EVALUATION OF THE REGULATORY REVIEW PROCESSES, QUALITY OF DECISION-MAKING AND STRATEGIC PLANNING IN THE GULF COOPERATION COUNCIL (GCC) STATES

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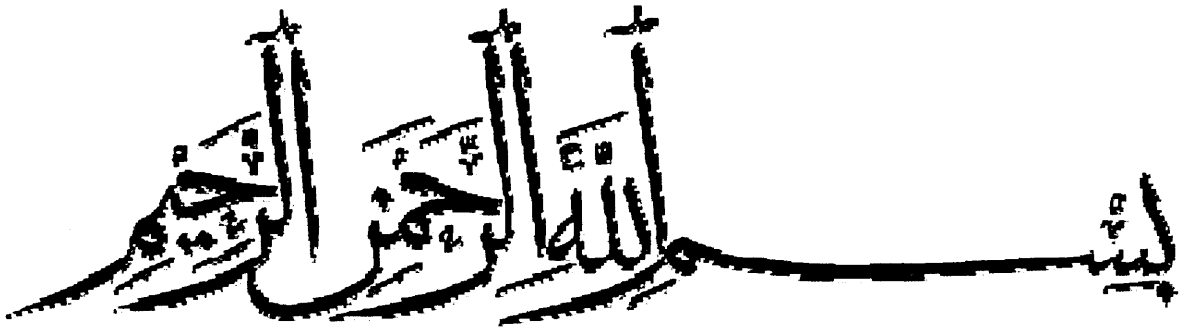

In The Name of Allah, Most Gracious, Most Merciful

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ABSTRACT

Regulatory authorities in both developed and developing countries share the responsibility of ensuring the access of safe and effective medicines to patients; however their structures, strategies, and practices vary significantly. The aim of this study was to evaluate the Gulf Cooperation Council (GCC) regulatory systems (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE) and Yemen) in order to develop a harmonised strategy.

A questionnaire was designed and completed by the seven GCC authorities to provide details of their review process and the quality measures used to improve their assessment procedures. The Kuwait Drug and Food Control (KDFC) authority was assessed to identify areas for improvement in the system. Metrics for medicines approved for the private and government sectors were collected together with their patients' access time using data obtained from the authority's archives. Another questionnaire was developed to assess and compare the strategic planning processes of the regulatory authorities in the seven Gulf States. Both questionnaires were tested for applicability and practicality in the GCC region and a pilot study was conducted with two selected authorities, after which they were distributed for completion by senior managers in each of the seven GCC authorities.

The results of the Kuwaiti regulatory system showed a significant decline ($p < 0.001$) in the number of medicines approved for the private sector from 180 to 129 products (2006 to 2009). In contrast, there was an increase in the number of medicines approved for the government sector from 22 to 48 products over the same period, but did not reach statistical significance ($p > 0.05$). Further analysis showed a significant decline ($p < 0.001$) in the patients' access time for New Active Substances (NASs) (26 to 11 months) and Existing Active Substances (EASs) (28 to 14 months) due to the enhanced political conditions and the improved performance of the authority. Furthermore, there was a significant decline in the registration time for government health supply (GHS) medicines from 10 to 7 months ($p < 0.05$) and for private sector medicines from 28 to 14 months ($p < 0.001$) over the same period.

The comparative study of the seven Gulf States showed that Kuwait and Yemen carry out a verification assessment for all applications. Bahrain and Oman conduct an abridged review while Saudi Arabia and UAE perform a full review for the majority of

their applications. Furthermore, the speed of the approval process in the GCC States depends on the types of products being registered (NASs or EASs), the quality of the submitted data, the level of interaction between the sponsor and the authority and whether parts of the review process are carried out in parallel or sequentially. Several GCC authorities lack the essential measures for conducting a quality review process such as Good Review Practice, assessment templates, Standard Operating Procedures and peer reviews. Finally, comparisons of the GCC strategic planning processes showed that the seven Gulf States shared common strategic parameters that can form a harmonised strategy, namely, the guidelines, SOPs, resources and Post-Marketing Surveillance (PMS).

It is hoped that the findings of this study will help the GCC authorities to improve approval time for the registration of new medicines by fully engaging in the quality review practices. Such improvements will fulfil the GCC central drug registration goals and encourage the pharmaceutical industry to use the GCC centralised system which is a step towards successful harmonisation of the regional regulatory systems.

CONTENTS

List OF ABBREVIATIONS

AMRAs : African American Regulatory Authorities

APG : American Pharmaceutical Group

ASEAN : Association of South-East Asian Nations

C&F : Cost and Freight

CDER : Center for Drug Evaluation and Research

CEO : Chief Executive Officer

cGMP: : Current Good Manufacturing Practice

CIF : Cost, Insurance and Freight

CMC : Chemistry and Manufacturing Control

CMR : Centre for Medicines Research

CMS : Central Medical Stores

CNS : Central Nervous System

CPD : Continuing Professional Development

CPP : Certificate of Pharmaceutical Product

CVS : Cardiovascular System

DRRS : Drug Registration and Release Superintendent

EAS : Existing Active Substance

e-CTD : Electronic Common Technical Document

EFQM : European Foundation of Quality Management

EMA : European Medicines Agency

EU : European Union

EURS : European Review System

GCC : Gulf Cooperation Council

GCC-DR : Gulf Cooperation Council Central Drug Registration

GCCU : GCC Central Registration Unit

GDP : Gross Domestic Product

GHS : Government Health Supply

GMP : Good Manufacturing Practice

GRP : Good Review Practice

HMRU : Herbal Medicines Registration Unit

HRC : Higher Registration Committee

ICH : International Conference on Harmonisation

IND : Investigational New Drug

IP : Intellectual Property

IT : Information Technology

KDFC : Kuwait Drug and Food Control

KSPICO : Kuwait Saudi Pharmaceutical Industry Company

MCC : Medicines Control Council

MRA : Medicines Regulatory Affairs

MD : Ministerial Decree

MHRA : Medicines and Health Products Regulatory Authority

MOH : Ministry of Health

MOU : Memorandum of Understanding

NAS : New Active Substance

NCE : New Chemical Entity

NDA : New Drug Application

OCD : Office Center Director

PDRU : Pharmaceutical Drug Registration Unit

PMDA : Pharmaceutical and Medical Devices Agency

PMS : Post-Marketing Surveillance

QA : Quality Assurance

QC : Quality Control

QP : Quality Policy

RC : Registration Committee

R&D : Research and Development

RH : Relative Humidity

RHI : Regional Harmonisation Initiatives

RIU : Release and Invoice Unit

SAC : Scientific Advisory Committee

SADC : Southern African Development Community

SC : Scientific Committee

SFDA : Saudi Food and Drug Authority

SOP : Standard Operating Procedure

TCR : Technical Committee for Registration

TCR&P : Technical Committee for Registration of Pharmaceutical Manufactures and their Products and Pricing of Products

TGA : Therapeutic Goods Administration

UPRU : Unclassified Product Registration Unit

US FDA : United States Food and Drug Administration

VMRU : Veterinary Medicines Registration Unit

WHO : World Health Organisation

GLOSSARY OF TERMS

Adverse event: any unfavourable and unintended sign in a patient or clinical investigation of a subject administered including a symptom or disease associated with the use of 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, Switzerland, Tanzania, Zambia and Zimbabwe.

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

Authorisation phase: Includes practices carried out when satisfactory outcomes of the evaluation phase has been reached. These are the product pricing process and the final decision making procedures.

Gulf Cooperation Council (GCC) Central Drug Registration: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE) and Yemen.

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

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

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 Authorisation covering the entire EU region is applied for, for example, for new biotechnological medicinal products and new innovative medicinal products. The applications for marketing Authorisation are then submitted to the European Medicines Agency (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.

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.

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.

Evaluation phase: Includes all the stages that involve the scientific assessment and quality control analysis carried out to ensure that the medicine is safe, efficacious and of the desired quality standard to be given to the patients. This phase consists of three stages, namely, the scientific assessment stage, the sponsor's interaction stage, and the sample analysis stage.

Existing Active Substance (EAS): An existing chemical, biological or pharmaceutical active substance includes a chemical, biological or radiopharmaceutical substance previously authorised as a medicinal product; an isomer, mixture of isomers, a

complex or derivative or salt of a chemical substance previously authorised as a medicinal product with the same properties with regard to safety and efficacy to that chemical substance previously authorised; a biological substance previously authorised as a medicinal product, which has the same molecular structure, nature of the source material or manufacturing process; a radiopharmaceutical substance which is radionucleotide, or a ligand previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide which has been previously authorised.

Goal: A stated aim; something specific the Planning Unit seeks to achieve or bring about in support of its mission. It is a broad statement describing a desired future condition or achievement without being specific about how much and when.

ICH Regions: European Union, Japan and USA.

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.

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.

Mission statement: A mission statement outlines the purpose of the existence of an organisation today. It focuses on today; it identifies the critical process (es); and it states the level of performance.

Mutual recognition procedure: The Mutual Recognition (MR) procedure utilizes the marketing authorisation 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 Authorisation 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.

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.

Objectives: Objectives are action-oriented and measurable steps towards the goals of an organisation. They are specific statements of desired short-term conditions or achievements; these include measurable end results to be accomplished by specific teams or individuals within time limits.

Patients' access: The active substance is made available for patients in the private and government sectors in any country.

Patients' access time: This is the time from the submission of the registration dossier to the Ministerial price approval of the new medicinal product.

Pricing time: The time from the registration of a new medicinal product to the Ministerial approval of the product price.

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.

Registration time: The time from the submission of the registration dossier to the registration of the new medicinal product.

Strategy: The direction and scope of an organisation over the long-term; which achieves advantage for the organisation through its configuration of resources within a challenging environment, to meet the needs of the public and to fulfil the stakeholder's expectations.

Strategic planning: A tool for organizing the present on the basis of the projections of the desired future. It is a road map to lead an organisation from where it is now to where it would like to be in five years.

Submission phase: The submission phase involves all the stages and processes carried out by the authorities' administrative staff prior the scientific assessment of the medicine. These include the receipt and validation stage and the queuing stage.

Values: Values are the collective principles and ideals which guide the thoughts and actions of an individual or a group of individuals (i.e., an organization). Values define the character of an organization – they describe what the organization stands for.

Vision statement: A vision statement outlines what an organization wants to be. It focuses on tomorrow; it is inspirational; it provides clear decision-making criteria; and it is timeless.

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CHAPTER 1

General Introduction

BACKGROUND

Effective Medicines Regulations

The regulation of medicines has evolved over the last five decades in response to serious adverse events in relation to medicinal products. The early regulatory standards were mainly related to ensuring the quality of pharmaceutical products and subsequent advances in the early 1960s led to the development of new standards for assessing the efficacy and safety of new medicines (Hill and Johnson, 2004).

Today, medicines are manufactured, marketed, distributed and dispensed across the globe. However, the globalization of pharmaceutical markets and production has also increased the spread and prevalence of medicines which are unsafe (Torstensson and Pugatch, 2010). Unsafe medicines can be divided into two categories, namely, counterfeit medicines which are deliberately forged and mislabelled with respect to identity and/or source and substandard medicines which have been legally authorised for manufacturing and marketing by a national or a regional regulatory authority, but do not meet the required quality or safety standards (Tortensson and Pugatch, 2010).

Currently, approximately 20% of countries have fully operational medicines regulations, 50% have regulations of varying capacity and 30% have either none or very limited drug regulation. Many developing countries are incapable of ensuring safety, efficacy and quality of the pharmaceutical products available in their markets because they are resource constrained in terms of staffing, standard systems, and training (WHO Drug Information, 2008).

The primary aim of drug regulation is protection of public health. However, it is claimed by some that the balance between controlling pharmaceuticals in the interests of ensuring public health and encouraging the development of the pharmaceutical industry has shifted in favour of the innovative industry. 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 expedite reviews and evaluations to approve new medicines in the shortest possible time. Furthermore, Hill and Johnson (2004) suggest that the political climate is currently in favour of multinational companies demanding the availability of new medicines for local patients in a timely manner without fully understanding the importance of supporting effective legislation to ensure

access to effective and safe medicines. However, 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 Role of Harmonisation of Drug Approval Systems

Given the major resources required to assemble registration dossiers for multiple submissions to a number of countries, there is a strong driving force towards promoting harmonisation in the format and the content of these dossiers. The establishment of the International Conference on Harmonisation (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 (WHO, 2002). Harmonisation involves the formation of effective networks between regulatory authorities (nationally, regionally and/or 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 Drug Information, 2008). The technical meaning of 'harmonisation' is the standardisation of technical requirements for medicines regulation (WHO Drug Information, 2008). These requirements relate to the quality, safety and efficacy of medicines and can differ in complexity from one country to another. In implementing harmonisation, all aspects of regulation are addressed to mitigate some of the problems associated with differing requirements between countries. Although the ICH group has intensified its work to cover non-ICH countries, it has been less successful in involving developing countries because harmonisation requires a certain level of socioeconomic development and a reasonable uniformity between existing regulatory systems (Saillot and Paxton, 2009). The ICH partners included the highly industrialized nations controlling the majority of the innovative industry, whereas most developing countries have generic markets with generic manufactures or none (Lilja et al., 2008).

Since its inception in 1990, ICH has evolved, through its Global Cooperation Group (GCG), to respond to the increasing global demands for drug development. The GCG was originally formed as a subcommittee in 1999 in response to the growing interest in ICH guidelines beyond the three ICH regions. A few years later, recognizing the need

to engage actively with other harmonisation initiatives, representatives from five Regional Harmonisation Initiatives (RHIs) were invited to participate in GCG discussions, namely, Asia-Pacific Economic Cooperation (APEC), Association of South East Asian Nations (ASEAN), Pan American Network on Drug Regulatory Harmonisation (PANDRH), Southern African Development Community (SADC) and the Gulf Cooperation Council (GCC) (Molzon, 2010). A further expansion of the GCG was agreed in 2007 and regulators were invited from countries with a history of ICH guideline implementation and/or where major production and clinical research are done (Australia, Brazil, China, Chinese Taipei, India, republic of Korea, Russia and Singapore) (ICH, 2011).

Regional Harmonisation

Cooperative action can be more effective in strengthening regulatory capacity at the national level, and the European Union (EU) centralized procedure is the largest established model for these systems. However, harmonisation within the EU took a number of years to develop to its current status. While the first EU Pharmaceutical Directive was issued in 1965, it was not until the 1990s that effective approaches for sharing regulatory processes and structures were really in place. Other regional initiatives include the ASEAN, the Andean Community, the Mercosur and the SADC (WHO Drug Information, 2008).

The seven Gulf Cooperation Council (GCC) States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) also took the initiative after the EU centralized procedure to improve patients' access to safe and effective medicines in the GCC Region. This was accomplished by strengthening the technical and administrative capacity of the individual GCC regulatory authorities. This envisaged that this collaborative mechanism could ensure a more transparent and streamlined process for the marketing authorisation of pharmaceutical products in the GCC Region.

The harmonisation of the regulatory processes in the GCC States has been a lengthy process. It 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 centralized registration system should be set up to monitor medicines and common guidelines be established for the participating authorities (Hashan, 2005). This was

followed by a series of GCC Ministerial Decrees relating to the establishment of a centralized 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. The remit of this committee ensures that the pharmaceutical companies apply satisfactory standards to guarantee manufacturing of quality, safe and effective medicines and to standardise their regulations with regards to medicines importation practices in the Gulf States.

The GCC Central Drug Registration (GCC-DR) Committee is composed of two members from each of the seven countries. The procedure is carried out by selecting two authorities alphabetically to review a registration dossier. However, all the GCC authorities are equally responsible for evaluating the quality, safety and efficacy of medicines and therefore all the seven states are provided with copies of the product registration dossier for their individual assessments. The seven member states meet four to five times a year to discuss the product review reports issued by the reviewers from each authority and the approval decision is made by agreement.

The central registration system has faced several criticisms with opponents 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 centralized authority. However, the effective collaborative efforts between the member states substantiated the support of the GCC-DR system for each GCC authority in improving the regulatory approval processes and operational efficiencies at the national level.

THE GULF COOPERATION COUNCIL (GCC) STATES: THEIR SIMILARITIES AND DIFFERENCES

The Gulf Cooperation Council (GCC) is a political and economic union involving six Arab States of the Arabian Gulf with shared economic and social objectives. It was created in May 25th, 1981 comprising Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates (UAE) (Figure 1.1). Therefore, these countries are often referred to as the GCC States.

Figure 1.1 Map of the seven Gulf Cooperation Council (GCC) States

Source: Adopted from Global Arab Network, 2010

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 structure of the GCC, demonstrated in Table 1.1, reveals that the total area of Gulf Region is 3,100,922 Km^2 with a total population of 61.5 million people having a median age of 26.4 years old and an average life expectancy of 73.8 years.

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

Country	Area / Km^2	Population	Median age (years)	Life expectancy at birth (years)	GDP ($)	GDP per capita ($)
Bahrain	760	738,004	30.4	75.4	28.27 billion	38,800
Kuwait	17,818	2,789,132	26.4	77.9	137.7 billion	51,200
Oman	309,500	2,967,717	23.9	74.0	72.8 billion	25,000
Qatar	11,586	840,926	30.8	75.5	100.8 billion	121,000
Saudi Arabia	2,149,690	25,731,776	24.9	73.9	590.9 billion	23,000
UAE	83,600	4,975,593	30.2	76.3	191.9 billion	40,000
Yemen	527,968	23,495,361	17.9	63.4	58.0 billion	2,500
Total	3,100,922	61,538,509	-	-	-	-
Mean	-	-	26.4	73.8	168.5	43,071

Source: Adopted from CIA World Factbook, 2009 and 2010 (accessed June 2010)

The largest country with the largest population and a dominating economy in the region is Saudi Arabia (CIA World Factbook, 2009 and 2010 data). The largest life expectancy at birth was shown to be in Kuwait while the highest median age was in Qatar. Yemen has the lowest GDP which may have had an impact on the life expectancy being the lowest in the region (63.4 years).

The demographic pattern of the GCC States may have an impact on the demand for pharmaceutical products in the region. During 2010-2020, the proportion of population over 65 years old is expected to grow from 2.7% to 4%. This population growth has averaged 3% per annum during 2004-2009, while the world population growth has risen 1% (ALPEN Capital, 2010). Older people generally need to seek more medical care and have more expensive health profiles than younger people. Improvements in life expectancy over the past quarter of a century have left the GCC with an increasing number of elderly people requiring care (Mourshed et al., 2007).

Furthermore, the increased urbanisation and per capita income in the GCC States have led people to consume unbalanced diets and aggravated lifestyle-related diseases such as diabetes and cardiovascular ailments. This has increased the market for drugs such as insulin. Although patents for many medicines are expiring, increasing lifestyle diseases would maintain revenue of the prescription medicines market in the long-term and encourage prospects for generic medicines manufacturers in the near future (ALPEN Capital, 2010).

The structure of the individual GCC regulatory authorities were explored through personal communication with key regulators in the region (Table 1.2). Five authorities are under the autonomy of the Ministry of Health 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. The seven GCC authorities regulate pharmaceutical products for human use with their main scope of activities revolving around marketing authorisation, post-marketing surveillance and quality control analysis. They also have a variety of other responsibilities depending on the size and resources available for each regulatory authority

Table 1.2 The structure, responsibilities and scope of activities within each of the seven Gulf Cooperation Council (GCC) regulatory authorities

Country		Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Name of Authority		The Pharmacy & Drug Control Department	Kuwait Drug and Food Control	The General Directorate of Pharmacy & 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	√	√	X	√	√	√	√
	GMP inspection		√	X	X	√	X	X
	Clinical trial authorisation	√	X	√	X	√	√	X

REGULATORY APPROVAL TIMES AND PATIENTS' ACCESS TO MEDICINES

The timeliness with which regulatory authorities approve new medicines for marketing affects healthcare professionals and patients. An unnecessarily long approval process delays access to new medicines that may improve patients' health status. Variation in the availability of drugs in different countries has been studied since the early 1970s (Rawson, 2000), and some marked differences have been found. The length of review time was perceived as one of the most important barriers to the pharmaceutical industry which is endeavoring to reduce the time required for review and approval of new applications (CMR Briefing 32B, 2001). Therefore, efforts have been made by many 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 (WHO, 2010). The timeliness with which national regulatory authorities approve new medicines has an effect on stakeholders, namely the pharmaceutical industry, patients and regulatory authorities (Anderson, 2004).

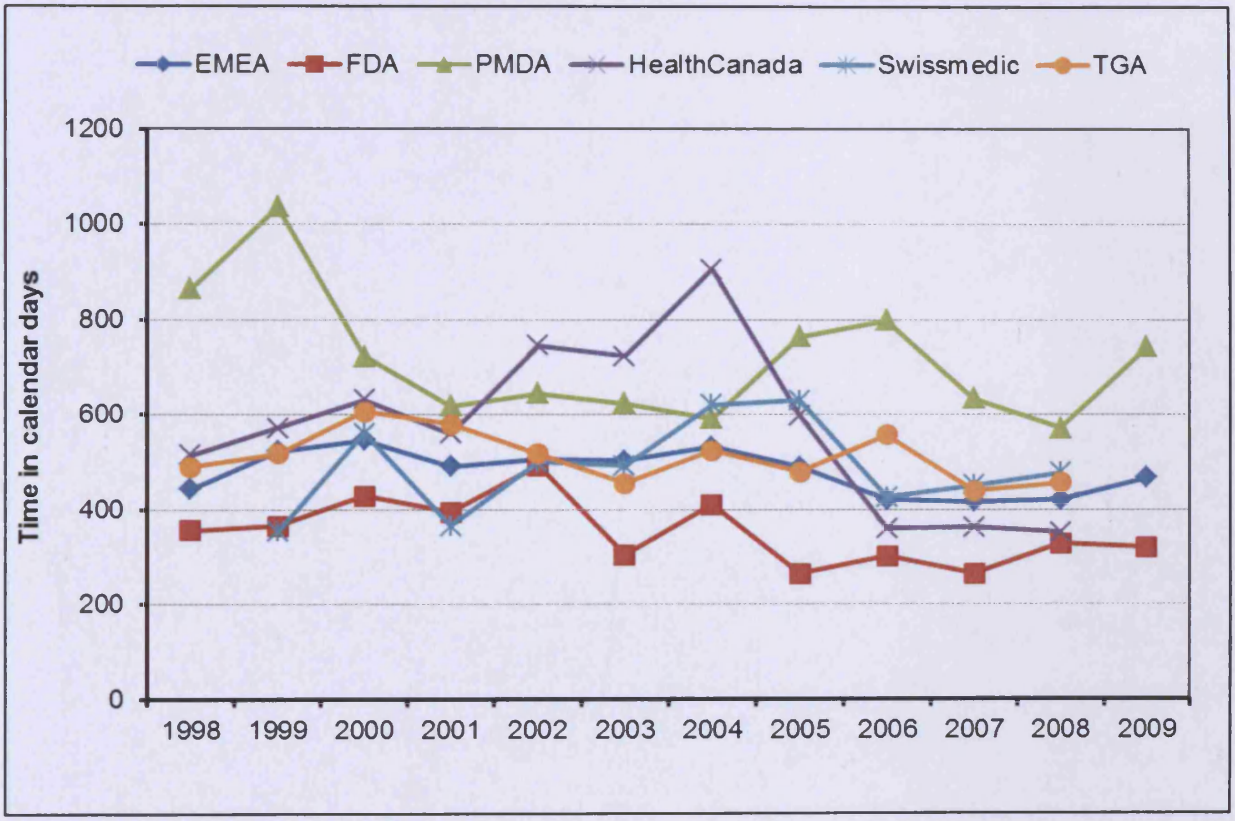
The length of the review process depends on the type of products being registered and the requirements of the approval process. Different countries impose different registration requirements on the manufacturers. However, it is possible to exploit these differences for the benefit of both the pharmaceutical industry and the regulatory authorities. For the manufacturers, registering new products in countries that have less requirements can help them produce evidence to support registration in other countries. On the other hand, such regulatory authorities will have the opportunity to compare themselves against other international systems. However, the first registering authority may not be sufficiently competent or recognised by the subsequent registering authorities. This may have an impact on the standard of the registration process of a pharmaceutical product elsewhere and the level of regulatory control in the countries where the product is approved. Therefore, authorisation by developed regulatory agencies not only leverages the standard of pharmaceutical products' registration elsewhere but provides an opportunity to establish a global market for the product in both developed and developing countries.

Furthermore, 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 is available and adequate. Many countries have legislative maximum times allowed for the review of dossiers. For example, the target time-frame for completing the review process in the EU centralized system is 210 days. This authorisation period has two points- known as 'clock-stops'- at day 120 and day 180. A time-scale of three months and one month, respectively, are enforced for applicants to respond and these periods maybe doubled upon request (EMA, 2009). The longest review time usually occurs when the benefits of the product are not apparent. This is used as a strong argument for carrying out the assessment at a regional level, rather than at a country level. The sharing of the evaluation work is currently what happens in the GCC-DR system, where the assessment process is shared amongst the GCC States and the decision is made by agreement. The challenge is not to implement a new centralised system, but to establish an effective method for sharing best practices, which include differences, amongst the countries to leverage the standard of the regulatory practices in each individual authority. The GCC-DR committee, with a total number of 14 members, two senior managers from each of the seven authorities, manages the GCC review process but is not able to function as a single authority, such as the United States Food and Drug Administration (US FDA) with approximately 3000 staff. Each country has its own authority with its respective identity that plays a prominent role in the overall functioning of the GCC-DR committee.

The efficiency of a review process is judged by the overall approval times from the time of submission of the new application to the date of patients' access to new medicines (Rawson, 2000; Anderson et al., 2002). Median times for patients' access (from the date of submission to the date of marketing authorisation) to new active substances (NASs) that were approved by six major authorities from 1998 to 2009 are demonstrated in Figure 1.2 (Patel et al, 2010). The median patients' access time achieved by the United States Food and Drug Administration continues to be the shortest amongst the six authorities. However, since 2006 there is an indication that the difference in the patients' access time between the six authorities has decreased, except for the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan which moved away from the other authorities when its review time increased in 2009.

This is the classic type of assessment that is carried out for comparing regulatory review processes to obtain information on trends and to demonstrate the impact of changes made to the review process over the years. However, such assessment provides limited information about the factors that influence the patients' access to new medicines (Hirako *et al.*, 2007).

Figure 1.2 Median times for patients' access to New Active Substances (NASs) in six mature markets (1998-2009)



Source: Adopted from Patel et al, 2010

An attempt was previously made to evaluate the length of the milestones and stages involved in the regulatory review processes for different authorities (Hirako et al., 2007) and a similar study of the GCC regulatory authorities was carried out by Hashan (2005) highlighting 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 lengths of the milestones and stages involved in the review process simply because the authorities did not have an electronic tracking system to monitor such activities.

Exploring the approval timelines in the Gulf Region would be worthwhile if the GCC regulatory authorities have managed to implement an electronic tracking system to monitor their approval times over the last 5 years; otherwise, the assessment of their approval timelines would remain to be a challenge for the current study.

The study carried out on established authorities assessed the review timelines, length of milestones and data points involved in the review process conducted in the United States, European Union, Canada and Australia. The data were obtained on applications for NASs that had not been previously approved by the authority in question, and were collected according to the year of submission rather than by the year in which the review process was completed. This method allowed meaningful comparisons to be made across these developed countries and identified variations in the length of the approval time in each authority (Hirako *et al.*, 2007). This study highlighted differences in timelines through variations in review practices and procedures. For example, in the Therapeutic Goods Administration (TGA), Australia, the advisory committee's evaluation procedure is an additional step to the scientific assessment process, while in the United States Centre for Drug Evaluation and Research (CDER), the advisory committees' evaluation process is part of the overall scientific assessment procedure. Likewise, Kuwait is the only authority that has a pricing department which is independent from the registration department and the pricing process is not part of the review process, while the pricing step in the other GCC authorities is part of the review process. Such factors may have an impact on the length of the approval time in any regulatory authority. The pricing step is an important part of the overall approval process in the Gulf States and, therefore, it should be addressed in future studies to make recommendations for improvement in the patients' access to new affordable medicines in the GCC Region.

EFFECTIVE REVIEW PROCESS: REGULATORY PERSPECTIVE

New medicines take years to develop and at every stage of the approval process, competent authorities review and assess research results. 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.

A strong, well-funded, consistent and transparent regulatory review system is essential to protect the public health and build confidence in the marketed medicines. Therefore, strengthening the regulatory authorities in the GCC Region is vital so that they have the expertise and tools to effectively evaluate new medicines. In general, the GCC authorities are structured differently and the scientific guidelines are not fully standardised and to solve this problem, they are consistently improving dialogue with each other and with the industry. To submit a new application in the GCC States, it is important to assess the regulatory review systems (regulations, directives and guidelines) and the regulatory requirements in each country. Differences in the pharmaceutical legislation and registration requirements can be determined from the administrative data (e.g. type of documents and certificates requested), from the pharmaceutical quality data (e.g. requirements for stability data) and from the clinical development data (e.g. placebo-controlled studies or comparative studies) (Horner, 2005). Therefore, it is very important to analyse and discuss especially the differences and similarities between the regulatory review processes carried out in the seven GCC authorities. To explore these, it is critical to identify key milestones and stages within each review process that can be benchmarked across the GCC Region (CMR Briefing 11, 1997).

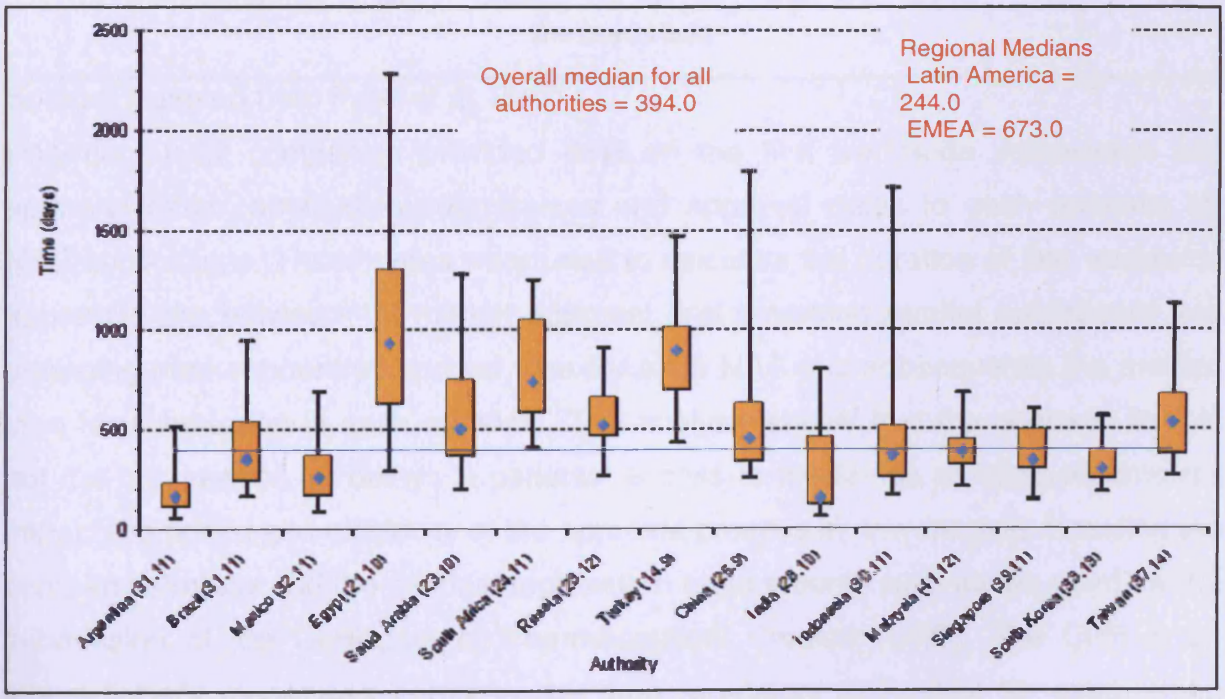
Regulatory approval times can also be influenced by the type of assessment carried out by different authorities. This was outlined in a study carried out among regulatory authorities in the emerging markets (Mallia-Milanes, 2010). This study showed that Singapore carries out three different review procedures, namely, the full, abridged and verification review. Full review involves products that have not yet received approval elsewhere. It takes 270 working days to be completed and is supported by external regulatory professionals (Foo, 2006). An abridged review is used for the majority of applications when the drug has been approved by a recognised regulatory authority, such as US FDA and EMA, before submission in Singapore. An Abridged evaluation takes approximately 180 working days. A verification review is carried out if the drug has been approved by at least two benchmark authorities. The evaluation takes four months and is mainly based on assessment reports but cannot be used for biological and biotech products (Foo, 2006). Argentina, was the only authority using

a verification assessment in the emerging market involving five other authorities (Mexico, Egypt, Saudi Arabia and Malaysia and Singapore) which conduct the abridged assessment for most of their applications (Perez, 2007).

The model of the review process carried out by the regulatory authorities is critical for pharmaceutical companies that are seeking to market new medicines in a timely manner. Therefore, in order to understand the type of model being used in each GCC State, it is necessary to examine the extent of their scientific review. Furthermore, the time taken for the completion of the regulatory approval process is also critical for the pharmaceutical companies in emerging markets (Walker *et al.*, 2005a, 2005b and 2005c) (Figure 1.3).

There are considerable differences between countries in the time taken to review medicinal products with median approval times ranging from one to three years. This difference was expressed analysing data on NASs approved between 2005 and 2009 in each authority (Figure 1.3) (Patel et al, 2010)

Figure 1.3 Regulatory approval times from date of submission to date of approval for New Active Substances (NASs) (2005-2009)

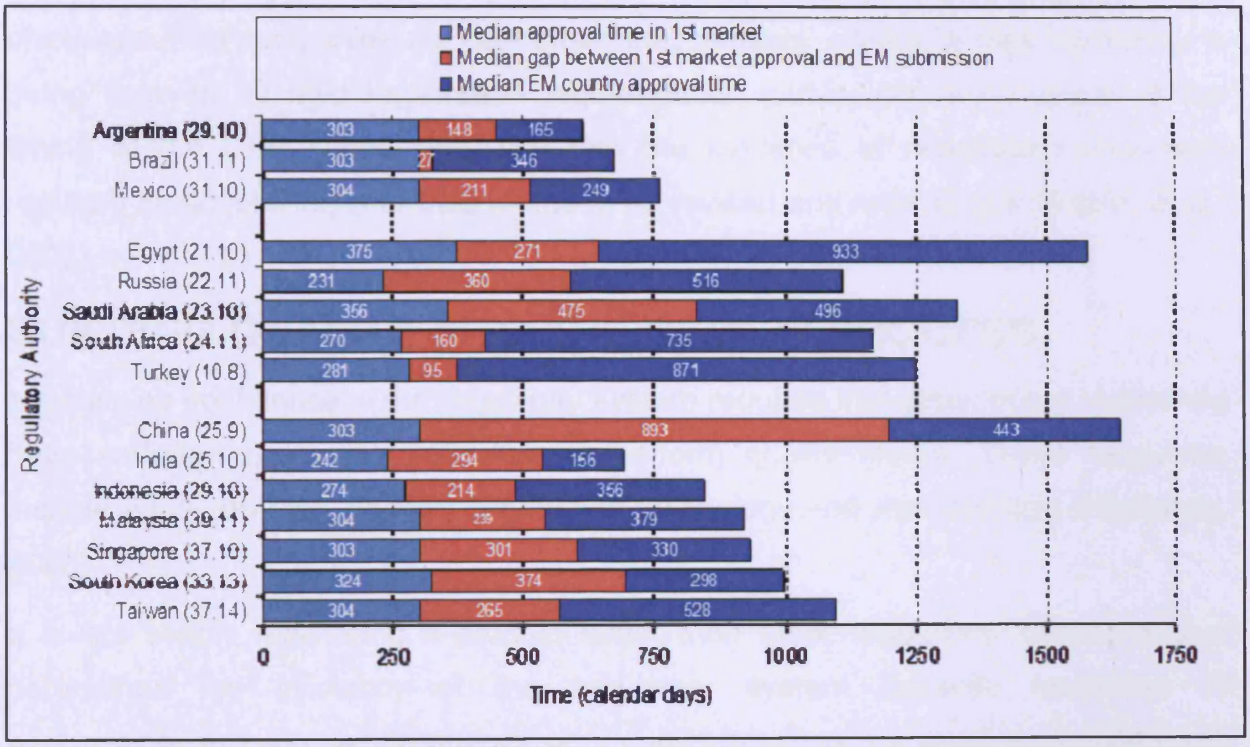


Source: Adopted from Patel et al, 2010

McAuslane et al. (2009) stated that there is a critical time interval between the approval by the first authority, usually in an ICH country, and subsequent submission for approval in another country. This was shown in the analysis of a composite of the

median interval durations for the first regulatory approval for a NAS application around the world, followed by submission and approval for the same compound to one of the emerging market authorities (Figure 1.4).

Figure 1.4 Median times for patients' access to medicines in Emerging Market (EM) countries for New Active Substance (NASs) (2005-2009)



Source: Adopted from Patel et al, 2010

Pharmaceutical companies provided data on the first worldwide submission and approval dates, application submissions and approval dates to each authority for NAS applications. These dates were used to calculate the duration of first worldwide approval, gap between 1st market approval and emerging market submission and emerging market country approval time for each NAS and subsequently the median time for submission in each authority. The analysis shows that the approval time is not the only reason for delays in patients' access to medicines as other parameters impact the speed and efficiency of the approval process in new markets including the company strategy and the national registration requirements such as the need for the submission of the Certificate of Pharmaceutical Product (CPP). The CPP is an internationally recognised certificate by drug regulatory authorities for establishing the status of a pharmaceutical product registration elsewhere. This document provides evidence that the medicinal product was produced under a comprehensive system of quality assurance, conforming to Good Manufacturing Practice (GMP)

standards as mandated by the World Health Organisation (WHO). It contains specific information such as the name of the product, the formulation, the manufacturer, packager, product license holder, and whether the product is marketed in the country where the CPP was issued. The extent of the authorities' reliance on the CPP depends on the type of review that is carried out by the importing country. However, pharmaceutical companies are concerned that patients' access to new medicines is being delayed by rigid registration requirements, particularly with regards to the timing of the CPP submission, and that the evidence of registration elsewhere required by developing countries needs to be revised and rationalized (Walker et al., 2007).

BUILDING QUALITY INTO THE REVIEW PROCESS

Maintaining confidence in the regulatory system requires that government authorities have sufficient resources and skills to perform quality review. These resources include adequate staff, budget, information technology and work facilities (Korteweg, 2003).

It is not simply registering a product faster than other regulatory authorities that determines the efficiency of the regulatory system because measures of performance through identification of poor quality products are much more important. There are four key determinants of the quality review process, namely an,

- Effective capacity development strategy that involves retaining staff through salary benefits as well as collaborations with other authorities for skill development.
- Efficient system of tracking application assessment and decision-making. Quality review requires the appropriate use of information technology.
- Effective networking with competent authorities to exchange best practices and to have appropriate insight into the capacity and performance of the authority.
- Accountability and transparency of the registration decisions. There is a range of interest groups that try to influence the authority's decisions, ranging from politicians to patients and clinicians. Strong and defensible decision-making is an authority's best protection against any influence.

Despite the considerable number of analytical and comparative studies on regulatory performance, there is limited research in the field of quality management, particularly the quality of the regulatory review process, the quality of decision-making, as well as

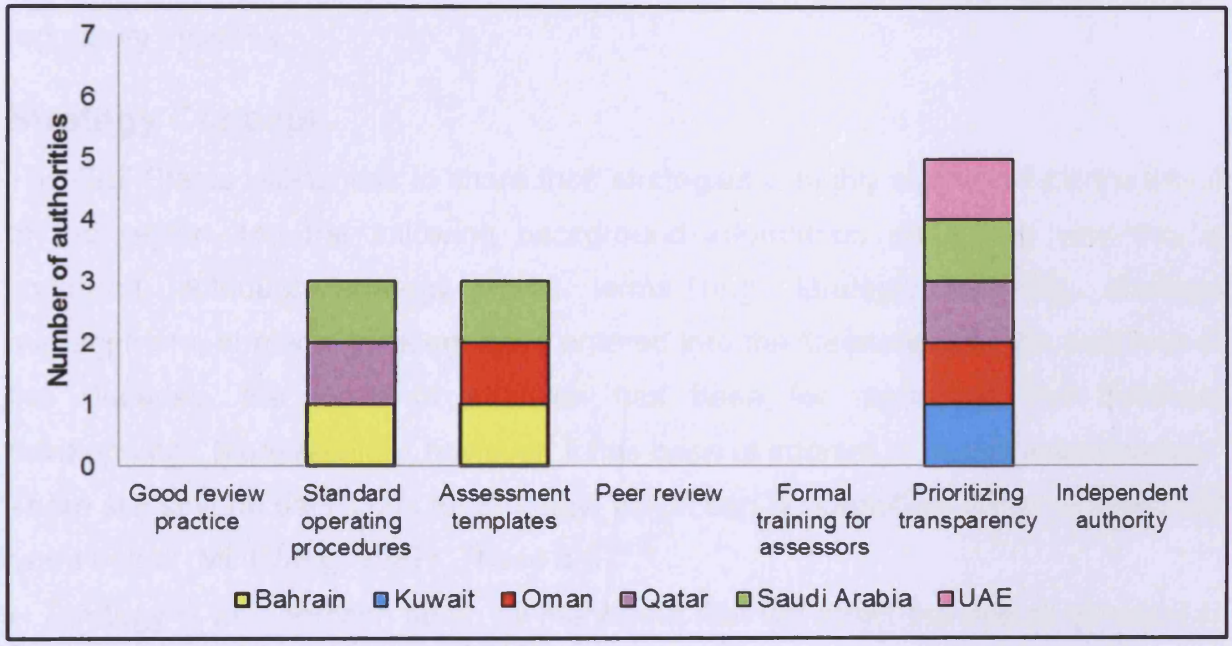
on the quality of the dossier submissions. The ultimate measure of success in the regulatory performance is the quality reviews and decisions, as well as the quality of the dossiers (United States Pharmacopeia (USP) Drug Quality Information Program, 2007; Karlton and Johnson, 1997; Cone and McAuslane, 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, 2006). 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).

Equally, both the authorities and the industry benefit from the consistency, thorough content, simplicity and overall the quality of the dossier (Zellerhoff, 2001). The quality of the dossier plays an important role in the achievement of a rapid regulatory review and approval of the new application (Karlton and Johnson, 1997). Poor quality complicates the review process and may negatively impact the confidence in the quality of the medicinal product and/or its manufacturer (Zellerhoff, 2001). Therefore, pharmaceutical companies are obliged to present high quality dossiers to maximize the efficiency of the review process and to increase the confidence in their systems (Abraham, 2002). Quality decision-making is also essential for any organisation that seeks maximum performance outcomes. Poor decision-making in the regulatory authorities results from the risk of performance failure or human errors (WHO policy perspectives, 2003). Furthermore, pharmaceutical companies are equally responsible for the quality of their decisions made at critical stages with regards to the benefit and risk for patients (Cone and McAuslane, 2006; Walker et al., 2007).

A study conducted by Hashan (2005) on the GCC regulatory authorities explored the quality measures used to improve the quality of the review and decision-making process in each of the six authorities (Yemen was not in the GCC group at the time). The study examined several aspects of quality that may have had an impact on the regulatory review process such as standard operating procedures (SOPs), good review practices (GRPs), peer review, assessment templates, transparency,

resources and training and continuing professional development programmes (Figure 1.5). This study revealed that many quality management tools did not exist in most of the GCC authorities and the ones which were present were being used differently by each authority which made it difficult to perform comparisons of the quality measures between the GCC authorities. In addition, the impact of the quality measures on the efficiency of the review process, such as SOPs and transparency, was not determined.

Figure 1.5 Measures used to improve the quality of the regulatory review process and decision-making in the Gulf Cooperation Council (GCC) States



Source: Adopted from Hashan (2005)

This was due to the lack of the electronic tracking and monitoring system of the review process in the Gulf States which made it difficult, if not impossible, to determine the impact of quality measures on the performance outcomes. Nevertheless, the previous study was the first to examine the quality management tools and to highlight areas where the quality of the GCC review processes was being monitored. It provided the opportunity to familiarise the Gulf authorities with the quality measures that could be of benefit for their regulatory review outcomes. Therefore, it is essential and reasonable to follow-on the progress made with regards to the current measures used to build quality into the review and decision-making processes in the GCC States.

STRATEGIC PLAN

The seven members of the Gulf Cooperation Council (GCC) decided to formulate similar regulations through their joint efforts to improve patients' access to medicines in the Gulf Region. The nature of the individual authorities makes the design of a harmonisation strategy rather difficult before a full evaluation of each of the seven authorities has been carried out. Therefore, a systematic planning process which involves identifying the status of the GCC authorities, their vision and mission statements, operating values, goals and objectives, priorities and monitoring their strategies and action plans are critical for the successful harmonisation of the GCC regulatory systems.

Strategy Concept

The Gulf States willingness to share their strategies is highly significant for the future of the region and the following background information underlines why this is important. Although strategy-related terms (e.g. strategic planning, strategic management, strategic thinking) have entered into the literature over the past four or five decades, the focus of attention has been for managers and business development. More recently, however, it has been of interest to healthcare providers. There are several definitions for strategy, which can be identified, some of which are listed below (Mintzberg, 1987). These are,

- Strategy is an approach taken by managers that will affect the overall direction of the organisation and will establish the organisation's future environment.
- Strategy is a way an organisation seeks to achieve its vision and mission. It is a forward-looking statement about an organisation's planned use of resources and deployment capabilities.
- Strategy is actions undertaken by managers to attain their goals.
- Strategy is a way of visualizing a future scene and doing everything possible in order to convert future scene into reality.

