Gulf States views and experiences, as well as pharmaceutical companies with the GCC centralised procedure over the past three years.

- It would be of value both to the member states and the rest of the world to understand from the seven Gulf States and the pharmaceutical industries what are the benefits of this new proposed system as well as the challenges.

Conclusion

In this research the Gulf Cooperation Council centralised procedure for the approval of pharmaceutical products was evaluated. The results demonstrated that the GCC-DR centralised procedure has contributed to a better review process both at the GCC-DR and national level. The GCC-DR needs to be revised and developed to an independent marketing authorization granting authority providing applicants with one license that covers all seven Gulf States. A new model for the GCC-DR CP has been proposed which should resolve many of the difficulties facing the GCC-DR currently and should improve its effectiveness and efficiency.

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Appendix 1

List of pharmaceutical companies respond to CACP

1	Abbott
2	Amriya Pharma
3	Apopharma Inc
4	AstraZeneca
5	B.Braun
6	CSL
7	Eli-Lilly
8	Glaxo Smith Kline
9	Glaxo Smith Kline Consumer Healthcare
10	Hospira
11	Hovid
12	Janssen
13	Jazeera Pharmaceutical Industries
14	Joriver
15	Kilitch
16	KSPICO
17	Leo Pharma
18	National Pharmaceutical Industries
19	Novartis Pharma AG, Basel, Switzerland
20	Oman Pharmaceutical Products
21	Pfizer
22	Pharmascience
23	Qatar Pharma
24	Ranbaxy
25	Reckitt Benckiser
26	Riyadh Pharma
27	Sandoz
28	SEDICO
29	Servier
30	SPIMACO