Advantages and Disadvantages of Strategy

The Gulf States have developed their internal strategies, which have considerable advantages as well as disadvantages.

Advantages of Strategy

- Strategy sets the direction of an organisation in order for it to sail cohesively through its environment.
- Strategy promotes coordination of activity. To focus effort without a strategy would result in chaos as people pull in different directions.
- Strategy defines the organisation. It provides a shorthand way for people to understand their organisation and to distinguish it from others and provides meanings plus a convenient way to comprehend what the organisation does.
- Strategy provides consistency, reduces ambiguity and provides order. In this sense, a strategy is like a theory: a cognitive structure to simplify and explain to the world, and thereby facilitate action.

Disadvantages of Strategy

- Strategic direction can hide the potential dangers that can be encountered during the course of its implementation. While direction is important, it is better to move slowly and carefully without looking too far ahead so that the resulting behaviour can be easily controlled and modified at a moment notice.
- "Group think" arises when effort is too carefully focused. There may be no peripheral vision, to open other possibilities. A given strategy can become too heavily embedded in the fabric of the organisation.
- Every strategy, like every theory, is a simplification that distorts reality. Strategies and theories are not really themselves, only representations (or abstractions) of reality in the minds of people who create them. No one has ever touched or seen strategy. This means that every strategy can have a misrepresenting or distorting effort. That is the price of having a strategy (Mintzberg *et al*, 1998).

The Model of Strategic Planning

In pulling together the Gulf States strategies, it is useful to have a "model" to follow. Although different models might have different steps or maybe they vary in the sequence of the steps, the strategic planning process essentially involves three stages and poses the following questions: Where are we now? Where do we want to be in the future? How are we going to get there?

Where are we now?

Every profession and every organisation is guided by a set of beliefs and values that communicate its identity and what it stands for. Core values describe collective principles and ideals that guide the thoughts and actions of individuals within an organisation (Zarkesh, 2008). Values shape the organisational mission, processes and goals (Seevers, 2000) and, therefore, it is critical to determine the values that the GCC authorities live by in order to prepare and implement a successful harmonised strategic plan.

All strategic planning approaches attempt to find an optional match between the resources and capabilities available within the organisation (strengths and weaknesses) and the external market conditions and environmental trends (opportunities and threats). This match or co-alignment, often called SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) results in a strategy, where efficacy translates into some level of corporate performance (Darden School of Business Administration, 2009).

Where do we want to be in the future?

While an organisation must continually adapt to its environmental status, there are certain core ideals that remain relatively stable and provide guidance for the organisation's strategic direction (Zarkesh, 2008 and Minzberg, 1998). These ideals are:

- *The Vision Statement*, which provides a picture of the organisation's future and allows a framework to be formulated for its strategy.
- *The Mission Statement*, which provides a brief description of the organisation's fundamental purpose and focuses on its existing status.
- *The Visionary Goals*, which describe what the authority desires to achieve in the future without being specific about when and how much to accomplish.
- *SMART Objectives*, which determines the Specific, Measurable, Attainable, Relevant and Time-bound steps that support the organisation's mission in order to achieve its ultimate visionary goals.
- *Driving Forces*, which are the motivating factors that every organisation needs to have to be successful in navigating its uncertain future.

How are we going to get there?

Given the information obtained from the environmental scanning and the collective core ideals which comprise the fundamental components of the strategic planning process, a strategic planning model can be proposed as an initiative to harmonise the GCC regulatory practices and to pinpoint areas where quality measures are mostly required to improve the registration procedures in the seven GCC authorities. This strategic background provides the rationale as to why this particular study is so valuable to the Gulf Region.

Drug regulation is an interplay between law and science, as well as between regulators and the pharmaceutical companies, with input and influences from patients and healthcare professionals. These stakeholders determine the identity of the regulatory environment in each of the seven GCC authorities which cannot be neglected in the course of the assessment of the regulatory practices in each country. A focused view of the regulatory review process and the quality measures currently used to improve the standard of the assessment procedure is critical to underpin the similarities and differences between the GCC regulatory authorities. However, these similarities and differences cannot be exploited unless they are placed in the context of the GCC harmonised strategic plan. In general, an effective harmonisation strategy requires an effective coordinated approach, legislations and administration at the country and regional level. Regional cooperation is needed to ensure that the regulatory capacity is sufficiently developed to meet the demands of the regulatory environment and to ensure that public health protection is the main purpose of achieving a quality review process for medicines which is a critical step to ensure patients' access to safe and effective medicines.

AIM AND OBJECTIVES OF THE STUDY

Aim

The aim of this study is to develop a strategic planning process for the GCC regulatory authorities which would enhance their similarities, minimise their differences and standardise regulatory practices across the GCC Region.

Objectives

- Assess the regulatory review process in Kuwait in order to develop an appropriate model for the evaluation of other GCC countries. (Chapter Three)
- Examine the trends in the submission, registration and pricing of pharmaceutical products and the associated approval timelines for patients' access to medicines in Kuwait. (Chapter Four)
- Identify and assess the models and activities related to the submission, review and regulatory action for new drug application in the seven GCC States. (Chapter Five)
- Determine the similarities and differences between the regulatory processes that occur during the review of product dossiers within the GCC authorities. (Chapter Six)
- Identify best practices in order to improve the standard of the regulatory review process in the GCC states. (Chapter Five)
- Evaluate the quality measures that the GCC member states are building into their regulatory review processes to ensure consistency, efficiency and transparency across the assessment procedures. (Chapter Six)
- Review the seven GCC authorities' vision and mission statements, goals, objectives and driving forces for change in order to determine their overall strategy for a successful GCC system. (Chapter Seven)
- Follow-on the progress of the quality measures adopted by the GCC regulatory authorities since the previous study conducted by Hashan (2005) to improve their review practices and the quality of their decision-making processes (Chapter Eight)

CHAPTER 2

Study Rationale and Methodological Framework

STUDY RATIONALE

Several key areas in the Gulf States were believed to be vital in regulating and monitoring the accessibility of medicines which have been recognised through a review of recently published literature and a series of informal dialogues with the senior managers within the seven Gulf Cooperation Council (GCC) regulatory authorities, namely,

- The timelines of the regulatory review processes within the targeted authorities
- The phases and milestones involved in each of the seven regulatory review processes
- The measures used to build quality into the GCC regulatory review processes
- The strategic planning process within each of the seven GCC regulatory authorities

Comprehensive literature search has identified lack of sufficient up-to-date published information about the regulatory review processes, quality measures and the strategic planning processes in the GCC Region. Therefore, it is recommended that information be collected to:

- Examine the performance of the regulatory review process in Kuwait and the rest of the Gulf States;
- Verify the quality measures used by the regulatory authorities to improve the assessment procedure;
- Assess the strategic planning processes within the GCC States to underpin areas for further improvement.

The aim of this research project is therefore to assess the regulatory environment for medicines within the GCC States with regards to all the procedures that involve the submission, registration and pricing of medicinal products as well as the strategies utilized by the seven authorities to improve their regulatory efficiencies and performances and to provide timely access of quality medicines to the local patients in the GCC Region.

Apart from presenting the rationale for carrying out all these studies, this chapter also reviews the appropriate methodological framework for the research project.

METHODOLOGICAL FRAMEWORK

Study Design

The selection of a study design is one of the most important decisions that need to be taken in order to answer the research questions. According to Yin (2003), the purpose of any academic research can be exploratory, descriptive or explanatory.

- Exploratory studies: exploratory studies aim for basic knowledge within the problem area (Zarkesh, 2008). These studies are appropriate when it is difficult to identify the problem and when important characteristics are hard to determine. They tend to start from a large pool of data that are narrowed as the research develops (Saunders *et al.*, 2002).
- Descriptive studies: descriptive studies are suitable when the problem is clearly structured but the intention is to simplify the matter to make it more understandable rather than identifying the causes of the symptoms. This is done by reducing the complicated problems into their component parts (Miles and Huberman, 1994).
- Explanatory studies: explanation means "making complicated concepts understandable by showing how their component parts fit together according to some rules" (Miles and Huberman, 1994). Explanatory research is used for studying the relationship between causes and effects and factors which together cause certain phenomena to be identified (Yin, 2003).

This research project aims to investigate the regulatory review processes and strategic plans in the seven Gulf Cooperation Council (GCC) regulatory authorities to develop a standardised assessment procedure through the establishment of a harmonised strategic plan for the GCC Region. Therefore, the main purpose is exploratory even though it can also be considered descriptive research. However, the study on approval timelines in Kuwait involves a set of hypotheses that will be tested statistically to provide an overview of Kuwait Drug and Food Control (KDFC) authority's performance over the four-year (2006-2009) period and therefore this particular study is considered explanatory as it evaluates the relationship between the authority's environment, political stability and the approval timelines of medicines in Kuwait. When considering the sample from which information will be collected, namely, the regulatory authorities located in the GCC States, together with the confidential nature of the data that will be gathered, it was decided that the most

appropriate technique for this research would be the use of a questionnaire technique.

Once the nature of the inquiry has been determined, two other issues need to be considered, namely, the duration of the study and the subjects to be included. Suitable study designs are reviewed here involving these two variables, namely, cross-sectional and longitudinal designs (Hua and David, 2009). Cross- sectional research involves the collection of data from different participants at one point in time within a narrow time span. There are several advantages of the cross-sectional studies such as saving in time and cost as these designs can collect a large amount of data over a short period of time (Anon, 2000). The research can be very short in study duration and can be executed with less difficulty and cost of maintaining contact with subjects than the longitudinal research. Another advantage which cannot be overlooked is mapping the similarities and differences between the authorities. This can be achieved by comparing the normative data collected through cross-sectional studies carried out with comparable criteria (Hua and David, 2009). One disadvantage of this cross-sectional research is that it this type is unable to trace a sequential developmental pattern of a particular change over time (Anon, 2000).

Longitudinal research involves a small number of subjects observed over a period of time, or repeatedly sampled at pre-determined intervals within a pre-determined period (Hua and David, 2009). The time scale varies significantly from a few weeks to a few years depending on the research question. However, longitudinal studies can address issues and support data collection methods in ways that are not possible with cross-sectional design. They allow for a large amount of data to be collected from every single individual over time and, therefore, are able to provide a more comprehensive and representative picture of the variables under investigation. However, longitudinal designs, by nature have a number of disadvantages. These include the challenge in maintaining contact and commitment from all participants in the study, as well as being time consuming and costly (Hua and David, 2009). Another form of research is comparing two similar subgroups and this is referred to as comparative research (Anon, 2000).

In order to achieve the objectives of the study with regards to the regulatory review processes and the measures used to build quality into the assessment procedures in the GCC States, the cross-sectional approach will initially be adopted. Depending on the level of response and the data obtained, the research may then be followed up by a systematic longitudinal study, should there be the need to determine particular changes and developments over time. With respect to the GCC strategic planning review, a cross-sectional approach will be adopted as the fundamental components and parameters of the strategic planning processes in the seven Gulf States will be measured at a specific point in time.

Data Collection Technique

Having decided to use a questionnaire technique, there are two possible approaches that could be used to collect data, self-administered questionnaires or semi-structured interviews. A key difference between these two is that the study participants complete questionnaires whereas interviews are completed by the interviewer based on a predetermined schedule to prompt and record the interviewees' responses.

Questionnaire

A self-administered questionnaire is useful when there is a need to collect information from the study participants within a reasonable time period. It is a structured technique for collecting primary data in a survey study using a series of structured questions for which the respondent provides answers. A well-designed questionnaire motivates the participant to provide complete and accurate information (Salant and Dillman, 1994). The main strengths and limitations of a questionnaire (McNamara, 2006; Passmore et al., 2002; Trochim, 2006) are as follows:

Strengths

- It is an inexpensive and efficient method where no special conditions or equipment are required. It can also be compiled anywhere and distributed easily.
- Information can be collected from a large group of people in a timely manner.
- The data collection can be anonymised, which might improve the response rate.
- Questions are standardised i.e. everyone answers the same questions. As the questions are consistent, the answers can easily be compared.

Limitations

- The recipients may be reluctant to complete and return the questionnaires, particularly by post.
- There is no opportunity to clarify what a question means.
- The choice of answers may be restricted, not allowing the respondents' views to be reflected accurately.
- Unless the researcher is present when the questionnaire is completed there is no certainty as to who has supplied the answers.

Semi-structured Interviews

Semi-structured interviews have a great deal in common with questionnaires as they are centred round a set of questions. The main difference is that they involve personal interaction either face-to-face, or by telephone, video conferencing etc. Normally, they would be on a face-to-face basis and, therefore, the interviewer has to avoid influencing the interviewee's responses.

A great deal of qualitative material comes from talking with people whether it be through formal interviews or casual conversations (Woods, 2006). If interviews are going to tap into the depths of reality of the situation and discover subjects' meaning and understandings, it is essential for the researcher to develop empathy with the interviewee and win their confidence and to be unobtrusive, in order not to impose one's own influence on the interviewee.

The main advantages and disadvantages of the interview technique (McNamara, 2006; Bourque and Fielder, 2003a; Trochim, 2006, Woods, 2006) includes:

Advantages

- Opportunity to obtain quick responses
- Interviewees are likely to talk more freely and produce more useful results due to the elements of empathy and closeness between the interviewer and interviewee
- The interviewer can explain the questions and give more information if necessary
- It is easier to obtain an accurate reflection of the interviewee's true feelings
- High response rate

Disadvantages

- The risk of leading questions which may direct the respondents towards giving biased answers
- Can be costly which is particularly true of in-home interviews, where travel time is a major factor
- Can be hard to analyse and compare

Due to the distance between the authorities and the researcher, the high costs involved, and the absence of face-to-face interactions, questionnaire is the more appropriate technique. This research seeks factual data and responses to categories related to the strategic planning processes within the Gulf Region. Also, it is reasonable to perform the pilot test on two pre-selected GCC regulatory authorities to understand if the participants are able to interpret the questions as intended.

Data Collection Method using the questionnaire technique

There are a number of methods available for collecting data using the questionnaire technique. Several factors should be considered when selecting the most appropriate method including 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 uses a printed questionnaire that is mailed to the study participants and allows them to respond at their convenience before returning it via mail or fax. Alternatively, e-mail can be used to deliver a questionnaire that maybe either completed electronically and returned via e-mail or maybe printed and returned by mail or fax. This method requires minimum resource to prepare; it enables privacy of responses and is relatively inexpensive, particularly if using e-mail. However, it does take time and requires follow-up to obtain responses. It can also be difficult to judge the quality of responses and to obtain accurate mailing lists or e-mail addresses and may risk being buried among unwanted "junk" mail (Diem, 2002a; Trochim, 2006).

Group-administered

A group-administered approach involves gathering a group of individuals together, administering the questionnaires and asking the group to complete them individually. This method ensures a high response rate and enables a full explanation of the study

to be given with the opportunity for questioning (Bourque and Fielder, 2003). It also improves the quality of responses particularly when the participants are unclear about the meaning of a question and requiring an explanation from the researcher. The disadvantages of this method are that time is limited for respondents to formulate their answers and the total turnaround time can be slow (Trochim, 2006).

Telephone-administered

Calling the participants by telephone, typically spontaneously, or by scheduling an appointment, can be used to collect data. It may be possible to use an automated system where users reply via a touch-tone telephone to a computer-based interview system. A rapid response is possible using this approach and it can be inexpensive if calling locally. Some of the problems encountered with this method include access limitations from answer machines, reliance on correct numbers and instantaneous credibility of the caller being established in order to complete the call. Time zones and language can also be a barrier (Diem, 2002a; Trochim, 2006). In addition, the time differences between different countries can be one of the problems which may lead to it being inconvenient to answer questions from the researcher's point of view. Text messages, to remind respondents, together with a mobile phone will be used in this study.

Web-based

Questionnaires can be posted on a web site to be completed by the study participants, typically remotely from individual computers. Web-based methods enable a quick and easy response and can be inexpensive if correct facilities and tools are available. However, this method relies on respondents having web access (Diem, 2002a).

Information Sources

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

The data source

For the Kuwait study all products (New Active Substances and Existing Active Substances) from Arab GCC, Arab non-GCC and international manufacturers, which have been approved for human use between 2006 and 2009 will be included.

Table 2.1 Regulatory Authorities in Gulf Cooperation Council (GCC) States

Country	Authority
Kingdom of Bahrain	Pharmacy and Drug Control Department
State of Kuwait	Pharmaceutical and Herbal Medicines Registration and Control Administration, Kuwait Drug and Food Control (KDFC)
Sultanate of Oman	General Directorate of Pharmacy and Drug Control
State of Qatar	Pharmacy and Drug Control Department
Kingdom of Saudi Arabia	Saudi Food and Drug Authority (SFDA)
United Arab Emirates	Registration and Drug Control Department
The Republic of Yemen	General and Supreme Board for Drug and Medical Appliances

Due to the use of manual recording for the 2005 data, and because there was no follow up or tracking system to monitor the efficiency of the work being handled, it was not possible to obtain data for 2005. Therefore, it was decided to exclude 2005 from the study and it was then decided to start the data collection from year 2006. The products which have complete information i.e. submission date, registration date, and pricing date, will be included in the total patients' access time. In the GCC study, investigations will be carried out on the regulatory review processes and measures used to improve the quality of the assessment procedures for all types of pharmaceutical products from all types of pharmaceutical companies (i.e. innovative or generic manufacturers). The evaluation of the strategic planning process of the seven GCC authorities involves the assessment of eight strategic parameters that can be used to establish the fundamental basis for a harmonised strategic planning process for the GCC region, namely, the guidelines, the standard operating procedures (SOPs), improving the review process, quality assurance (QA), post-marketing surveillance (PMS), resources, budgeting, and changing requirements.

Data Collection Procedure

Using mail delivered questionnaires to collect data allows for confidentiality and/or anonymity if required. A name or identifier will be used for follow-ups and to match data collected at different point in time for within group comparisons. Anonymous procedures do not enable follow-ups (Diem, 2002b). For this reason confidential procedures will be used for each of the questionnaires considered for this study, particularly where data are aggregated to avoid identification of individual participants.

Data Collection Monitoring and Timeline

A face-to-face meeting and telephone interviews will take place to follow-up on the data to be obtained from the Kuwait Drug and Food control (KDFC) authority to closely observe the regulatory review processes and the approval timelines in Kuwait as a model of the regulatory systems in the GCC region.

In addition, face-to-face meetings with all the Directors and General Directors of the seven GCC regulatory authorities will take place in Kuwait and/or other GCC States where the GCC Central Registration Committee meeting will be held. The participants will be asked to provide information on:

- The regulatory review processes in each authority, which will then be standardised into an individual report for each country in word documents which will be sent to each authority for auditing, correction and comment.
- Their feedback about the questionnaire that explores the regulatory review process and building quality into the assessment procedures in the GCC States. Attempts will be made to clarify the sections of the questionnaire considered by the participants as unclear.

The GCC strategic planning processes require telephone-interview and an email delivered questionnaire in order to:

- Observe similarities and differences in the strategic plans of the regulatory systems in the seven GCC States;
- Determine the driving forces for change that shape the future direction of the GCC regulatory systems.
- Collect feedback about the Strategic Planning Process questionnaire from the GCC regulatory authorities. Attempts will be made to clarify areas of the questionnaire which maybe unclear to the participants.

Questionnaire Development

A questionnaire will be developed based on tested and evaluated questionnaires previously used in studying ICH countries (McAuslane et al., 2006). Through a series of consultations with experts and key regulators, it will be possible to test the applicability of the questions to the regulatory systems in the GCC Region through conducting a pilot study consultation with two selected GCC authorities. The

questionnaire (Appendix A) will address the regulatory review processes and building quality into the review processes in the GCC States.

Another questionnaire will be developed to assess the strategic planning processes of the regulatory authorities in the seven GCC countries. Following a series of consultations with experts from CMR International Institute for Regulatory Science and the GCC regulatory authorities, a pilot study consultation will be conducted with some of the authorities in the GCC Region.

Chapters three, four, five, six and seven will aim to provide evidence to establish consensus on topics for which 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 the 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). They allow a greater role for the qualitative assessment of evidence (Van Teijlingen et al, 2006).

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. This "agreement" includes the extent to which each participant agrees with the issue under consideration and also the extent to which participants agree with each other: the consensus element (Jones and Hunter, 1995). The features of consensus methods are described in Table 2.2.

Table 2.2 Features of Consensus Methods

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

Source: Adopted from Jones and Hunter, 1995

Consensus Development Conference (CDC) Method

Developed by the US National Institutes of Health in 1977, CDC is a formal method of gaining feedback that is 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

This approach was developed in the USA in the 1960s. A highly structured meeting is organised to collect information from appropriate experts about a given topic or issue. It involves two rounds in which panellists 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 (Van Teijlingen et al., 2006). This method focuses on a single goal, e.g. the definition of criteria to assess the appropriateness of a gene therapy invention, rather than eliciting a range of ideas and therefore it will not be appropriate for studies considered for this research project.

Delphi Approach

The Delphi technique was developed in the 1960's by RAND (a non-profit institution that helps to improve policy and decision-making through research and analysis). Since then the method has been adopted and interpreted widely in health services research to obtain judgement from expert panels by systematically collecting and aggregating informed opinions from a group on specific issues. Assessment of the application of this method has more recently indicated considerable variation in process and thus the term 'Delphi Approach' is more appropriate (Shulmoski and Hartman , 2007).

In essence, the Delphi approach uses repeated rounds of questionnaires, interspersed by controlled feedback, that seek to gain a reliable consensus of opinion from a group of experts while avoiding the biasing effects that may occur in face-to-face meetings through dominance. The first round involves application of an unstructured questionnaire that aims to gain responses about a broad subject or question(s) from which subsequent questionnaires are derived using summarized

findings from previous questionnaires. Expert panellists responses are treated in the strictest confidence, thereby avoiding an identifiable link between a specific opinion and an individual. This anonymity promotes a sense of freedom to express opinions without negative repercussion. Panel experts are encouraged to revise previous responses in subsequent iterations after reviewing new information submitted by other experts. This multiple iteration process is used as a means of accomplishing group consensus (Annells et al., 2004).

The Delphi approach is useful for situations where individual judgments must be tapped and combined in order to address a lack of agreement for incomplete state of knowledge (Hsu and Sandford, 2007). It is viewed as a useful communication tool for generating debate as opposed to reaching conclusions. Therefore, the feedback between questionnaire rounds enables participants to share their wide range of direct knowledge and experience that will be educational and may stimulate new ideas and, in itself, be highly motivating (Powell, 2003). The technique can be a quick, inexpensive and a relatively efficient way of combining the knowledge and abilities of an expert group on a particular issue. On the downside, it has been noted that consensus approach may result in a dilution of the best opinion and that the anonymity of the technique may lead to accountability of views expressed or encourage hasty decisions (Powell, 2003). The Delphi approach has also been criticised for not being evidence-based

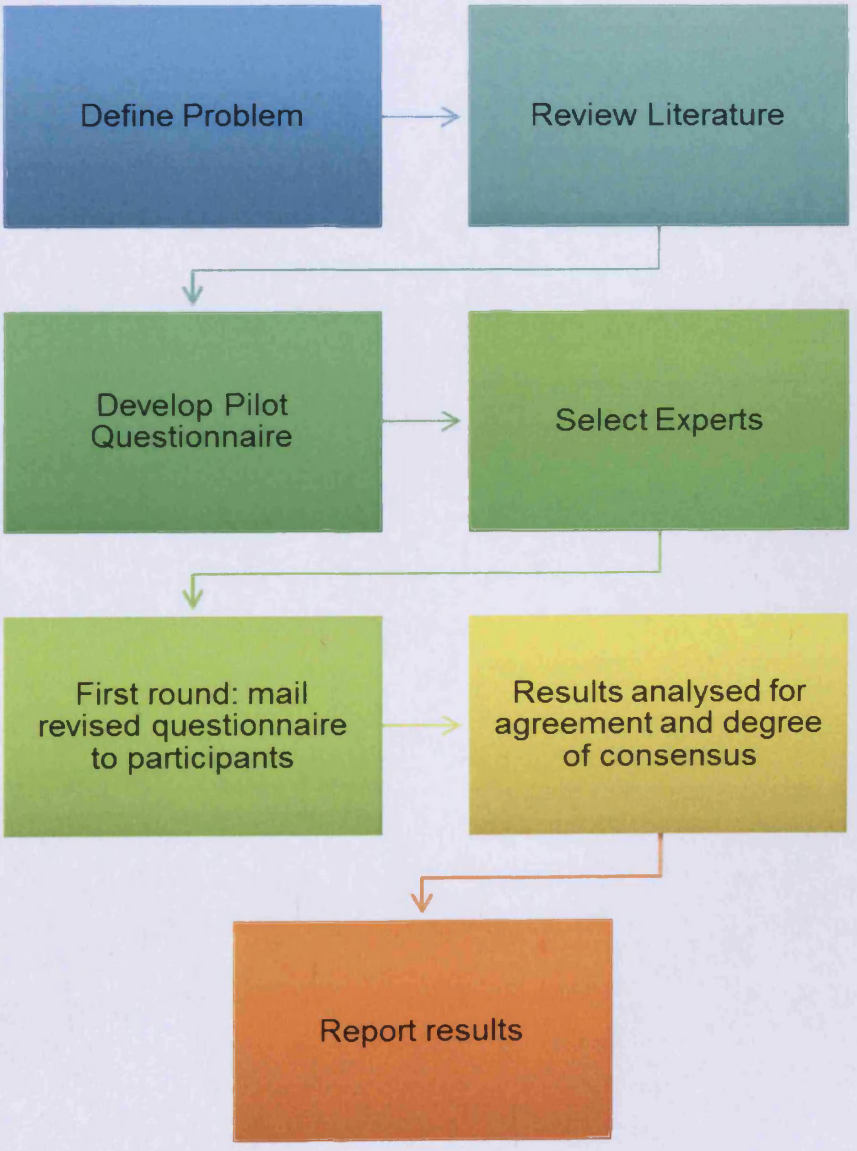
For the purpose of this study, the essence of the Delphi approach will be used to develop consensus of opinions in each of the previously defined topic areas as well as collect information that can be used as scientific evidence (Figure 2.1). It is, therefore, imperative that detailed information be 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, results from the questionnaire will be aggregated and analysed before being reported back to participants.

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 GCC countries (i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE and Yemen). In order to close this gap and improve the regulatory performance, it is vital to understand the regulatory review practices and the strategies undertaken to achieve effective and standardised assessments across the Gulf Region. Therefore, the following study plan was developed to capture data on the regulatory environment in these countries. These were then subjected to a significant scrutiny to fulfil the objectives of the study.

Figure 2.1 The Delphi Approach to be used in this study



The thesis consists of five core chapters that investigate four major areas in the GCC drug regulatory field, namely,

Chapter three: A detailed assessment of the regulatory review process will be carried out in Kuwait selected as an example of a medium-sized authority in the GCC Region.

Chapter four: A detailed investigation of patients' access timelines (i.e. the registration time + the pricing time) to new medicines over the period from 2006 to 2009 in Kuwait selected as a representative model for the approval timelines in the GCC region.

Chapter five: A comparative study of the regulatory review processes in the seven GCC States.

Chapter six: A comparative study of the measures and tools used to build quality into the regulatory review procedures in the seven GCC States.

Chapter seven: An evaluation of the strategic planning processes in the seven GCC States.

The outcomes of the study will be combined to identify the major areas that require further improvement to achieve a standardised and efficient regulatory review process for the GCC region. The following methods will be employed to collect the required data, namely to:

1. Obtain a list of the senior personnel in each regulatory authority in the GCC Region.
2. Review of the literature on the subject of regulatory review process and building quality into the assessment practices.
3. Carry out consultation with regulatory experts and senior managers in the GCC regulatory authorities.
4. Develop two questionnaires to be completed by the key regulatory managers in the GCC States to assess and compare the review processes, quality tools, and strategic plans in each of the seven regulatory authorities.
5. Prepare two reports as a result of the assessment of the GCC regulatory review systems and the strategic planning processes shared with the Gulf States.

The steps outlined above will be used as the basis for the preparation for the relevant chapter in this thesis.

Study Instruments

The sequence of events to be carried out to achieve the aims of this study will start with an evaluation of the regulatory approval timelines in Kuwait. This is a lengthy process which involves collecting data on the registration and pricing dates in 2006 and 2007 from the KDFC archives, and following up on the completion of these data for 2008 and 2009. During the course of collecting data on the approval timelines in Kuwait, the questionnaire on the regulatory review process and building quality into the assessment procedures will be prepared for distribution to the seven GCC States for completion. The questionnaire was originally designed and utilised by CMR International Institute for Regulatory Science in a number of emerging markets (McAuslane et al., 2006a). This questionnaire comprises three main parts, namely, the key milestones in the registration of medicines, the regulation of clinical trials and building quality into the assessment and registration process in the emerging markets. The three parts were carefully revised to confirm their appropriateness with the current regulatory status of the Gulf States. It was known that the GCC authorities do not conduct clinical trials and, therefore, the regulation of clinical trials was excluded from the study. Furthermore, items covered in the original questionnaire on the regulatory review models in the GCC countries were carefully examined to confirm their suitability to the fundamental structures and core practices within each GCC regulatory review process. This is to ensure that all the main points were thoroughly identified and assessed and that all the data pool was complete. Data were collected on applications for New Active Substances (NAS) and Existing Active Substances (EAS) that had not previously been approved by the authority in question. The methodology was based on identifying review stages and milestones that could be compared across regulatory authorities; in spite of any differences between the individual regulatory procedures. It is crucial to understand the individual regulatory systems in the GCC Region and carry out a comparative analysis to understand the best practices shared by the seven GCC States and the commonly identified gaps in the region that require further attention to improve the quality of the review processes and approval timelines in the GCC Region.

The second questionnaire on the strategic planning processes will then be developed and prepared for distribution to the seven GCC authorities. The questionnaire consists of eight parts each having its own instructions for completion. Each part

evaluates different aspects of the strategic planning processes of the regulatory authorities in the GCC Region as follows:

1. General characteristics of the organisation and respondent
2. Vision and mission statements and organisational values
3. Organisational goals and objectives
4. Analysis of organisation's Strengths, Weaknesses, Opportunities and Threats (SWOT Analysis).
5. Organisational Short-term (1-2 years) and Long-Term (3-5years) Strategic plans
6. Organisational driving forces for change
7. Methods for approving and documenting strategic plans in each GCC authority.
8. General comments not covered by the questionnaire.

It is critical to understand the shared strategic needs of the GCC authorities to be utilised during the course of establishing a harmonised regulatory strategy that will close the common gaps identified in the comparative evaluation of the regulatory review processes and the quality measures used to improve the assessment procedures in the seven GCC authorities.

Psychometric evaluation of the study instruments

There are a number of fundamental principles that need to be considered when developing measurement instruments. There are seven psychometric principles that will be assessed in this study, namely, the applicability and acceptability, practicality, confidentiality, validity, reliability and sensitivity (responsiveness).

Applicability and acceptability

Applicability of the study instrument ensures the appropriateness of its content for 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). Another critical aspect is the acceptability of the study instrument by the study participants and whether they are willing to respond to the questions. 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).

Confidentiality and anonymity of the participants

Anonymity and confidentiality of participants are central to ethical research practice in social research (Crow and Wiles, 2008). Where possible, participants in this study will be assured that every effort will be made to ensure that the data they provide cannot be traced back to them in reports, presentations and other forms of dissemination. The primary method researchers use to preserve anonymity and confidentiality is the use of pseudonyms for participants and also for the location of the research (Crow and Wiles, 2008). There are several issues that such practices raise. One is that it is difficult for researchers to know how far to take anonymisation of individuals in order for them not to be identifiable, given that research findings may be presented to a variety of audiences. A second issue is that research participants hold differing views about the desirability of anonymisation, presenting researchers with difficult choices between respecting the preferences of those participants who wish to be identifiable and those who prefer to remain anonymous (Crow and Wiles, 2008).

Practicality

The practicality of the instrument must also be considered when assessing its appropriateness to the purpose of the study. 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., 1981). Indicators of the participants' lack of comfort include low response rate, high refusal rate, missing responses and administration time (Ware et al., 1981).

Validity

Kaiser and Smith (2001) define validity as "... the most fundamental consideration in developing and evaluating tests. The concept refers to the degree to which evidence and theory support the interpretations of test scores entailed by proposed uses of tests". Essentially, the concept of validity is whether or not an indicator/instrument measures what it claims it does and when investigating sensitive issues this can be complex. There are a variety of methods by which validity can be assessed. The three types of validity most commonly used are content, criterion and construct.

Content Validity

This assesses the extent to which questions in a survey 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

This assesses how the observed values of the indicator compare with another related measure. The aim is to correlate a new indicator with reference to a previously well-established indicator ('gold standard') (Anon, 2001). Piloting the questionnaires before using the final version in the main study participants assess the practicality and applicability of questions and will ensure that they are clear, feasible and unambiguous.

Construct Validity

This is the most rigorous approach to establishing validity (Guyatt et al., 1993). This type of validation requires assembling empirical evidence to support the inference that a particular instrument measures what it is supposed to measure. Construct validity involves comparisons between measures and examines the logical relations that should exist between a measure and the characteristics of the system being studied (Guyatt et al, 1993). Sub-types of construct validity include convergent validity (positive correlation with a related measure) and discriminate validity (a low correlation coefficient is obtained when the measures are of unrelated constructs (Saw, 2001).

Sensitivity

Sensitivity is related to the instrument's ability to detect and measure change when it has occurred (Higginson and Carr, 2001; McLeod et al., 2008). Differences among groups (approval times, milestones, quality measures, strategic parameters, years of study, and the authorities) will be checked to test the instrument's ability to detect differences if they really exist (sensitivity) (Dimoliatis et al., 2010).

The questionnaires will be developed based on established psychometric principles to collect data from the participating regulatory authorities. Pilot testing with two authorities is a critical step to increase the confidence about the clarity, feasibility and

suitability of the questions for the GCC Region. Following the pilot study, changes will be made to the questionnaires in order to incorporate the feedback obtained and the lessons learned. Once the appropriateness, convenience, relevance and clarity of the questionnaire are ensured from the pilot study, it will then be distributed to the rest of the GCC authorities for completion.

DATA ANALYSIS AND PROCESSING

Data processing and analysis will be carried out using Microsoft Excel™. Where data is quantitative, descriptive statistics such as mean and median will be used and where data are qualitative, content analysis will be used to generate major themes. Where consensus is being sought in a study it will be defined in a variety of ways from the use of percentage levels and ranking to less specific alternatives, such as reference to the agreement of the majority of participants.

Quantitative Analysis

Hypothesis Testing

Setting up and testing hypotheses is an essential part of statistical inference. A hypothesis is a specific statement of prediction that describes in concrete (rather than theoretical) terms what to expect in a study (Trochim, 2006). Not all studies have hypotheses as some studies are designed to be exploratory where no formal hypotheses need to be tested. These studies explore areas more thoroughly in order to develop some specific hypotheses or predictions that can be tested in future studies; such as the exploratory study of the regulatory review processes, quality measures adopted and the strategic planning processes in the seven GCC authorities conducted in order to pinpoint areas for improvement. However, a formal hypothesis will be necessary to examine the differences in the regulatory approval times of pharmaceutical products in Kuwait between 2006 and 2009. The best way to determine whether a statistical hypothesis is true would be to examine the set of collected data and if they are not consistent with the statistical hypothesis, the hypothesis is rejected (Trochim, 2006). The way to formally set up the hypothesis is to formulate two hypothetical statements, one that describes the study predictions (Null Hypothesis, H0), and one that describes all the possible outcomes with respect to the hypothesised relationship (Alternative Hypothesis, H1). Hypothesis testing consists of four steps (Akindeinde, 2010), namely,

- Setting the hypothesis: this involves stating the null and alternative hypothesis in such a way that they are mutually exclusive. That is, if one is true, the other must be false.
- Formulating an analysis plan: the analysis plan describes how to use sample data to evaluate the null hypothesis. The evaluation often focuses around a single test statistic.
- Analysing sample data: the value of the test statistic is determined (mean, median, proportion, test score, percentage) as described in the analysis plan.
- Interpret results: the decision rule described in the analysis plan will be applied. If the value of the test statistic is unlikely, based on the null hypothesis, the null hypothesis will be rejected.

Statistical Testing

A statistic is a quantity that is calculated from a sample of data used to give information about unknown values in the corresponding population. Statistical inferences make use of information from a sample to draw conclusions (inferences) about the population from which the sample was taken (Easton and McColl, 2004). This study will utilize a variety of statistical inferences, depending on the type of data being analysed. Therefore, most of these data will be presented in bar charts to illustrate key features in the distribution of the data.

The sample mean will be used for estimating the population mean (the "middle" value) as well as the median (the value half way through the ordered data set, below and above which there lies an equal number of data values). 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 picture produced consists of the most extreme values in the data set (5^{th} and 95^{th} percentile values), the lower and upper quartiles (25^{th} and 75^{th} percentile values), and the median (Easton and McColl, 2004). Where appropriate, alternative statistics will be used to make inferences about the data presented, namely, regression analysis, correlation analysis, Mann-Whitney U-Test and Kruskal-Wallis test.

Regression

Regression analysis is a statistical tool for the investigation of relationships between 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 and McColl, 2004).

Correlation

Correlation analysis can be used to show the strength of a relationship between two variables. It is often used as a descriptive tool in non-experimental research. Two measures are *correlated* if they have something in common. The intensity of the correlation is expressed by a number called the *coefficient of correlation* which is denoted by the letter *r*. A correlation coefficient 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. There is negative correlation whenever one variable has a high value and the other has a low value, or vice versa meaning that the direction measurement is opposite, to the other. A correlation coefficient of 0 indicates that there is no linear relationship between the variables (Easton and McColl, 2004).

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, 2000; Easton and McColl, 2004).

Kruskal-Wallis test

The Kruskal-Wallis test is a non-parametric 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 (median), if at all. 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 and McColl, 2004).

Qualitative Analysis

The ultimate goal of analysing data is to treat the evidence fairly, to produce compelling analytical conclusions and to rule out alternative interpretations. When analysing the data collected, the intentions are to find answers on the study objectives. 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 organise the data so that the final conclusion can be drawn and verified.
- Data display: taking the reduced data and displaying it in an organised 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 present 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. This allows for a better focused analysis and helps the researcher to elaborate a cognitive map in order to understand local incidents and interactions.

In this study, a set of steps is followed in order to analyse the generated data. The two questionnaires will be piloted with two GCC regulatory authorities before the appropriateness of the final questionnaires is determined. They are then emailed to the targeted key regulators in the rest of the authorities for completion at pre-scheduled dates. After the completed questionnaires are returned, the data will then be analysed and reduced where the required data is abstracted according to pre-set targeted information in each GCC authority. 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. Finally, conclusions from the analyses will be drawn based on patterns of similarities and differences which are discovered in the data reduction and data display processes.

SUMMARY

- The chapter describes the rationale for carrying out the study on the seven GCC regulatory authorities.
- The various methodologies, techniques and instruments that will be used in analysing the data obtained from the seven GCC regulatory authorities have been described.
- A detailed description of the developmental technique of the two questionnaires has also been provided and how the information obtained from these questionnaires will reduced, analysed and displayed in an organised manner.
- Methodological choices related to database management, data processing and data analyses are described.
- The data collected from the GCC regulatory authorities revolve around three major areas, namely, the regulatory review processes and milestones, the quality assurance measures used to improve the assessment practices, and the strategic planning processes for the regulatory systems within the seven GCC States.

CHAPTER 3

Evaluation of the Regulatory Review System in Kuwait

INTRODUCTION

Medicines in Kuwait are regulated for quality, safety and efficacy standards, price control and patent protection. Kuwait has 40 years experience in drug regulatory practices and plays a prominent role in the Gulf Cooperation Council (GCC) Region (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, and Yemen). The regulatory system started with a small quality control laboratory in 1967 where all pharmaceutical products imported into the country used to be analysed to ensure that they were of the desired quality standards. A registration certificate used to be issued according to the quality control laboratory analysis results on samples of the pharmaceutical product under registration. Kuwait began facing significant challenges reflecting the rapid advancement of the regulatory services with limited resources possibly influencing patients' timely access to medicines. These challenges gave the regulatory authority no choice but to review and update its regulatory practices.

In 1980, the first Ministerial Decree (M.D.) 302/80 was issued to regulate the submission of the drug registration dossier and is considered the appropriate guide for the regulatory reviewer to ensure that all the required documents are submitted. These documents assure the authority that the pharmaceutical product being registered is of the desired quality, safety and efficacy. Since 1980, pharmaceutical companies were required to comply with the M.D. 302/80 for each pharmaceutical product intended for registration in Kuwait. Being an oil-rich country, financial resources have never been the problem in this aspect. It is the lack of proper knowledge and the appropriate expertise in the regulatory field, which is impeding the development of more advanced regulatory services. Although there are a few discussions on the development of quality measures in the regulatory review processes of authorities in the emerging markets, there is only one major study on this area and this is limited to the regulatory practices in the Gulf States (Hashan, 2005). The Kuwait regulatory system was considered briefly as part of the critical evaluation of the GCC regulatory authorities. The literature has focused on the quality measures in the regulatory authorities for major markets, such as EU, North

America and Japan and a number of studies have been carried out in these regions (Anderson, 2004).

Therefore, the scope of this chapter was to: a) obtain data and information on how Kuwait is conducting its quality review process; b) identify factors affecting applications and approvals of medicines in Kuwait from the regulatory authority's perspective; c) determine the standard procedures being performed to ensure the quality of the review process; and d) identify the main reasons that are driving the authority to build quality into its review process and its decision-making. The responsibility of the review process rests with the Registration Department in Kuwait Drug and Food Control (KDFC). This department is headed by the Drug Registration and Release Superintendent (DRRS) and has six units: Pharmaceutical Drug Registration Unit (PDRU), Veterinary Medicine Registration Unit (VMRU), Unclassified (Borderline) Product Registration Unit (UPRU), Herbal Medicines Registration Unit (HMRU), Release and Invoice Unit (RIU), and The GCC Central Registration Unit (GCCU).

The Kuwait regulatory system was closely assessed and evaluated as a model system to obtain a deeper insight into the areas that need to be addressed to improve the regulatory services for better patient access to safe medicines in Kuwait. It was then possible to perform the same assessment on the rest of the GCC countries described in Chapters six and seven to pinpoint the similarities and differences in the areas of concern addressed in the Kuwait project. This study utilized a questionnaire, which was revised and updated to fit the current status of the regulatory systems within the GCC region.

OBJECTIVES

The main objectives of this study were to:

- Critically evaluate the regulatory review process in Kuwait
- Identify the key milestones and stages of the review process.
- Assess the quality measures used to ensure consistency, transparency, timeliness and competency in the review process.
- Identify opportunities for better regulatory practices in Kuwait through understanding the Authority's quality of decision-making processes.

METHODS

Study Participants

The study involved the Drug Registration and Release Superintendent (DRRS) who is responsible for decision-making, setting and implementing policies, procedures, and guidelines for the regulatory review system within the authority, and the director of the authority who approves and authenticates the decisions made by the DRRS.

Data Collection Process

A questionnaire was designed which enables details of the regulatory review process in Kuwait to be determined and completed by the DRRS (Appendix A). Key milestones and quality review measures were addressed in the questionnaire.

The questionnaire was previously utilized to analyse the regulatory environment in a number of emerging markets (McAuslane et al., 2009). Parameters and sections within the original questionnaire were carefully assessed and selected to confirm that they are in accordance with the authority's foundation and core practices. This is to ensure that fundamental details were identified and evaluated and that all the data pool was complete. Data were collected on applications for New Active Substances (NASs) and Existing Active Substances (EASs) that had not previously been approved by the authority. After completing the questionnaire, the data was then standardised into a word document for the auditing, correction and comment by the authority's key participants.

RESULTS

PART I Model of Assessment in Kuwait

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

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 authorised by one or more recognised 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 authorisation(s).

Abridged model (type II assessment)

This model also 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 pharmaceutical quality (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 recognised agency elsewhere is a pre-requisite before the local authorisation 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 authorised by a reference authority before the local authorisation can be finalised.

The data assessment models for scientific review were explored for Kuwait to identify the type of scientific review used in the authority. The survey results indicated that KDFC authority uses a 'verification review' for all major applications. However, Kuwait carries out a unique practice whereby the pharmaceutical product, being

considered for approval, must be marketed elsewhere for at least 12 months before it can be registered in Kuwait. This requirement may be waived, depending on the product type, if evidence of registration in recognised international reference agencies such United States Food and Drug Administration (US FDA), Medicines and Health products Regulatory Agency in UK (MHRA), European Medicines Agency (EMA), Therapeutic Goods Administration in Australia (TGA), Health Canada, SwissMedic and/or GCC Drug Registration (GCC-DR) System.

Data requirements and assessment

The Kuwait review process is carried out according to the Ministerial Decree (M.D.) 302/80 that is used as a reference guide for the scientific reviewers and companies about the requirements of the registration process in Kuwait.

There are four types of applications that were investigated by the survey to highlight the data requirements for a successful registration procedure, namely,

1. Products authorised in one or more reference countries
2. Products authorised elsewhere but not in a reference country
3. Not authorised elsewhere at the time of application
4. Priority/Fast-track products

The most important registration requirement is the Certificate of Pharmaceutical Product (CPP) and it is a determining factor for the successful completion of the approval procedure in Kuwait. The CPP covers all the information required about the product manufacturer, packager, product license holder, shelf life, composition, GMP status of the manufacturer and product characteristics and it is required at the time of the submission, but the application is not refused if the CPP is missing. However, it must be submitted before granting the registration approval. Failure to submit the CPP will delay the approval and the registration certificate will not be issued until the CPP is submitted in its original format and authenticated by a consulate or an embassy. This practice is applied to the four types of applications stated above.

The authority requires another evidence of authorisation that provides the list of countries where the product is registered and marketed for at least 12 months. This list does not replace the CPP but is required in addition to the CPP to demonstrate its clinical effectiveness in patient populations in other countries. The list of countries is

considered as an appropriate solution for the shortage of experts required to conduct proper safety and efficacy review of the product.

In case of products not authorised elsewhere at the time of application, Kuwait is reluctant to proceed with the completion of the review process of such products until it is registered in another country. However, if the CPP is from a country with a recognised regulatory authority, the registration process will be expedited. Furthermore, Kuwait requests Chemistry/Manufacturing/Control (CMC) data to ensure that the product is of the desired pharmaceutical quality according to internationally recognised pharmacopoeia standards. This includes,

1. Finished product specifications with detailed methods of analysis. The reviewer verifies the submitted data to provide the quality control laboratory with the complete analytical details to carry out the sample analysis on products under registration.
2. Original certificate of analysis of finished products from the manufacturer. This is to be used as a benchmark document in the quality control laboratory to compare it with the quality control analytical results of products under registration.
3. Full stability studies in tabulated format demonstrating the product stability on two conditions:
    a. Long-term stability studies at 30°C/65% Relative Humidity (RH) for three different batches covering the full proposed shelf life of the product.
    b. Accelerated stability studies at 40°C/75% RH for three different batches covering a period of six months.

Kuwait places great emphasis on the accelerated stability data in their assessment of the stability studies because of the climatic conditions in Kuwait that could adversely affect the stability of the product.

4. Raw material specifications with detailed methods of analysis. This is an important requirement but it is only requested for documentation and is only examined if there is a queries such as a problem with the source of the raw material.

An assessment template is used by the reviewers to provide a standardised content and format of the data to be presented to the DRRS, who evaluates the presented report, queries and questions raised during the assessment process. He/she then

recommends his/her decision to the Director of the authority accordingly. The non-clinical and clinical data must be submitted to the authority but they are only examined when there is a query. These studies are only required for New Active Substances (NASs) as an evidence of their safety and efficacy. For products which are not authorised elsewhere, depending on the type and medical urgency of the product, a selective review may be performed in detail.

For priority review and fast-track products, the registration dossier is taken out of the queue and verified for data completeness. The reviewer ensures that all the required documents are available and presents his/her queries to the DRRS to recommend the decision to the director. The authority recognises the medical urgency and the importance of some products, and therefore priority review and fast tracking is considered imperative in some cases.

The authority is also required to ensure that the product characteristics (dosage form, strength, ingredients, indications and dose, warnings and precautions) as well as the product labeling information are identical to the one which is authorised in the country that exports in Kuwait.

The Kuwait review is considered a process that does not necessarily rely on information sources other than the Ministerial Decree 302/80. This Decree was issued in 1980, and the authority has stated its intention to update its contents in line with developments of the regulatory review practices around the world. However, reference to additional data that are not included in the application depends on the motivational level and enthusiasm of the reviewer. The appointed reviewer has the full choice to refer to other agencies' internal assessment reports as and when they are available, reports available on the Internet, and/or general Internet searches to obtain additional information on the product.

PART II Kuwait Regulatory Review Process

A map of the review process in Kuwait is given in Figure 3.1. It is a simplified representation of the main steps in the review of New Active Substance (NAS) and Existing Active Substance (EAS) applications. The map represents the review and authorisation of a product that is approved on the first cycle basis (i.e. does not include a second cycle for products approved subject to the submission of additional data). Furthermore, it does not include the steps that follow the refusal of an

application (hearing, appeals, etc). The procedures for the review and authorisation of medicines are performed within the pharmaceutical drug registration unit (PDRU) under the supervision of the DRRS.

Company registration

It is Kuwait's practice that separates the company registration from the product registration. For a pharmaceutical company to access the local market, it must appoint a local agent to represent it in Kuwait. This is a one-off process that is required as a prerequisite for the registration of all the company's products. So before submitting any product of a new manufacturing company, the local agent must present an original letter of appointment from the pharmaceutical company, which must be authenticated by the Kuwait embassy or consulate in the country of origin.

The letter of appointment must clearly state that the selected local agent is the company's sole/exclusive agent in Kuwait. This is critical to define the legal status of the medicine and the officially responsible representative of the principal manufacturer in Kuwait. Another requirement to register a pharmaceutical company is the GMP certificate in its original format from the health authority in the country of origin and authenticated by Kuwait embassy or consulate. This certificate states that the manufacturer is periodically inspected by the relevant health authority and that it follows strict current Good Manufacturing Practice (cGMP) guidelines to ensure the production of products with the desired quality standard. Finally, an original manufacturing license from the health authority in the country of origin must also be available and must be authenticated by the Kuwait embassy or consulate.

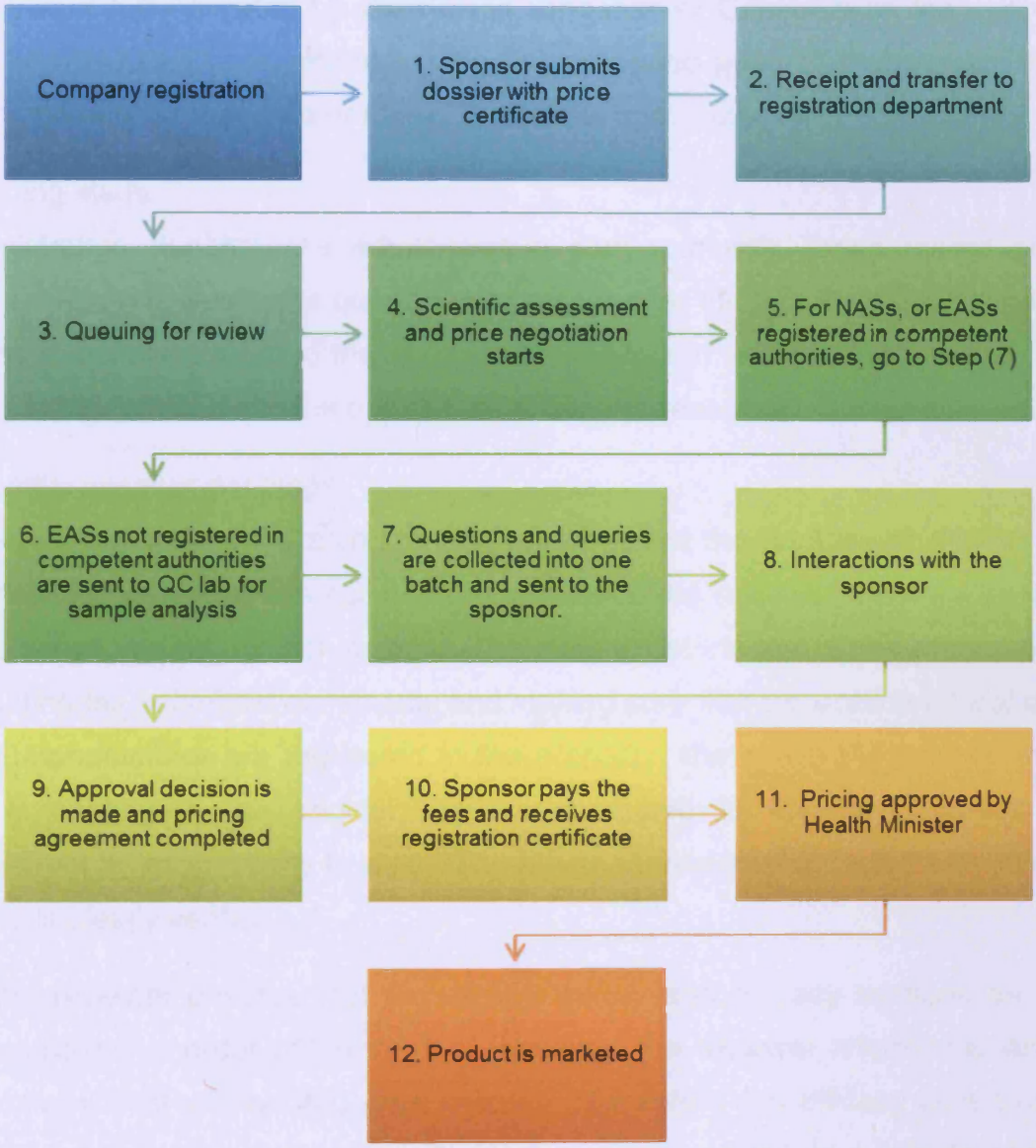
Product registration

The review process for the registration of pharmaceutical products was examined and described in detail as follows (Figure 3.1),

1. Submission stage

The registration dossier is submitted to the authority with an official request letter from the local agent to register the product. The date of submission is manually recorded by the director's administrative staff.

Figure 3.1 The regulatory review process map for Kuwait



2. Receipt stage

The Director officially accepts the registration file and transfers it to the registration department where it is received by the DRRS and transferred to the Registration department's administrative staff to be placed in the queue. During this time, the department's administrative staff transfer the price certificate submitted in the file to the pricing department to begin the pricing procedure. The product will not be reviewed unless the price certificate is submitted to the authority. The Drug Registration and Release Superintendent (DRRS) assigns a reviewer for the file at this stage.

The price certificate is a legal document produced by the principal pharmaceutical company and authenticated by the Kuwait Embassy or Consulate in the exporting country to the KDFC authority indicating the proposed price of the product in the exporting country as well as other GCC States (as applicable).

3. Queuing stage

The registration department's administrative staff manually keeps record of the product registration files in the queue and is responsible for clearing the files from the queue by transferring them to the appointed reviewers in an organised manner. The date of transfer of the file to the appointed reviewer is recorded.

4. Scientific assessment stage

The scientific assessment starting time is recorded but the duration of this stage is not calculated. However, it is estimated that it takes the reviewer no more than one week to review the registration dossier. The reviewer starts the assessment process by validating the submitted documents and making sure that the applicant/local agent and the manufacturer are registered in the authority, the active ingredient's patent status is confirmed, the original CPP is submitted in the WHO format and authenticated by an embassy or a consulate, and an evidence of registration in other countries is clearly verified.

Then, the reviewer ensures that the quality, safety and efficacy sections are in a clear unambiguous order within the file. However, the reviewer attempts to assess the pharmaceutical quality/CMC data in detail. The safety and efficacy data must be submitted but they are not investigated unless a query is raised on a specific product. In this case, the safety and efficacy assessment may or may not be carried out by the originally assigned dossier reviewer, depending on his/her level of expertise in this area. In certain cases, particularly for New Molecular Entities (NMEs), the safety and efficacy studies are transferred to an external expert in a local hospital or health institution to perform clinical evaluation and provide a clinical opinion on the new medicinal product.

5. Quality control analysis stage

In general, NASs do not go through the quality control analysis stage because the authority relies on the certificate of analysis submitted by the sponsor from the manufacturer. Also the authority may not have the reference pharmacopoeia that

they can rely on to carry out the analytical testing on the NASs. EASs, on the other hand, must pass the quality control testing. The quality control stage affects the overall approval timeline, and failing the tests will either delay or terminate the whole approval process. NASs and EASs registered in countries with developed regulatory systems (Such as US FDA and EMA) are exempt from this analytical stage, because KDFC depends on the credibility of the review processes carried out by these authorities.

If the manufacturing company submits an evidence of authorisation by a recognised competent agency such as USFDA, EMA, MHRA, TGA, SwissMedic, Health Canada, or the GCC Central Registration Committee (GCC-DR), the authority will waive such QC testing and will grant the registration approval if all the required documents are completed. As a general rule, the evidence of registration in a recognised competent agency is equally required for both NAS and EAS manufacturers. Products produced by innovative companies, which are not registered in these authorities, are not accepted for registration until the company provides such evidence. Products produced by EAS manufacturers, which are not registered by reference agencies, are able to register their products if the NAS version is registered and marketed in Kuwait and if they pass the QC analysis. In addition, EAS manufacturers must be able to demonstrate bioequivalence between their product and the registered NAS comparator.

6. Interaction with sponsor

Questions are collected as they arise during the scientific assessment and quality control testing and then they are transferred to the DRRS who decides on the suitability of the queries raised during the review process. The questions and queries are sent to the sponsor in one batch. The authority places no limits on the sponsor's response time and the review process ceases at this stage. The sponsor is permitted to meet with the DRRS or the Director to discuss issues stated in the queries form.

7. Final decision-making

When all the requirements are completed, the DRRS proposes the approval decision to the director of the authority who signs the registration certificate upon his approval of the recommendation made by the DRRS. The sponsor pays the registration fees of 100KD (340US$) and receives the registration certificate.

8. Pricing agreement

The registration certificate will not permit the product's access into the market before the ministerial pricing approval is published in the local official business magazine "Kuwait Today". Once the price is approved by the minister, the local agent is allowed to order the first shipment of their new registered product for Kuwait.

The pricing department in Kuwait is independent from the registration department. The main responsibility of this department is to ensure that the product price is reasonable for patients. The local agent must submit an original price certificate, authenticated by Kuwait embassy or consulate in the country of origin. There are four price categories that the authority requires in the certificate, namely:

- C&F price to Kuwait (and another GCC States if applicable)

C&F stands for 'Cost and Freight'. Both the initials and phrase are used in offers and contracts for the sale of goods (in this case medicines) to indicate that the quoted price includes the cost of the freight to a named destination as well as the cost of the goods. In some cases pharmaceutical companies submit CIF price which stands for 'Cost, Insurance, and Freight'. This phrase is used in an offer or a contract for the sale of goods indicating that the quoted price includes the combined cost of the goods, insurance, and the freight to a named destination. CIF price is always higher than the C&F price. However, the submission of either one is acceptable as it depends on the contractual agreement between the principal company and the local agent.

The C&F to other GCC States is also required, as applicable, to compare between the submitted C&F prices in the region. There are a number of problems that have to be considered in making comparisons between C&F (or CIF) prices submitted to GCC States such as whether the medicine is marketed in any of the GCC countries, the inclusion of the insurance cost which increases the CIF value above the C&F and the differing practices at the GCC customs services. C&F (or CIF) price must be submitted to the authority to be used in the pricing formula, along with the current exchange rates to generate the final price to be proposed to the Health Minister for approval. The price regulators ensure that the medicines sold in Kuwait are not over-priced.

- Ex-factory price in the exporting country

The seller owns the goods until they are picked up at the factory and the ex-factory price is the cost of the goods at the point of their pick-up from the factory. This price is required for the purpose of comparison of the medicines cost at different levels of transport to Kuwait. However, ex-factory price is not used in the pricing formula.

- Wholesale price in the exporting country

This is the price of goods purchased through wholesale. Medicines are purchased by the pharmacies from the local agents through wholesalers and these have a lower price than medicines sold in retail pharmacies. This is required for the purpose of comparison between the wholesale price in the exporting country and the calculated local wholesale price according to the formula used by the pricing department.

- Retail price in the exporting country (and in UAE if applicable)

This is the price paid by the consumer (in this case the patient) to the dealer (in this case the pharmacy). The retail price is calculated by the pricing department, using the pricing formula. UAE retail price is required from the local agent (when available) for the purpose of comparison between retail prices in Kuwait and UAE. Some comparative assessment is carried out between the calculated price of medicines in Kuwait and other GCC States. However, the assessment lacks the health technology evaluation with respect to cost-effectiveness of medicines. The pricing formula used to calculate the proposed retail and wholesale prices is:

Retail Price = C&F X Exchange Rate X 1.55
Wholesale Price = C&F X Exchange Rate X 1.29

The profit margins for wholesalers and retailers in Kuwait are controlled by the authority as follows:

Local Agent Profit	29%
Pharmacy Profit	26%
Pharmacy Profit on Wholesale	20%
Total Profit Margin on C&F	55%

Once a reasonable price is reviewed, negotiated and agreed with the local agent, the Director recommends the calculated price to the Health Minister who makes the final decision to approve the marketing of the registered product.

Before mid-2009, the pricing procedure used to start after completing the registration process and issuing the registration certificate to the local agent. The Director of the authority recognised the importance of speeding the access of new medicines to local patients and therefore made a wise decision to start the pricing process in parallel with the registration process. All discussions and negotiations are carried out during the review process so by the time the registration certificate is issued; the authority will have finalised the pricing agreement with the local agent/sponsor.

Key milestones in the review process

All pharmaceutical products must go through all the milestones involved in the registration phase (Table 3.1). However, pre-approved NASs (and EASs registered in countries with recognised regulatory systems) are not analysed in the quality control (QC) laboratories except in certain circumstances. Although, post-approval samples from shipments of all approved NASs and EASs are sent to the QC laboratory to be analysed before they are released onto the market. This process creates an uncertainty with regard to the time taken from approval to marketing of the product. Table 3.1 shows that the authority estimated the receipt time to be about seven days, and during this time the product dossier is officially accepted by the Director of the authority and transferred to the registration department where it is officially received by the DRRS.

Table 3.1 Estimated timelines for Key milestones of the review process in Kuwait

Milestone	Estimated timeline (calendar days)
Receipt Stage	7 days
Queue Stage	14-56 days
Scientific Assessment	7 days
Quality Control Analysis	7-14 days
Sponsor Response	No limit
Registration Procedure	>30 days
Pricing Procedure	120-180 days
Overall Patient Access Time	180 days

The DRRS then sends the dossier to the administrative staff within the registration department for queuing. The queue time is estimated to be between two to eight weeks depending on the urgency and importance of the product. When the product is ready to enter scientific assessment stage, the authority estimates this time to be around seven days. The quality control analysis time is estimated to be seven to fourteen days. Following questions and queries the sponsor is not given a time limit to respond to the authority but the scientific review clock stops at this stage. Once the response is received, the appointed assessor presents the conclusion to the DRRS who recommends the final decision to the director. A positive opinion is given to the sponsor once the decision is made by the DRRS and confirmed by the director and the final registration certificate is signed. This process takes less than 30 days. However, the product is still not available to patients until the pricing procedure is finalised and approved by the Health Minister which can take between 120 and 180 days (Table 3.1).

PART III Building Quality into the Assessment and the Registration Process

Quality in the assessment and registration process is important to KDFC as it ensures consistency, transparency, timeliness and competency in the review process. The authority is striving to develop and implement a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public. The purpose of this section is to obtain an insight into the strategies, measures and resources that KDFC has in place to develop and maintain quality in their review process.

General measures used to achieve quality

The KDFC implements one important quality measure, which is the use of "assessment templates" to provide a standardised content and format of all scientific reviews. Assessment templates present the data to the DRRS in a precise, concise and organised manner to enable him/her to make the appropriate decision.

However, the authority does not have Good Review Practice (GRP) guidelines or Standard Operating Procedures (SOPs) to ensure acceptable quality of the review process. Peer reviews are not practiced by the authority for new applications submitted for registration in Kuwait, but peer reviews are carried out as part of the

GCC centralized procedure where two reviewers from two GCC states are appointed to review the same product file and raise their reports to the GCC Central Registration Committee where the decision is made in a conference meeting by the seven member states.

Quality management

The KDFC recognises the importance of implementing quality measures and is very supportive to any new practices that can be employed to improve the quality of the review process in Kuwait. The authority's enthusiastic support to improving the quality management system comes from its eagerness to increase the efficiency, to minimize errors and to ensure consistency in the review processes conducted by the assigned reviewers.

This is achieved by undertaking activities to bring continuous improvement in the assessment and authorisation process, namely:

1. Reviewing assessors' feedback and taking necessary action
2. Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action
3. Using an internal tracking system to monitor the consistency, timeliness, efficiency and accuracy of the review process.
4. Having a 'post-approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain company's comments.

There is no specific department or unit that has the full responsibility of performing these activities but a QA unit was established in 2008 to monitor the quality of the registration process for new medicines. This unit is not involved in the details of the review process, but it does monitor the outcomes of the approval process and the performance of the reviewers. The authority intends to set clear responsibilities for the QA unit to involve more activities that can achieve consistent improvements in the assessment and approval practices.

Quality in the review and assessment process

The authority provides guidelines on request to assist the pharmaceutical companies in the registration of medicinal products and the requirements are set out in the Ministerial Decree 302/80. Senior pharmacists within the authority are currently updating this Decree. In addition, applicants are allowed to meet with the authority's

key personnel to discuss the registration process prior to submitting a new application. This provides them with a potential opportunity of understanding the authority's review procedures and requirements before going through the process. However, the level of contact between the sponsor and the authority's personnel is controlled. The reviewing staff are not permitted to meet with the sponsors without the DRRS's or the director's approval. Extensive formal contact between the sponsor and the key personnel occur during the assessment process. This includes scheduled meetings, teleconferencing, and emails. This form of contact motivates the sponsor to follow-up on the registration requirements and enables them to negotiate certain questions and queries raised during the assessment process.

Training and continuing education as an element of quality

Unfortunately the authority does not currently have any formal training programs for assessors. Training is mainly carried out through induction, where a new employee is provided with a scheduled orientation to be introduced to all the departments and units in KDFC. A time period is set from one week up to one month in each department or unit and after the orientation program is completed the director places the employees in the department that is most short staffed. The authority sets no formal examinations or requirements for completion of the orientation program, but it must be completed in order to be eligible to work in the authority. The director is flexible with the candidates needs and interests because the most important goal of employing a new member of the staff is to maintain the best level of performance which is highly affected by the employees personal interests and ambitions.

Transparency of the review procedure

'Transparency' is the ability and willingness of the authority to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry. In general, KDFC assigns medium priority to transparency:

- Public: KDFC responds to public queries on an individual basis or through published reports in newspapers and local magazines
- Professional: KDFC responds to queries from all health professionals on an immediate basis but some delays could be encountered due to work carried out manually.
- Industry: KDFC always responds to queries coming from the industry.

The authority strives to answer all queries from the public, health professionals, and the industry as openly and transparently as possible, but at the same time, they are very cautious with the kind and amount of information being released as there are many specialised and technical practices that may not be fully comprehended by the general public and media. The authority is under a great deal of public, media and political pressure and must be careful about any statements they may be required to release.

However, the KDFC identified four main drivers for assigning resources to activities that can enhance openness of the regulatory system:

- Need to increase confidence in the system
- Press and media pressure
- Political will
- Public Pressure

Transparency is a major responsibility and it significantly contributes to the effectiveness of the authority's resources and capabilities. The KDFC is often questioned as to why so little information about the approved drug is provided to the medical community, researchers and consumers. The same concept applies to the lack of the industry's transparency. However, pharmaceutical companies are incapable of obtaining the information they need about the stage of their product assessment from the authority. Some companies are persistent in their follow-ups with their products and are constantly pressurising the authority's senior managers to approve them in the minimum possible time. Furthermore, companies are not provided with detailed reason(s) for rejecting a product.

Drivers and barriers facing the review process in Kuwait

KDFC senior managers are eager to improve the quality of the review process and to maximize its performance through achieving efficiency, precision, credibility and consistency in their assessment practices. There are several motivating factors identified by senior managers in KDFC, that contribute to accomplishing the desired effectiveness and efficiency of the authority's review procedures and decision-making for new applications, namely:

- KDFC is a key regulatory authority in the GCC region. The successful completion of registration process of a product in Kuwait facilitates the registration process in other GCC authorities such as Oman and UAE. This practice is currently changing to enhance the GCC-DR system, and the GCC States, particularly Saudi Arabia and UAE, are requesting the GCC registration to obtain marketing authorisation in individual States.
- The reviewers are highly experienced and are working efficiently within the scope and capacity provided by the authority.
- Senior managers are highly supportive of any improvement in the system within the scope of their capabilities and responsibilities
- A variety of scientific qualifications is available to suit the regulatory needs.

On the other hand, the KDFC is facing several obstacles that are hindering its ability to make new medicines available in timely manner, namely:

- Lack of quality assurance guidelines and policies
- Lack of project management plans in place
- No electronic handling for the submission, assessment, analysis and documentation of the product dossiers.

DISCUSSION

It has been recognised that Kuwait has an efficient regulatory review system which streamlines the registration of new medicines, provided that they have been approved in a 'major' reference country. Products with US, UK, EU, Canadian, Australian, Swiss, or Japanese approvals usually experience little difficulty in gaining access to the market. Life-saving and emergency products are taken out of queue for priority evaluation as the authority realises the medical importance of these products for local patients. Registration fees are relatively low at US$340 per product with no fees charged for product variations or renewal. The low cost is due to the small local manufacturing industry, which renders Kuwait being largely dependent on imports.

This study has evaluated the regulatory review process in Kuwait and the various milestones and stages constituting it. It also addresses various measures, which may have critical effects on the quality of the review process in Kuwait.

Model of the Regulatory Review in Kuwait

This study addressed the review model undertaken by KDFC for both NASs and EASs. The guidance for review set for the assessors is the Ministerial Decree (M.D.) 302/80 which is concerned with the requirements of the product registration dossier. It is currently being updated by the authority's key personnel and the new version will be released after the Ministerial approval has been given. There are several regulatory practices that are considered unique to Kuwait that are addressed in this study. These practices may or may not have a positive impact on the review process carried out by the authority but they do demonstrate, however, that Kuwait has a rational registration system that recognises the drivers and the barriers to achieving a reliable and efficient review process.

One of the most distinctive practices undertaken by KDFC is that products manufactured by innovative and generic manufacturing companies are not sent to the Quality Control (QC) laboratory for analysis if they are registered in countries with competent regulatory authorities. This process increases the authority's confidence in the product's quality, safety, and efficacy and overcomes its shortage in skill sets required to perform a highly specialised review for the product. Dossiers for New Chemical Entities (NCEs) typically involve between 100 and 800 binders of data (Health Canada, 2006). The time taken to review and evaluate such dossiers is a common measure of the performance of a drug regulatory authority, which unfortunately puts pressure on small authorities to keep up with international standards set by agencies such as USFDA and the EMA (Hill and Johnson, 2004). It is understandably difficult for KDFC, being a small developing authority, to undertake a full assessment. Therefore, the authority performs a 'verification review', rather than a full review, concentrating on the evaluation of quality and the product information documents. Thus, the basis for decision-making is generally trusting the assessment performed by well-resourced and experienced agencies.

The KDFC's most important document that can markedly affect the approval time of any product is the Certificate of Pharmaceutical Product (CPP). This is the focus of the authority's whole review process and it is compulsory for companies to submit the original CPP, in WHO format, authenticated by an embassy or a consulate. It is considered the birth certificate of any pharmaceutical product where all product particulars are legally stated such as the name, dosage form, shelf life, manufacturer,

product license holder, packager, GMP status, the summary of product characteristics, and the marketing status of the product in the exporting country. However, the KDFC has particular concerns about products that are regarded as ' for export only' and clarification from the manufacturer is requested accordingly. The reason for this request comes from the authority's concern that developed authorities may not pay full attention to product specifications if the manufacturer indicates that such a product is only for export to another country, especially a developing country. An appropriate practice, that the authority needs to consider to ensure that manufacturers of 'for export only' products are of the desired standard, is the conduct of GMP inspection of the manufacturing site(s) whether based in developing or developed countries. Currently, some GMP inspections are performed on the local manufacturer (Kuwait Saudi Pharmaceutical Industry Company- KSPICO) and as part of the GCC centralized process. No GMP inspections are carried out on any international manufacturing sites for the registration of products in Kuwait. The KDFC relies on the GMP certificate and the manufacturing license submitted at the point of the company registration.

Having an officially registered local agent is a critical practice in developing countries to ensure that the product is legally under the full responsibility of one local representative of the principal company who follows up the product's pre- and post-marketing status within the country and enables the authority to have a locally approved representative with whom they can directly liaise in case of any product related issues. The registration of a pharmaceutical company is an important first step for the registration of its own products. It saves the company the time spent during the validation stage to check the status of the applicant for every single product submitted for registration. Instead, the authority enforces the practice of registering the company and its local agent, who will then be fully responsible for following up on the registration of its products.

The registration of NASs in Kuwait is simpler than the registration of EASs. For an NAS, a company is required to submit a dossier that contains data about the pharmaceutical quality of the product. The assumption is that by providing evidence of registration in other competent authorities, the KDFC generally trusts the assessment carried out by these authorities and is therefore able to streamline the registration requirements and accept the NAS without the need to perform QC testing

or to evaluate the submitted clinical studies for the approval. The drug is therefore assumed to be clinically effective and safe if it is registered in a strongly controlled market like the EU or USA. This also applies to EASs registered in reference authorities. However, NASs are not accepted for registration until they are registered in countries with developed regulatory systems, while EASs not registered in reference agencies, must pass the QC analysis and prove to be interchangeable with the NAS in terms of efficacy and safety. Kuwait requests limited clinical data in the form of bioequivalence studies which show that the EAS is bioequivalent to the NAS. Bioequivalence presents the first challenge for the EAS registration because many EAS manufacturers find it difficult and costly to perform high standard controlled trials that compare the proposed EAS with the NAS.

The second challenge that faces the KDFC and the companies is that KDFC refuses to register an EAS if the NAS is not marketed in Kuwait. The authority requires that the submitted EAS is capable of demonstrating a satisfactory safety and efficacy profile and bioequivalence to the NAS marketed in Kuwait. The third challenge is the availability of sufficient statistical and pharmacokinetic skills within the authority to properly assess the bioequivalence studies. Kuwait has 15 scientific reviewers, none of whom have had any formal training in assessing bioequivalence studies. They all gained the experience through personal efforts and job experience. However, there are several ways of improving the authority's skill sets, such as utilizing user-friendly software, attending additional training programs, and the use of external experts.

Key Milestones of the Review Process in Kuwait

The total number of the staff members working in the Pharmaceutical Drug Registration Unit (PDRU) is 30, 15 of whom are pharmacists performing the review process. Reviewers evaluate the pharmaceutical quality of medicines. However, the KDFC understands that medicines are not normal commodities, and the ultimate public health protection relies on the benefit-risk profile demonstrated by the product through the regulatory review process. The authority lacks the skill sets required to assess the safety and efficacy data of the medicines and approves products based on pharmaceutical quality data, relying on the registration and marketing of the product in other countries with competent authorities. The pressure on regulators in Kuwait includes having to respond to the political force, media critiques, the culture of

personal interests, the public needs for access of new medicines, and the industry demands for entry of their product onto the market within the shortest period of time. The regulators strive to balance these responsibilities by making high quality medicines available to the public through an efficient and reliable review process.

New Product Submission Process

In certain mature agencies, such as US FDA and Health Canada, the regulatory review process consists of two main stages, namely, the investigational new drug (IND) and the new drug application (NDA). During the IND, the medicine is required to pass the pre-market review process in order to be approved for regulatory assessment. Pre-clinical studies are carried out to evaluate the safety of a drug and to provide information about the existence and extent of adverse effects prior to testing in clinical trials. If the pre-clinical studies are promising, clinical trials are conducted to assess the existence of potential therapeutic value that may outweigh the risks (e.g. adverse effects or toxicity) associated with its proposed use; the manufacturer can, then, file for NDA with the relevant agency (Health Canada, 2006). An NDA contains all pre-clinical and clinical information obtained during the testing phase and information on the chemical make-up and manufacturing process, pharmacology and toxicology of the compound, human pharmacokinetics, results of the clinical trial and proposed labeling (Lipsky and Sharp, 2001). These are similar to the contents of the product registration dossier submitted to the KDFC for approval. The authority is therefore skeptical about approving products that are not assessed, approved and marketed in countries with developed regulatory systems.

New Product Assessment Process

At the time that the new medicine is selected for review, the administrative staff member transfers all the files to the assigned reviewer. The reviewer is fully responsible for validating and scientifically evaluating the product dossier, listing all the possible queries, questions and missing data in one form to be sent to the local agent/sponsor. The validation stage 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. This is more convenient and less time consuming for developed agencies, while it is considered time consuming for the KDFC being a small agency that performs a simple verification review.

After completing the scientific assessment, the product enters the QC analysis stage. NASs and EASs registered in countries with reference agencies are exempt from this analytical stage. Upon passing the QC analysis, the DRRS recommends the approval to the Director of the authority who authenticates and issues the registration certificate. Interaction occurs directly between the authority and the manufacturing company in Canada and USA. In Kuwait, however, communication occurs between the authority and the local agent, because the KDFC is limited in its ability to make risk-benefit assessments and has inadequate resources to perform effective post-marketing surveillance (PMS). Therefore, regulators need to interact with a legitimate local representative who is legally responsible for the entire product's pre- and post-marketing status. The local agent faces considerable pressure from the pharmaceutical company and the regulatory authority proving and sustaining credibility, integrity, and honesty in their interactions with the two parties. They must demonstrate that their fundamental ethical goal which is to ensure access to safe and effective medicines in Kuwait and must avoid any detrimental expression of being a sole 'profit-making company' to any of the two parties. A recent improvement involves the addition of a requirement to submit Post-Marketing Surveillance (PMS) reports as part of the safety studies which include cases of Adverse Drug Reaction (ADRs) and Adverse Drug Events (ADEs) that occurred during the use of the medicinal products by patients in other countries.

Priority Review

Products that are considered lifesaving or medically urgent are prioritised for review in Kuwait. These are categorized as fast-track submissions. They are reviewed more quickly with shorter approval time than non-fast-track submissions. This is similar to 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 risk-benefit profile is better than that of existing therapies (Health Canada, 2008a). US FDA, on the other hand, has a different system for fast approvals which includes accelerated approvals, fast-track reviews, and priority

reviews. The first two categories affect the development process before the sponsor submits a marketing application to the agency (Thaul, 2008). The priority review relates only to the applications' place in the review queue, which is one that coincides with the Kuwaiti and Canadian Priority Review systems mentioned above. Priority review in USA applies to major advances in treatment or where no adequate therapy exists. The difference between KDFC and the other two comparator agencies is that Health Canada and US FDA do not prioritise the review of products for serious or life-threatening conditions because they must establish the evidence of their safety and efficacy during the development stage in order to be medically recognised as lifesaving products.

Pricing Review and Agreement

It is important to evaluate the quality, safety and efficacy of the medicinal product to protect the public health, however, ensuring that the product price is affordable by the local patients is another important aspect to be considered. The pricing process can markedly affect the timely access of medicines to the patients in Kuwait. Therefore, the Director decided to commence the pricing procedure in parallel, rather than at the end of, the review process. The Pricing department is responsible for regulating the price charged by pharmaceutical companies for medicines sold in Kuwait to wholesalers, pharmacies and local agents. Each party is allowed a calculated profit margin that is controlled by the KDFC price regulators. By examining this profit margin, which is fixed by the government at 55%, it is clearly understandable why the medicines in Kuwait are considered expensive. The government is making significant efforts to reduce these prices and the profit margin was reduced from 71% to 55% in 2005. However, other factors involved in the pricing of medicines, such as inflation and exchange rates, cannot be controlled by the KDFC.

Unfortunately, the Kuwaiti authority does not perform cost-effective analysis of medicines marketed in the private sector, and pharmaceutical companies set prices to ensure appropriate profits in countries such as Kuwait. In addition, the Kuwaiti government is spending more than US$ 2billion on the health sector each year and providing the public with medicines free of charge. The authority is not paying attention to the affordability of medicines available in the private sector, and the full

implication of the current situation has been a shift of patients towards government hospitals and the failure of pharmaceutical companies to achieve profits in the private sector. A clear sense of value of a medicine being considered for marketing is an advantage during the negotiation process and could improve the access to quality medicines in the private sector at affordable prices (Lopert et al., 2002)

Evaluation of Quality Measures used in the Review Process in Kuwait

Regulators in Kuwait are eager to promote consumer protection and support public health by achieving effective and timely regulatory judgments based on the quality of the review process. The KDFC, as many other small developing agencies, lack the appropriate expertise and resources that ensure the conduct of high standard review practices such as GRP, SOPs, peer reviews and other quality assurance tools to ensure consistency, transparency, timeliness and competency in the review process. Thus, this study explores the quality measures that are currently available in the KDFC to identify areas of improvement and provides an insight into the strategies, measures and resources that KDFC has in place to develop and maintain quality in its review process.

General quality measures used in the review process

Unfortunately, Kuwait is still not adopting Good Review Practice (GRP) which may be due to the lack of the required expertise, and the formal training programs for reviewers. The KDFC regulators recognise the urgency of standardising the overall documentation and ensuring timeliness, predictability, consistency and high quality review reports as a result of implementing GRP. However, the KDFC lacks the political influence to convince the minister and the parliament members to accomplish this quality measure. Standard operating procedures (SOPs) are another quality measure that is deficient in the regulatory practices. The importance of implementing SOPs is fully understood by the regulators, but they explained that M.D. 302/80 is used as in SOP because it guides the reviewer through the data and the documents required in a complete application. Furthermore, Kuwait uses assessment templates that set out the content and format of the written scientific reviews for the reviewers in a clear, unambiguous manner. SOPs and assessment templates are sufficient for the conduct of a simple verification review in Kuwait.

Long, thorough and complicated full-reviews carried out by developed agencies require the availability of detailed SOPs that enable the assessors to precisely follow the routine review procedure without losing the quality and effectiveness of the review outcomes. Nevertheless, it is essential that the KDFC regulators seriously consider the implementation of SOPs in the regulatory review practice if they have the intention and the desire to improve the standard of the review process in Kuwait. Unwritten SOPs and guidelines may become erratic and even lead to questions about the transparency of law enforcement (Hashan, 2005).

The Kuwaiti review process relies entirely on three key persons: the reviewer, the DRRS, and the Director. The DRRS appoints the reviewer who is responsible for validating and scientifically assessing the product dossier. Therefore, the quality of the review depends on the reviewer's level of experience, qualifications, knowledge and the level of enthusiasm in carrying out the assigned task. There are 15 reviewers for pharmaceutical products in the KDFC with a range of experience from few months to 30 years. This wide range demonstrates the difference in the quality of the review process from one reviewer to another. Moreover, some reviewers are keen to produce the best possible review reports and have a great interest in continuously learning and improving their individual practices, while some others are only carrying out the jobs they are assigned to achieve without demonstrating any enthusiasm in improving the quality of their performance and outcomes. Peer review may be an essential determinant that should be seriously considered by the DRRS and the Director of KDFC to ensure optimal quality review, especially if the reviewer has less than six months experience in conducting a review process. In the TGA, for example, there is a multilayered peer review process during which applications are evaluated a second time by more experienced reviewers to ensure that a correct decision is made initially (Anderson, 2004). The DRRS fully relies on the assigned reviewer's report to recommend the approval decision to the Director who makes the final decision. In addition to peer review, joint review is another important tool of quality in the review process. It is performed as part of the GCC central registration process, where two authorities are assigned alphabetically to review a product submitted for the central registration, where the outcome is discussed in a conference meeting and the decision is made by consensus.

Quality management

The DRRS has the responsibility for ensuring the consistency, efficiency and accuracy of the review process. Therefore, establishing an effective communication style between the authority and the local agent is critical to bring about continuous improvement in the assessment and registration process. The DRRS must have the experience and the skill of managing and scrutinising the feedback from the assessors and the local agent without negatively affecting the quality of the review process. In that case, peer review is essential to help the DRRS provide the companies with more accurate and reliable feedback.

In the US FDA, for example, more dialogues occur among the review team members throughout the process. Medical officers and statistical reviewers work particularly closely and sometimes carry out a joint evaluation. Members of a review team are located close to one another to encourage more interaction. Multidisciplinary teams review the NDAs and meet throughout the review process to discuss the status of their reviews and to share ideas. The NDA review process adequately integrates information across the review disciplines (Rehnquist, 2003).

The management team in KDFC has the responsibility to ensure the quality of the review process. Therefore, an attempt to establish a quality assurance (QA) unit was made in 2008. This unit is responsible for ensuring that the reviewers' as well as the QC analysts' performance meets the authority's demands and expectations. However, this unit is not yet officially approved as part of the KDFC structure and therefore its scope of responsibility cannot yet be enforced. The unit consists of two pharmacists which is a small number to achieve the desired quality assurance task for the authority. The KDFC's perception of achieving quality in the review process relies on the outcome of the review at different managerial levels from the reviewer to the DRRS to the Director. However, in the absence of written official SOPs for the review activities within the authority, the role and efficiency of checking and supervision as a QA method becomes questionable. In the USA, the quality assurance staff (QAS), who monitor the quality and consistency of the review activities, reside in the Office Centre Director (OCD). The QAS also provides an oversight for committees created to ensure conformity with FDA regulatory policies

and procedures, such as the FDA refusal-to-file and clinical hold policies. The head of these staff reports directly to the biologic center director (Sensabaugh, 1998).

Quality in the review and assessment process

The only official written guide for both the reviewers as well the industry is the M.D. 302/80. For reviewers it acts as an SOP that directs them through the routine review process. For the industry, on the other hand, it assists the applicants in the registration of medicinal products. A hard copy is provided to the local agents upon submitting an official request. Another important determinant of a good quality review process is the authority's willingness to provide pre-submission advice that allows the applicant an opportunity to understand the requirements of the registration process more clearly, and it also informally introduces the authority to the new proposed product and the importance of this product for local patients.

The KDFC permits the applicant to establish the contact with the technical staff only upon the approval of the Director or the DRRS. This is to prevent the culture of bribes and corruption from creeping into the system (Fattore and Jommi, 1998). The most effective tool to circumvent any distortion is the use of an electronic system for handling the regulatory review procedures, which is still deficient in the KDFC. All submissions, reviews, follow-ups and tracking procedures are handled manually. This results in several errors, misplaced files and documents and missing data, which can markedly affect the credibility of the work being carried out by the authority's staff.

Training and continuing professional development (CPD) programmes

Training and CPD is an important element of quality that can markedly affect the standard of the scientific review performed by an assessor. The US FDA has taken several steps to encourage reviewers to participate in professional development activities. A policy was put in place to allow the reviewers to spend up to one day a week participating in professional development activities as well as conducting extensive internal training programs that include a broad range of classes from statistics to technical writing and good review management principles (Rehnquist, 2003). Unfortunately, the KDFC does not conduct official training on the review process for new reviewers when they join the authority. The new reviewer

(Pharmacist) is trained by other experienced colleagues and there is no obligatory training program for any reviewer to achieve the desired level of expertise. Lack of such important QA tools does not provide confidence in the KDFC's reviewer's ability to produce high standard review reports and therefore, it will negatively affect the quality of the final decision-making. In fact, senior managers are encouraged to attend training courses and CPD programmes. However, the KDFC should seriously consider training programmes that particularly include the reviewers, because decision-makers depend on the review reports issued by the assessors to make the final approval decisions. Training and continuing education programmes should be compulsory for reviewers and other members of the authority's staff.

Transparency of the review procedure

Transparency is another critical determinant of the quality of the review process. It demonstrates the authority's willingness to provide information on its activities to both the informed public (which includes health professionals) and industry (Hill and Johnson, 2004). Transparency in pharmaceutical regulation in Kuwait is considered crucial. However, this study found that KDFC regulators are skeptical about releasing all the details to avoid unnecessary political or media criticisms. This can be understandable as the authority realises that the information maybe too specialized and that the public would not fully comprehend the authority's decision(s), particularly when the media exaggerates the case. However, there are certain situations where full transparency is essential and can affect the credibility of the regulatory authority. An example of these cases is the recent review of antidepressant trials registered with US FDA. It showed that antidepressant trials with negative results were much less likely to be published than trials with positive results. This influenced the public trust of FDA (Vitry, 2008). Another crucial point to be considered is the regulatory decision that involves value judgments in balancing data about the benefits and harms of medicines (The Ontario Health Technology Advisory Committee (OHTAC), 2010). These value judgments should be disclosed with reasons for regulatory decisions. This would help patients make their own choices about whether the medicines are suitable for them (Editorial Executive Committee, 2005).

There are considerable media critiques and public suspicions about the integrity of the decisions made by KDFC regulators. Pharmaceutical companies make significant profits following the successful registration and pricing of their product(s). This places

the regulators under a great deal of public scrutiny because of the possibilities of conflict of interests and/or corruption. Thus, transparency in pharmaceutical policy-making is required to maintain public trust in the KDFC.

It is simplistic to think that speeding up the registration processes without paying attention to the importance of market control and assurance of quality will improve patients' access to medicines. The KDFC regulators are capable of setting a framework for registration that has its key function "the protection of public health", and at the same time as "improving access". This is because they have the key assets to achieve such a framework being an important authority in the GCC region, having experienced reviewers, having an efficient registration system, and highly supportive and enthusiastic regulators. However, pressure always stands in the face of any successful system. These obstacles can hinder the authority's ability to be in line with the advanced and developed agencies. Kuwait has the financial ability to support any improvements in the regulatory system, but the main deficiency lies within the shortage of QA policies and project management plans as well as the lack of electronic handling of the regulatory procedures. This is probably due to the fact that KDFC is under the autonomy of the Ministry of Health (MOH). It is 100% funded by the government and its budget is part of the whole MOH budget. Kuwait regulatory authority works independently from all the other divisions and departments within the MOH. Its important role is not being sufficiently recognised by the government officials which makes it very difficult for the regulators to persuade the politicians of the significance of having an effective regulatory system in order to ensure that the authority is financed to achieve the desired level of regulatory services. It is important to educate the politicians and the government officials that drug regulation is essential rather than a luxury. It is also essential that parliament considers separating the KDFC from the MOH control to become a fully independent authority funded partly by the government and partly by registration fees. This shift in power of autonomy could bring in the advanced regulatory practices and programs that improve the quality of the regulatory review process in Kuwait.

SUMMARY

- The Kuwait regulatory review process involves the registration of the pharmaceutical manufacturer and its sole agent in Kuwait before commencing the registration of its pharmaceutical products.
- The validation of a registration dossier is part of the scientific assessment stage in Kuwait in which a simple verification review is performed by the appointed assessor.
- Safety and efficacy studies are required for the registration of medicines but they are only examined when there is a query.
- EASs must demonstrate interchangeability with the currently registered NASs in Kuwait and, therefore, bioequivalence studies must be submitted by the pharmaceutical company to be assessed by the appointed assessor in the KDFC.
- NASs and EASs which are registered in recognised regulatory authorities do not face the QC analytical testing and the approval process is significantly expedited accordingly.
- The product price is calculated using a special formula by the pricing department. In addition, some comparative assessment is carried out between the calculated prices in Kuwait and other GCC States as applicable. However, the assessment lacks the health technology evaluation with respect to cost-effectiveness of medicines.
- The overall target patient access time to medicines is six months which includes the registration and the pricing time.
- The authority does not implement GRPs, SOPs, or peer reviews to enhance the quality of the review process. However, assessment templates are used to achieve clarity and consistency in the final review reports.

- Joint reviews are performed as part of the GCC-DR procedures where two GCC authorities are appointed to review the registration dossiers and submit their reports to the GCC-DR committee where the final approval decision is made collectively by the seven member states.

- The Ministerial Decree (M.D.) 302/80 is considered a suitable guideline for both the assessors and the industry that guides them through the successful completion of the review process of the medicines in Kuwait.

- The KDFC does not have any formal training programs for the assessors and new pharmacists are trained by experienced colleagues on how to conduct the review of new medicines.

- Kuwait assigns medium priority to the transparency of the information on its activities to the public and the media because the information maybe too specialised to be comprehended by the public and caution is practiced when providing any statement that might be misinterpreted by media and politicians.

CHAPTER 4

Evaluation of the Regulatory Review Time in Kuwait

INTRODUCTION

The regulatory approval of medicines can be a complicated process that is frequently considered as being unreasonably long. Critics often complain that the pharmaceutical approval process, which is too slow and too costly, could have a negative effect on patients' health when life-saving anti-cancer and anti-HIV drugs are involved (Brower, 2002). Drug regulatory agencies worldwide have recognised the importance of review timelines in their work and endeavoured to achieve an improvement in this area (Mutlib, 1996).

The timeliness with which national regulatory authorities approve new medicines for marketing affects healthcare professionals and patients. An unnecessary long approval process delays access to new medicines that may improve patients' health status (Rawson, 2000). From a public perspective, the rationale for rapid access to safe and effective therapeutic products is simple. The nation as a whole benefits socially and economically when everyone enjoys the best possible health (Health Canada, 2006). The KDFC has long encountered criticism of its review process and timelines by the industry, media, politicians and the regulators have been struggling to expedite the approval process although it is still unclear whether a faster and streamlined approval process is indeed better for the public.

Patients' access to medicines in many emerging markets largely depends on approvals made by the mature agencies such as the United States Food and Drug Administration (US FDA) and The European Medicines Agency (EMA), in order to avoid duplication of effort and to enable optimal use of limited resources. However, if registrations in these recognised agencies are not evidenced, patients' access to new medicines may be delayed. Furthermore, some routine procedures cause unnecessary barriers to the timely approval to new medicines. Different data requirements involve additional work, time and money on the part of the company and slow down drug development (Tsui, 2009).

This study identifies the timelines of the approval process in Kuwait which are governed and regulated by the three stages of the approval process namely, submission stage, registration stage and pricing stage.

OBJECTIVES

The objectives of this study were to,

1. Compare and contrast the number of applications submitted, registered, and priced for various pharmaceutical products over the four-year period from 2006 to 2009.
2. Compare the timelines for patients' access to various pharmaceutical products over the period from 2006 to 2009.
3. Determine the registration and pricing timelines of New Active Substances (NASs) from major therapeutic groups over the period from 2006 to 2009.
4. Determine the speed of patients' access to New Active Substances (NASs) and Existing Active Substances (EASs) over the period from 2006 to 2009.

METHODS

Study Participants

The study participants involved the senior managers in the Registration and Release Department and the Pricing Department in Kuwait Drug and Food Control (KDFC) authority. These participants are responsible for organising the review and pricing systems and monitoring the submission and approval times.

Data Collection Process

Face-to-face meetings with the Director of KDFC and the Drug Registration and Release Superintendent (DRRS) took place in Kuwait in 2008 and 2009. Further meetings were held with the senior technical staff and reviewers in the Registration and Pricing Departments with the Director's approval. They provided data on the regulatory review process and approval timelines in the form of word documents. In December 2009, the four-year data were provided after auditing and approval was made by the DRRS. The data consisted of the number of submitted, registered and priced medicines over the period from 2006 to 2009. The median registration and pricing times were calculated for New Active Substances (NASs) and Existing Active Substances (EASs). The data were further scrutinized to obtain the median registration and pricing time for NASs for various therapeutic groups submitted and approved during this period. Moreover, the data included Government Hospital Supply (GHS) medicines which are provided to the citizens free of charge and are

not included in the pricing system. However, the registration time is the determining factor for the timely access of these medicines to patients. Therefore, data for the trends of registration of GHS medicines were also obtained from the authority.

Compounds Included in the Study

All products (NASs and EASs) from the Gulf Cooperation Council (GCC) Arab, Non-GCC Arab, and international pharmaceutical manufacturers, approved for human use and accessed by patients in 2006, 2007, 2008 and 2009 in Kuwait, were included in this study. Therapeutic groups for NASs were specified for the purpose of this study and GHS medicines were also included to further review the patients' access time to medicines in the government health sector. The aim of collecting data on such specific categories was to cover the complete range of pharmaceutical products reviewed, approved and marketed in the private and government sectors over the period from 2006 to 2009.

Hypotheses

The study examined the following hypotheses,

1. There was an increase in the number of pharmaceutical products submitted, registered and priced between 2006 and 2009.
2. The number of products made available to patients from International, Gulf Cooperation Council (GCC) Arab, and Non-GCC Arab pharmaceutical companies did not change from 2006 to 2009.
3. Patients' access time to medicines in Kuwait did improve over the period from 2006 to 2009.
4. Patients' access time was significantly longer for EASs in comparison with NASs over the period from 2006 to 2009.
5. There was no difference in the registration time of GHS medicines from 2006 to 2009.
6. There was a decline in the median time for patients' access to NASs for each major therapeutic groups over the period from 2006 to 2009

Data processing and analysis

The patients' access time is defined as the time from submission of the new application to the time of price approval by the Minister of Health. This involves two phases, the registration time, which is the time from the submission to the registration of the new medicine, and the pricing time, which is the time from the registration to the pricing approval by the Minister of Health.

From this study, the following three major areas were examined, namely, (1) trends in submission, registration and pricing of new pharmaceutical products over the period from 2006 to 2009; (2) changes in the approval timelines for various medicines over the period from 2006 to 2009; and (3) the rate of patients' access to medicines over the period from 2006 to 2009. Non-parametric tests were applied for the analysis of the data generated in this chapter (see chapter two for further details).

RESULTS

For the purpose of clarity, the results in this chapter will be presented in three parts: Part I: Trends in submission, registration and pricing (2006-2009); Part II: An evaluation of patients' access timelines for pharmaceutical products in Kuwait (2006-2009); and Part III: Trends in regulatory submissions and approvals of new active substances (NASs) for major therapeutic groups (2006 - 2009).

The senior regulators in the Drug Registration Department and the Pricing Department provided the data from 2006, 2007, 2008, and 2009 (Table 4.1).

Part I: Trends in Submission, Registration and Pricing of Pharmaceutical Products in Kuwait (2006-2009)

Submission

The number of approved products in any regulatory authority can be affected by many factors. For example, the number of dossiers submitted to the authority and the number of reviewers in the registration section (Hashan, 2005).

Table 4.1 Data type and definitions collected from the Kuwait Drug and Food Control (KDFC) authority

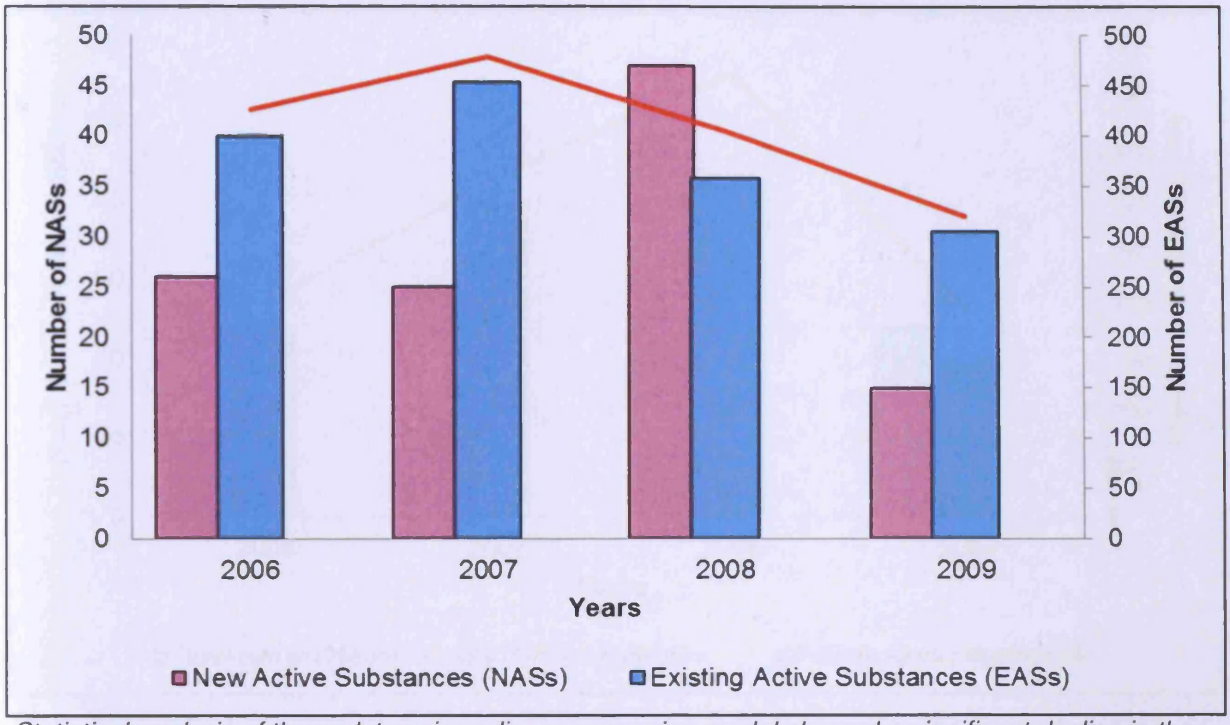
Data Type	Definition
Brand name	A legally protected name given to a drug by the manufacturing company.
Composition	The combination of the pharmaceutical chemical ingredients that form the final medicinal product
Therapeutic groups	Drugs are classified by therapeutic groups—that is, by the disorder or symptom they are used to treat. For example, drugs used to treat high blood pressure are called antihypertensives.
Date of submission	Date of submission of new drug for registration. New applications require the submission of an updated product dossier to KDFC.
Date of registration	Date of issuing the final registration certificate to the pharmaceutical company as a proof of approval of their product.
Date of pricing	Date of final ministerial approval of the product price.
Registration time	Time from submission to registration of a pharmaceutical product
Pricing time (market access)	Time from registration to the final pricing approval by the health minister
Overall patients' access time	Overall time from the date of submission to the date of pricing of the new pharmaceutical product

Kuwait is no exception and the number of approved products varies from year to year due to these and other factors. This section evaluates the trends in pharmaceutical products' submissions, registrations and pricings by analysing the data provided by the Kuwait authority.

When the data obtained from the KDFC for the four-year period (2006-2009) was examined, the results showed an overall significant decline ($p < 0.05$) in the total number of submitted pharmaceutical products for review from 426 products in 2006 to 320 products in 2009 (Figure 4.1). The total number of submitted products included New Active Substances (NASs) and Existing Active Substances (EASs).

Statistical analysis using a linear regression model showed that the decrease in the overall number of submitted NASs was not statistically significant ($p > 0.05$), while it was highly significant for EASs ($p < 0.01$).

Figure 4.1 Total number of pharmaceutical products submitted for registration (2006 – 2009)



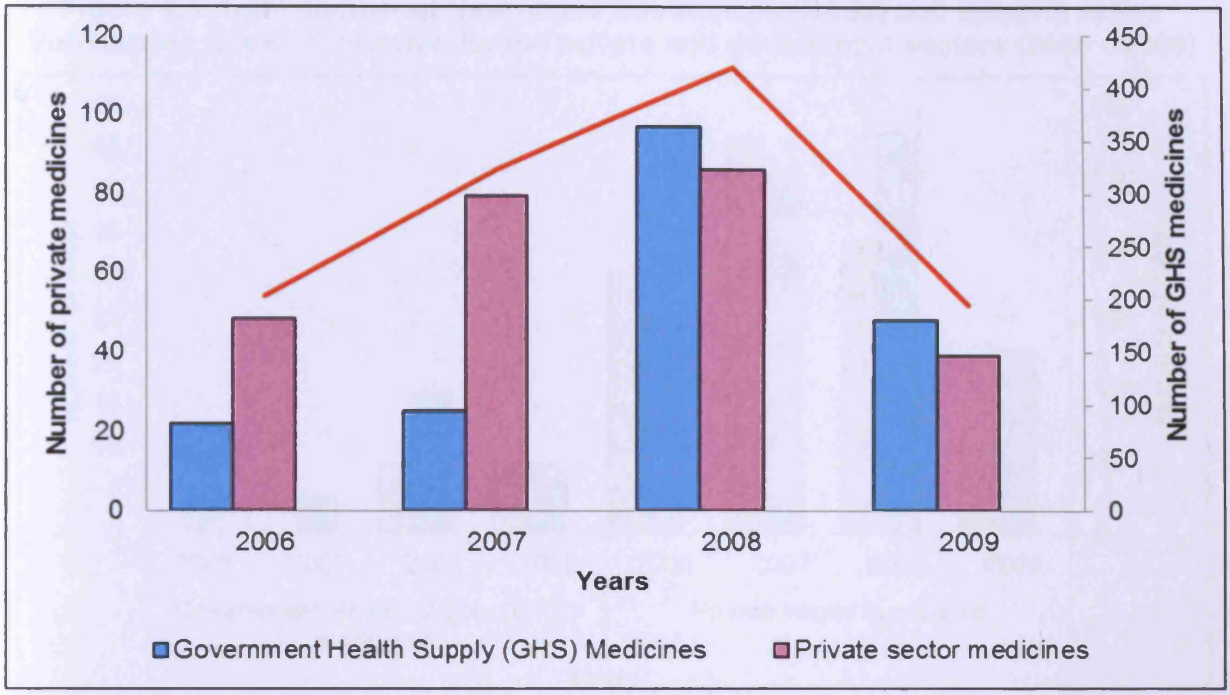
Statistical analysis of these data using a linear regression model showed a significant decline in the number of all medicines submitted from 2006 to 2009 ($p < 0.05$).

Examining the trend of pharmaceutical products submitted during the four-year period, a peak in 2007 reaching 478 products was observed. This was due to the increased number of EASs submitted for registration in that year. The number of submitted NASs doubled from 25 products in 2007 to 47 products in 2008. These peaks in the number of EASs and NASs in 2007 and 2008, respectively, were due to the authority's efforts to reduce the backlog problem during this period which encouraged the pharmaceutical companies to submit more products for registration.

Registration

The trend for pharmaceutical products registered in Kuwait was evaluated and two major outcomes were identified. The first outcome was related to the total number of pharmaceutical products reviewed and registered in Kuwait including medicines sold in the private sector (community pharmacy, private hospital pharmacies and health centres) and the government sector as Government Health Supply (GHS) medicines which are provided to the patients free of charge (Figure 4.2).

Figure 4.2 Total number of registered pharmaceutical products for the government and private sectors (2006-2009)

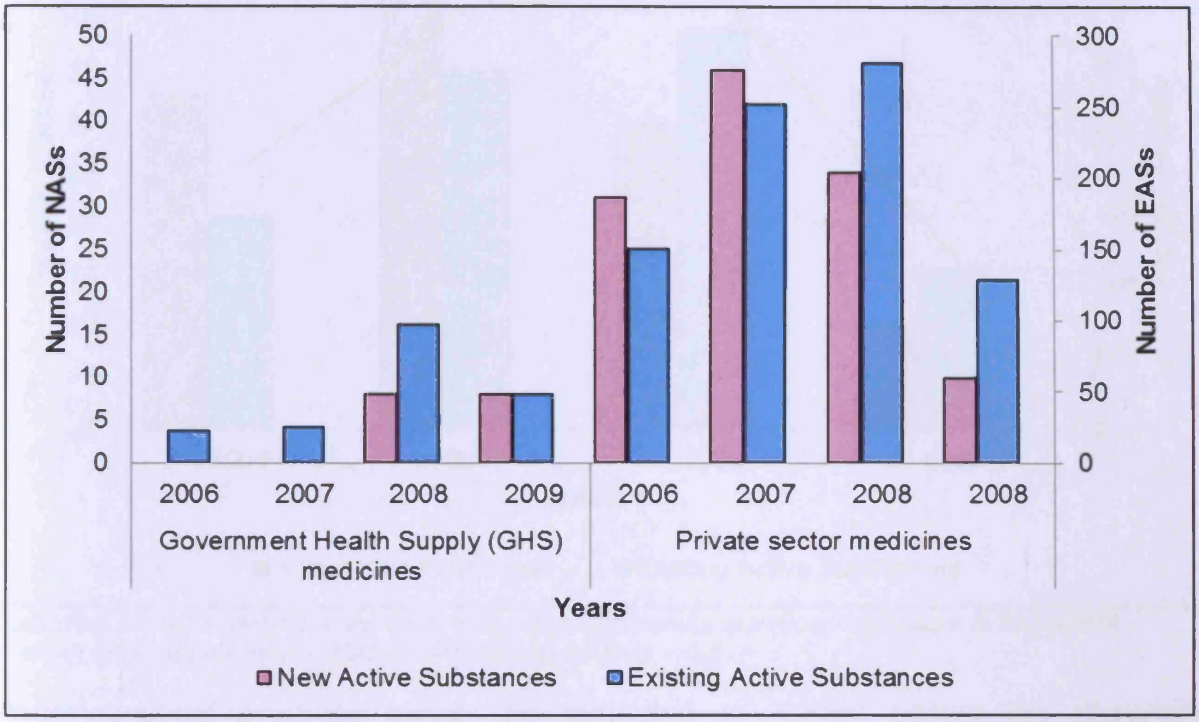


This trend showed a steep and continuous rise in the total number of registered products from 203 products in 2006 to 323 products in 2007 and 420 products in 2008. This can be attributed to the large number of submissions that occurred in 2007 (478 products) which increased the reviewers' workload to expedite the review process and register more products to overcome the backlog problem (Figure 4.2). As a result of the authority's successful efforts, the number of registered products returned to 195 products in 2009 which is similar to that which occurred in 2006 (203 products) (Figure 4.2).

The second outcome was revealed through further examination of the data which determined the total number of the NASs and EASs registered for the private sector and the government sector as GHS medicines. Both NASs and EASs demonstrated similar trends over the four-year period where the largest number of registrations occurred in 2007 and 2008, respectively.

No NASs were registered for the government sector in 2006 and 2007 as the government focused on providing generic medicines to patients. However, the government responded to the increasing public demand for the availability of quality, safe and effective medicines in government hospitals and, therefore, eight NASs were registered as GHS medicines in 2008 and 2009, respectively (Figure 4.3).

Figure 4.3 Total number of New Active Substances (NASs) and Existing Active Substances (EASs) registered for the private and government sectors (2006 – 2009)

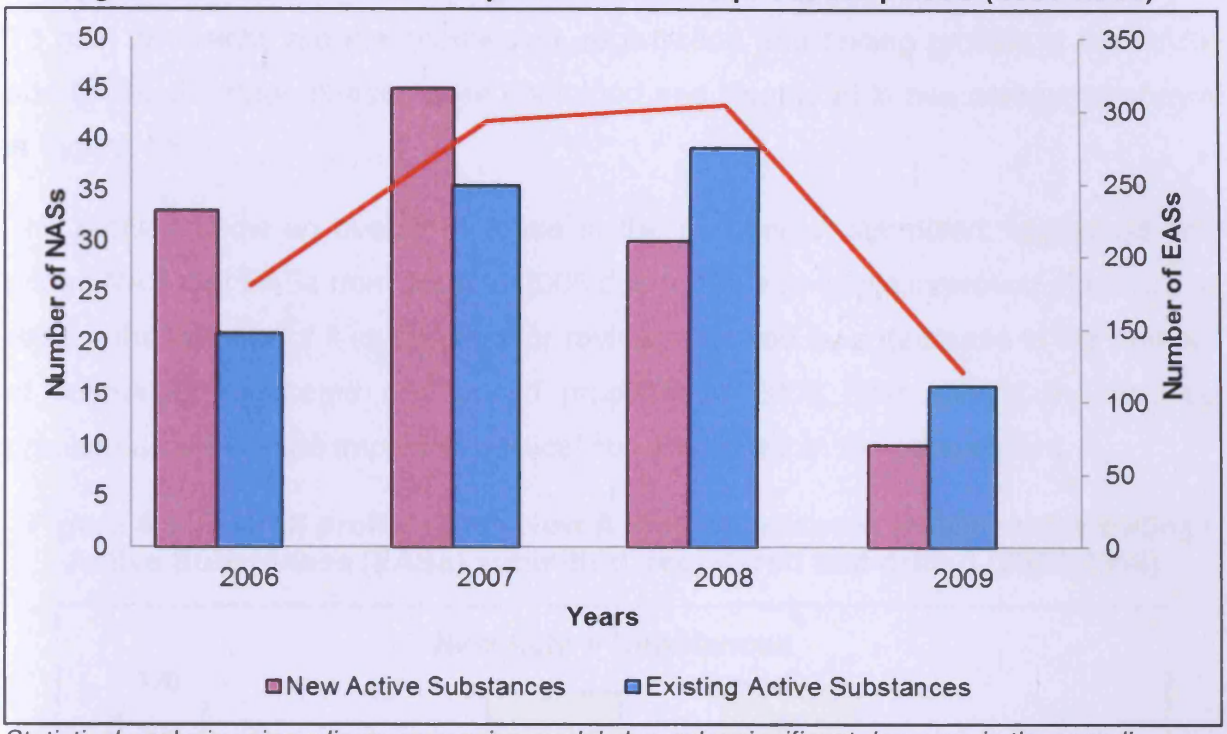


Statistical analysis using a linear regression model showed a significant increase in the overall number of NASs registered for the government sector from no products in 2006 to eight products in 2009 ($p < 0.05$) while it showed a significant decrease in the number of NASs made available to patients in the private sector from 31 products in 2006 to 10 products in 2009 ($p < 0.001$). The analysis also showed that the increase in the overall number of registered EASs from 22 products in 2006 to 48 products in 2009 was not significant ($p > 0.05$) while the decrease in the number of EASs registered for the private sector from 150 products in 2006 to 129 products in 2009 was significant ($p < 0.01$).

Pricing

The number of priced pharmaceutical products followed a similar trend to the number of registered pharmaceutical products over the period from 2006 to 2009 (Figure 4.4). There was a steep increase in the priced products from 180 in 2006 to 293 and 304 products in 2007 and 2008, respectively. This increase was attributed to the political changes in the government that resulted in six Ministers of Health being replaced within three years.

Figure 4.4 Total number of pharmaceutical products priced (2006-2009)



Statistical analysis using a linear regression model showed a significant decrease in the overall number of priced NASs and EASs from 2006 to 2009 ($p < 0.01$)

Pharmaceutical products cannot be marketed in Kuwait before the Minister's approval is granted for the product price after it has been calculated and proposed by the pricing department in KDFC (Figure 4.4).

With these changes, delays occurred and the increasing number of products waiting to have price approval by the next Minister was inevitable. However, by the end of 2008, the political situation began to stabilise and a sharp decline of priced products occurred from 304 products in 2008 down to 121 products in 2009, which indicated that the authority was able to tackle the problem of pending price approvals in 2007 and 2008 resulting in a significant overall decline in the number of priced products from 180 in 2006 to 121 in 2009 ($p < 0.01$) which indicated that the authority was able to obtain the Ministerial price approvals for most of the pending products despite the obstacles encountered from the political conditions.

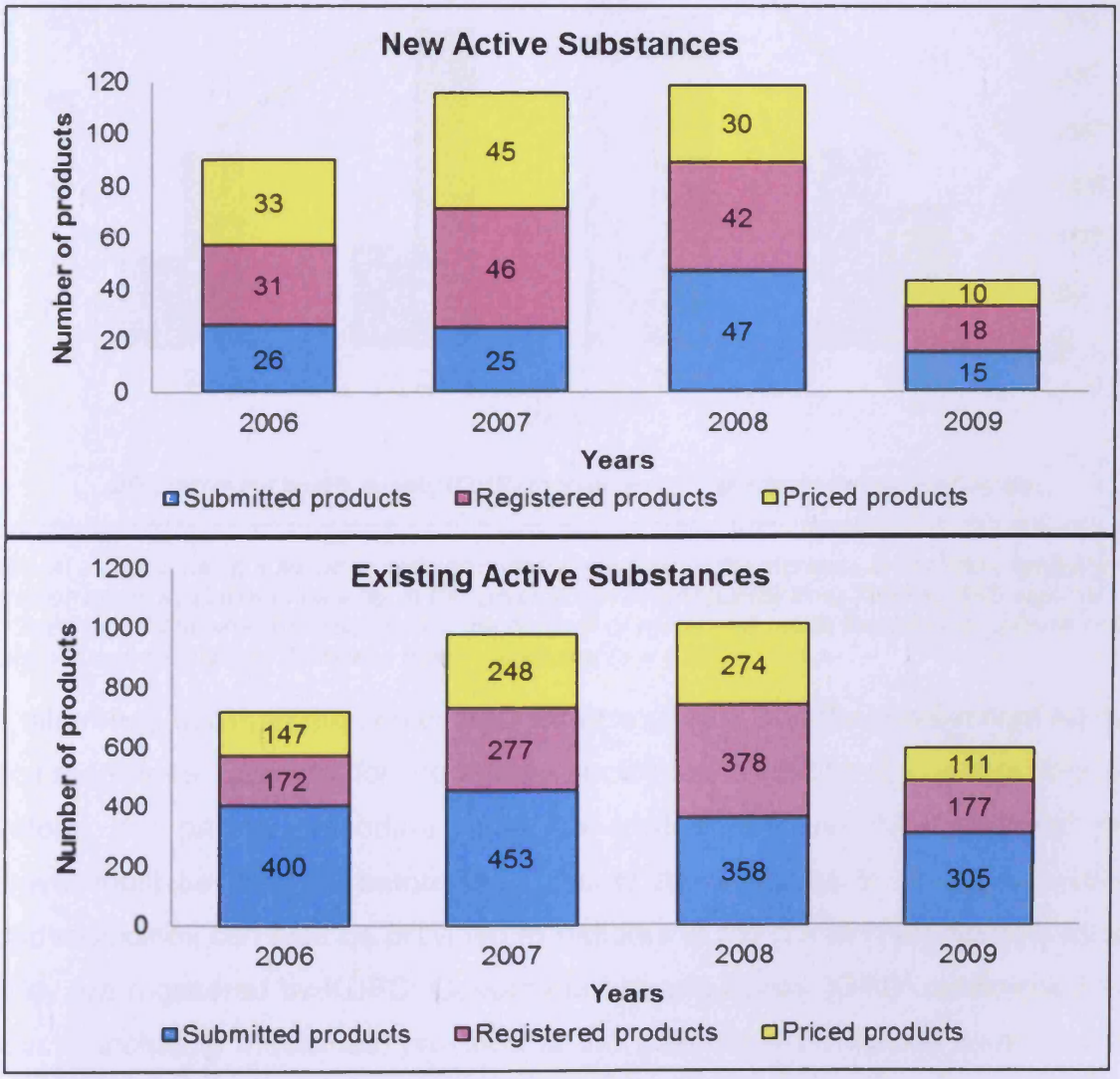
All the priced products are made available to patients through the private sector by community pharmacies, private hospitals and health centres. The largest numbers of NASs and EASs receiving price approval occurred in 2007 and 2008, respectively and this corresponded to the outcomes revealed from the number of registered products in these two years.

Comparisons of submission, registration and pricing timelines

To gain an insight into the submission, registration and pricing profiles of the NASs and EASs, the three phases were combined and illustrated in one context as shown in Figure 4.5.

The profiles show an overall increase in the number of submitted, registered and priced NAS and EASs from 2006 to 2008 due to the authority's improved efficiency to reduce the number of files pending for review, followed by a decrease in the number of submitted, registered and priced products in 2009 after solving the backlog problem as well as the improved political conditions within the government.

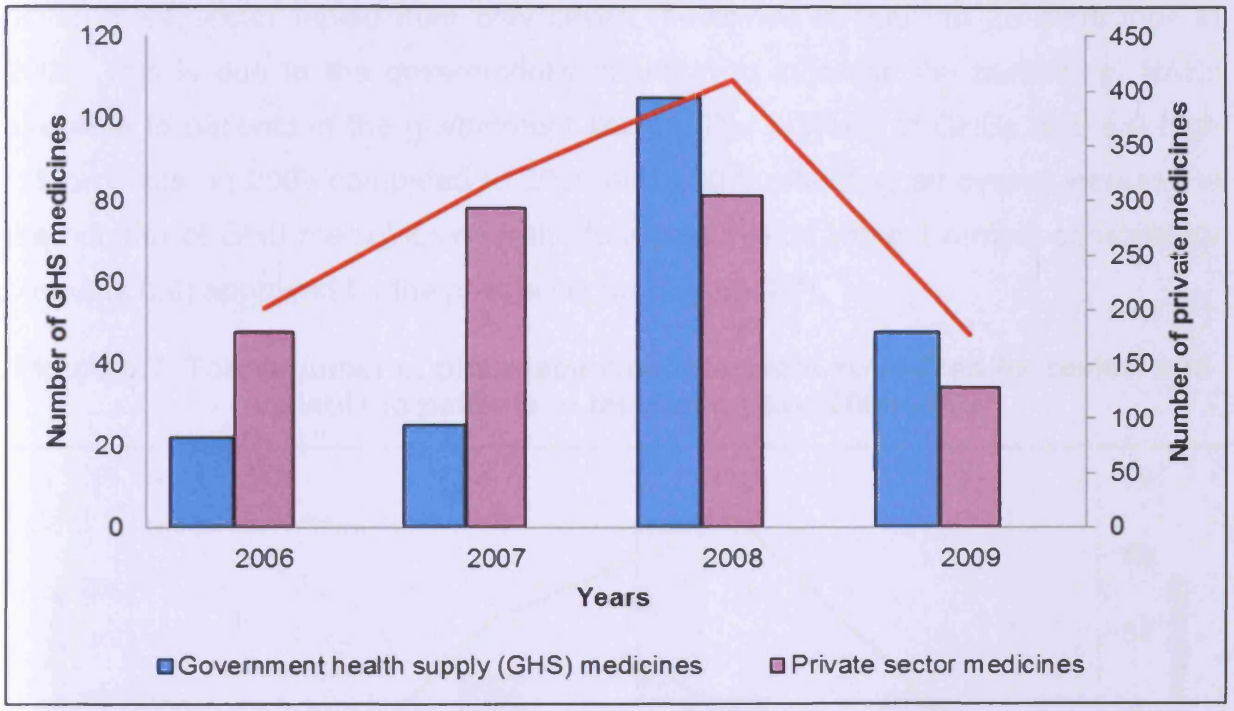
Figure 4.5 Overall profile of the New Active Substances (NASs) and Existing Active Substances (EASs) submitted, registered and priced (2006-2009)



Comparison of the availability of medicines in private and government sector

Further assessment of the data revealed that the largest number of medicines available to patients in the government and the private sectors occurred in 2008 with a total number of 409 products which is an evidence of the authority's intention to reduce the backlog problem and increase the efficiency of the registration process (Figure 4.6).

Figure 4.6 Total number of pharmaceutical products made available to patients in the private and the government sectors (2006-2009)



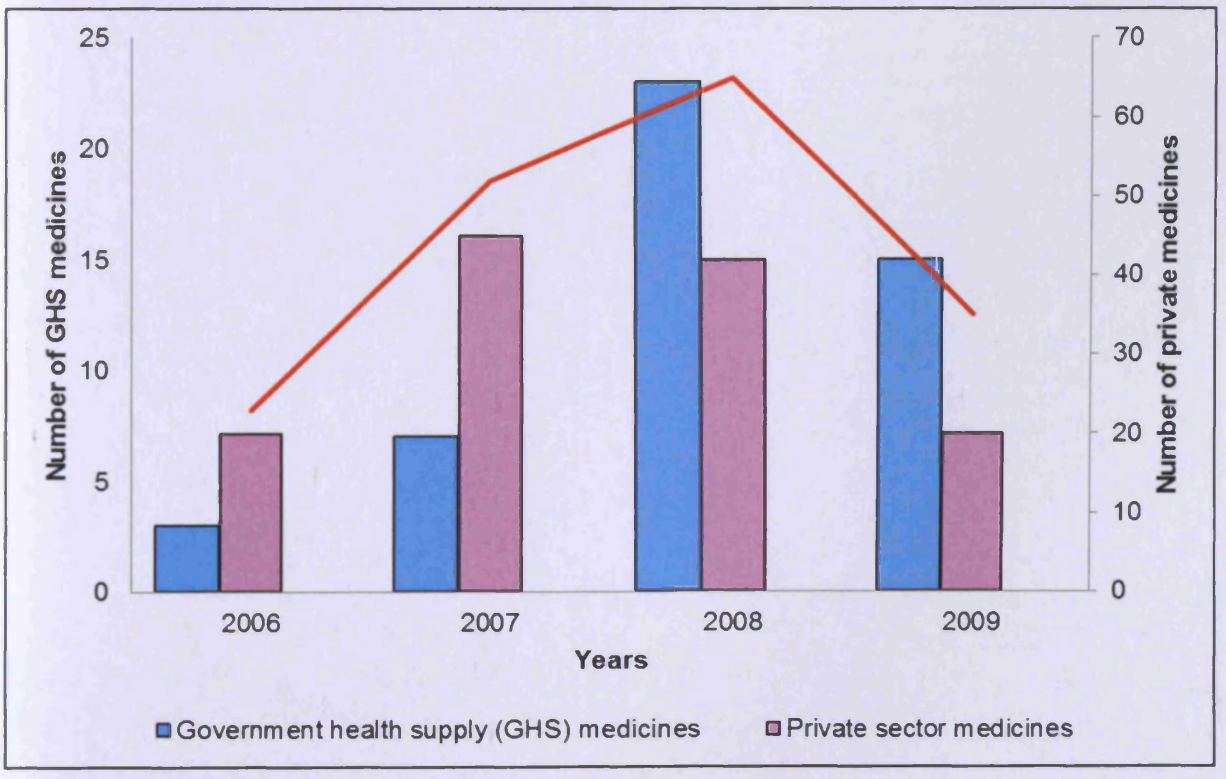
Statistical analysis using a linear regression model showed that the increase in the total number of medicines made available to patients in the government sector (GHS) from 2006 to 2009 was not significant ($p > 0.05$) while the decrease in the number of medicines made available to patients in the private sector from 2006 to 2009 was highly significant ($p < 0.001$).

The difference between the two categories (the private and the government sectors) is that medicines approved for the private sector are priced by the government and, therefore, the pricing procedure must be carried out and the ministerial price approval must be reached before the patients have access to the new medicine. Priced medicines can also be provided to patients in the government sectors as long as they are registered by KDFC. Government health supply (GHS) medicines are all products, including medicines, provided to the government hospitals, health centers and pharmacies in the government sector. Once the medicine is registered by the

authority, it is the responsibility of the Central Medical Stores (CMSs) to make the orders and fulfill the need of the patients in the government sector.

The number of products submitted for review and made available to patients in the private and the government sectors in each year (2006 to 2009) was determined. The study revealed that the largest total number of medicines submitted for review and available to patients was 65 in 2008, followed by 52 medicines in 2007. This is part of the authority's efforts to increase the efficiency of the registration and pricing processes. However, the number of medicines submitted and approved for the government sector tripled from only seven medicines in 2007 to 23 medicines in 2008. This is due to the government's intention to increase the number of NASs available to patients in the government sector. The number of GHSs was still high (15 products) in 2009 compared to 2006 and 2007, reflecting an overall increase in the number of GHS medicines over the four-year period while it remain constant for products (20) approved for the private sector (Figure 4.7).

Figure 4.7 Total number of pharmaceutical products submitted for review and available to patients in the same year (2006-2009)



Statistical analysis using a linear regression model showed that the increase in the overall number of medicines submitted, registered and priced in the same year over the period from 2006 to 2009 was significant ($p < 0.01$)

Comparisons between registration and pricing timelines for different therapeutic areas

This study assessed the number of NASs submitted, registered and priced from each therapeutic group over the period from 2006 to 2009. This was to determine the profile of the new safe and effective medicines that were available to patients in Kuwait. Ten therapeutic groups were examined, namely, infections, cardiovascular system, malignant disease and immunosuppression, central nervous system, endocrine system, obstetrics/gynecology/urinary tract disorders, eye/ ear/ nose/ oropharynx, respiratory system, gastro-intestinal system, and musculoskeletal and joint diseases. The outcomes of this study showed that there are four dominant therapeutic groups with the largest number of NASs made available to patients each year over the four-year study period. These are, medicines for the cardiovascular, central nervous system, malignant/immunosuppression and endocrine disorders.

Moreover, the study revealed that most of the NASs were made available to patients in the private sector (Table 4.2). Only four cardiovascular medicines and two malignant disease and immunosuppressant medicines in 2009, and one musculoskeletal and joint disease medicine in 2008 were NASs which were approved as GHS medicines.

Comparison between number of products submitted and approved for different pharmaceutical companies

This study provided an insight into patients' access to medicines in Kuwait from different pharmaceutical manufacturing companies. Three categories of pharmaceutical companies were identified for the purpose of this study, namely,

1. GCC-Arab Pharmaceutical Manufacturers: these are GCC manufacturing companies located in any of the seven Gulf States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE and Yemen) and producing pharmaceutical products locally.

2. Non-GCC Arab Pharmaceutical Manufacturers: these are manufacturing companies located in any of the Arab states outside the GCC Region.

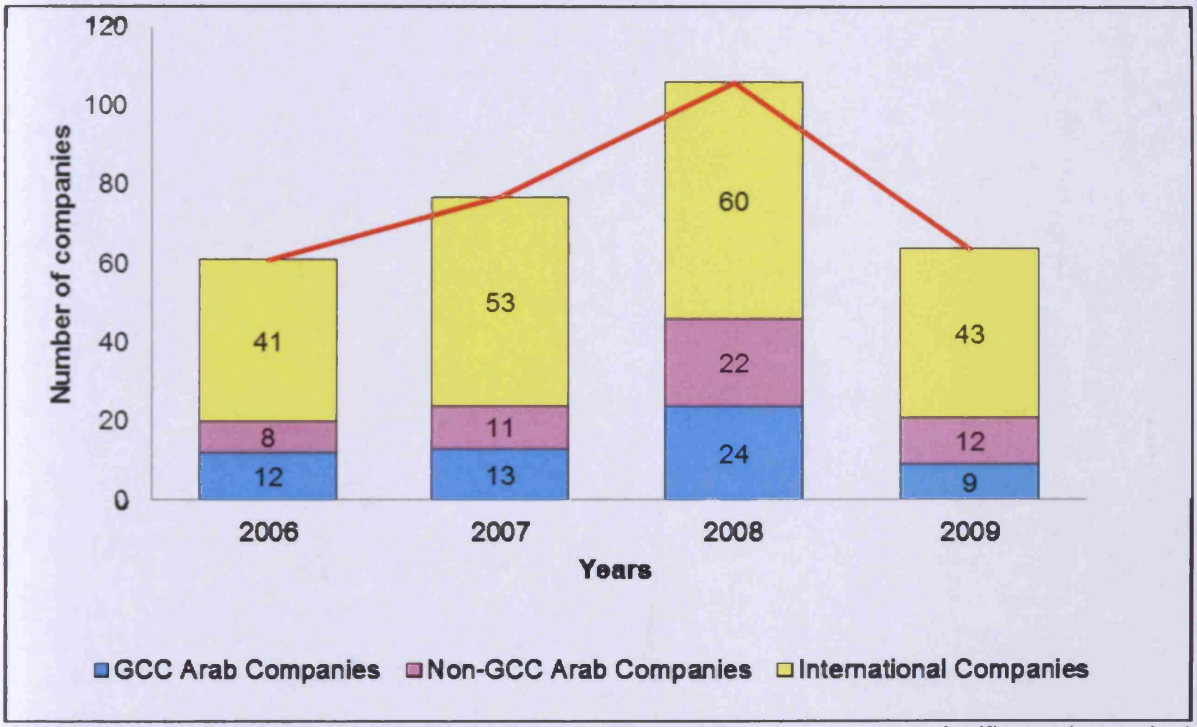
3. International Pharmaceutical Manufacturers: these are manufacturing companies located outside the Arab world.

Table 4.2 Number of New Active Substances (NASs) available to patients from various therapeutic groups (2006 – 2009)

	Submissions					Registrations					Pricing Approvals				
Year	2006	2007	2008	2009	Total/ year	2006	2007	2008	2009	Total/ year	2006	2007	2008	2009	Total/ year
Infections	1	1	2	2	6	2	3	2	0	7	2	3	2	0	7
Endocrine System	7	2	6	2	17	2	8	4	0	14	2	8	4	0	14
Cardiovascular System	3	4	16	4	27	6	7	9	11	33	6	7	9	7	29
Malignant Disease/ Immunosuppression	2	3	0	4	9	9	5	1	2	17	9	5	1	0	15
Central Nervous System	2	0	2	5	9	4	6	3	2	15	4	6	3	2	15
Obstetrics/Gynecology/Urinary Tract Disorders	1	0	2	0	2	2	1	0	1	4	2	1	0	1	4
Eye/ear/ nose/ oropharynx	3	2	0	1	6	2	4	2	0	8	2	4	2	0	8
Respiratory System	0	0	1	0	1	0	1	2	0	3	0	1	2	0	3
Gastro-Intestinal System	0	1	1	1	3	0	0	1	1	2	0	0	1	1	2
Musculosketal & Joint Diseases	3	1	0	1	5	0	0	4	0	4	0	0	3	0	3
Total Per Year	**22**	**14**	**30**	**20**	**86**	**27**	**35**	**28**	**17**	**107**	**27**	**35**	**27**	**11**	**100**

The number of pharmaceutical companies registering medicines every year from 2006 to 2008 increased for each of the three specified categories (Figure 4.8). A reduction was then experienced from a total of 106 products in 2008 to 64 products in 2009 due to the large numbers of approvals achieved in 2007 and 2008. In general, however, there was no significant change in the total number of pharmaceutical companies registering medicines over the period from 2006 to 2009 ($p>0.05$).

Figure 4.8 Number of pharmaceutical companies registering medicines (2006-2009)



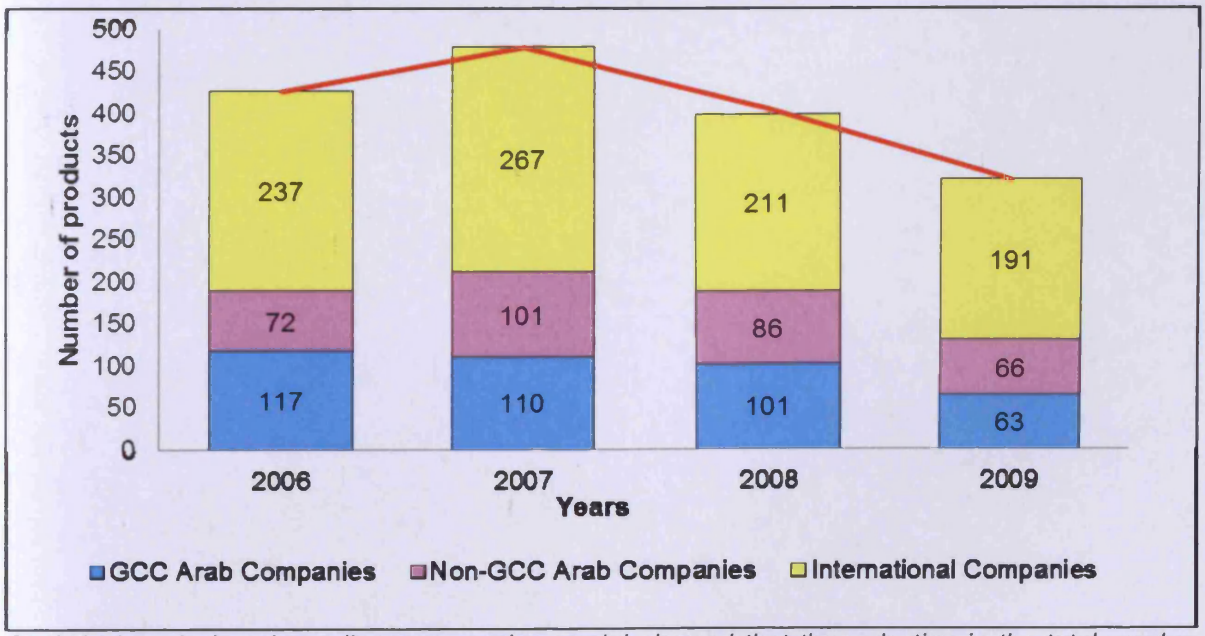
Statistical analysis using a linear regression model showed that there was no significant change in the number of GCC Arab companies and Non-GCC Arab companies registering medicines ($p > 0.05$) but there was a significant change in the number of International companies registering medicines over the period from 2006 to 2009.

The largest number of pharmaceutical companies registering products for the private and government sectors each year from 2006 to 2009 were international companies resulting from greater interest in the GCC market. The smallest number of pharmaceutical companies registering products in Kuwait are the Arab Gulf Cooperation Council (GCC Arab) manufacturing companies. The GCC Region is in the process of developing its local manufacturing capability specifically in Saudi Arabia, UAE and Oman. Kuwait prioritizes the registration of GCC manufactured pharmaceutical products because all GCC-Arab manufacturers are reviewed, inspected and registered by the GCC central registration committee which is sufficient

evidence for the approval of the product for marketing in Kuwait. The Non-GCC Arab manufacturing companies are also small in number. This is due to the strict national regulations that require evidence of registration in countries with developed regulatory systems. Non-GCC Arab manufacturers had experienced some difficulty in registering products in Kuwait because they were not able to provide evidence of registration elsewhere. Kuwait advices these companies to seek GCC centralized approval to be able to obtain recognised evidence of registration which would increase their chance of approval in Kuwait.

An overall reduction in the number of submissions was seen in all the pharmaceutical companies over the period from 2006 to 2009 (Figure 4.9). This together with the reduction in the overall number of submissions from international companies were statistically significant ($p < 0.01$). However, the reduction in the numbers of submissions from the GCC Arab and Non-GCC Arab companies over the period from 2006 to 2009 was significant ($p < 0.05$). One reason for this decline was related to the large number of submissions made in the first three years (2006, 2007, and 2008), being the highest for all three categories in 2007, due to the companies' increased enthusiasm to register more products as a result of the increased efficiency of the registration process.

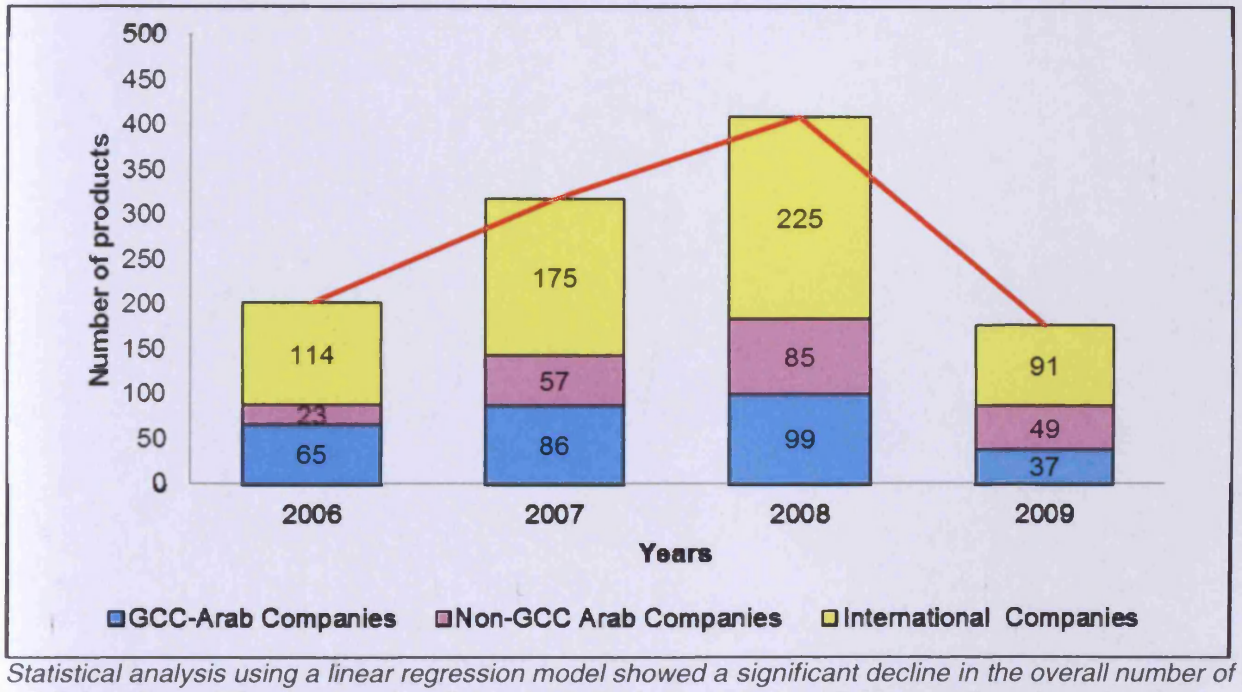
Figure 4.9 Number of pharmaceutical products submitted by the GCC Arab, Non-GCC Arab and International pharmaceutical companies (2006-2009)



Statistical analysis using a linear regression model showed that the reduction in the total number of submissions from all pharmaceutical companies was statistically significant ($p < 0.01$)

Finally, an assessment of the total number of products available to patients in the government and the private sector from each of the three categories of the pharmaceutical companies revealed that international companies were the dominant category in each year. There was an upward trend in the number of medicines available to patients from 2006 to 2008 by the three categories. However, the numbers significantly dropped for all companies in 2009 ($p < 0.05$) due to the smaller number of submissions made in this year compared to previous years as well as the large number of registration made in previous years which reflected the number of submissions and approvals that occurred in 2009 compared to previous years (Figure 4.10).

Figure 4.10 Number of pharmaceutical products available to patients in the private and government sectors from the GCC Arab, Non-GCC Arab and International pharmaceutical companies (2006-2009)



Statistical analysis using a linear regression model showed a significant decline in the overall number of medicines from all three categories of pharmaceutical companies available to patients from 2006 to 2009 ($p < 0.05$)

The largest overall number of medicines available to patients in the private and government sectors were from international companies followed by the GCC Arab companies over the period from 2006 to 2009. The overall number of medicines available to patients from the Non-GCC Arab companies were the smallest over the period from 2006 to 2008, but it was higher than those from the GCC Arab companies in 2009. In general, there was a decline in the number of medicines available to

patients from international and GCC Arab companies over the four-year period. This was related to the decline in the number of submissions over the same period. However, there was a general increase in the number of Non-GCC Arab companies from 2006 to 2009 which may be related to the consistency in the number of their submissions throughout the four-year period as well as improved follow-up and feedback from the Non-GCC Arab companies to gain approval of their medicines.

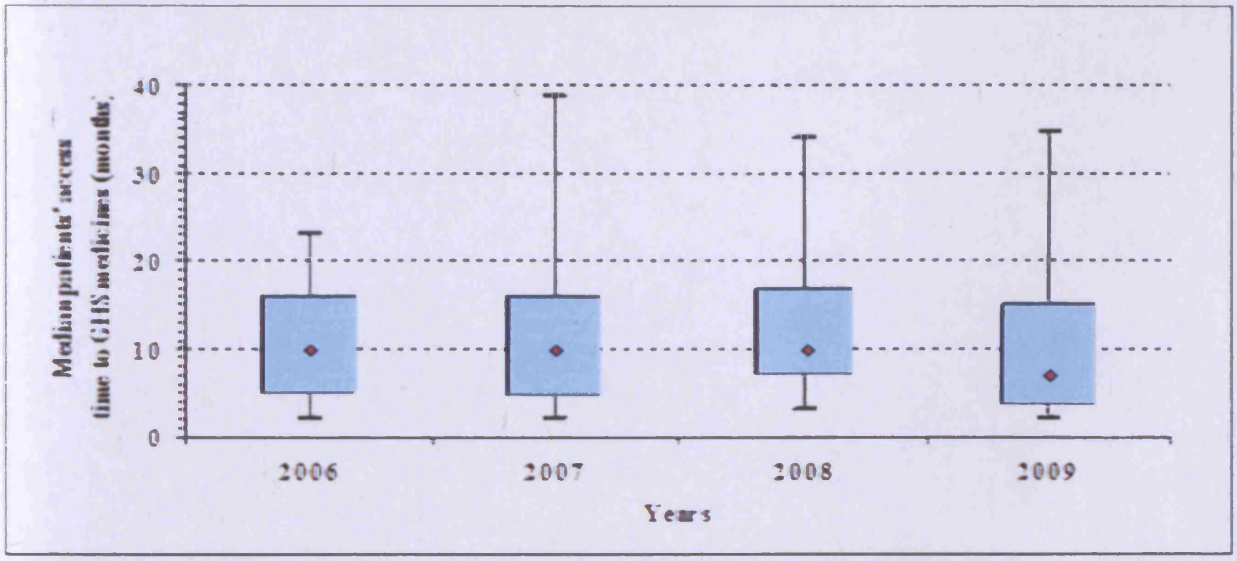
Part II: An evaluation of patients' access timelines for pharmaceutical products in Kuwait (2006-2009)

The time from submission to patients' access for all pharmaceutical products (government health supply (GHS) medicines, medicines for the private sector, NASs and EASs) in Kuwait between 2006 and 2009 were examined using these boxplots to demonstrate a change in the median time for patients' access to medicines.

Comparison of submission to approval time gap (patients' access time) for government health supply (GHS) medicines

The median patients' access time did not vary (10 months) for the GHS medicines over the period from 2006 to 2008, but it declined to seven months in 2009 (Figure 4.11). Statistical analysis using on-way analysis of variance showed that there was a significant decline ($p < 0.05$) in the patients' access times across the four-year period (2006 to 2009).

Figure 4.11 Patients' access time to government health supply (GHS) medicines in Kuwait (2006-2009)



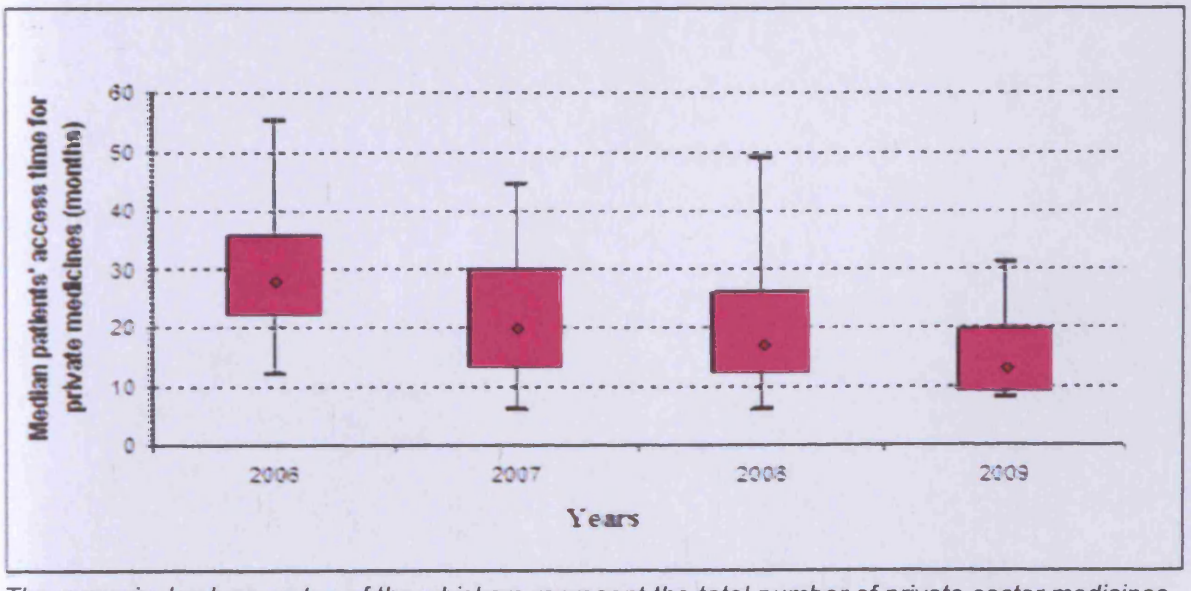
The numerical values on top of the whiskers represent the total number of GHS medicines available to patients from 2006 to 2009.

Further comparisons between one year and another using Mann-Whitney U-tests showed that the difference in patients' access times between 2006 and 2007 was not significant ($p > 0.05$). The difference was also found to be not significant from 2006 to 2008 ($p > 0.05$). However, the differences in patients' access times between 2006 and 2009 and from 2008 and 2009 was found to be statistically significant ($p < 0.01$). The reason for this decline was due to the political stability and the reduced backlog.

Comparison of submission to approval time gap (patients' access time) for private medicines

The median patients' access times for private sector medicines decreased from 28months in 2006 to 13months in 2009 (Figure 4.12). Statistical analysis using analysis of variance across the four-year period showed that there was a significant difference in patients' access times for private sector medicines (2006-2009) ($p < 0.001$). Further analysis was carried out using Mann-Whitney U-Test to examine the difference in the median patients' access time of private sector medicines over the same period. The difference was found to be significant ($p < 0.001$) and was represented in the steady decline in the number of medicines available to patients in the private sector from 2006 to 2009 (Figure 4.12). This decline was attributed to the KDFC's efficiency to expedite the availability of medicines to patients in Kuwait and to reduce the backlog from previous years.

Figure 4.12 Patients' access time to private sector medicines in Kuwait (2006 – 2009)

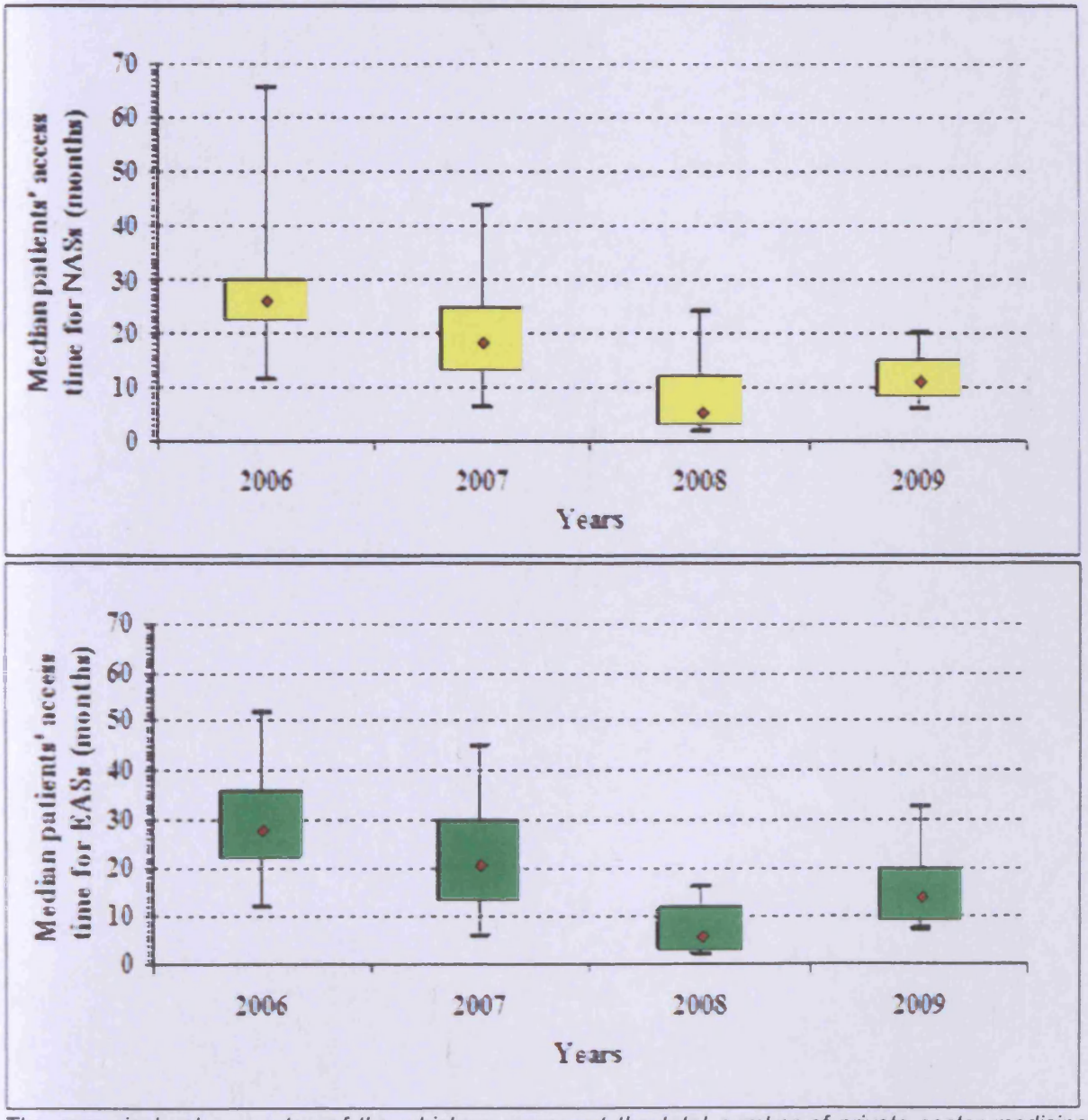


The numerical values on top of the whiskers represent the total number of private sector medicines available to patients from 2006 to 2009.

Comparisons between patients' access time to private sector medicines for NASs and EASs

It has been observed that the number of medicines available to patients in the private sector is larger than those in the government sector. Therefore, using the analysis of variance test and the Mann-Whitney U-Test the change in patients' access time to NASs and EASs in the private sector was assessed (Figure 4.13).

Figure 4.13 Patients' access time to New Active Substances (NASs) and Existing Active Substances (EASs) in the private sector in Kuwait (2006 -2009)



The numerical values on top of the whiskers represent the total number of private sector medicines available to patients from 2006 to 2009.

With regards to the NASs, the results obtained from performing the analysis of variance test showed that the difference was highly significant ($p < 0.001$) with a decline in the median patients' access time for NASs from 26 months (2006) to 11 months (2009). The shortest patients' access time was 5.5months in 2008 which was related to the increased efficiency of the registration process during that year. Further analysis using Mann-Whitney U-Test showed that the changes in the patients' access time for NASs in the private sector were also highly significant ($p < 0.001$) between all years except for 2006 and 2007 where the change was not significant ($p > 0.05$) (Figure 4.13).

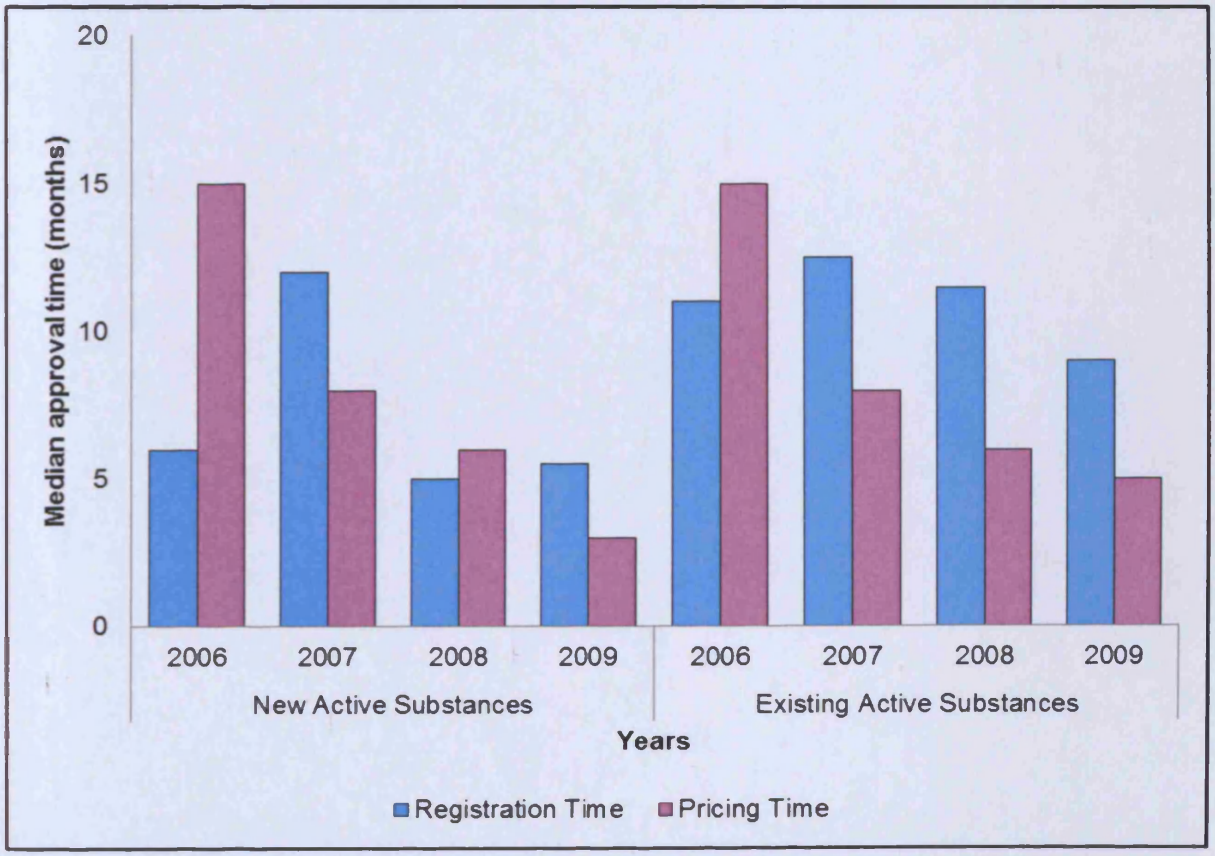
With regards to EASs, the difference across the four-year period was also significant ($p < 0.001$) with a decline in the median patients' access time for EASs from 28 months in 2006 to 14 months in 2009. KDFC was most efficient in year 2008 which was evidenced by the shortest median patients' access time of six months. Furthermore, the comparison between years using the Mann-Whitney U-Test showed that the changes in the patients' access time for NASs in the private sector were highly significant ($p < 0.001$) throughout the four-year period (Figure 4.13).

When the median time for patients' access to medicines was assessed for NASs and EASs, the results showed a constant median registration time for NASs over the period from 2006 to 2009 of five to six months, the target time set by the authority. The median registration time peaked at 12 months in 2007 due to the large number of submissions and the backlog problem for the KDFC, but the number declined to be within the overall target time in 2008 (Figure 4.14).

However, the median pricing time for NASs (Figure 4.14) showed a steady decline from 15 months in 2006 to three months in 2009 due to the significant ministerial changes that occurred over that period. By the end of 2008, the ministerial parliament was finally stabilised which was reflected in the ministerial price approval times for 2009. The median registration time for EASs did not vary significantly either throughout the four-year period. The median pricing time for EASs followed the same profile as for the NASs and reduced from 15months (2006) down to 5months (2009) due to the enhanced political conditions and the improved performance of the KDFC authority. In addition, the calculated median time for patients' access to medicines in Kuwait showed that it was longer for EASs than NASs (Figures 4.13 and 4.14).

However, further examination showed that this difference was due to the difference in their registration time and not their pricing time as the ministerial pricing approval occurs twice or three times a year where a group of registered products (NASs and EASs) are presented to the Minister of Health with their proposed prices in a supplement to be approved and published in the national Journal "Kuwait Today" around the same time. Therefore, there is no difference in the median pricing time for NASs and EASs (Figure 4.14). Statistical analysis using Mann-Whitney U-test was carried out to compare the median time for patients' access to NASs with those for EASs over the period 2006 to 2009.

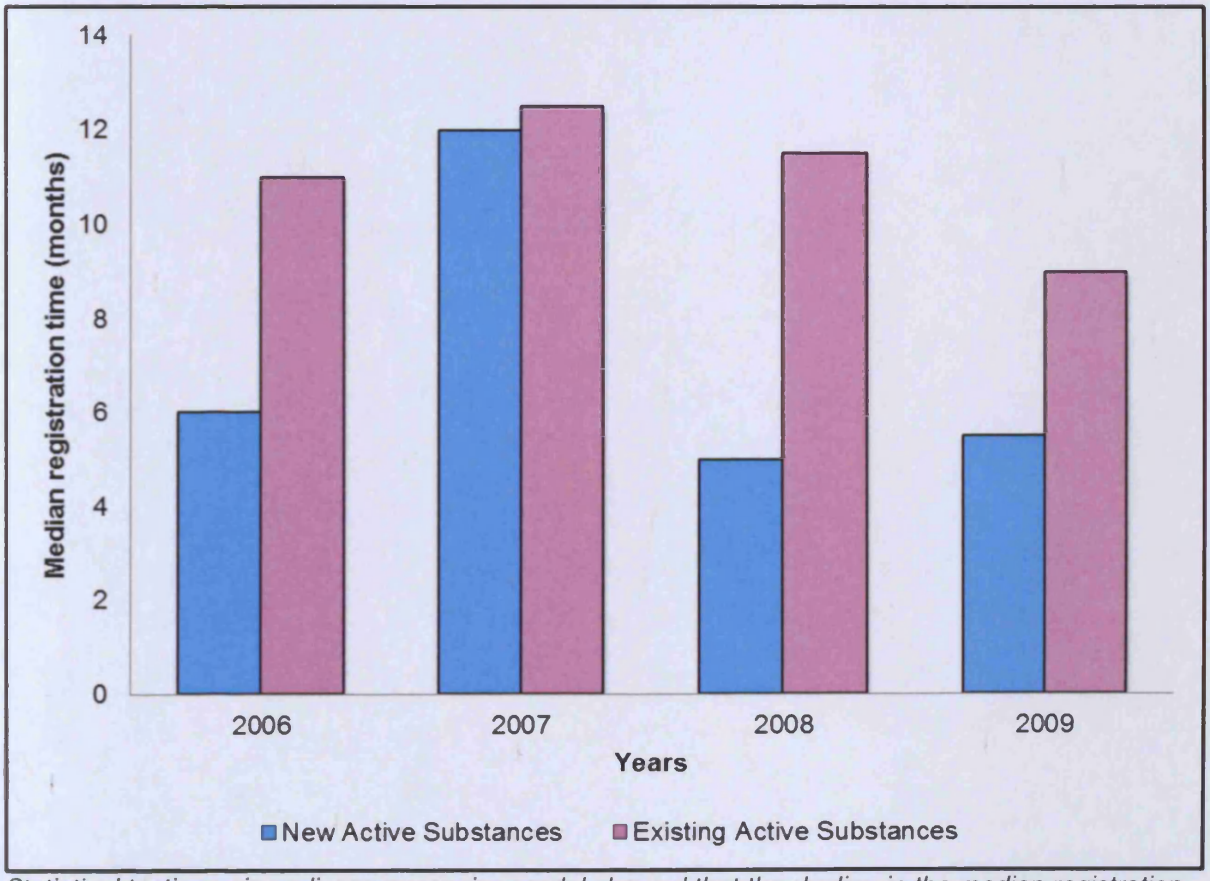
Figure 4.14 Median registration and pricing times for patients' access to New Active Substances (NASs) and Existing Active Substances (EASs) in the private sector (2006-2009)



Statistical analysis using the Mann-Whitney U- test over the years from 2006 to 2009 showed that the difference in the overall patients' access times (registration time plus pricing time) between the new active substances (NASs) and existing active substances (EASs) were not statistically significant in years 2006, 2007 and 2008 ($p > 0.05$). However, the difference between the two categories was significant in 2009 ($p < 0.01$).

The analysis showed that the difference was not significant when the two groups where compared in years 2006, 2007 and 2008 ($p > 0.05$), while it was significant in year 2009 ($p < 0.01$). Furthermore, a statistical analysis using analysis of variance was carried out to examine the registration performance outcome over the period 2006 to 2009. The analysis showed that the overall decline in the median registration time from 2006 to 2009 was not significant for NASs ($p > 0.05$), but it was significant for EASs ($p < 0.001$) (Figure 4.15).

Figure 4.15 Median registration time for New Active Substances (NASs) and Existing Active Substances (EASs) in the private sector (2006-2009)



Statistical testing using a linear regression model showed that the decline in the median registration time from 2006 to 2009 was not significant for NASs ($p > 0.05$) while it was highly significant for EASs ($p < 0.001$).

Trends in number of pharmaceutical products made available within specific time frame in Kuwait

This part of the study focused on the number of medicines that were made available in the private and government sectors within a specified time category (Table 4.3).

Four categories were examined to determine the performance of the KDFC authority over the four-year study period, namely, the number of pharmaceutical products made available to patients in the government and private sectors in less than six months, within six to twelve months, within 12 to 24 months and over 24 months.

Table 4.3 Number of pharmaceutical products made available to patients during a specific interval (2006-2009)

Categories	Government Health Supply (GHS) medicines					Private sector medicines				
	2006	*2007*	*2008*	*2009*	*Total/ interval*	*2006*	*2007*	*2008*	*2009*	*Total/ interval*
Within 6 months	7	12	23	25	67	0	21	19	5	45
6 to12 months	10	5	51	18	84	11	37	63	12	123
12 to 24 months	0	2	25	12	39	45	113	117	59	344
More than 24months	0	0	9	5	14	96	120	84	18	318
Total/Year	17	19	99	65	204	152	291	283	94	830

The assessment revealed three major outcomes, namely,

- More medicines were made available to patients in the government sector over the period from 2006 to 2009 in less than six months. This was the result of the government's efforts to meet the public demands of providing more medicines to patients in the government hospitals and health centres.
- The number of GHS medicines decreased with the increasing time interval while the number of medicines in the private sector increased with the increasing time interval. This is due to the pricing process which is not included in the approval process of GHS medicines. This process is totally dependent on the time of

obtaining the Ministerial approval to the proposed price of medicines and it can take anywhere between three to six months in a stable political condition.

- The largest number of GHS medicines was registered within six to 12 months. In contrast, the largest number of private sector medicines was approved within 12 to 24 months. This difference was due to the pricing stage which was carried out after granting the registration approval for the pharmaceutical product until June 2009. The system was altered then from that time to perform the pricing process in parallel with the scientific assessment of the registration dossier.

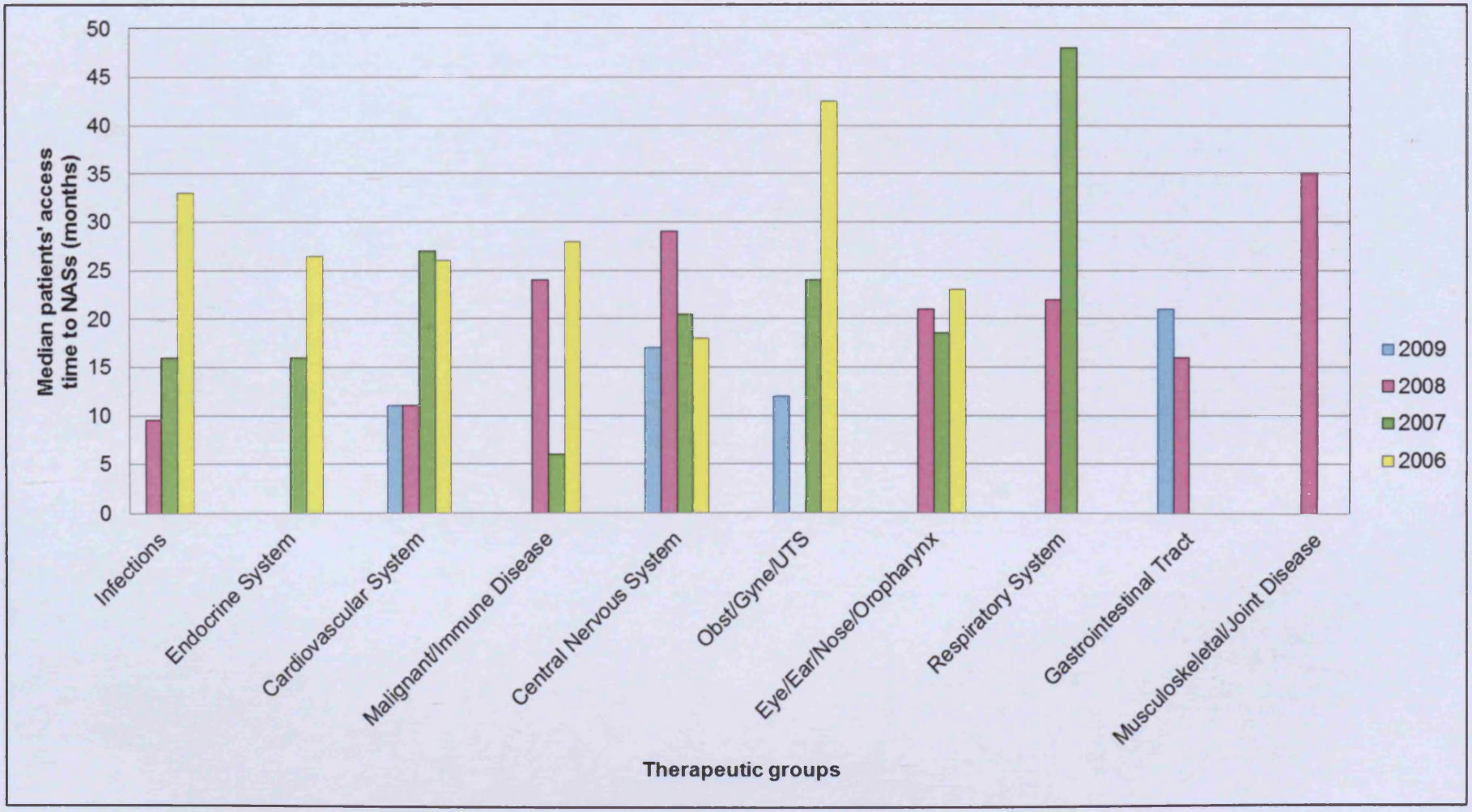
Part III: Trends in regulatory submissions and approvals of New Active Substances (NASs) for major therapeutic groups (2006 - 2009)

The number of NASs from different therapeutic groups made available to patients in Kuwait varied from one medicine for respiratory disorders to 27 medicines for cardiovascular disorders (Table 4.2). A total number of 107 NASs from different therapeutic groups were registered; seven of these were GHSs. The most commonly submitted, registered and priced medicines were cardiovascular, endocrine, central nervous system, and malignant and immunosuppressive disease medicines.

The median time for patients' access to medicines (median registration time plus median pricing time) to NASs in the private and government sectors was assessed for the ten selected therapeutic groups (Figure 4.16). The longest patients' access time was 48 months for the medicines for treatment of the respiratory disorders which were approved in 2007 followed by 43 months for Obs/Gyna/UTS registered in 2006. These long patient access times were related to the backlog of pending files handled by the regulators as well as delays in the submission of the Certificate of Pharmaceutical Product (CPP) and/or evidence of registration in recognised regulatory authorities.

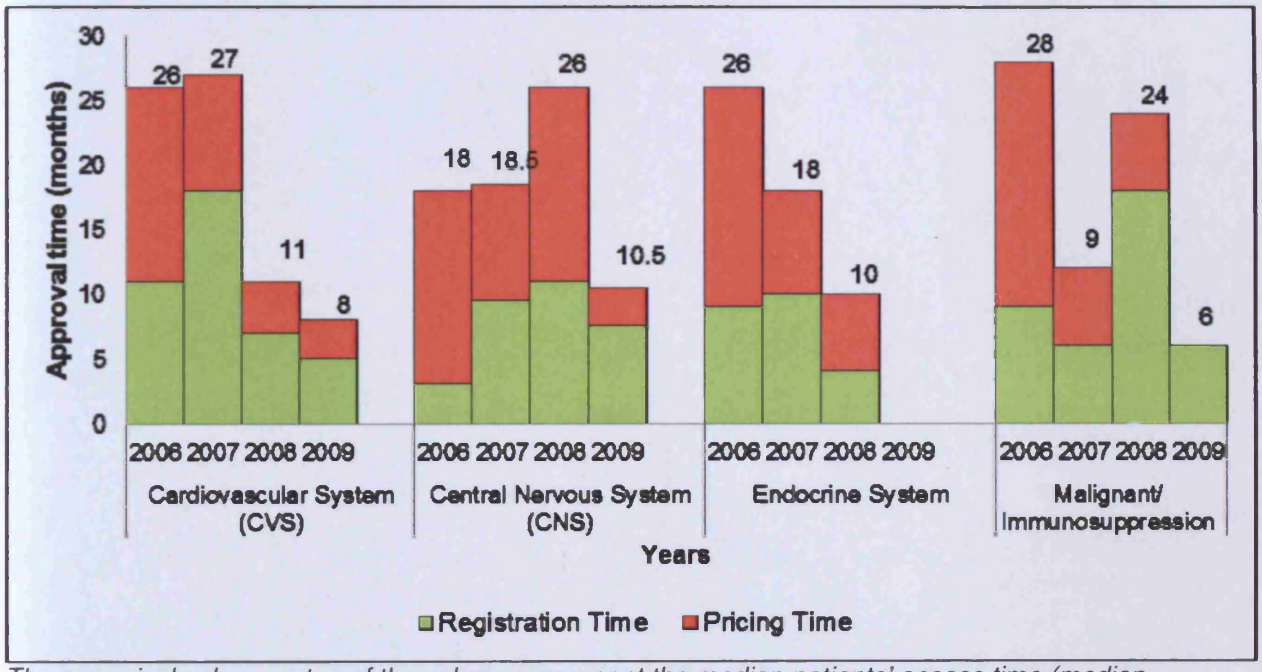
The analysis of the patients' access time to NASs involved the four largest therapeutic groups mentioned above which dominate the pharmaceutical market in Kuwait to obtain an overview of the speed of patients' access to NASs registered and priced between 2006 and 2009.

Figure 4.16 Median patients' access time to New Active Substances (NASs) for various therapeutic groups in the private and government sectors (2006-2009)



A review of the approval profiles for the major therapeutic groups showed a significant difference in the patients' median access time throughout the four-year study period (Figure 4.17). Due to the small number of NASs approved from each therapeutic group, statistical analysis using (linear regression model) was used to assess the significance of the change in the patients' median access times (2006-2009).

Figure 4.17 Median registration and pricing time for New Active Substances (NASs) from major therapeutic groups (2006-2009)



The numerical values on top of the columns represent the median patients' access time (median registration time + median pricing time) for new active substances (NASs) from the major therapeutic groups.

Patients' access time to medicines is the sum of the registration time and the pricing time. In general, the median time for patients' access to NASs for Cardiovascular System (CVS) and Endocrine disorders significantly declined ($p < 0.05$) over the period from 2006 to 2009. The median time for patients' access to NASs for Central Nervous System (CNS) and the Malignant Diseases and Immunosuppressive disorders also decreased, but analysis showed that this change was not significant ($p > 0.05$). The median time for patients' access to medicines peaked for CVS, CNS and malignant disease and immunosuppressant medicines in 2006, 2007 and 2008 due to KDFC's backlog problem.

Furthermore, trend of medicines for endocrine disorders showed a steady decline in their approval times from 2006 to 2008 with no NASs approved for the endocrine system in 2009 (Figure 4.17). Two NASs for malignant and immunosuppressive disorders and four CVS medicines were approved in 2009 as GHS medicines. No NASs for malignant disease and immunosuppressive disorders were approved for the private sector in 2009 and, therefore, both medicines were available to patients in the government sector with a median registration time of six months (Figure 4.17).

The differing patterns of patients' access to NASs from different therapeutic groups were attributed to the authority's assessment requirements which may or may not include the need for clinical evaluation by external experts. This can be a lengthy process and has an impact on the overall approval timeline. Another reason that plays a role in such differences is the sponsor's response time to the authority's requirements and the level of communication between the two parties.

DISCUSSION

This study was designed to review trends in patients' access time to pharmaceutical products in Kuwait over the period from 2006 to 2009. The outcomes revealed that the largest number of medicines submitted for review and approved for the private and government sectors occurred in 2007 and 2008. The authority went through a period when pharmaceutical companies increased the number of submissions to obtain the Kuwaiti registration approval which was used as an evidence of registration in a competent authority; along with Oman, Saudi Arabia and/or UAE; to expedite products submitted to the Gulf Cooperation Council (GCC) Central Registration committee. Many generic and innovative manufacturers increased their efforts to obtain the GCC-DR approval in order to facilitate entry into individual GCC markets. This effort on the part of the pharmaceutical companies had an impact on the number of submissions and approvals in Kuwait. By assessing the approval timelines for pharmaceutical products in Kuwait, it was found that the median time for access to all pharmaceutical products approved for the private and government sectors experienced a significant and steady decline over the four-year study period. Furthermore, the number of pharmaceutical products available to patients in the government sector in less than six months experienced a general increase from 2006 to 2009 while the majority of the private sector medicines were registered in more than 12months. This is due to the

pricing procedure which does not apply to GHS medicines which are provided to national patients free of charge.

The largest number of submissions, registrations and pricings occurred for the cardiovascular system (CVS), central nervous system (CNS), endocrine system, and malignant disease and immunosuppressant medicines during the period from 2006 to 2009. This was due to the growing local demand for these medicines in Kuwait. This study examined the outcomes from the four major therapeutic groups and revealed that there was a general decline in median time for patients' access to these medicines over the period of study.

This study examined five hypotheses and their respective findings are discussed below.

Hypothesis 1: There was an increase in the number of pharmaceutical products submitted, registered and priced between 2006 and 2009

The number of pharmaceutical products submitted, registered and priced peaked in 2007 and/or 2008 due to the authority's efforts to decrease the backlog of pending registration dossiers. However, the numbers declined towards 2009 for these three categories resulting in a slight overall reduction in the number of medicines submitted and available to patients over the four-year period. The decline was found to be significant and therefore, this hypothesis was rejected. However, the increased number of registered and priced medicines in 2007 and 2008 encouraged the pharmaceutical companies to submit more applications for approval in Kuwait. This placed more pressure on the KDFC regulators to reduce the backlog and achieve the timely approval of safe and effective medicines. In 1988, a similar situation occurred in Canada when the Department of National Health and Welfare took steps to improve the Canadian system for evaluating and approving medicines with a mandate that the backlog of new drug submissions was to be eliminated within three years. However, it was not easy to turn a government department around and even though the Canadian government achieved some progress two years into the three-year plan, the Directorate still faced some problems and the backlog still existed while more submissions were being made every year (Rafuse, 1991). The KDFC authority is obliged to continuously track the build-up of pending files, as this problem can never be permanently eliminated. The use of external experts to review the pending dossiers

maybe the best solution for this problem to reduce the workload on the internal reviewers but this may suggest a possible impact on the quality of the review process.

Hypothesis 2: The number of products made available to patients from International , Gulf Cooperation Council (GCC) Arab, and Non-GCC Arab pharmaceutical companies did not change from 2006 to 2009.

International companies were the largest group registering products every year in Kuwait. Many of the companies increased the number of their submission to the Kuwaiti authority to obtain registration approval as evidence that would support their GCC-DR approval. The increase in the number of pharmaceutical products made available to patients peaked in 2008 and then declined in 2009. Statistical examination showed that there was a significant overall decline in the number of products available to patients from 2006 to 2009. Therefore, this hypothesis was rejected.

Furthermore, the GCC States are making efforts; particularly Saudi Arabia, UAE and Oman to improve their local manufacturing capabilities and the production capacity for the local population. The Non-GCC Arab companies face strict national regulations and the requirement to submit evidence of registration in countries or regions with competent regulatory systems. This burden has been largely reduced by directing the Non-GCC Arab companies towards submitting their products for GCC-DR approval. This effort is being enhanced by some GCC authorities, particularly Saudi Arabia and UAE, which are currently requiring the GCC-DR approval to obtain local marketing authorisation of new medicines.

In Kuwait, there is only one local manufacturer of pharmaceutical products. This manufacturer is not fully capable of meeting the local demands of medicines and therefore international imports dominate the market. The registration fees are also relatively low, compared with the rest of the region, at US$340 per product, with no fees for renewals. The low cost is due primarily to the fact that Kuwait only has a small local manufacturing industry, and is therefore heavily reliant on imports which makes it difficult to adjust to the demand for the GCC-DR approval as a condition for patients' access to medicines in Kuwait. However, in order to increase the local production, the government is considering raising the drug registration fees, to over US$2000 per product (Business Monitor International (BMI), 2008).

Hypothesis three: Patients' access to medicines in Kuwait did improve over the period from 2006 to 2009

There was a significant decline in the median time for patients access to NASs and EASs in Kuwait over the period from 2006 to 2009. Therefore, this hypothesis was accepted. There are many factors which affect the speed of patients' access to new medicines in Kuwait, namely,

- The improved stability in the ministerial parliament which resulted in an improved pricing timeline and, therefore, reduced patients' access time to new medicines.
- The improved communication between the pharmaceutical companies and the KDFC regulators resulting in better follow-up of the registration and pricing requirements and, therefore, improved patients' access times to medicines in Kuwait.
- The increasing number of products handled by the KDFC in 2007 and 2008 is an indication of the additional efforts and resources provided, which in turn, contributed to the improved performance during the four-year period.
- The focused responsibility of the reviewing staff positively influenced the approval times and compensated for any shortage in the number of reviewers.

The median time for patients' access to medicines approved for the private and the government sectors have also significantly decreased from 26 and 10 months to 11 and 7 months, respectively, from 2006 to 2009. which is a significant improvement even though this is not yet near the authority's overall target approval time of six months. Therefore, this hypothesis was accepted.

A study carried out by the World Health Organisation (WHO) 1998 to 1999 on 10 developing regulatory agencies showed that KDFC's new patients' access times of 12 months were similar to some countries such as Estonia with an average approval time for new products of nine months, 12 months in Cuba and 14 months in Australia (Hill and Johnson, 2004).

Hypothesis 4: Patients' access time was significantly longer for EASs in comparison with NASs over the period 2006 to 2009

In general, the median time for access to NASs and EASs in Kuwait changed from 2006 to 2009 and the time taken to register an EAS was double that for a NAS. This is due to the quality control analysis stage which can be lengthy. Furthermore, the EASs must demonstrate bioequivalence compared with existing registered innovative

products and bioequivalence studies must be submitted for evaluation by the KDFC authority. However, the pricing time experienced a sharp decline from 15 months to three months for NASs, and from 15 months to five months for EASs, which explains the overall significant reduction in the median patients' access time to NASs and EASs over the period from 2006 to 2009. However, the overall patients' access time was longer for EASs than NASs although statistical tests showed no significant difference between median times for patients' access to NASs and EASs from 2006 to 2008, but did show a significant difference between the two categories in 2009. Therefore, this hypothesis was rejected for the years 2006 to 2008 but accepted for 2009.

The 10-country study by WHO, referred to earlier, demonstrated the average time taken to register innovative and generic products in 10 developing authorities. The study showed that Zimbabwe was the only country that took a longer time to register generics compared to new active substances in 2004 with the average registration time for a new product being only 4.5 months while it reached 18 months for generic products. Kuwait follows the same pattern as Zimbabwe. The median patients' access time to generic medicines in Kuwait is 14 months while it is 8.5 months for new products.

Hypothesis 5: There was no difference in the registration time of GHS medicines from 2006 to 2009

Analysis of the pattern and speed of patients' access to GHS medicines showed that the government recognises the importance of increasing the number of free products available to patients in government hospitals and pharmacies to improve the quality of life and public health protection in Kuwait. This study revealed that the number of GHS medicines increased by more than two fold from 22 to 48 EASs and from zero to eight NASs throughout the study period.

The median time for patients' access to new medicines remained constant (10 months) from 2006 to 2008. Statistical analysis also showed no significant difference in the median patients' access time during this period. However, the median time for patient's access to medicines declined to seven months in 2009 and this decline was shown to be significant (from 2006 to 2009 and from 2008 to 2009). Therefore, this hypothesis was rejected.

Kuwait's Minister of Health is currently planning to ensure that public hospitals and pharmacies are stocked with medicines in the major therapeutic categories to prevent patients paying higher fees at private pharmacies. The increase in the GHS medicines was also noticed through an improvement in the patients' access time to new medicines in government hospitals and pharmacies in Kuwait. All NASs, and over 50% of the EASs, were approved in less than twelve months for the government sector. This indicates the government's enthusiasm and commitment to make the desired medicines available to the patients in the shortest possible time.

Hypothesis 6: There was a decline in the median time for patients' access to NASs for each major therapeutic group over the period from 2006 to 2009

The findings of this study showed that the median time for patients' access to NASs for cardiovascular and endocrine system disorders significantly declined over the period from 2006 to 2009. However, medicines for the central nervous and malignant/immunosuppression disorders showed a slight decrease in their median patients' access time over the same period, but this decline did not reach statistical significance. Therefore, this hypothesis was accepted.

There are several factors leading to differences in the approval time for different therapeutic groups. In some cases, clinical study files are sent to hospitals for clinical evaluation which can 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 are faced with long pricing time which cannot be controlled because the price approval has to be obtained from the Minister of Health. The minister approves prices two or three times a year depending on the political stability of the government. Changing the minister more than six times in three years negatively impacted the overall patients' access time to new medicines from 2006 to 2008. However, a large number of products were registered and priced in less than twelve months each year during the study period. For example, the median patients' access time for anti-infective medicines and anti-malignant/immunosuppressive medicines were 9.5 months and six months in 2006 and 2007, respectively. This was attributed to the fast completion of the review process and obtaining the price approval from the minister of health during a temporarily stable political environment.

The data obtained from the Kuwaiti authority demonstrated that four major therapeutic groups were in demand by the public, namely, CVS, CNS, endocrine and malignant/immune disease medicines. It is recommended that external specialists are contracted to assess medicines from each of these therapeutic groups rather than current situation where pharmacists in the registration department are reviewing medicines from all therapeutic groups. Also, it is recommended that a priority be given to the major therapeutic groups for which there is the greatest need in Kuwait.

SUMMARY

- The KDFC authority made a significant improvement to the overall patients' access time to medicines in the private and government sectors in Kuwait over the period from 2006 to 2009.
- International companies were the largest group registering products every year in Kuwait as a result of the increasing importance of the GCC centralized procedure and the growing demands of the GCC pharmaceutical market.
- Pharmaceutical companies increased the number of submissions and registrations in 2007 and 2008 to obtain the Kuwaiti registration approval which was considered sufficient evidence to support the GCC-DR approval along with Saudi Arabia, Oman or UAE.
- Patients' access time to EASs was slightly longer than for NASs between 2006 and 2008, but it was significantly longer in 2009.
- Patients' access time to NASs for CNS and malignant diseases and immunosuppressive disorders slightly decreased over the four-year period.
- The patients' access time to NASs for CVS and endocrine disorders significantly decreased over the period 2006 to 2009.

CHAPTER 5

Comparisons of the Regulatory Review Processes in the Gulf Cooperation Council (GCC) States

INTRODUCTION

Modern day licensing began in the 1940s with the formation and constitution of the World Health Organisation (WHO), and its recommendation that global standards be established in relation to the safety, quality and efficacy of biological, pharmaceutical and similar products, and extending this to their labeling and advertising (Crout, 1998). However, there is little conformity between countries worldwide as to how the review is conducted including, what stages comprise the process, who carries out each stage, what criteria are employed, how long it takes, or, indeed, whether there is a review process at all. About 30% of WHO member states either have only a very rudimentary drug regulatory authority or none at all, while only 20% are thought to have a well-developed drug registration system (Ratanawijitrasin *et al.*, 2002).

This chapter focuses on the Gulf Cooperation Council (GCC) States: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, and Yemen. These seven GCC regulatory authorities have the same goals and regulations to protect local consumers from harmful and detrimental effects of medicines by ensuring the availability of medicinal products of desirable quality, safety, and efficacy in each country. However, the practices and strategies involved in carrying out the regulatory review processes vary across the seven authorities. From the pharmaceutical industry's perspective, the regulatory review of new medicines is the culmination of a research and development process that has taken between 12 to 14 years (McAuslane *et al*, 2004), and estimates about the cost of developing a new drug vary widely, from a low of $800 million to nearly $2 billion per drug (Masia, 2008). Therefore, this study uses a structured approach to collect comprehensive data on the regulatory review process across the GCC region. The assessment is based on the argument that, despite the noticeable differences between different regulatory processes, the processes are made up of a set of basic stages sufficiently similar to allow meaningful comparisons (Hirako *et al.*, 2007). All the GCC authorities 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 (Hashan, 2005).

It is recognised that individual authorities have various experiences and knowledge that could be of value to each other through the comparison of various systems and

sharing of best practices to the advantage of all. With this in mind, this study was conducted to compare the review practices in the seven GCC States.

This chapter evaluates the key stages in each review process to determine the commonly shared milestones of the regulatory review process across the seven states. The key milestones in the approval process, which are recognised and shared in most of the GCC States are defined in Table 5.1.

Table 5.1 Definitions of key milestones identified in the Gulf Cooperation Council (GCC) regulatory review processes

Review Phases	Key Milestone	Suggested Definition
Submission Phase	Receipt Stage	The authority may request a pre-submission document for the application to be accepted, for example notification to submit from the sponsor.
	Queuing for Review	This is the stage where the received applications are pending for action to begin.
	Validation Stage	This may include administrative procedures such as checks on completeness of the dossier to include all the documents required, check on legal requirements, status of the company, local agent, manufacturer etc.
Evaluation Phase	Scientific Assessment	The assigned member of the scientific committee or a pharmacist from the department carries out the scientific assessment and generates a report. Sometimes the registration committee assesses the pharmacist's report and makes the final registration decision. In some systems the clock stops when questions are asked and sponsor's time can be measured and deducted from the authority review time.
	Questions to Sponsor	May be batched and sent at one time or asked throughout the review process, in which case the *sponsor's time* is not easily measured.
	Quality Control Analysis	The National Quality Control Laboratory analyses the pharmaceutical product as a requirement for registration and generates a report.
Authorisation Phase	Pricing Process	All GCC authorities carry out the pricing of products before they are allowed to enter the local market, but they differ in their pricing procedure and the final price approval.
	Authorisation Process	This is the process after the scientific review while the formal authorisation is issued. It may be extended by pricing negotiations and finalisation of analytical and/or GMP checks.
	Approval Time	This is the time interval from the submission stage to the final issue of the registration certificate.

OBJECTIVES

The objectives of this study were to,

- Identify the model(s) of the review which is being undertaken by each of the GCC authorities.
- Assess and identify the stages and activities related to the submission, review and regulatory action for new drug marketing applications in the seven GCC authorities.
- Determine the similarities and differences between the regulatory processes that occur during the review of product dossiers within the GCC authorities.
- Identify best practices in order to harmonise targets and improve the standard of the regulatory review processes in the GCC states.

METHODS

Study Participants

The regulatory bodies which are responsible for the regulation of pharmaceutical products in five of the Gulf States (i.e. Bahrain, Kuwait, Qatar, Oman, and UAE) are under the auspices of the respective governments. Saudi Arabia and Yemen are independent, stand-alone, authorities.

Data Collection Procedure

A questionnaire was designed which enabled details of the regulatory process to be determined (Appendix A). A face-to-face meeting with the senior personnel from the region took place in Kuwait, March 2010. The aim of the meeting was to introduce the participating authorities to the research goals and objectives and to provide an overview of the contents of the questionnaire used to collect the data required for this research study.

All authorities were able to complete the questionnaire on time. The data were then standardised into a word document for the purpose of comparison. The resulting reports were sent to the authorities for auditing, correction and comment by July 2010. At the end of this month, the participating authorities were contacted by email to confirm the accuracies of the information contained in the respective country reports.

The questionnaire was originally designed and utilised by CMR International Institute for Regulatory Science in a number of emerging markets (McAuslane, 2006a). It comprised three main parts, namely, the key milestones in the registration of medicines, the regulation of clinical trials and building quality into the assessment and registration process in the emerging markets. The three parts were carefully revised to confirm their appropriateness with the current regulatory status of the Gulf States. It was known that the GCC authorities do not in general conduct clinical trials and, therefore, the details were excluded from the study. Furthermore, items covered in the original questionnaire on the regulatory review models in the GCC countries were carefully examined to confirm their suitability to the fundamental structures and core practices within each GCC regulatory review process. This is to ensure that all the main points were thoroughly identified and assessed and that all the data pool was complete. Data were collected on applications for New Active Substances (NAS) and Existing Active Substances (EAS) that had not previously been approved by the authority in question. The methodology was based on identifying review stages and milestones that could be compared across regulatory authorities; in spite of any differences between the individual regulatory procedures.

RESULTS

The seven authorities share similar goals, objectives and obligations to safeguard public health when assessing the safety, quality and efficacy of medicines before they are authorised for marketing. This study revealed that the GCC States are no exception to any other authority in the world, and in order to achieve this target; each country has laws, strategies, and regulations to approve and market pharmaceutical products. Therefore, for the purpose of clarity, the results will be presented in two main parts: Part I addresses the regulatory review process in individual Gulf States, and Part II provides a comparative assessment of the review milestones between the GCC States.

Part I: Regulatory Review Process in the Individual Gulf States

Pharmaceutical companies are obliged to demonstrate evidence of their product's quality, safety and efficacy standards and must submit data to the regulatory authorities reporting reasonable biological and chemical activities in order to be considered for registration for human use. Further evidence of the product's

registration and marketing in other countries is required prior to making the final approval decision.

Models of assessment in the GCC authorities

This chapter explores review model(s) for the scientific assessment in terms of the extent to which data is assessed in detail by the authority rather than relying on the results of assessments and reviews carried out elsewhere. Many authorities apply a different level of data assessment to different applications, according to the type of product and/or its regulatory status with other authorities.

Three basic types have been identified (refer to chapter three for complete definitions) as a result of discussions with regulatory authorities and workshop reports from CMR International Institute for Regulatory Science (McAuslane et al., 2006a), namely, the verification model (type I assessment), the abridged model (type II assessment) and the full review model (type III assessment). The models of the review process carried out in the GCC States significantly vary according to the respondent's perceptions and views of their own review practices. The level of data assessment in each authority depends on the type of product and/or its regulatory status with other authorities. The three types of assessment models were explored and the extent of the scientific reviews was examined for each GCC authority.

Four GCC authorities stated that they perform an abridged assessment (Bahrain, Oman and UAE). This is a critical practice to ensure the appropriateness of the product under local conditions. Bahrain carries out 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. UAE conducts an abridged review for biological and biotech products because they are only registered if they are approved by advanced regulatory authorities and conducts a full review for other major applications. Saudi Arabia is the only country that performs a full review for all types of applications, while Kuwait, Qatar and Yemen carry out a verification review for all registration dossiers.

A verification review requires that the new medicine should be approved in countries with advanced and competent regulatory authorities to ensure that a full reliable review has been conducted before it can be made available to local patients. A full review requires the availability of qualified and multidisciplinary experts in various

areas of the regulatory science field. The outcomes of this study are shown in Table 5.2.

Table 5.2 Models of assessment and the extent of the scientific review in the Gulf Cooperation Council (GCC) authorities

Type of review model	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Verification review (Type I)	✓	✓	×	✓	×	×	✓
Abridged review (Type II)	✓	×	✓	×	×	✓	×
Full review (Type III)	×	×	×	×	✓	✓	×
Similarity to locally registered product							
Fully identical	✓	✓	×	✓	✓	✓	✓
Mostly identical	×	×	✓	×	×	×	×
Closely Similar	×	×	×	×	×	×	×
Extent of scientific review							
1. Chemistry and Manufacturing Control (CMC) data							
Extensive assessment	✓	✓	✓	✓	✓	✓	NA*
Reviewed when necessary	×	×	✓	×	×	×	×
2. Nonclinical data							
Extensive assessment	×	×	×	×	✓	✓	✓
Reviewed when necessary	✓	✓	✓	✓	×	✓	×
3. Clinical data							
Extensive assessment	×	×	×	×	✓	✓	✓
Reviewed when necessary	✓	✓	✓	✓	×	✓	×
Addition information obtained from							
Other agencies' internal review reports	✓	×	×	✓	×	×	✓
Reports available on the internet	✓	✓	✓	✓	×	✓	✓
General Internet search	✓	✓	✓	✓	×	✓	×

**Not Applicable*

Furthermore, the extent of the scientific assessment was evaluated in the seven GCC authorities and the results revealed that six GCC authorities perform detailed assessment on the pharmaceutical quality (CMC) data (Table 5.2). The six authorities have assessors with the required skills and experience to evaluate the CMC data. Yemen, however, is the only authority that uses external reviewers to verify the non-

clinical and clinical data and stated that the CMC assessment is not applicable in their review process. The authority conducts a form of a verification assessment of the clinical an non-clinical studies to ensure that the medicine is safe and effective to be approved for marketing in Yemen.

In Oman, an extensive assessment is only performed when the product is not authorised in countries with reference agencies. In contrast, non-clinical and clinical data are assessed extensively in Saudi Arabia for all products while they are only studied in detail in UAE for products which are not authorised by reference agencies. Bahrain, Kuwait, Oman and Qatar perform the non-clinical and clinical assessment when there is a critical issue or a complaint with regards to the safety of the medicine after it has been approved for marketing. This may be an attempt to conserve resource by not duplicating effort made by reference agencies to carry out non-clinical and clinical assessment in these four authorities.

The regulatory review processes in the seven GCC States

In this part of the study, three common phases are thoroughly examined and described for each GCC regulatory review process, namely, the submission phase, the evaluation phase and the authorisation phase. These data reflect the situation at the time when study was carried out (2010) and subsequent changes in the regulatory environment will need to be monitored.

Regulatory Review Process in Bahrain

Bahrain has a unique medicines policy that clearly states the aims, the current situation and the objectives of the Bahraini medicines control system. It is called the "Bahrain Medicines Policy- BMP". The goal of the policy is to serve as a guide for action and commitment to provide good quality, safe, and effective medicines which are rationally used and provided at reasonable costs for the people in Bahrain, and for coping with new developments in the field of pharmaceuticals (Bahrain Ministry of Health, 2008). The regulatory review process in Bahrain is illustrated in Figure 5.1 comprising of critical steps that form substantial parts of the review process.

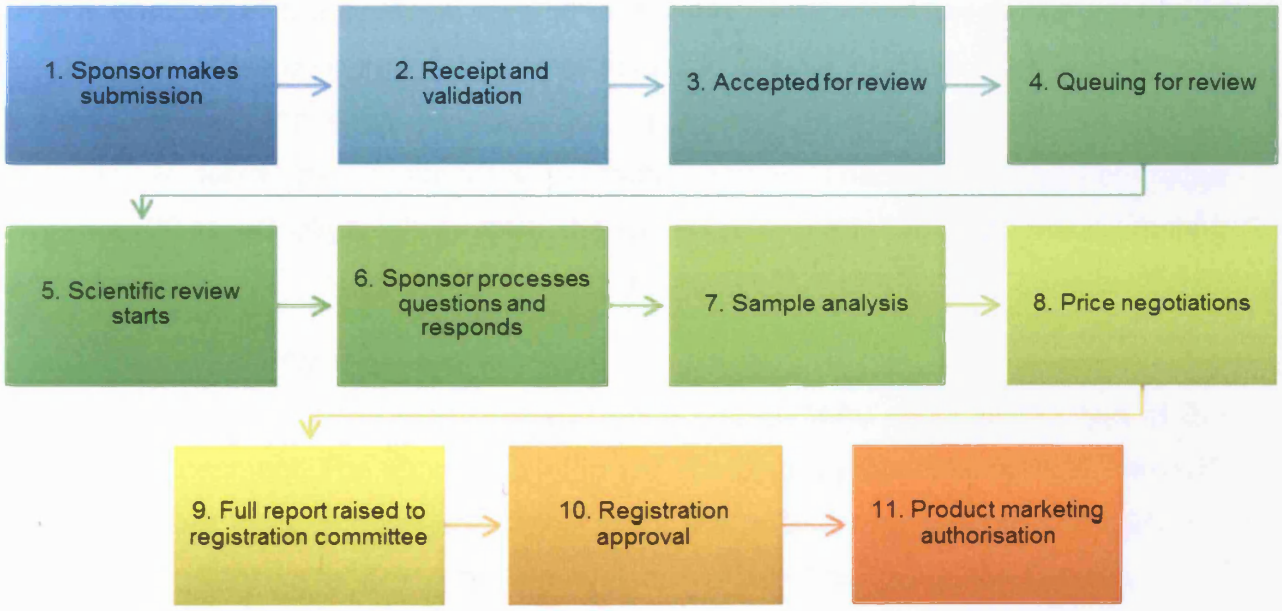
The Submission Phase

Initially, the sponsor submits the product registration dossier with the complete documents for the official acceptance of the dossier to be made. The authority did not specify information about the logistics involved at the receiving stage.

However, the dossier is validated before it is accepted for review and the following items are checked accordingly,

1. Legal status of applicant/local agent
2. GMP status of manufacturer
3. Patent/IP status of active ingredients
4. Acceptable format of the application
5. Organised format of the registration dossier including the three sections of scientific data (quality, safety and efficacy)
6. The CPP authenticated by the respective embassy or consulate general

Figure 5.1 The regulatory review process map for Bahrain



The target validation time within the authority is two weeks after which it is officially accepted for review once all the missing data has been provided and the date of acceptance is recorded. The Bahraini authority refuses an incomplete application and generates an official letter indicating the missing data and a time period of two to four weeks for the application to be completed. The dossier, then, joins the queue for a period of two to eight weeks before entering the scientific assessment stage. The

authority recognises the medical urgency of the priority review process and therefore emergency, lifesaving and important medicines are always taken out of the queue for the accelerated review process.

The Evaluation Phase

When the product enters the scientific assessment stage, the dossier is split into three sections, which are assessed in parallel by the appointed reviewer who completes a product assessment template and collects all the resulting questions as they arise during the review into one batch for the sponsor including the laboratory requirements. After sending the queries, the sponsor is given a time limit of six weeks to respond and all inquiries regarding the product labeling information are negotiated with the sponsor during the evaluation phase. The sponsor holds meetings with the authority's staff to discuss any questions that arise during the assessment. Finally, the product is sent to the quality control laboratory to carry out sample analysis to determine the eligibility of the product for approval.

The procedures of the scientific committee for the assessment stage are integrated into the authority's own internal/external scientific review process. The committee's experts (internal and external) carry out the review process and the authority is mandated to follow the committee's recommendations. The time for the committee review is 30 to 90 days, after which the decision is made to grant the marketing authorisation.

The Authorisation Phase

The pricing process is the final step and price negotiations occur at the end of the scientific assessment. The sponsor is informed of a positive scientific opinion within 90 days of issuing the authorisation. At this point the pricing negotiations and scientific assessment procedures are complete and the product is ready for approval. The company is now required to pay the fees to receive the registration certificate and the product is ready to be marketed in Bahrain.

The key milestones in the approval process and target approval time in Bahrain are illustrated in Table 5.3. The authority has not set a target time for the scientific assessment stage and therefore it was not possible to calculate the final product approval time.

Table 5.3 Key milestones in the regulatory review process of Bahrain

Milestone	Target time (Calendar days)
Validation time	14
Queue time	14 to 56
Scientific assessment time	Not set
Sponsor response time	42
Expert committee time	30 to 90
Authorisation procedure time	30 to 90
Overall approval time	Not set

Regulatory Review process in Kuwait

The regulatory review process in Kuwait focuses on the quality review for pharmaceutical products to be authorised for marketing in Kuwait (Figure 5.2).

Figure 5.2 The regulatory review process map for Kuwait

The most important goal of the Kuwaiti review process is to ensure that (a) the product is registered and marketed in countries with recognised and competent regulatory authorities for at least twelve months, (b) that the product meets the desired, internationally recognised, quality standards to ensure that the product was manufactured for its intended use, (c) that the product is stable for the entire proposed

shelf life and for six months under the stressed conditions of 40°C/75% relative humidity, and (d) the product price must be reasonable and affordable for local patients.

The Submission Phase

The review process starts with the local agent (or the sponsor) submitting the registration dossier along with a covering letter to the Director of Kuwait Drug and Food Control (KDFC) officially requesting the registration of the pharmaceutical product. The authority, then, transfers the registration dossier to the registration department and the Drug Registration and Release Superintendent (DRRS) acknowledges the receipt and appoints a reviewer to undertake the assessment of the dossier. The product is placed in a queue for review by the department's administrative staff member who is responsible for keeping a record of the dossiers to be transferred to the appointed reviewing staff member.

The Evaluation Phase

After entering the scientific review stage, the reviewer evaluates the Chemical and Manufacturing Control (CMC) data focusing on the following data,

1. Product specifications and detailed methods of analysis of the finished products with the reference pharmacopoeias.
2. Full stability studies in tabulated form addressing the proposed product shelf life.
3. Raw material specifications and their methods of analysis as well as the reference pharmacopoeia.

Even though the authority does not evaluate safety and efficacy data, it considers documentation of such data as an important part of a successful approval process. Therefore, sponsors must ensure that safety and efficacy data are submitted to the authority along with all other registration documents. These are addressed when further investigations are necessary and then the following procedure occurs. The authority indicates that innovative companies must submit clinical studies as a major requirement for a successful approval of their NAS. Clinical studies are sent to the relevant specialised hospital or health institutions for evaluation by clinical experts and a report is sent back to the regulatory authority stating the clinical effectiveness of the product on selected patient volunteers, and whether there is a significant clinical need for such a medicine in Kuwait. The authority appends this report to the scientific

assessment report. In case of an EAS, the sponsor must submit bioequivalence studies to provide evidence of bioequivalence between the locally marketed NAS and its EAS counterpart under registration.

Kuwait requires suitable facilities, the expertise, resources, and proper settings to be able to conduct the desired standard safety and efficacy assessments. Therefore, the main focus of the authority is on the pharmaceutical quality data that provide the assurance that the drug was formulated for its intended use. Furthermore, administrative documents such as the certificate of pharmaceutical product (CPP), the list of countries where the product is registered and marketed with the registration dates, the good manufacturing practice (GMP) certificate and a manufacturing license authenticated by the health authority in the country of origin, are the official documents that are requested from the sponsor to overcome the shortage in resources and expert capacities to evaluate the safety and efficacy studies. For completion of the review process, NASs do not enter the quality control analysis stage as long as the sponsor has provided complete pharmaceutical quality documents to ensure that this product is of the desired quality. Once this is achieved, the NAS is ready for approval. EASs, however, are sent to the QC laboratory for sample analysis. The results must comply with analytical results and ranges provided by the manufacturer's certificate of analysis of the finished product. Moreover, the results must not be outside the ranges and limits provided by the innovative company's patent counterpart. Furthermore, to overcome the lack of Post-Marketing Surveillance (PMS) capacity, the authorities request the PMS reports as part of the safety studies submitted in the registration dossier.

After reviewing the dossier, questions are collected as they arise during the scientific assessment and sample analysis. These are sent to the sponsor after the drug registration and release superintendent (DRRS) has given their advice by signing the question/query form. The authority places no limit on the sponsors' processing time and the scientific assessment clock stops at this point until a reply is received from the sponsor. This step affects the overall approval time when delays in the sponsor's reply are encountered. However, the authority does not exclude it from the review process but considers its impact on the final approval time.

The Authorisation Phase

When the full assessment has been successfully completed, the final approval decision is made by the DRRS which is officially endorsed by the director of the authority. At this stage, the pricing negotiations have been completed and an agreement has been reached. Once the review and pricing procedures are completed, the product is finally approved and the sponsor is then required to pay the fees to receive the registration certificate. The agreed product price is listed in the next supplement to be presented for approval by the Health Minister. Once the Minister approves the price, it is officially published in the locally distributed business magazine called "Kuwait Today", after which the product is ready to be marketed.

The key milestones in the approval process and the associated timelines in Kuwait are illustrated in Table 5.4. The target approval time in Kuwait is 120 to 180 days for both NASs and EASs. However, this timeline is not fully enforced due to many interfering factors that hinder its implementation such as the clock stop during the sponsor's response time with no specific time limit for the sponsor to process the authority's questions and queries. Nevertheless, if the sponsor does not respond to the authority's question within a maximum period of two years and is still willing to complete the registration process in Kuwait, the original dossier is returned to the sponsor and a new application must be made.

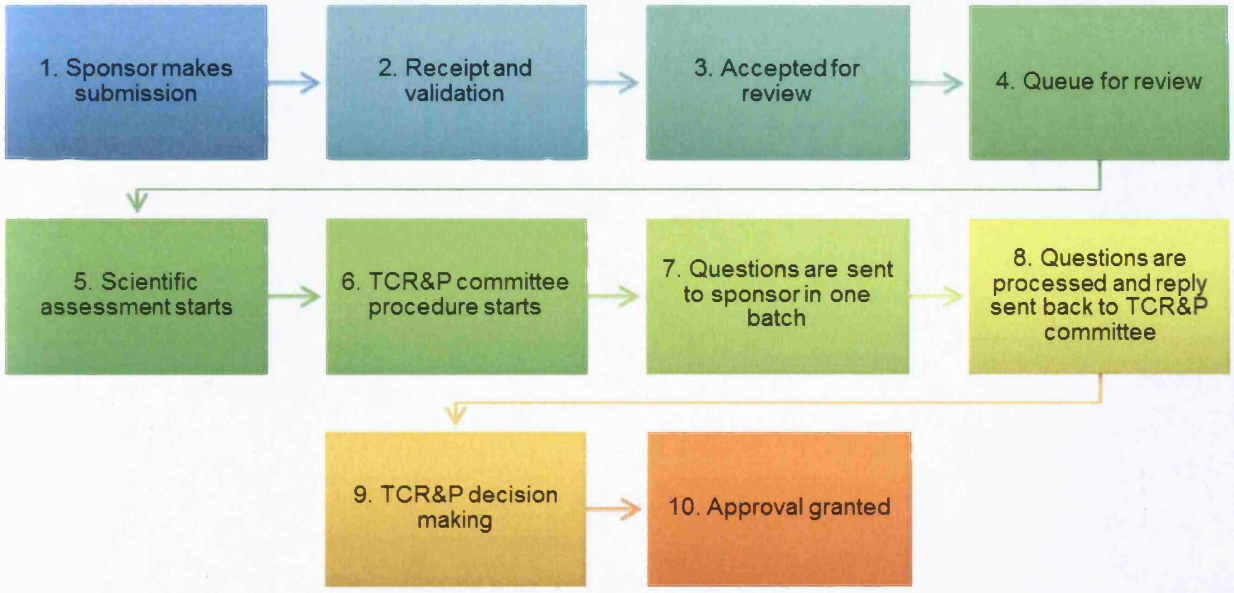
Table 5.4 Key milestones in the regulatory review process of Kuwait

Milestone	Target time (Calendar days)
Receipt time	7
Queue time	14 to 56
Scientific assessment time	No limit
Sponsor response time	No limit
Authorisation procedure time	>30
Pricing procedure time	120 to 180
Overall approval time	180

Regulatory Review Process in Oman

A thorough evaluation of the regulatory process in Oman was undertaken and the milestones identified. The regulatory review process in Oman comprises ten stages which are considered critical and have an impact on the approval time of medicines (Figure 5.3).

Figure 5.3 The regulatory review process map for the Oman



The Submission Phase

As a common practice, the sponsor submits the product registration file to the authority. All documents must be completed for official acceptance. The following items are checked at the validation stage,

1. Legal status of the applicant/local agent
2. GMP status of the manufacturer
3. Organisation of the registration dossier
4. Certificate of a Pharmaceutical Product (CPP) authenticated by the respective embassy or consulate general.

If the application is incomplete, the dossier is rejected and a new application must be made after providing the missing data. After receiving the product dossier the company must pay the registration fees within one week. Once the validation stage is successfully completed, applications join the queue and have to wait for two weeks

before being allocated for review. There is no official priority review procedure for fast track medicines but lifesaving products are unofficially prioritised.

The Evaluation Stage

The product enters the scientific review stage, and data on quality, safety and efficacy are assessed in parallel. The safety and efficacy parts are reviewed in the drug control department and the quality part by the quality control laboratory department. There is a formal record for the starting time of the scientific assessment. In the primary scientific assessment procedure, an internal reviewer in the drug control department completes a scientific product report, detailing the trade, generic names, indication and country of origin. Then, the product assessment report is sent to the scientific committee for evaluation. This committee assesses the product report and generates questions, queries and concerns relevant to the product's quality, safety and efficacy.

The committee also examines any queries that are raised during the assessment process. These questions are returned to the reviewer to be collected in one batch for the sponsor after the scientific committee has given its advice. After sending the questions and queries to the sponsor, there is a time limit of 90 to 180 days given to sponsors to reply to the questions which are entirely dependent on the type of queries addressed, whether they are related to major or minor issues. The sponsor can meet with internal staff to discuss questions and queries that arise during the assessment but they are only permitted to meet the directors and/or section heads. The drug control department refers the marketing authorisation application assessment report and their recommendation to the registration committee within 90 days of its receipt and the registration committee makes a decision within 30 days from the date of receipt. The registration committee consists of members from two directorates in the Ministry of Health 1) six members from the Directorate General of Pharmaceutical Affairs and Drug Control and 2) two members from the Directorate General of Medical Supply and all members are pharmacists. Meanwhile, 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, or if it is registered in the GCC Central Drug Registration (GCC-DR) or in a recognised regulatory agency.

The Authorisation Phase

Finally, the registration committee is responsible for granting the marketing authorisation and pricing of the product after completion of the review process. A

product registration certificate is issued within two weeks after the committee has provided a positive decision about the product registration which is signed by the chairperson of the registration committee. If the registration committee rejects the application, the sponsor can appeal within 60 days from the date of receiving the committee's decision; otherwise, a whole new submission is required after a 60-day period.

The key milestones in the approval process and the target approval time in Oman are illustrated in Table 5.5. The length of the scientific assessment and, therefore, the approval time depends on the type of product being reviewed and the regulatory requirements to register such a product, whether they are major or minor requirements.

Table 5.5 Key milestones in the regulatory review process of Oman

Milestone	**Target time (Calendar days)**
Validation time	1
Queue time	14
Scientific assessment time	90
Sponsor's response time	90 to 180
Registration committee time	30
Authorisation procedure time	14
Overall approval time	120

Regulatory Review Process in Qatar

An evaluation of the regulatory review process in Qatar was undertaken and the milestones were identified. The regulatory review process in Qatar is illustrated in Figure 5.4 and consists of thirteen critical steps that have an impact on the overall time of patient access to the medicines.

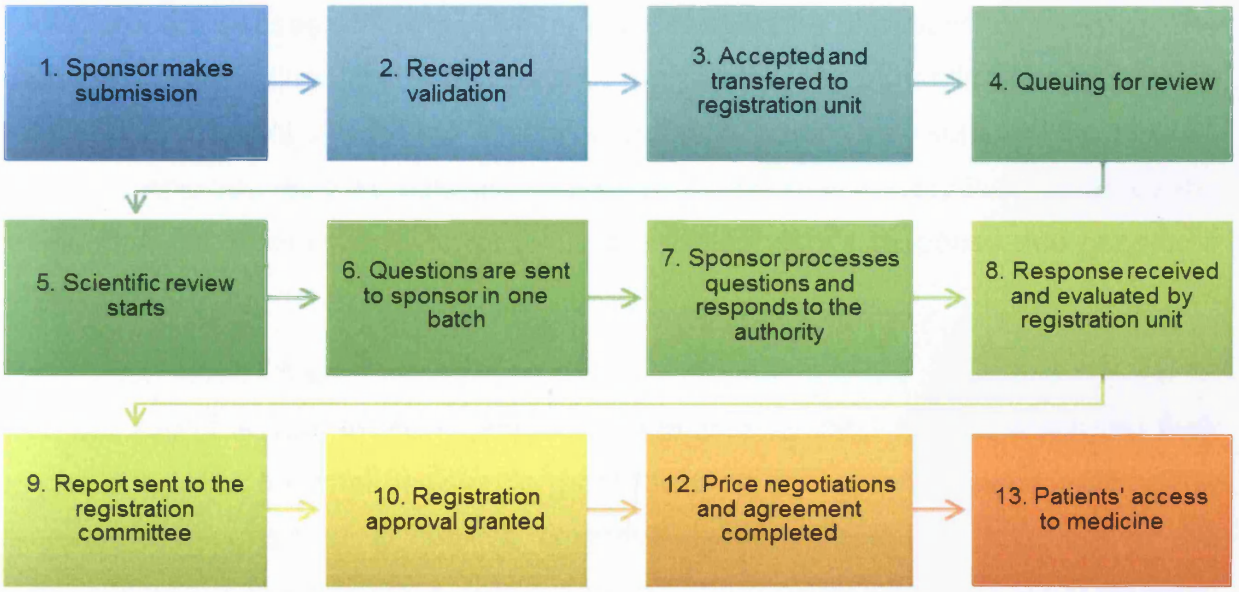
The Submission Phase

The regulatory review process in Qatar begins with the sponsor submitting the registration dossier to the department containing the complete documents for a successful and timely review process.

There are no formal requirements at the submission phase, but there are items that must be checked at the validation stage for the file to be accepted for review, these are:

1. Legal status of the applicant/local agent
2. GMP status of the manufacturer
3. Patent/IP status of the active ingredient
4. The CPP authenticated by the respective embassy or consulate general
5. The complete dossier in the acceptable format

Figure 5.4 The regulatory review process map for the Qatar



No specific time is targeted for the validation process. The date of acceptance is not formally recorded and if the application is incomplete, a request for the missing data is sent to the applicant and the dossier remains pending for a period of up to one year during which the sponsor must complete the missing data. Once the missing data is provided, the product dossier is held in a queue after validation for 60 to 90 days. The department recognises the medical urgency of certain medicines and therefore, priority products are sometimes taken out of the queue to be reviewed urgently.

The Evaluation Phase

During the scientific assessment process, the registration dossier is split into quality, safety and efficacy and the appointed reviewer, who is a technical staff member, reviews all parts in parallel. The reviewer must complete a product evaluation template and type all the resulting queries into one batch for the sponsor.

There is no separate negotiation of the product labeling/product information after the scientific opinion is given or before the approval is given. The negotiation of the product labeling takes place during the scientific assessment process. There is no set time limit for the scientific assessment stage. All questions are collected into one batch and sent to the sponsor after the committee has given its advice. The scientific review process ceases while the sponsor is processing the questions (clock stop). The sponsor is given a time limit of 365 days to reply to the department's queries and can hold official meetings with the senior managers within the authority to discuss questions and queries that arise during the assessment. The reply is received by the registration unit where the reviewer evaluates the sponsor's response and generates a final report.

The Authorisation Phase

The final report is sent to the registration committee for their review, which, on their agreement, make the final decision to grant the product marketing authorisation. The sponsor is informed of a positive scientific opinion 30 to 90 days before the authorisation is issued. No fees are applied and the registration certificate is released to the sponsor on request.

The pricing negotiation is the final step to be performed after granting the marketing approval of a pharmaceutical product. After a pricing agreement is reached and the registration certificate is released, the product price is published in the local official Gazette and then the product can be marketed in Qatar.

The key milestones in the approval process and target approval times in Qatar are shown in Table 5.6. The authority does not set a target time for the validation, scientific assessment and the pricing of the medicines. Therefore, it was not possible to determine the overall target approval time.

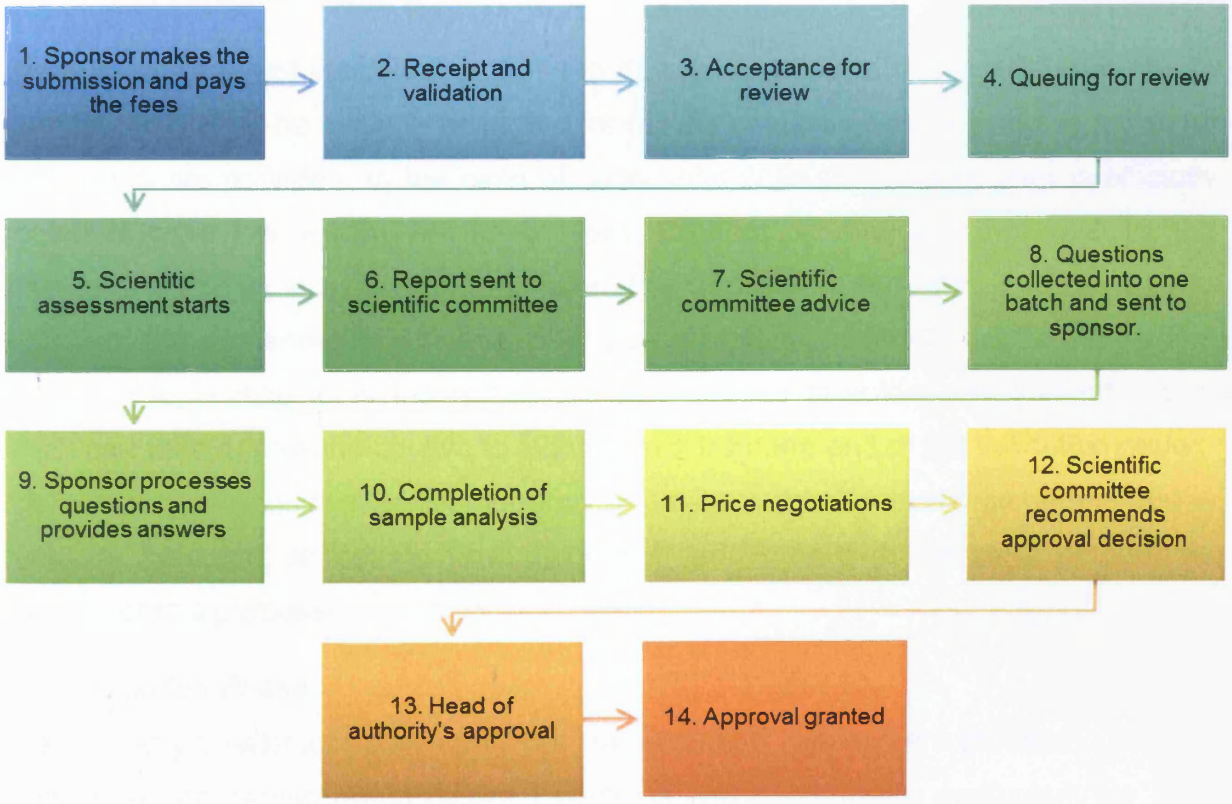
Table 5.6 Key milestones in the regulatory review process of Qatar

Milestone	Target time (Calendar days)
Validation time	Not set
Queue time	60 to 90
Scientific assessment time	Not set
Sponsor's response time	365
Pricing procedure time	Not set
Authorisation procedure time	30 to 90
Overall approval time	Not set

Regulatory Review Process in the Kingdom of Saudi Arabia (KSA)

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 comprises thirteen steps which are critical to the whole process (Figure 5.5).

Figure 5.5 The regulatory review process map for Saudi Arabia



The independent resourcing and provision of the necessary expertise was a requirement to implement highly sophisticated review practices which ensures patients' access to medicines with the desired quality, safety and efficacy standards.

The Submission Phase

The authority's approval process starts with the sponsor submitting the product registration dossier to the authority online. The applicant has to pay the application fees in order to submit the application form and schedule an appointment to deliver the hard and electronic copy of the product file. The sponsor must ensure that the dossier contains the complete documents for it to be officially accepted for assessment.

The authority acknowledges the receipt of the dossier and starts the validation process. The following items are checked at the validation stage:

1. Legal status of the applicant
2. GMP status of the manufacturer
3. Acceptable format with the correct sections of scientific data
4. Certificate of Pharmaceutical Product (CPP) authenticated by the respective embassy or consulate general.

The authority's target validation time is ten days after which a decision is made as to whether the file will be officially accepted for review or will be pending until the missing documents are provided. In the case of successful validation, the dossier is officially accepted for review. Incomplete applications are kept pending and a request for the missing documents is sent to the sponsor. The applicant has a period of 60 days to reply with the requested documents otherwise a new application must be made. The accepted application joins the queue for entering the scientific assessment stage, which can take approximately two to eight weeks from the end of the validation period. The authority realises the medical urgency of having a priority review procedure and is therefore planning on setting new guidelines and standard operating procedures (SOPs) for this purpose.

The Evaluation Phase

The authority's technical staff carry out the scientific assessment process. Different procedures are carried out in different sections and departments particularly for New Chemical Entities (NCEs) and biological products. In the scientific assessment stage,

the reviewing staff assess the quality, safety and efficacy data in parallel. The dossier is split into three separate parts and an appointed staff member thoroughly reviews all parts of the dossier including the clinical trial section and product literature. The reviewer must complete a scientific assessment form; detailing the product specifications such as the trade name, indication, and the country of origin. External experts are utilised to evaluate the product dossier and to present a detailed assessment and recommendation, a clinical opinion on the product, as well as to advise the authority's staff on specific technical issues related to the review process and the product details. The product's labeling information is also evaluated during this stage and no negotiation process is carried out separately on the labeling and packaging of the product under registration. After completing the assessment, a report is generated by the reviewer and presented to the scientific committee containing a detailed assessment of the product dossier and all the questions and queries arising during the review stage. The scientific committee is an integral part of the whole review process and is therefore consulted after the assessment process has been completed. Questions and queries are collected into one batch as they arise during the assessment process by the assigned reviewer, who must report them to the scientific committee to make the necessary recommendations. The target time for the sponsor's response is limited to 30 days and the 'sponsor time' for questions answered after the scientific committee procedure is calculated. The sponsor can meet with the internal staff to discuss questions and queries that were produced during the assessment procedure. However, there are no guidelines or SOPs to aid the negotiation process. The product enters the quality control laboratory to assess its quality in parallel to the scientific assessment stage according to internationally recognised standards and pharmacopoeias. The sample analysis is a vital step, depending on which the final approval may or may not be granted.

The Authorisation Phase

Towards the end of the scientific assessment, the authority requests the sponsor to submit the price list outlining the price of the product in countries where it is marketed. The pricing unit proposes a price to the scientific committee according to the internal pricing guidelines. Product pricing is an essential part of the whole approval process, depending on which, the approval may or may not be granted. The scientific committee recommends its decision to the head of the authority on the product

registration and pricing. Following a positive recommendation from the committee and the head of the authority, a registration certificate is issued to the company or the local agent will finally receive the registration certificate.

The key milestones in the approval process and target approval time in the Saudi Food and Drug Authority (SFDA) are shown in Table 5.7. The overall approval time for NASs is 290 days while it is 165 days for EASs. The authority has set a target time for each one of the milestones in order to achieve timely patient access to new medicines.

Table 5.7 Key milestones in the regulatory review process of Saudi Arabia

Milestone	Target time (Calendar days)
Validation time	10
Queue time	14 to 56
Scientific assessment time	180 to 245
Sponsor response time	30
Expert committee time	30
Authorisation procedure time	<30
Overall approval time	EAS: 165 NAS: 290

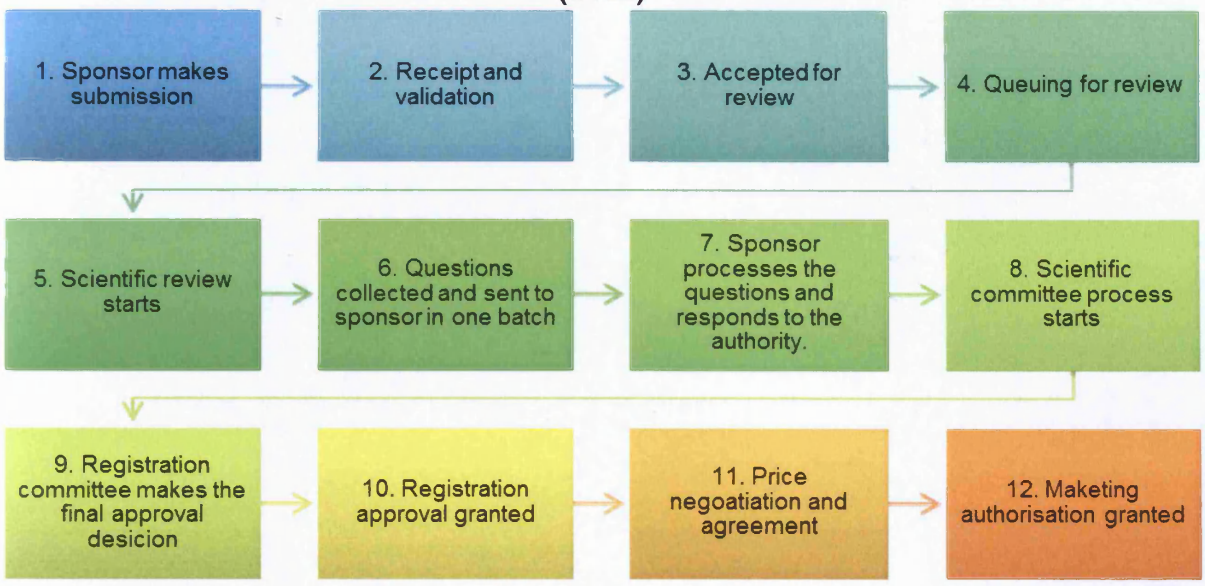
Regulatory Review Process in the United Arab Emirates (UAE)

An evaluation of the regulatory review process of the UAE was undertaken and the milestones were identified for comparative purposes. The regulatory review process in UAE consists of twelve critical stages that are considered essential and comprise a significant part of the review procedure (Figure 5.6).

The Submission Phase

The sponsor submits the registration dossier, which must contain all the required data to pass the validation stage and become accepted for review. An appointment is then arranged with the department's administrative staff to submit the product for registration and an appointment sheet and evidence of the manufacturing site registration must be presented at this stage.

Figure 5.6 The regulatory review process map for the United Arab Emirates (UAE)



Items checked at the validation stage include:

1. Legal status of applicant/local agent
2. Patent/IP status of the active ingredients
3. Evidence of payment of the relevant fees
4. The CPP authenticated by the respective embassy or consulate general.
5. A completed application in an acceptable format
6. The correct sections of scientific data (quality, safety, and efficacy)

The validation process is performed within 24 hours from submission and the decision as to whether to accept, refuse, or hold the product dossier is made accordingly. Once all the documents are available, the product is officially accepted for review. In the case of lifesaving products, applications can be accepted followed by submission of the CPP. The date of the file acceptance is formally recorded. However, if the application is incomplete, the file is refused and a new application must be made. In such cases with minor deficiencies, the missing data is recorded within the checklist included in the receipt form. The file can be pending for acceptance and a request for the missing data is sent to the applicant. The time limit depends on the individual case and the relevant justification letter(s). After completing the validation process, product dossiers are held in the queue for 60 to 180 days for innovative and GCC products, 180 to 365 days for generics and more than 365 days for generics when there is an equivalent available in the local market.

Priority products are always taken out of the queue for accelerated review. Innovative and GCC products are given priority, followed by other generics. Generics having more than six equivalents in the market are directed to the GCC Central Drug Registration System (GCC-DR). The authority regards the backlog of applications as a problem so they depend on the GCC-DR as a way of dealing with this issue.

The Evaluation Phase

The dossier is split into the three sections; quality, safety and efficacy; which are all reviewed together by the same appointed reviewer. The reviewer must complete a product evaluation template and print all the resulting requirements into one report for the sponsor. The start of the scientific assessment is not recorded. The sample analysis is carried out in parallel with the review process and the results accompany the product evaluation report. There is no time limit set for the scientific review process. During the scientific assessment, questions and queries are collected as they arise to be sent to the sponsor in one batch. Batched questions are sent to the sponsor after the committee has given its advice but the scientific review does not cease while the sponsor is processing the questions, although the sponsor is given a time limit of 90 days to respond. However, the authority is not enforcing this time limit on the companies. The sponsor can hold meetings with the agency staff to discuss questions and queries during the assessment.

The scientific committee, for the scientific assessment stage, is integrated into the authority's own internal and external scientific procedure. The committee review time is not recorded but the target time for the committee procedure is one week. The department staff is mandated to follow the scientific committee's recommendations. All reports of the scientific committee are then discussed in the higher registration committee after the scientific committee has given its opinion. There are no separate negotiations of the product labeling/ product information after the scientific opinion or before the approval is given. The required changes are communicated to the company together with other conditions to be fulfilled and the company can ask for an appointment to clarify its position, but negotiations in general are not opened as the enquiries usually go to the company after the higher registration committee meeting and the decision (approved, delayed, conditional approval, or rejected) is stated on the form. The correspondence and other communications with the sponsor comes in the form of a post-meeting sheet issued for each product.

The Authorisation Phase

The higher registration committee is the committee that is responsible for granting the final approval for a product, which is of political and administrative rather than of technical membership. The registration committee reviews the scientific committee report and makes a decision to grant marketing authorisation for a product accordingly. The sponsor is informed of a positive scientific opinion 30 to 90 days before the authorisation is issued in the form of a post-meeting sheet issued after the higher committee's decision, where all the decisions of scientific committees and questions are listed for the company to fulfil. At this time, the product is priced but not marketed until the sponsor fulfils all conditions listed in the post-meeting sheet.

Pricing is the final step when no product will be issued a registration certificate before it is priced and the price proposed by the company is not necessarily agreed to, but the company is given an opportunity to appeal once more, or maximum twice, for the final price. Pricing negotiations start after granting the registration approval of the medicine. When the review process and pricing agreement are finalised, the sponsor pays the fees and the department issues the registration certificate to the company, which is approved by the Deputy Minister of Health who authorises the product for marketing in UAE.

The key milestones in the approval process and target approval time in UAE are demonstrated in Table 5.8. The authority does not set a target time for the scientific assessment or the pricing process, and therefore it is not possible to provide a specific target approval time.

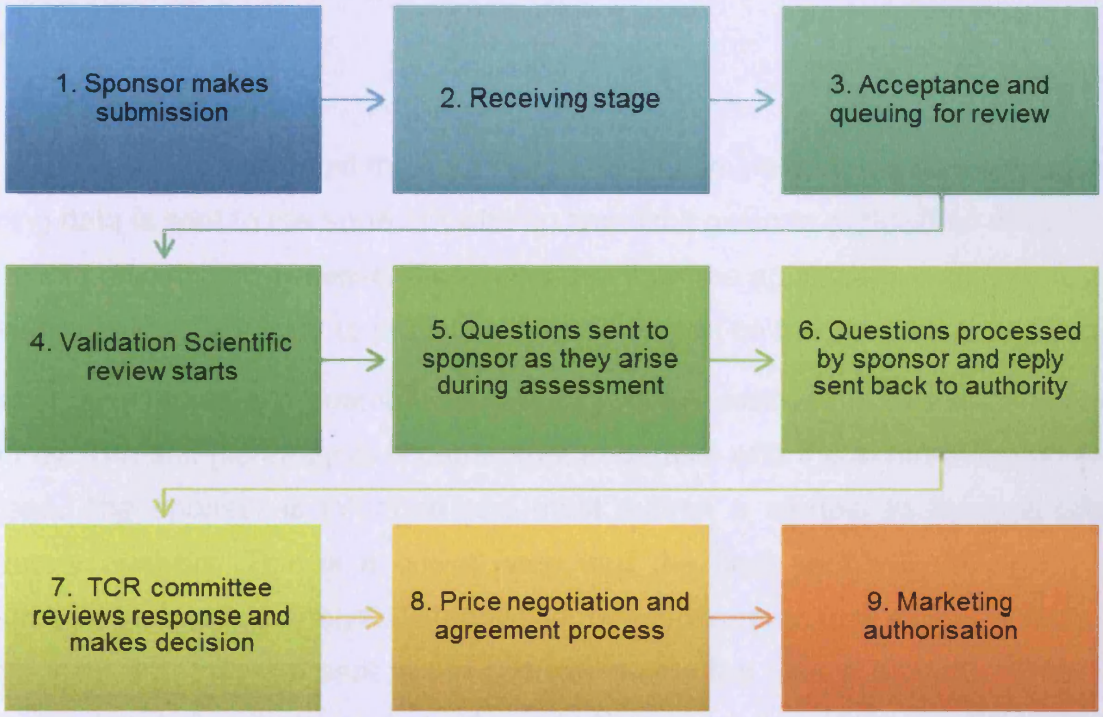
Table 5.8 Key milestones in the regulatory review process of United Arab Emirates (UAE)

Milestone	**Target time (Calendar days)**
Validation time	Immediately
Queue time	60 to 180 days for innovative and GCC products 180 days for generics 365 days for generics with available equivalents
Scientific assessment time	Not set
Sponsor response time	90
Scientific committee time	7
Authorisation procedure time	30 to 90
Overall approval time	Not set

Regulatory Review Process in Yemen

Yemen partially joined the Gulf Cooperation Council (GCC) in 2004 particularly in the fields of health and sport. Yemen's limited financial capabilities has given the government no other option but to allow full independence of the drug regulatory authority, fully funded and relying entirely on the application fees. Despite the limited resources, Yemen's regulatory approval procedure is illustrated in Figure 5.7.

Figure 5.7 The regulatory review process map for Yemen



The Submission Phase

Once the sponsor submits the registration dossier to the authority and the file is officially received, it is transferred to the relevant department to be validated and scientifically assessed. There is no official priority procedure, but the authority realisses the medical urgency of prioritizing the review of selected products. Therefore, lifesaving products are taken out of the queue to enter the review stage. The backlog is considered a problem by the authority, which is being addressed by keeping them pending until a decision is made on actions to be taken accordingly. The product dossier is validated before the scientific review.

The validation process is integrated into the scientific assessment procedure where the following issues are validated along with the full review,

1. Legal status of the applicant/ local agent
2. GMP status of the manufacturer
3. Whether the company has paid the correct fee
4. A CPP is required at the time of application but it can be submitted before granting the authorisation and must be authenticated by the respective embassy or consulate general.

The Evaluation Phase

The dossier is held pending if the information is not complete, and a request for the missing data is sent to the applicant with no time limit given to reply. Data on quality, safety and efficacy are assessed in parallel and then the application is transferred to an external expert reviewer to provide a clinical opinion on the product.

There is no contractual agreement for carrying out this task within deadlines set by the authority. The sample analysis is carried out in parallel with the external expert review process. The sponsor is informed and must submit a sample to the authority for laboratory analysis. This is a critical step and the final approval depends on the outcome of the sample analysis. Meanwhile, questions may arise any time during the assessment and they are sent to the sponsor during the review process. There is no time limit for sponsors to reply to the questions and the response time after the assessment process is not calculated. The sponsor can meet with the internal staff to discuss questions and queries listed in the authority's query form.

The Technical Committee for Registration (TCR) is an integral part of the review process and they must be consulted after the reviewers have completed their assessment of the product and generated a report on the scientific data. The committee procedure takes a period of approximately 30 to 60 days and the authority is mandated to follow TCR's recommendations. The TCR committee is responsible for reviewing and making recommendations on scientific aspects of the product. A *Product registration form* is generated from this recommendation. Separate negotiations may be performed for product labeling/ product information after the scientific opinion is given but before the approval is granted.

Sometimes the TCR committee requests a change in the product name, the volume, the outer package and the product information leaflet.

The Authorisation Phase

The price negotiations are carried out after granting the approval and therefore will not delay the registration approval but may delay the market entry if a price agreement is not reached. Granting of market authorisation depends on the sample analysis, which is carried out in parallel with the scientific assessment. Following a positive recommendation from the TCR committee, registration approval will be issued and the company and local agent must then pay the registration fees before obtaining a registration certificate. It takes about 180 days from receiving a positive scientific opinion to issuing the registration certificate. This positive opinion is based on the documents submitted and reviewer's report. Finally, the product can be marketed once the two main parts of the review process are successfully completed, namely the registration approval and product price.

The key milestones in the approval process and target approval time in Yemen are shown in Table 5.9. The authority has not set any target time for the validation, scientific assessment and the sponsor's response time. However the authority has a target approval time of six to twelve months for the pharmaceutical products.

Table 5.9 Key milestones in the regulatory review process of Yemen

Milestone	**Target time (Calendar days)**
Validation time	Not set
Scientific assessment time	Not set
Sponsor response time	Not set
Expert committee time	30 to 60
Authorisation procedure time	180
Overall approval time	180 to 365

Part II- A Comparison of the Regulatory Review Processes in the Seven Gulf States

This part describes a comparison between the regulatory review processes conducted by the seven GCC regulatory authorities. Similarities and differences between these processes were reviewed to provide a common account of the practices that may impact the approval time in these GCC authorities.

For the purpose for establishing a common ground for the comparative study, the regulatory review processes were considered to be performed in three phases, namely, the submission phase, the evaluation phase and the authorisation phase.

Submission Phase

The submission phase involved all the stages and processes carried out by the authorities' administrative staff prior to the scientific assessment of the medicine. These include the receipt and validation stage and the queuing stage (Table 5.10).

Receipt and validation stage

The seven authorities record the date of receiving the registration dossier and five authorities carry out a validation process to ensure that the documents submitted for registration are complete before they can be accepted for review (Table 5.10). Kuwait and Yemen accept the dossier for review and carry out the validation process as part of the scientific assessment stage where all questions, queries and missing data are requested from the sponsor after completing the scientific review process. Nonetheless, all the GCC authorities request the availability of the initial basic registration requirements, namely,

1. The certificate of pharmaceutical product (CPP) authenticated by the respective embassy or consulate general.
2. The GMP status of the manufacturer
3. The acceptable format of the dossier with the clearly organised sections of quality, safety and efficacy.
4. The legal status of the applicant

Table 5.10 The submission phase in the Gulf Cooperation Council (GCC) regulatory review processes

Task	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Receipt and validation							
Validation exists	✓	×	✓	✓	✓	✓	×
Authenticated CPP required	✓	✓	✓	✓	✓	✓	✓
GMP status of manufacturer	✓	✓	✓	✓	✓	✓	✓
Acceptable format of the registration dossier	✓	✓	✓	✓	✓	✓	✓
Legal status of the applicant	✓	✓	✓	✓	✓	✓	✓
Patent protection	✓	✓	✓	✓	✓	✓	×
Applicant response time with the complete missing data (days)	14-30	×	×	365	60	×	×
Validation time (days)	14	7	1	×	10	1	60-90
Fees range (GBP)							
<500	✓	✓	✓	×	×	✓	×
500-5000	×	×	×	×	×	×	✓
>5000	×	×	×	×	✓	×	×
Queuing Stage							
Queuing exists	✓	✓	✓	✓	✓	✓	×
Queue time (days)	14-56	14-56	14-56	60-90	14-56	NAS: 60-180 EAS: 180-365	×
Backlog problem	×	✓	×	×	×	✓	✓
Priority review exists	✓	✓	✓	✓	✓	✓	✓

The patent protection status of the active ingredient is relevant to six authorities, while it is not applicable in Yemen because of its lower GDP compared to the other Gulf States which enabled the government of Yemen to allow patients' access to affordable generic medicines and to prevent the monopoly of the overpriced medicines which are protected by patents (Medecins San Frontiers (MSF), 2005).

Furthermore, all the GCC authorities, except Qatar, apply fees for the evaluation and registration of medicines. The range of fees, however, varies significantly from country to country according to the funding structure and the services provided by each authority. The 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. 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 improve their resources such as increasing the number of expert reviewers, developing the information technology (IT) structure, and establishing training and continuous education programmes. Without proper funding, the authorities will always face difficulties in improving their regulatory systems.

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 UAE performing the validation process immediately after submission while Bahrain takes 14 days to complete it. The seven authorities vary significantly in their perceptions on how to handle the validation process. For example, while other authorities recognise the importance of the validation stage, Kuwait indicated that it is a time consuming process particularly for developing authorities that carry out a simple verification assessment.

Queuing stage

A queuing process was identified in all the Gulf authorities except Yemen which did not specify the existence of a queuing stage although a form of a queuing system is carried out to deal with the backlog problem and to expedite the review of important products (Table 5.10). All the GCC authorities carry out priority reviews because they recognise the therapeutic urgency of many medicines. However, Saudi Arabia expressed concerns in conducting priority reviews without having a set of guidelines and standard operating procedures (SOPs) that direct them towards proper decisions. 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 several months unjustifiably delays patients' access to medicines (Table 5.10).

Evaluation Phase

The evaluation phase includes all the stages that involve the scientific assessment and quality control analysis carried out to ensure that the medicine is safe, efficacious and of the desired quality standard to be given to the patients (Table 5.11). This phase consists of three stages shared by the seven GCC authorities, namely, the scientific assessment stage, the sponsor's interaction stage, and the sample analysis stage.

Table 5.11 The evaluation phase in the Gulf Cooperation Council (GCC) regulatory review processes

Task	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Scientific Assessment							
QSE* assessment carried out in parallel	✓	✓	✓	✓	✓	✓	✓
Internal reviewers exist	✓	✓	✓	✓	✓	✓	×
External reviewers exist	×	✓	✓	×	✓	×	✓
Scientific committee exists	✓	×	✓	×	✓	✓	✓
Overall assessment time (days)	×	×	90	×	180-245	×	×
Sponsor's interaction							
Contact with agency staff permitted	✓	✓	✓	×	✓	✓	✓
Clock stop during sponsor's response time	×	✓	✓	✓	✓	×	×
Questions collected in one batch	✓	✓	✓	✓	✓	✓	×
Sponsor response time (days)	40	×	90-180	365	30	60	×
Sample Analysis							
Parallel to the scientific review	×	×	✓	✓	✓	✓	✓
After the scientific review	✓	✓	×	×	×	×	×
Impacts the overall approval time	✓	✓	✓	✓	✓	✓	✓

**QSE= quality, safety and efficacy*

Scientific Assessment Stage

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. Internal reviewers assess the quality, safety and efficacy dossiers in six GCC states, while Yemen

depends on external reviewers to provide a clinical opinion about the medicine. Being a self-sufficient authority with a low fee structure in a country with a low GDP value ($58 billion) and a population of 23 million people (CIA World Factbook, 2009, accessed in June 2010), hiring internal reviewers would be costly and, therefore, employing external reviewers without a legal agreement between the two parties is the most appropriate cost-effective option for Yemen.

External reviewers, however, are only used by a few other authorities. In Kuwait, for example, clinical studies for certain NASs are sent to selected clinical experts in government hospitals to conduct clinical evaluation and provide the Kuwaiti authority with a clinical opinion about the medicine. Oman also hires external experts to provide advice on certain technical issues under no contractual agreement with the authority. Saudi Arabia has an expert panel which consists of 10 to 15 specialists that are not committed to a contractual agreement and provide a detailed assessment report and recommendation, a clinical opinion on the medicine and technical advice to the authority's staff. In general, investing time and resources to acquire skill sets using external assessors is advantageous as it may add a broader perspective to the GCC authorities that could benefit the review process so that the submitted data is more reliable and valid. External experts can also help answer specific technical or clinical questions such as whether registering a product is necessary for local patients (Dimmitt *et al.*, 2007).

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. It is considered valuable by advanced regulatory authorities to have committees review the scientific assessment reports and make an appropriate recommendation about the final product approval decision as this provides in essence a peer reviewed system which in turn adds to the quality of the review.

Sample Analysis Stage

In general, the sample analysis stage is an essential part of the review process that impacts the overall approval time for medicines in the seven GCC authorities (Table 5.11). It is carried out in parallel with the scientific assessment stage in some countries (Oman, Qatar, Saudi Arabia, UAE and Yemen) and after the scientific assessment in other countries (Kuwait and Bahrain) with the outcome of the sample analysis affecting the final approval decision. Nonetheless, the GCC authorities waive the analytical stage for products registered in Kuwait, Saudi Arabia, Oman, UAE, 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).

Sponsor Interaction Stage

The sponsor's interaction process is where all the communications occur between the sponsor and the authority with regards to the registration of a new medicine in each GCC State (Table 5.11). 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 six GCC authorities. Yemen, however, communicates these questions to the sponsor as they arise during the assessment process. In Bahrain, Kuwait, Oman, and UAE, interaction with the sponsor is permitted with the internal staff under the supervision of the person in charge, while Saudi Arabia expressed concerns with regards to the logistics of the communication process between the sponsor and the authority's internal staff, specifying the need for proper guidelines and SOPs on how to monitor the sponsor-staff interactions. Qatar applies restrictions to the handling of the authority's communication process with the sponsor and limits these interactions to official letters, emails, faxes or scheduled meetings with senior managers only. Effective interaction and the ability to communicate efficiently are necessary to synchronise opinions and ideas between the communicating parties. Without a means to communicate, the authorities will become isolated and important issues which may impact the overall outcome of the review process may well be overlooked or underestimated.

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 system but they target a specified limit for the sponsor response time (see Table 5.11). 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 minimises the backlog problem

Authorisation Phase

The authorisation phase includes practices carried out when a satisfactory outcome of the evaluation phase has been reached. These are the product pricing process and the final decision-making procedures (Table 5.12).

Pricing Process

Pricing agreement has a significant impact on the overall approval time. The pricing of a medicinal product is finalised prior to its importation into the GCC States. However, in four states (Bahrain, Kuwait, UAE and Yemen) the pricing procedure starts when the registration dossiers are submitted and goes in parallel with the scientific assessment process, while it is carried out at the end of the scientific review stage in other states (Table 5.12).

The Kuwait regulatory authority is the only authority that has a separate pricing department. Once the product is registered and the proposed price is calculated and compared against others in the GCC region, the director of the authority presents the price to the pricing committee, chaired by the Deputy Minister of Health to finalise the pricing decisions which are subsequently approved by the Health Minister.

The pricing step in other Gulf States is part of the regulatory review process and registration committees can be responsible for both the product registration and pricing decisions. Because of its political sensitivity, the medicines' prices are approved by the Minister of Health in Kuwait, Qatar and UAE, and by the Head of SFDA in Saudi Arabia.

Table 5.12 The authorisation phase in the Gulf Cooperation Council (GCC) regulatory review processes

Task	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Pricing procedure							
Parallel to the scientific review	✓	✓	×	×	×	✓	✓
After the scientific review	×	×	✓	✓	✓	×	×
After issuing the registration approval	×	×	×	×	×	×	×
Pricing decision	RC*	Minister	TCR&P*	Minister	Head of authority	Minister	TCR
Impacts the overall approval time	✓	✓	✓	✓	✓	✓	✓
Decision-making process							
Separate negotiation for product labeling/ information	×	×	✓	×	×	×	✓
Final approval decision maker	RC*	DRRS*	TCR&P*	RC*	Head of authority	HRC*	TCR
Time from reaching positive scientific opinion to final approval (days)	30- 90	<30	<30	30 -90	<30	30-90	>180
Overall approval time (days)	×	180	120	×	EAS: 165 NAS: 290	×	180-365

*RC= Registration Committee; DRRS= Drug Registration and Release Superintendent; TCR&P= Technical Committee for Registration of Pharmaceutical Manufacturers and their Products and Pricing of Products; HRC= Higher Registration Committee; TCR= Technical Committee for Registration

Decision-making stage

In general, most authorities do not perform separate negotiations about the product information or package insert after the scientific opinion is reached or prior to issuing the final approval, as any requirements are communicated to the company during the evaluation phase which must be fulfilled by the sponsor (Table 5.12). However, if there are points that require further clarification, they can be dealt with in official face-to-face meetings or by any other means of communication with the person in charge.

Bahrain, Qatar and UAE were not able to specify their target approval time as there are several factors involved in their judgments such as the types of products being registered (i.e. whether they are NASs, EASs, or therapeutically important or lifesaving products), the quality of the submitted dossiers and the level of follow-up and interaction between the pharmaceutical company and the authority. The other four authorities described in Table 5.12 showed slight differences in their overall target approval times with the shortest one in Oman being 120 days. The time taken from reaching a positive opinion by the scientific committee to the final approval decision varies considerably across the region taking less than 30 days in Kuwait, Oman and Saudi Arabia, less than 90 days in Bahrain, Qatar and Saudi Arabia, and over 180 days in Yemen. 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 authorisation time without any justifiable reason related to the quality of the overall submitted registration dossiers.

DISCUSSION

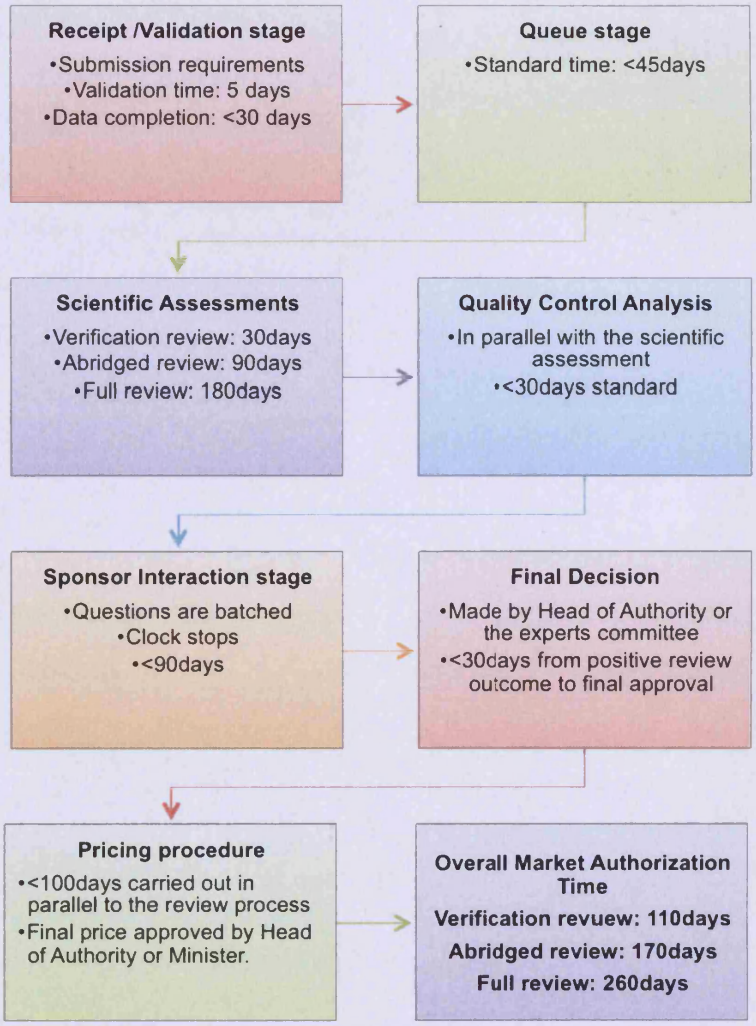
The rationale for this study was to gain a better understanding of the Gulf Cooperation Council (GCC) States regulatory review processes so that comparisons between these authorities can be made.

The study initially examined the regulatory review models which may have an impact on the approval timelines in each of the seven GCC States. Definitions of the types of assessment models were provided to the regulators to enable them to respond accurately to the relevant questions. Without these definitions, the authorities may perceive their assessments to be sufficiently detailed to be described as full review models. The findings of this study showed that four authorities use the verification model (Bahrain, Kuwait, Qatar and Yemen), three undertake the abridged model (Bahrain, Oman and UAE), and two use the full review model (UAE and Saudi Arabia). Bahrain performs a verification review on biological and biotech products because they are not accepted for review without being approved in countries with recognised regulatory authorities, while they perform an abridged review on all other applications. UAE uses a similar approach, but carries out an abridged review on biological and biotech products because they are only accepted for review if they are

registered in reference authorities while they perform a full review for all other major applications. A similar situation was highlighted in a study carried out in emerging markets which showed that Argentina routinely uses the verification review for new active substances and major line extensions (Walker et al., 2007 and McAuslane et al., 2009). However, the Argentinian authority currently has limited capacity to undertake the full assessment model for products which have not previously been registered in a competent agency. In Singapore, an abridged review model is used for most of its applications (Health Science Authority (HSA), 2008) This model saves times, effort, and resources by avoiding duplication of efforts made by recognised regulatory authorities. Therefore, the authorisation of a product in a benchmark agency is a prerequisite to the abridged model (McAuslane et al., 2009). However, the Singaporean Health Services Authority (HSA) is equipped with the resources and capabilities to perform a full evaluation of quality, nonclinical and clinical data for products which have not been approved in any other country (Foo, 2006).

A common ground for a standardised review process in the GCC Region was generated by identifying the stages shared by the GCC review processes and defining the most appropriate timeline for accomplishing each milestone efficiently and effectively (Figure 5.8). The receipt and validation process is the first contact between the sponsors and the regulatory authorities. Although Kuwait and Yemen have a slightly different approach for implementing the validation process, it is considered necessary by the other five GCC authorities and certainly by advanced regulatory authorities such as the United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA). Validation is an important checking point to ensure the correctness and completeness of the submitted data before entering the scientific assessment stage. However, it should not be a lengthy procedure and requires the use of an advanced information technology system (IT) and the appropriate human resources specifically to complete the validation task successfully in a timely manner. Online submission of registration dossiers is the future approach for the regulatory authorities worldwide to expedite the submission procedures.

Figure 5.8 The proposed standardised regulatory review process map for the Gulf Cooperation Council GCC regions



The following issues are considered to be fundamental requirements for the submission of a complete registration dossier,

- An online application form for pharmaceutical product registration
- The Certificate of Pharmaceutical Product (CPP) authenticated by the respective embassy or consulate general
- The status of the product applicant
- The good manufacturing practice (GMP) status
- The patent protection status
- Payment of the registration fees
- Appointment schedule to submit the locally acceptable format of the registration dossier

Saudi Food and Drug Authority (SFDA) is the first GCC authority to be able to process the electronic submission which is conducted by internationally recognised agencies. For these agencies, the accepted format for an electronic submission is the Common Technical Document (e-CTD) (Roth, 2008). 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 make better decisions (TGA, 2009). GCC authorities showed considerable differences between their validation times from one to 14 days. In addition, if the application is incomplete, time is also allocated for the sponsor to complete the missing data which ranges from 14 days to more than 365 days across the GCC States. The electronic submission minimises the risk of there being missing data while the authority's staff members ensure that the submitted dossiers are valid and accurate. However, the validation process should be performed in a reasonable time allowing for accurate checking of the submitted documents. By examining the current GCC validation times as described in Figure 5.8, it is possible to minimise steps that may cause unnecessary delays in the overall approval time. Therefore, five days should be allowed depending on the number of submissions and the availability of human resources.

Furthermore, due to the clarity and specificity of the submission requirements, the sponsor should be able to fulfill them in the minimal period of time and, therefore, a maximum of 30 days can be applied to allow sufficient time for the sponsor to complete or amend the submitted data (Figure 5.8). The overall receipt and validation stage should be carried out according to set guidelines and standard operating procedures (SOPs) as well as the availability of appropriate facilities and human resources to support the electronic submission and carry out the accurate and efficient validation process.

The queuing process is straightforward and allows proper handling of the received registration dossiers in an organised fashion. However, the lack of regular monitoring of queue time could lead to a backlog. Managing the priority review is another important issue that is recognised by all the GCC authorities 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 priority review. Therefore, appropriate human 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. It is suggested that 45 days should be the maximum queue time for standard reviews while fast-track/priority review products can be taken out of the queue as necessary. This allows for sufficient time to handle the pending dossiers by the authority's technical staff in an organised manner without negatively affecting the final approval time.

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 attention on providing the appropriate skill sets and the facilities as well as establishing appropriate guidelines, SOPs, training and continuing education programmes, and the electronic handling of the review process to implement the desired good review practices (GRPs) by the GCC authorities. External expert review is an important part of the review process which may be underestimated by many authorities because drug evaluation requires the collaboration of scientists in many different disciplines such as benefit-risk assessment, post-marketing surveillance studies, clinical evaluation, toxicological studies, and bioavailability and bioequivalence assessment. Kuwait, Oman and Saudi Arabia use external experts to provide recommendations, clinical opinions and/or technical advice to the authority without any contractual agreements on working within specific guidelines or deadlines set by the authorities. China performs an interesting external expert selection process whereby the internal reviewers evaluate all the applications first and if there are challenging issues based on preliminary review, internal reviewers organise an advisory committee meeting monthly to have a consulting discussion with selected temporary experts in the relevant areas before making the final approval decision. This has the advantage of ensuring the availability of experienced experts in the advisory committee and productive discussion during the meeting. In addition, during the review process, internal reviewers interact with external experts and drug developers to reduce the uncertainty about the drug's safety and effectiveness based on the submitted information (Lu and Huang, 2010). Having a committee of external experts in various scientific disciplines within the medicines safety and efficacy fields is a useful practice for most GCC authorities to support the internal review process which only pays attention to the pharmaceutical quality dossier and the quality control analysis of

pharmaceutical products. However, there should be a rational time limit for the scientific assessment process which includes the fundamental sections of the registration dossier assessed by internal and external reviewers namely, the quality, safety and efficacy sections.

The scientific assessment time is not determined in five GCC authorities. Oman and Saudi Arabia specified a time limit of 90 days and 180 to 245 days respectively. It is essential to have a target time for the scientific assessment and to monitor this in order to prevent delays that may impact the final approval time. In the United States Food and Drug Administration, (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. 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 rendered the agency to hire an additional 300 employees within five years with funds from user fees (Rehnquist, 2003).

The GCC sometimes perform in-depth scientific reviews although, in general, they carry out abridged or verification reviews. Therefore, it is suggested that 180 days be allocated for a full review of safety and efficacy while 90 days might be appropriate for an abridged review whereas 30 days should be adequate for a verification review. However, hiring sufficient experts, utilising suitable training and continuing educational programmes, establishing appropriate guidelines and the availability of facilities and information technology and resources to aid the review process requires adequate funding to achieve the desired objectives of the review process.

The sample analysis stage is a common practice and is performed either in parallel or sequentially with the scientific assessment in the GCC states. Even though no information was provided regarding the sample analysis timeline in the GCC authorities, there was a general agreement that it has a considerable impact on the overall approval time. However, having a time limit for the sample analysis stage can improve the handling of the analytical procedure to meet the target time with the

required quality control test results. 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 timely patient's access to the medicine (Figure 5.8).

After completing the scientific assessment and sample analysis procedures, the questions and queries should be collected into one batch to be sent to the sponsor. These questions, along with the scientific review reports from the external experts, internal reviewers, quality control (QC) laboratories, and the batched questions should be presented to the scientific committee which consists of experts from several scientific disciplines related to the drug regulatory and clinical fields.

Five authorities have scientific committees that evaluate the assessment reports and questions prior to communicating with the sponsor. This is a useful practice that should also be considered by Kuwait and Qatar because having a scientific committee has two main advantages, namely,

1. The variety of expertise in the scientific committee can provide the knowledge and recommendations on scientific issues of the product that may be overlooked by the internal reviewer.
2. Committee members are not individually held accountable for its level of performance or decision-making as all the members make decisions collectively that ultimately affect patients' health.

Since some GCC authorities use external experts under no contractual agreements, creating a temporary working committee of several external experts, which are typically dissolved after issuing the recommendations, to review the scientific reports and make recommendations to the decision-maker in each authority, would be a suitable option. This approach is carried out by the Chinese authority where external experts in each advisory committee meeting are selected from a database based on specific fields related to the issues for discussion (Lu and Huang, 2010)

Clock stop is another important approach which is not fully enforced in the GCC authorities but practiced in Kuwait, Oman, Qatar and Saudi Arabia to control the overall approval time. EMA is obliged by its regulations to reach a decision within 210 days, though the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data (EMA, 2009). This compares well with the average of 320 days taken by the US FDA (Patel et al., 2010). However, the approval time in FDA includes the sponsor's response time (Thaul, 2008). The US FDA stated that clock

stop for a fixed period of time would offer the sponsor an opportunity to respond to the drug regulatory letters while protecting the remaining clock time for FDA reviewers to complete the review process (US FDA, 2010b). In China, the clock stops when the Center for Drug Evaluation issues an action paper (e.g., approval, recommendation, or refusal). If the Center for Drug Evaluation requests more data to demonstrate the safety and efficacy of the new drug, it has 15 days to review supplemental data for fast and accelerated reviews and 4 months for standard reviews (Deng and Kaitin, 2004). Therefore, the sponsor's response time of 90 days is a suitable practice to be performed by the GCC authorities applying the clock stop approach to oblige the sponsor to meet the deadline and to allow more time for the reviewers to complete the assessment of the submitted data.

Although the pricing process has a significant impact on patient's access time to medicines, it is considered a separate procedure from the review process. Advanced regulatory authorities have independent committees or units for the pricing of medicines. In Health Canada, for example, a specialised Medicines Pricing Board is responsible to monitor and report the prices of NASs and EASs in Canada (Health Canada, 2006). This approach prevents the pricing step from being integrated into the review process and causing delays to the final approval time. Prior to 2009, Kuwait used to start the pricing procedure after the official registration of the product was finalised. However, the Director of the authority changed this approach to carry out the pricing procedure in parallel with the review process to minimise the time delay for patients' access to the new medicine. The proposed time of 100 days allows sufficient time to complete the pricing step during the review process (Figure 5.8).

Another approach which may be underestimated by the GCC authorities, is the cost-effectiveness of the medicines which are intended to show the relationship between resources used (costs) and the health benefits achieved (effects) for a medicine (Neumann and Johannesson, 1994). Differential pricing is an effective approach to applying an affordable price for the medicines in the GCC States but it does not value the health outcomes of the new medicine. Therefore, cost-effective analysis is an approach that might be included in the pricing process in the GCC States. Currently the GCC authorities only perform comparative price assessment with each other and with other countries such as Algeria, Lebanon, Egypt, Belgium, Germany and Switzerland in order to ensure that medicines are affordable for the local patients. This

process may currently be the available choice due to the lack of expertise in the Health Technology Assessment (HTA) field. However, the GCC authorities may not continue to avoid the importance of value-based pricing of medicines and will need to consider obtaining experts in this area to improve the criteria for determining the availability of affordable medicines in the region. Expertise in the HTA field can be obtained from collaborating with competent authorities to conduct training programmes for assessors as well as encouraging the pursuance of academic research projects in this field. Cost-effective analysis of medicines, however, requires a set of guidelines and allocated resources in addition to the appropriate expertise. This may take a long period of time and, therefore, the current comparative pricing process is preferably carried out in parallel to the review process and then a separate and fully equipped department may need to be established to conduct cost-effective analysis of medicines in the future.

After setting all the conditions, the senior management will be capable of making the final decision about the medicine according to several factors, namely,

- The complete electronic submission of the registration dossier
- The scientific committee's recommendations, where the external experts provide their clinical, technical and scientific opinions about the safety and efficacy of the product.
- The internal pharmaceutical quality review report which addresses the Chemistry and Manufacturing Control (CMC) data from the registration dossier.
- The outcome of the sample analysis to ensure that the product has the desired quality to be administered to local patients.
- The cost-effectiveness of a medicine to aid appropriate decision-making of the value of the medicine being registered

Once the decision-makers have the complete and accurate information about the medicine, it is possible to make the final approval decision with confidence that the registered medicine will be safe, effective, valuable and of the desired quality to local patients in the seven GCC States.

According to the proposed standardised GCC regulatory review process illustrated in Figure 4, an overall target approval time of 110 days for a verification review, 170 days for an abridged review and 260 days for a full review were suggested. These timelines may be considered challenging when compared with the target approval

times of 180 days in Kuwait which conducts a verification review, 170 days in Oman which conducts an abridged review and 260days in Saudi Arabia which conducts a full review. Therefore, it is suggested that the authorities should adjust their assessment processes according to the type of product and the model of review(s) being conducted.

The GCC Central Drug Registration (GCC-DR) aims at standardising the registration processes of pharmaceutical products in the Gulf Region. This is implemented by focusing on the collaborative efforts between the seven member states to ensure the availability of safe and effective medicines in the region. This standardisation process is considered to be the GCC's platform for exchange of knowledge, skills and best practices on the assessment of pharmaceutical products. Therefore, in order for the GCC centralised process to be successful, the Gulf States should optimise the use of their resources to increase the level of their expertise and improve the standard of their review practices. The future GCC-DR system should be able to comprise seven GCC regulatory authorities capable of performing an abridged review for the pharmaceutical products in order to standardise their models of assessment, increase the trust and confidence between each other, conserve the regional resources by reducing duplication of efforts made by reference agencies, and perform an independent review of the product in terms of its use in the GCC regional conditions.

SUMMARY

- Three assessment models are conducted in the GCC region. Kuwait and Yemen perform the verification review, Bahrain, Oman and Qatar carry out an abridged review while Saudi Arabia and UAE conduct a full review for the majority of their applications.
- The GCC regulatory authorities share common regulatory review practices that are critical in the establishment of a standardised review process for the GCC region.
- The differences identified in the seven review processes were mainly due to the order of the steps carried out or the time spent in carrying out a certain procedure.
- 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.
- The GCC authorities should consider setting guidelines and increasing resources to achieve the desired standard of the regulatory review practices in the region.

CHAPTER 6

A Critical Evaluation of the Quality Measures in the Gulf Cooperation Council (GCC) Regulatory Review Systems

INTRODUCTION

Drug regulatory authorities are constantly challenged to develop and improve their capacity to regulate pharmaceutical products. Therefore, it is critical to develop regulations based on two broad objectives: 1) to provide technical assistance in establishing and implementing effective strategies for monitoring quality and correcting deficiencies (Brown et al, 1998), and 2) to refine existing methods to ensure optimal regulatory services through an applied quality management programme. The regulations must be broad enough to address all the essential issues, but flexible enough to be applied to specific problems.

In the world of medicines regulations, the term 'quality' is associated with data on the pharmaceutical characteristics of the medicinal product and the processes for chemical and manufacturing control (CMC). Increasingly, however, the term 'quality' is also being used in discussions of the drug regulatory process itself. It is not enough to measure regulatory performance in terms of timelines and the speed of the review process alone. The quality of the process, from the construction of the dossier to the ultimate regulatory decision must also be monitored and added to the equation (McAuslane et al., 2006b).

Past attempts to compare review processes of different regulatory authorities have been hampered by insufficient public information, together with the complexity of the processes themselves. Even though, for some authorities, a review performance is becoming more transparent, the lack of uniformity between countries puts considerable limitations on the interpretation of different review times (CMR R&D Briefing 11, 1997). Different pressures on regulatory authorities from the general public for rapid access to new medicines have led health authorities world-wide to seek new measures for improving their own review processes. However, regulatory authorities are faced with the responsibility of reducing review timelines as well as maintaining the quality of the review procedures. To achieve this aim, the regulatory authorities should have a legal basis for all its functions, sufficient human and financial resources, access to appropriate scientific expertise, and to a quality control laboratory. However, different regulators have different definitions of 'quality', but they all agree that the term is defined in the light of the provider's standards and patient's expectations. The quality of the review process stems from the quality of care

provided to the public and the degree of quality is the extent to which the care provided is expected to achieve the most favourable balance of benefits and risks (Donabedian, 2005; Brown et al., 1998).

In order to assess the quality of the review process conducted in the GCC authorities, a clear understanding of the current situation, an identification of the practices and standards, the level of expertise and technical support as well as the accessibility to procedures and information within the authorities are essential. Therefore, the regulatory functions involved in the review procedures were examined and a comparative view of the quality measures were established to produce a valuable insight into aspects of the Good Review Practices (GRPs) in the GCC authorities.

OBJECTIVES

The objectives of this study were to,

1. Assess how each GCC regulatory authority is building quality into the assessment and registration process

2. Compare and contrast the measures used to build quality into the review processes and to establish opportunities for exchange of better practices amongst the GCC regulatory authorities

4. Identify drivers and barriers to carrying out a quality review of medicines and to make them available to meet patients' needs

METHODS

Study Participants

The seven GCC regulatory authorities were asked to participate in this study (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE), and Yemen) and a 100% response rate was achieved. The questionnaire was sent out in March 2010 and the feedback was finalised by June 2010. The GCC countries have the unique advantage of sharing similar economies and culture, the same language, similar historical background and political characteristics. This advantage is the main factor that plays a prominent role in the success of the GCC central drug registration (GCC-DR) system. Therefore, the GCC regulatory authorities, being in their developing

stage, were chosen for comparison and to achieve standardisation on the basis of these similarities; unlike the systems of the mature agencies such as the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), Health Canada, and Australia's Therapeutic Goods Administration (TGA) which are advanced and complex and differ significantly from one country to another.

Data Collection Procedure

A questionnaire was designed which enabled details of the regulatory process to be determined (Appendix A). A face-to-face meeting with the senior managers from the region took place in Kuwait in March 2010. The aim of the meeting was to introduce the participating authorities to the research goals and objectives and to provide an overview of the contents of the questionnaire used to collect the data required for this study. All authorities were able to complete the questionnaire on time and the data were then standardised into a word document for the purpose of comparison. The reports that were generated were sent to the authorities for auditing, correction and comment by July 2010. By the end of this month, the participating authorities were contacted by email to confirm the accuracy of the information contained in the reports provided. Unclear questions or areas with respect to the questionnaires were discussed and clarified by phone and/or email.

The questionnaire was previously utilised to analyse the regulatory environment in a number of emerging markets (McAuslane et al., 2009). However, a series of consultations with senior managers in each of the above regulatory authorities were carried out and the questions were carefully revised and assessed to ensure that they were appropriate for the current status of the GCC regulatory authorities. The final questionnaire examined the activities that contribute to the quality of the decision-making process and measures adopted to improve consistency, transparency, timelines and competency in the review processes.

The questionnaire was piloted with two GCC authorities, Kuwait and Saudi Arabia, along with obtaining consultations from the senior managers in the region. The advice provided by the GCC experts was used to make amendments to the questionnaire so that it would suit the local regulatory status in the region. Elements of the activities used to measure and assess quality in the regulatory review process were, therefore, determined and utilised for the benefit of this study accordingly.

The questionnaire consists of six sections (general measures used to achieve quality, quality management tools, communication as an element of quality, training and continuing education as an element of quality, transparency of the review procedure and the drivers and barriers to achieving a quality review process) each with its own instructions and explanations. Moreover, open-ended and close-ended questions were used in the questionnaire and the study participants were able to provide detailed explanations to clarify points related to the questions. All sections are focused on evaluating different aspects of the quality measures used in the regulatory review process in each GCC regulatory authority.

Section One: General measures used to achieve quality

This information allowed a comparison of quality measures used officially across the seven GCC authorities. The regulatory authorities are continuously developing and implementing a variety of measures to improve quality standards and to meet the expectations of the industry and the general public. Therefore, it was critical to assess the quality measures currently in place within each GCC regulatory authority and, where none, their plans to introduce such measures in the foreseeable future. A list of the assessed quality measures with their definitions are given in Table 6.1.

Table 6.1 The general measures used to achieve a quality review process

Quality Measure	Definition
Quality Policy	Overall intentions and direction of an organisation related to quality as formally expressed by top management.
Good Review Practice (GRP)	A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports
Standard Operating Procedures (SOPs)	Written documents that describe in detail the routine procedures to be followed for a specific operation.
Assessment Templates	Set out the content and format of written reports on scientific reviews.
Peer Review	An additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during assessment of a dossier or at the time of sign-off.
Shared and Joint Review	A shared review is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A joint review is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken such as the GCC system.

Section Two: Quality Management Tools

Quality management tools can be considered to have two main components: quality assurance and quality improvement. Quality management is focused not only on product/service quality, but also the means to achieve it. It uses quality assurance and control of processes as well as products/services to achieve more consistent quality. In the context of this study, means for assuring and improving a quality in the review process were assessed, namely, the quality audit and feedback, the scientific committee review, and the existence of the quality assurance (QA) infrastructure.

Section Three: Communication as an element of quality

This section assessed practices used to ensure quality in the review process using the element of effective communication between the authority and the applicant in order to exchange critical information and official guidelines to assist the industry in the registration of medicines. Furthermore, the level of interaction with the applicants during the assessment of the registration dossier was examined to understand its impact on the efficiency and effectiveness of the decision-making in each authority.

Section Four: Training and continuing professional development (CPD) as an element of quality

This section was related to the training and continuing education of assessors working within the authority, including those employed on a full-time basis and those contracted for specific assessments where necessary.

Furthermore, it assessed whether the training was followed by an examination once it was completed. The level of cooperation and collaboration between the GCC authorities and other authorities in the training and/or CPD programmes for reviewers was evaluated and whether external speakers were invited to provide informative lectures to the reviewers within the authorities.

Section Five: Transparency of the review procedure

This section examined 'transparency' in terms of the ability and willingness of the authorities to assign time and resources to providing information on its activities to both the public (which includes health professionals) and the industry. Transparency was measured in terms of the level of information made available and how important

the authorities believe that increased transparency is to determine the quality of the review processes.

Section Six: Drivers and barriers

The purpose of this section was to identify the most common reasons for introducing quality measures as viewed by each participating authority as well as to understand the unique positive qualities and the major impediments they are facing in carrying out the review of new medicines to making them available to meet patients' needs. Each authority was asked to provide three factors that make a major contribution to the effectiveness and efficiency of its review procedures and decision-making processes and three factors that act as barriers to making new medicines available in a timely manner through their regulatory process.

RESULTS

Questionnaire response rate

All the regulatory authorities in the seven GCC states (100%) agreed to participate in the study and completed the questionnaire. For some questions, additional explanations were provided by the authorities. The responses obtained from the senior managers in each of the seven authorities represent their experiences during the year of this study (2010). However, variations can occur in practice due to continuous changes in the regulatory systems in the GCC Region.

General Measures used to Achieve Quality

Six quality measures were considered critical in the evaluation of the regulatory review process in the GCC states, namely, joint and shared review (JR/SR), peer review (external and internal), assessment templates, standard operating procedures (SOPs), Good Review Practice (GRP), and a Quality Policy (QP). The GCC authorities completed all the questions and, where questions were not applicable, no response was provided. However, the answers received were sufficient to provide the required information for the study. Furthermore, the respondents had the opportunity to express their comments and viewpoints in more detail for each question.

The measures currently used by each GCC regulatory authority to achieve quality in the review process are shown in Table 6.2. The results indicated that a joint review is the only quality measure shared by all seven GCC authorities. It is a practice that is

performed by all the authorities for the GCC central drug registration (GCC-DR) system, where a dossier is reviewed by each authority and the outcome is discussed in a conference meeting after which the decision is made by consensus. The other quality measures are practiced in some authorities while other authorities have plans to implement them in the future.

Table 6.2 Current measures used to achieve quality in the Gulf Cooperation Council (GCC) review processes

Quality measure	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Quality policy	✓	✓	×	×	×	✓	✓
Good Review Practice (GRP)	✓	×	×	×	×	×	×
Standard Operating Procedures (SOPs)	✓	×	✓	✓	×	✓	×
Assessment Templates	✓	✓	×	×	✓	✓	✓
Internal Peer Reviews	✓	×	✓	×	✓	✓	✓
External Peer Reviews	×	×	✓	×	×	✓	×
Shared/Joint Reviews	✓	✓	✓	✓	✓	✓	✓

Quality Policy

This is the overall intentions and direction of an organisation related to quality as formally expressed by top management. It aims at improving the performance of the reviewers, and the activities involved focus entirely on the term "quality" of the review process. To establish whether the review process is acceptable and the registration procedure fulfils the desired quality standard, a quality policy must be decided by the top management for the achievement of satisfactory results. Four out of seven authorities stated that they have quality policies (Bahrain, Kuwait, UAE, and Yemen) whereas the other three authorities are planning to introduce them in the foreseeable future (Table 6.2)

Good Review Practice (GRP)

The seven authorities were asked whether they implement a GRP system. GRP was defined as a code about the process and documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness predictability, consistency and high quality reviews and review reports (Table 6.1). Unfortunately, only Bahrain stated that they implement the GRP system. Kuwait explained that the Ministerial Decree 302/80 is being used as an appropriate guidance for both assessors and the industry through the scientific assessment process. However, Kuwait, as well as the other GCC states, is planning to implement the full GRP system in the future. GRP has been introduced in all well-established authorities, for example, Canada initiated it in 2004 while it has been conducted for more than a decade by the US FDA (Health Canada, 2008b; Garrett, 2009) (Table 6.2).

Standard Operating Procedures (SOPs)

This measure is defined as the formal documents that clearly and accurately describes how an individual or organisation should be performing a certain task. A standard operating procedure (SOP) is a compulsory document which describes the regularly recurring operations relevant to the quality of the investigation. The purpose of SOPs is to carry out the procedures correctly and always in the same manner and should be available at the place where the work is done.

In the GCC States, four out of seven countries use SOPs for the guidance of scientific reviewers (Bahrain, Oman, Qatar, and UAE) whereas the other three expressed their intentions to implement this quality measure in the near future (Table 6.2).

Assessment templates

Five out of seven authorities in the GCC region use assessment templates for reports on the scientific review of a New Active Substance (NAS) and an Existing Active Substance (EAS) (Bahrain, Kuwait, Saudi Arabia, UAE and Yemen). These templates are an important quality measure that set out the content and the format of the written scientific assessment reports. Oman and Qatar indicated that they intend to introduce assessment templates in the near future (Table 6.2).

Peer review

Peer review is an additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during the assessment of a dossier or at the time of sign-off. It can occur internally at different levels within an authority which can help to build quality into the review process. Five out of seven authorities stated that they perform internal peer reviews (Bahrain, Oman, Saudi Arabia, UAE and Yemen) through their established scientific committee that evaluates the reviewer's assessment reports, while only two authorities (Oman and UAE) stated that they also carry out external peer reviews to ensure that the registration dossier is of the desired quality. Kuwait and Qatar do not perform peer reviews in any shape or form and the review is totally dependent on the qualification and experience of the reviewer. However, Qatar has a registration committee that makes the final approval decision should the assessment report shows positive outcomes. In Kuwait, the drug registration and release superintendent (DRRS) reviews the scientific report made by the assessor and makes the final decision.

Shared/joint reviews

All the GCC authorities stated that they conduct joint reviews as part of the GCC central drug registration (GCC-DR) system. A Joint review was described as a procedure where the whole dossier is reviewed by each authority and the outcome is discussed before the decision is taken by agreement between the seven states. The GCC States took this initiative from the European centralised procedure where joint reviews of the registration dossier is carried out by the EU member states. In a shared review, however, each authority takes responsibility for reviewing a separate part of the dossier. This is not applicable in the GCC regulatory system. A shared review is conducted internally within different divisions of the State Food and Drug Administration in China (Deng and Kaitin, 2004). Shared reviews are rarely carried out in well-established authorities. However, Memorandums of understanding have recently been signed between the TGA, SwissMedic, Health Canada, and Health Science Authority (HSA) in Singapore in order to facilitate the opportunity for these four agencies to carry out shared and joint reviews (Health Science Authority (HAS), 2010).

Quality Management Tools

Quality audits and Feedback

When the GCC authorities were asked about activities they are undertaking to achieve continuous improvement in the assessment and registration process, two responses were provided by the GCC authorities, namely, reviewing the assessor's feedback (Bahrain, Kuwait, Qatar, Saudi Arabia UAE and Yemen) and the stakeholder's feedback (Bahrain, Kuwait Oman, Qatar and Saudi Arabia) to take the necessary action accordingly (Table 6.3).

Table 6.3 Quality audit and feedback activities carried out to improve the quality of the assessment and registration process in the Gulf Cooperation Council (GCC) States

Activities that bring improvement in the review process	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Reviewing assessors' feedback and taking necessary action	✓	✓	×	✓	✓	✓	✓
Reviewing stakeholders feedback and taking necessary action	✓	✓	✓	✓	✓	×	×
Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy)	✓	✓	✓	×	✓	×	×
Carrying out internal audits and using findings to improve the system	✓	×	✓	✓	✓	×	×
Having external quality audits by an accredited certification body to improve the system	×	×	✓	×	×	×	×
Having a 'post-approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments.	✓	✓	×	×	×	✓	×

Four authorities have an internal tracking system to monitor the quality of the review process (Bahrain, Kuwait, Oman and Saudi Arabia). However, in general, the GCC authorities lack the appropriate electronic tracking system that monitor the impact of

each of the review milestones and the activities performed with these milestones on the overall approval time. Furthermore, the study showed that four authorities carry out internal audits (Bahrain, Oman, Qatar and Saudi Arabia). However, the logistics behind conducting such audits are questionable. Some regulators view an internal audits as reassessing the review by a senior assessor to ensure that it is of the required quality standard while others view it as an independent activity performed by a separate section/unit on different departments or processes (Table 6.3).

External audits can be carried out by accredited certification bodies such as the International Organisation for Standardisation (ISO), the European Foundation for Quality Management (EFQM) or by WHO audits. Unfortunately, Oman was the only authority that engages in external auditing by accredited certification bodies to improve the quality of its registration process. External audits are essential to provide an objective opinion on the quality of the review process, discover errors that may be overlooked by the internal reviewers and educate regulators on the importance of the current regulatory issues that need to be considered in the process of improving the quality of the assessment and decision-making process.

Post-approval feedback is another important practice to provide the sponsor with an opportunity to improve the quality of the submitted data after issuing the registration approval of a medicinal product. On the other hand, the authority will also benefit from the objective pre-approval discussion about issues that could impact the consistency, accuracy, transparency and timeliness of the approval process. This exchange of constructive feedback between the two stakeholders can have a significant impact on the quality of the review and decision-making outcomes.

Quality assurance Infrastructure

Finally, when the authorities were asked whether they have dedicated departments or units for the quality assurance of the assessment and registration process, only Kuwait and Yemen stated that they have one each. Kuwait has a small unit consisting of two pharmacists. However, the unit is does not yet officially exist in the current organisational structure of the authority and its functions are not fully regulated or enforced.

UAE stated that the quality assurance department does not exist for the assessment and registration process but it does exist as an independent department reporting to the CEO of the Medical Practices and Licensing, to which the Registration and Drug Control Department reports. Nevertheless, their work has not been fully implemented yet.

Scientific Committee procedure

The study also examined the existence of committees and their associated procedures involved in the review process. Committees are a necessary aspect of organisations of any significant size (say, more than 15 or 20 people) and they are a way to formally draw together people of relevant expertise from different parts of an organisation who otherwise would not have an appropriate way to share information and coordinate actions.

They may have the advantage of widening viewpoints and sharing responsibilities. They can also be supported with experts to recommend actions in matters that require specialised knowledge or technical judgment. After assessing the committee's procedures as an element to improve the quality of the registration of medicines in each authority, it was found that Kuwait and Qatar do not have scientific committees that are integrated into the their assessment procedure and therefore they were not included in this part of the assessment (Table 6.4).

However, Qatar does have a registration committee that makes the final approval decision. In four authorities (Saudi Arabia, Yemen, Oman and Bahrain), the committees are responsible for assessing the applications and making the final approval decision. However, in UAE, separate scientific committees exist for each area e.g. stability, quality control, GMP, bioequivalence studies, minor variations and internal peer reviews, and external screening committee. All reports of the scientific committees are then discussed in the higher registration committee after the scientific committees have given their opinions and the higher registration committee then makes the final approval decision.

Table 6.4 Description of the scientific committees in five Gulf Cooperation Council (GCC) authorities

Description	Bahrain	Oman	Saudi Arabia	UAE	Yemen
Committee	RC*	TCR&P*	SAC*	SC*+HRC*	TCR*
Meeting frequency	Once a month	Every 2weeks	Once a week	Every 2months	Once a week
Number of members	8	8	19	Average 5	14
Committee reviews all applications (NASs/EASs)	×	✓	✓	✓	✓
Committee reviews selected applications (NASs/EASs)	✓	×	×	×	×
Committee review complete dossier	×	×	✓	×	✓
Committee reviews assessment reports from reviewers	✓	✓	×	✓	×
Committee makes the final approval decision	✓	✓	✓	×	✓

*RC= Registration Committee; TCR&P= Technical Committee for Registration of Pharmaceutical Companies and their Products and Pricing; SAC= Scientific Advisory Committee; SC= Scientific Committee; HRC= Higher Registration Committee; TCR= Technical Committee for Registration

Information Technology (IT) infrastructure

Finally, the study showed that Saudi Arabia is the only authority that is placing considerable effort on applying electronic system to improve the quality of the review process such as e-CTD and electronic tracking systems. Companies are able to access the status of the applications in SFDA electronically to find out the stage of the registration procedure of their product. Four authorities (Oman, Saudi Arabia, UAE and Yemen) stated that they have an electronic system for registering and tracing applications (Table 6.5).

Table 6.5 Electronic facilities for registering and tracking applications in the Gulf Cooperation Council (GCC) States

Electronic facilities	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Electronic system for registering and tracking application available	×	×	✓	×	✓	✓	✓
Tracking application that are under review and identifying the stage in the process	×	×	✓	×	✓	✓	✓
Signalling that target review dates have been exceeded	×	×	✓	×	✓	×	×
Recording the terms of the authorisation once granted	×	×	✓	×	✓	✓	✓
Archiving information on applications in a way that can be searched	×	×	✓	×	✓	✓	✓

The most prevalent electronic facilities shared by the four authorities were found to be,

1. An electronic system for registering and tracking applications
2. Tracing applications that are under review and identifying the stage in the process
3. Recording the terms of the authorisation once granted
4. Archiving information on applications in a way that can be searched

Even though these facilities are available, the level of advancement of the system can differ between the four authorities particularly compared to the advanced system in the SFDA. Only two authorities (Saudi Arabia and Oman) have an electronic system to signal delays in the review process, which is an important tool to help the authorities control and monitor the approval timeline for pharmaceutical products.

Communication as an element of quality

The most prevalent method for providing official information and guidelines to assist the industry in the registration of medicinal products is 'on request'. UAE provides the guidelines in the customer service desk, as they are available during official office hours on purchase basis. Three authorities (Oman, Saudi Arabia and Yemen) provide

official guidelines through the official authority's website which is the most convenient method for the companies (Table 6.6). Four authorities (Kuwait, Qatar, UAE and Yement) provide information and guidelines to the industry on request. Bahrain, Kuwait and UAE provide pre-submission advice to the sponsor and applicants can receive details of the technical staff in Bahrain, UAE and Yemen to be contacted to discuss the registration requirements during the review process.

The level of contact that the pharmaceutical companies have with the authority staff during the assessment process was evaluated. In general, formal contact through scheduled meetings and official letters as well as informal contacts through telephone, email, or fax occur between the sponsors and the authorities were observed (Table 6.6).

Table 6.6 The interactive relationship between the sponsor and the Gulf Cooperation Council (GCC) regulatory authorities

Methods of communicating regulatory information and guidelines to the industry	**Bahrain**	**Kuwait**	**Oman**	**Qatar**	**Saudi Arabia**	**UAE**	**Yemen**
Through the authority's official website	×	×	✓	×	✓	×	✓
On-request	×	✓	×	✓	×	✓	✓
Through official publications	✓	×	×	×	×	✓	×
Pre-submission advice is provided	✓	✓	×	×	×	✓	×
Applicant receives details of the technical staff that can be contacted to discuss the application during the review process	✓	×	×	×	×	✓	✓
Level of contact with the authority's staff during the review process							
Extensive formal contact (including scheduled meetings)	✓	✓	×	×	×	✓	×
Extensive informal contact (frequent telephone or email contacts)	✓	×	×	×	×	✓	×
Some formal contact (possibly of meetings)	×	×	×	✓	✓	×	✓
Some informal contact (possibly of telephone or email contacts)	×	×	✓	✓	✓	×	×

It may be an extensive form of contact as in Bahrain, Kuwait and UAE or less extensive as in Oman, Saudi Arabia, Qatar and Yemen. The importance of keeping the lines of communication between the two parties cannot be overemphasised, and a successful and timely completion of the review process largely depends on the degree and quality of the communication between the parties. This communication is particularly useful when pre-submission advice is required by the sponsor to have a better understanding of the registration system and the associated requirements to approve their pharmaceutical product. This occurs in Bahrain, Kuwait and UAE. Furthermore, a rational practice to enhance the communication is when it is allowed to occur between the pharmaceutical company and the authority's internal staff. This practice is carried out in Bahrain, UAE and Yemen. However, the other authorities apply restrictions to such practices to prevent the culture of corruption from creeping into the system.

Training and Continuing Education as an element of quality

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 specialised training in the carrying out a quality review process. Such training can be given within the authority, by external specialists, or external courses can be attended, if necessary abroad. In certain cases it may be worthwhile to second someone to another authority for a certain period to get in-service training and experience in a different regulatory culture.

Ideally, 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 in existing procedures or adoption of new practices to improve the overall performance of the reviewing staff. Tests to assess the proficiency of the reviewer are another ideal method to ensure that the required knowledge and skills have been successfully absorbed by the reviewer.

Training and continually educating the reviewers in the GCC regulatory authorities is essential to ensure the work is carried out in a professional manner. The internal reviewer in the GCC authorities has to be a pharmacist, but the question arises as to whether this pharmacist receives the proper training to be a qualified regulatory assessor. This section evaluates the element of training and continuing education in

the quality of the review process in the GCC Region. Only Saudi Arabia and UAE specified that they conduct formal training for the assessors. Other authorities do not have formal training or continuing education programmes but they do conduct other educational methods for the assessors (Table 6.7).

Table 6.7 Training and continuing professional development in the Gulf Cooperation Council (GCC) regulatory authorities

Methods for training assessors	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Induction training	✓	✓	×	✓	✓	×	×
On-the-job training	✓	×	×	✓	✓	✓	×
In-house training	✓	×	×	×	✓	✓	×
External speakers invited	✓	×	×	×	✓	✓	✓
External courses	✓	×	✓	×	✓	✓	✓
Post-graduate degrees	✓	✓	✓	×	✓	×	×
Participation in international conferences/workshops	✓	✓	✓	✓	✓	✓	✓
Placements and secondments in other regulatory authorities	✓	×	×	×	×	×	×
Tests performed after completion of training	×	Partly	×	Partly	×	×	×
Training is required for professional advancement	Partly	×	×	✓	×	✓	✓
Collaboration with international agencies in the training for assessors	WHO	×	WHO	WHO	WHO, World Bank, TGA	WHO	×

All the GCC authorities participate in international conferences and workshops. Attending such events is considered important to remain updated with the latest developments in the drug regulatory field around the world. Other forms of training are shared by some GCC authorities but none of the authorities focused on examining the knowledge of the trainees after completing the training programme because training is not a compulsory practice for internal and external reviewers nor for any member of their respective committees.

The seven authorities stated various forms of training conducted throughout the GCC Region. Bahrain stated that they conduct all types of training assessed by this study,

including attending external courses, placements and secondments in other regulatory agencies and inviting speakers in the authority. However, the relevance of these training programmes to the review procedure and the reviewing staff is not clear. Most of the GCC authorities believe that they have continuing education programmes but these programmes are not necessarily focused on the review process. Saudi Arabia is believed to be the first country to take a positive initiative towards properly training the reviewers in the new Saudi Food and Drug Authority (SFDA).

Post-graduate degrees are encouraged in Bahrain, Kuwait, Oman and Saudi Arabia through government scholarships to developed countries with the aim of optimising the quality of the regulatory systems. Four authorities (Bahrain, UAE, Yemen and Saudi Arabia) invite speakers to the authorities to present their knowledge and expertise to the internal reviewers. Nevertheless, in all cases, questions are raised as to whether training conducted in any authority is focused on reviewers or decision makers, or both.

Collaboration with other agencies in the training of assessors is performed by five authorities (Table 6.7). Kuwait stated that they are fully dependent on the opportunistic training programmes provided by the Ministry of Health in collaboration with international agencies e.g. WHO to all healthcare professional which rarely, if any, include training programmes for regulatory reviewers. Yemen is also lacking such a practice, probably due to financial resources to participate in educational programmes provided by international agencies. The other five GCC authorities specified their collaboration with WHO in training their reviewers, with SFDA also cooperating with the World Bank and TGA (Table 6.7). Collaboration with international authorities is an essential tool for the GCC authorities to be able to prosper and remain competitive; growing along with the global advancement of international competent regulatory systems.

Transparency of the review process

Transparency is an important element to ensure that the review process is heading towards the desired direction and producing the quality standards that are acceptable to both the authority and other regulatory stakeholders (Figure 6.8).

Table 6.8 Transparency as an element of quality in the Gulf Cooperation Council (GCC) regulatory review procedure

Level of priority assigned to transparency	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
High	✓	×	✓	✓	✓	✓	✓
Medium	×	✓	×	×	×	×	×
Low	×	×	×	×	×	×	×
Incentives for establishing transparency							
Political will	✓	✓	✓	×	✓	✓	×
Press and media attention	×	✓	×	✓	✓	×	×
Public pressure	×	✓	×	✓	×	×	×
Better staff moral and performance	✓	×	×	✓	✓	✓	✓
Need to provide assurance on safety safeguards	×	×	✓	×	✓	×	✓
Need to increase confidence in the system	✓	×	✓	×	✓	×	✓
Detailed reasons for rejection of an application is given to the company	✓	×	✓	✓	✓	✓	×

All the authorities believe that transparency is essential in their relationships with the public, professionals and the industry. However, Kuwait was the only country that assigned medium priority to transparency. Since each authority needs to establish a level of transparency to the public, media and the industry, it was deemed critical to assess the authorities' drivers for assigning resources to activities that enhance the openness of the regulatory system (Table 6.8). It was found that no one incentive was shared by all seven GCC States and that the three most prevalent incentives in the GCC region were:

1. Political will
2. Better staff moral and performance
3. Need to increase the confidence in the system

The availability of information to the general public on the performance of the regulatory authority was explored in each GCC State. It was found that six authorities provide information about the approved products to the public, health professionals and the industry (Table 6.9).

Table 6.9 The level of transparency assigned to provide information to the public in the seven Gulf Cooperation Council (GCC) States

Information available to the public	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Approval of products	✓	✓	✓	×	✓	✓	✓
Approval times	×	×	×	×	✓	×	×
Summary of the grounds on which the approval was granted	×	×	×	×	×	×	✓
Product price	×	✓	×	×	✓	×	×
Information is available							
Through official journals/periodical publications	×	✓	×	×	✓	✓	×
On-request	✓	✓	✓	×	×	✓	✓
From official internet website	✓	×	✓	×	✓	×	×
Methods of self-tracking the progress of applications							
Electronic access to the status of application	×	×	×	×	✓	×	×
Email contact	✓	✓	×	×	×	✓	×
Telephone contact	×	✓	×	×	✓	✓	×
Formal meeting with the person in charge	✓	✓	✓	✓	✓	✓	✓

Any information can generally be obtained on request, or from the authority's official website or from official journals and periodical publications in some countries. However, the most prevalent method of providing information to the public about the registration and assessment of pharmaceutical products was found to be 'on request', which is specified by five out of seven authorities.

Pharmaceutical companies are able to track the progress of their own applications in the GCC States (Table 6.9). The most common method shared by the seven authorities is a formal meeting with the head of section. Even though email and telephone contacts are internationally recognised as official methods of communication between companies and authorities, they are only stated by three out of seven GCC authorities as official mechanisms of application follow-ups for pharmaceutical companies. Saudi Arabia is the only authority that allows electronic access to studies of the application. However, it is believed that telephone and email contacts are the most efficient tracking methods available for companies in the GCC States and companies are always using them more than other methods of contact.

An important tool for a transparent regulatory system is the availability of a website. Six GCC regulatory authorities stated that they have websites (Bahrain, Oman, Qatar, Saudi Arabia, UAE and Yemen). In general, Bahrain, Oman and Yemen provide information on product approvals and guidelines to the pharmaceutical industry. Qatar did not specify the type of information provided to the public or the industry through the website while Saudi Arabia, being an independent authority, has a more informative website than the other five authorities, providing information on product approvals, timelines, prices, regulatory information and guidelines through the SFDA's website.

Drivers and barriers

The most important reasons for the introduction of quality measures in each GCC authority and the activities performed by the GCC authorities to bring about improvement in their regulatory review processes is shown in Table 6.10.

No one reason was shared by the seven GCC states. However, the most commonly stated reasons were to minimise errors, to ensure consistency and to increase efficiency in the GCC review systems.

The purpose of this section is to identify the GCC authorities' perceptions of their distinctive positive qualities and the major impediments they are facing in carrying out the review of new medicines and making them available to meet patients' needs.

Table 6.10 Reasons for introducing quality measures in the Gulf Cooperation Council (GCC) review and decision-making process

Reasons for introducing quality measures	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
To minimise errors	×	✓	✓	✓	✓	✓	✓
To ensure consistency	✓	✓	×	✓	✓	✓	✓
To be more efficient	✓	✓	✓	✓	✓	×	×
To increase transparency	×	×	✓	×	×	✓	×
To Ensure stakeholder satisfaction	✓	×	×	×	×	✓	×
To reduce cost	×	×	×	×	×	×	✓

Each one of the seven authorities were asked to list three unique factors that make a major contribution to the effectiveness and efficiency of its review procedures and decision-making processes and three unique factors that act as barriers to making new medicines available in a timely manner through the regulatory process (Table 6.11).

It can be seen that no single driver or barrier was common to all GCC authorities. Surprisingly, each factor emerged from an authority's distinctive environment depending on the political situation, the governmental autonomy and level of resources available to achieve the desired standard of the regulatory services. However, it is common in all authorities that reviewers are pharmacists, and employing reviewers from other scientific disciplines such as biostatisticians, pharmacologists, toxicologists and physicians are not currently being considered by any authority. In addition, it is a common deficiency in all states that the number of IT staff is minimal compared to other activities.

In Kuwait and Bahrain, the secretarial staff perform some IT work, mainly because IT practices are not fully developed in these authorities. SFDA senior managers focused on applying electronic practices for the registration and assessment procedures and for the industry follow-up of the progress of the submitted application.

Budget is also a common controlling factor for the quality of the review process, because Kuwait, UAE, Bahrain, Qatar and Oman are dependent on the Ministry of Health in obtaining their annual budget which is mostly focused on basic needs such as employees' salaries.

Table 6.11 Drivers and barriers to quality review and decision-making process in the Gulf Cooperation Council (GCC) States

Country	Drivers	Barriers
Bahrain	Easy access Good communication Clear guidelines	No accreditation from trusted drug authorities Inadequate PMS studies Marketing status in the country of origin
Kuwait	Well established system Supportive government Variety of scientific qualifications	No QA policy system in place No project management planning No electronic handling for product dossier
Oman	Good tracking system Following a scheme of assessment Good management plan Reviewers are well qualified, trained and experienced	Shortage of experience and personnel No independent budget No internal quality policy
Qatar	Need of access of new drugs to patients Emergence of new diseases The desire for advancement	Shortage in manpower Increasing workload due to growing market Weak follow-up
Saudi Arabia	E-communication with applicants E-environment (EURS, ECTD).	Delayed response of companies Inappropriate responses from companies
UAE	Utilising reference countries' approvals Flexibility and understanding	Lack of human resources Lack of laboratory technical resources. Complex administrative and hierarchy structure and appointments systems
Yemen	Well trained qualified persons Written SOPs for reviewers Archiving information database	Current programmes need updating Registration department and QC laboratory are overloaded with products and applications. Shortage in working facilities (e.g. computers, technical references)

DISCUSSION

This chapter focused on the extent to which quality measures and good review practices are being applied to the review processes of the seven GCC regulatory authorities, namely, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE and Yemen. The activities performed to assess methods of communication and transparency as well as the availability of training and continuing education programmes were also determined.

Quality is a comprehensive and multifaceted concept (Brown *et al.*, 1998). Previous studies have concluded that it is not sufficient to measure the regulatory performance in terms of the speed of the approval process alone. The quality of the regulatory review process, from the construction of the dossier to the final regulatory decision must also be examined (Cone and McAuslane, 2006). This approach which was used

in this study challenges the concept as to whether the GCC authorities carry out the regulatory review process in a consistent, efficient, organised and effective manner. This proposition is illustrated below.

The results of the study showed that the seven GCC regulatory authorities have a range of quality measures that vary from one country to another such as the quality policy, good review practices (GRPs), standard operating procedures (SOPs), and assessment templates (Table 6.2). The study showed that the joint review practice was reported by all the seven authorities as part of the GCC centralised procedure where each authority assesses the registration dossier and the outcome from each authority is discussed in a conference meeting and the decision is made by agreement of all the GCC-DR committee members. This is a positive result as performing joint reviews by the seven GCC authorities is a sign of consistency, stability, and standardisation in the GCC regulatory review processes. The GCC centralised system is based on a strong cooperation between the seven member states and is considered as an effective monitor for consistency and quality in the review process. 'Assessment templates' is another commonly used quality measure by most of the GCC States, which is an important sign of consistency and uniformity in the GCC review processes. It is an effective way to ensure that documentation is valuable, accurate, and acts as an outline to follow when developing or documenting data for the review process. However, good review practice (GRP) is the least implemented quality measure in the Gulf Region. The importance of implementing and maintaining 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). However, GRPs were only introduced in the advanced regulatory authorities over the last ten years and the use of SOPs and assessments templates should be the focus to improve the quality of the review process in the GCC States.

The GCC authorities were also found to be focused on 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 minimise errors in the system. Therefore, quality systems should be regularly reviewed to ensure that they are working effectively. Continual improvement activities include

reviewing feedback from assessors and stakeholders, carrying out internal tracking systems to monitor consistency, timeliness, efficiency and accuracy, undertaking internal audits as well as external audits by accredited certification bodies to improve the system and performing "post-approval" discussions with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments. Oman was the only authority that undertakes external quality auditing, while four authorities out of seven stated that they do perform internal quality auditing. However, if these authorities lack the guidelines and SOPs for their procedures, then the quality of their internal audits would be questionable. It is an essential practice in competent authorities to perform audits as they provide constructive feedback which could enable the authorities to further improve their quality management tools through further exploring good practices performed in advanced regulatory authorities. Another issue is that only a few authorities carry out 'post-approval' discussions with the pharmaceutical companies. This is an effective practice which should be considered by the GCC States because it allows the system to improve. Without the post-approval feedback, both the sponsor and the authority will assume that the system is producing the desired results. However, since the processes are never free from human errors, there will be a need to focus on the areas that need improvement for the two parties to be able to make the necessary adjustments to produce better results or perform more efficiently during the next cycle (Compass West Consulting, 2008).

The ability of the regulatory authority to apply quality measures and carry out quality audits to identify areas for improvement in their systems depends on the existence of the quality assurance infrastructure within each authority. This infrastructure is concerned with both the quality of the products themselves and all the activities and services that may affect quality (WHO, 2001). Unfortunately, only Kuwait and Yemen have independent and dedicated quality assurance (QA) departments for assessing and/or ensuring quality in the assessment and registration procedure. However, the practice of QA in such authorities is questionable without the existence of guidelines and SOPs for the QA personnel. In many countries drug quality assurance systems are inadequate because they lack the necessary components including adequate drug legislations and regulations with sufficient resources and infrastructure to enforce them (Torstensson and Pugatch, 2010). Investing time and resources on establishing a dedicated QA unit/department in each GCC authority is an important practice to

monitor all activities aimed at ensuring that patients receive a product that meets established specifications and standards of quality, safety and efficacy.

Another important quality management tool is the existence of an expert committee for the scientific assessment and registration of pharmaceutical products. Most GCC authorities have expert committees. Kuwait is the only country that does not have a committee and their assessment process depends entirely on the reviewer's assessment report and the drug registration superintendent's (DRRS's) final decision. Qatar does not have a committee for the scientific assessment of medicines but the final decision is made by the registration committee. Other GCC authorities recognise the importance of having scientific committees for the review process. The advantage of relying on a group of experts' decision-making instead of one individual is access to the group's collective wisdom, as well as the ability to spread an increasing management workload over a number of people. Another advantage would be the diffusion of responsibilities where the individual's part in a group decision weighs less heavily on him/her than an individual decision would (Muir, 2007). The existence of expert scientific committees is essential when decisions are made at critical stages as the new medicine moves from the assessment stage to the final patients' access stage. A significant finding of this study shows that the committees in five GCC authorities vary considerably in their characteristics and functions. In Oman and UAE, the expert committees review assessment reports for all NAS and EAS applications. In Saudi Arabia and Yemen, on the other hand, expert committees review the complete dossier for all NAS and EAS applications. Bahrain is the authority where the expert committee review assessment reports for selected NAS and EAS applications. Four authorities have an expert scientific evaluation committee that makes the final approval decision. In UAE, however, the expert committee comprises several scientific subcommittees with an average number of five members in each one. Each committee is specialised in evaluating a separate discipline such as stability, quality control analysis, GMP, bioequivalence studies, minor variations, internal peer reviews, and external screening. These committees present their assessment reports to the higher registration committee (HRC) which reviews the assessment reports and makes the final approval decision accordingly. The various committee procedures in the Gulf States is comparable to other regions in the world. For example, China and India review the complete dossier while South Korea and Canada review the assessment reports of selected applications (Mallia-Milanes, 2010).

Communication is another important element for building quality into the review process. Regular contact with the industry is necessary to provide the scientific and regulatory advice, to inform the applicant about the progress of the review process, and to provide post-approval feedback to the industry on the quality of the dossier (Mallia-Milanes, 2006). Communication takes many forms and shapes and is more than just talking and listening and there are many areas where improvement in communication can minimize risks of errors in the system and improve the relationship between the two parties (Panting, 2003). In this study, Bahrain, Kuwait and UAE carry out extensive formal and/or informal contact with the industry to clarify issues during the assessment process. However, some formal and/or informal contact is carried out in the other four authorities. Formal contacts include scheduled meetings and official letters submitted to the authorities and informal contacts include telephone calls, emails, and fax. Whatever the contact methods might be, it is essential to keep abreast of them to enhance the quality of the review process. The authorities also need to use effective methods to communicate important regulatory information and official guidelines to the industry. The most effective method of achieving this is by the use of official Internet websites for the authorities. Although six authorities stated that they have websites, the level of transparency provided to the public and the pharmaceutical industry is questionable. SFDA's website is considered the most informative providing regulatory information and guidelines to the industry, product approvals, timelines, and prices. There are a number of reasons why each GCC authority should have a focused and informative website, namely,

- It is a predictable feature of any competitive regulatory authority and the public simply expects its existence in the web.
- It is readily accessible to visitors at their convenience, which is an important characteristic to facilitate the registration procedure.
- It saves time because the website provides all the required information and reduces the need for the time-wasting calls, emails, and scheduled meetings.
- It can project a professional image of the organisation.
- It can help keep up with the developing regulatory field.
- It can collate valuable information about the authority's events and new developments.
- It can introduce the regulatory authority to the world.

Therefore, all GCC authorities should take advantage of the web presence to improve the quality of their communication with the industry. Four authorities provide the official guidelines on-request which is a simple straightforward feature that is conducted by most organisations around the world. Two authorities publish their guidelines in official periodical publications, and this is another effective communication practice that can positively affect the quality of the review process because it keeps the required information readily available and continuously updated for the public and the industry.

The continuing professional development (CPD) of assessors is an essential criterion for quality reviews. This should include regular training that focuses on improved practices; scientific and technological advancements, as well as knowledge and skills transfer. Abdul Halim and Ali (1992) described training as the process of acquiring specific skills to perform a task better. They also state that organisations facilitate the employees' learning through training so that their modified behaviour contributes to the attainment of the organisation's goals and objectives. The ultimate objectives of training and continuing education are (1) to make the employees as well qualified as possible to carry out their job, and (2) to make the employees qualified to perform in positions of greater difficulty and responsibility. The results of this study showed that only Saudi Arabia and UAE stated the existence of formal training and continuing education programmes for their assessors. The other five authorities do not have official programmes but they do carry out some form of training. The most prevalent method is the participation in international conferences and workshops. The other common methods shared by four authorities in the region are the external courses, post-graduate degrees, and inviting external speakers for the internal reviewers. Such importance was also given by the authorities in a number of the emerging markets to participate in workshops and conferences which raised the issue as to whether the most effective learning techniques are being used. Furthermore, no compulsory training is carried out for internal or external experts or for the members of the scientific committees. The lack of such a crucial quality assurance tool raises a question about the ability of the reviewer to carry out a quality review process. Furthermore, placements and secondments are overlooked and it should be further explored by the authorities in the GCC Region. These systems enable the assessors to gain experience and knowledge in the area of dossier assessment from more experienced assessors. An example of this kind of collaborative training occurs

between United States Food and Drug Administration (US FDA), Australia's Therapeutic Goods Administration (TGA) and Health Canada under the Memorandum of Understanding (MOU) and confidentiality agreement between the three authorities to better enable them to share information on the review and evaluation of new product submissions, product investigation and enforcement activities and post-market safety of therapeutic products (Health Canada, 2006). It also sets the stage for other, more specific, collaborative projects for exchanging regulatory information, including expert visits, joint training initiatives, participation in scientific advisory bodies and development of guidance documents. Another effective collaborative approach is the implementation of twinning reviews whereby a developing country regulator would assess a pharmaceutical dossier in consultation with, or alongside, a reviewer from a well-resourced regulatory agency. An example of a twinned review occurred in 2008 which was organised by the WHO and involved regulatory training sessions in joint reviews and assessment of full regulatory dossier by regulators from African Medicines Regulatory Authorities (MRAs), the EMA and WHO (Moran et al., 2010). These collaborative activities are essential and the possibilities of establishing them with the advanced regulatory authorities should be further explored by the GCC senior regulators.

The GCC authorities recognise the importance of transparency for the improvement of the review process. Kuwait was the only authority that assigned medium priority to transparency even though they openly answer all queries from the public, professionals, the industry, the media and the politicians. However, Kuwait is cautious with the kind of information being released to avoid misinterpretation of specialised data that otherwise may not be fully understood by the public and the media. Having said that, the study showed that the extent of the information available from the GCC authorities was limited, with most of the authorities only publishing the approval dates of the marketing authorisation of applications. Saudi Arabia provides the most information to the public compared to all the six GCC States. It is important to provide substantive information on the decision criteria that was used to approve or reject a product, which is a practice that is not common in the GCC Region. Transparency of information and decision-making was believed to support and maximise the impact and political acceptability of the centralised drug review in Australia, Canada, New Zealand, and the United Kingdom (UK) (Morgan et al., 2006). Therefore, transparency is a discipline that requires further attention to ensure quality in the GCC review

process. In order for the transparency to be enhanced in the GCC States, a set of measures need to be addressed (Bertolini, 2006). Guidelines, legislations as well as rights and obligations of the regulatory authorities in regulatory instruments (e.g. laws, regulations and licenses) should be clarified, and predictability of the regulatory outcomes should be achieved by reassuring stakeholders that the regulatory decisions are made according to established rules and processes. Flexibility in setting out parameters and methodologies is important but it needs to be handled carefully. Certain methods should be introduced gradually and through negotiations with stakeholders. Autonomy of the regulatory authorities should be protected from interference of special interests and should be balanced with accountability. Stakeholders should be able to challenge the regulatory decisions and the regulators should openly discuss their decision and provide clear justifications once decisions are made. In addition, stakeholders (regulators, consumers, policymakers and industry) should participate in the decision-making process by providing the regulators with useful information about their views and about the possible consequences of a regulatory decision. Open access to information should be allowed (e.g. new legislations, regulatory decisions and consultant's reports) for all stakeholders in a timely and cost-effective manner, taking into consideration the literacy rate, the type of audience receiving the information and the use of technology (e.g. websites) in deciding the best way to disseminate the information.

An underlying resource is required to support robust quality in Information Technology. This is fundamental for handling, management and tracking large amounts of data and documents. Four authorities stated the presence of an electronic system to register and track applications, to identify the stage of the review process, to record the terms of approval once granted and to provide an efficient archiving system for each authority. Saudi Arabia and Oman use the IT system to signal any delays of the review process from the targeted approval date. However, the extent to which these IT systems are impacting the quality of the review process in the GCC States should be further explored.

The GCC authorities have stated a variety of drivers and barriers to achieving a high quality review. The seven countries have well established authorities that demonstrated experience in the registration process, a good degree of communication, a cooperative attitude, and the desire for continuous development. However, they lack the resources to help them implement the standard quality

measures in the review process. They require the human resources, the proper funding, the internal structure, the IT infrastructure, and the work facilities to achieve the desired quality standards. 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 assurance of quality. Given the pressures that arise from legitimate business interests of the multinational pharmaceutical manufacturers, there needs to be support for regional activities designed to ensure quality in the registration systems. This includes ensuring that there is adequate capacity to cover the required resources and the proper guidelines at a country level to assess and control the quality of medicines. One way to increase the level of resourcing in the GCC authorities is to educate the politicians and governments that drug regulation is essential rather than a luxury and their support is vital for the ultimate protection of the public health.

SUMMARY

- The seven GCC States shared similar characteristics that were the fundamental factors that enabled the successful comparison of the quality measures between their regulatory review processes.
- This study showed that the GCC authorities have a range of quality measures in place and undertake a number of activities to improve the review process and they stated their intentions to implement further quality measures in the foreseeable future.
- The GCC authorities deploy some form of training and continuous education programmes for their reviewing staff as well as carrying out joint reviews as part of the GCC-DR system.
- The GCC authorities perform a range of activities to improve communication with the pharmaceutical industry and transparency to the public as they recognise the importance of being open and transparent, although limited information is made available to the public.

CHAPTER 7

An Evaluation of the Strategic Planning Process for the GCC Regulatory Authorities

INTRODUCTION

The Gulf Cooperation Council (GCC) was established on May 25th 1981 with the six Arab States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and UAE). The GCC's primary role is to formulate standardised regulations in various fields such as economics, finance, trade, customs, tourism, health, legislation and administration, establish scientific research centres, encourage cooperation with the private sector and strengthen ties between their people. Yemen has joined the GCC only in the healthcare and sports initiatives in 2004.

Throughout the three decades, since the establishment of the GCC, the Gulf States have experienced major challenges in view of the rapid change in the regulatory environment around the world. However, because of their strategic importance, position in the world and rich oil resources, they present significant potential for the growth of the pharmaceutical market. This growth, together with the increase in the price of medicines, has encouraged the GCC authorities to build their individual regulatory systems to deal with the considerable challenges in the pharmaceutical market. However, they realised that the pace of development in their individual markets is currently becoming significant.

The growth of the pharmaceutical market in the Gulf Region is 7% with an expected increase in the pharmaceutical sales to US$ 10.8 billion in 2020 from US$ 5.6 billion in 2010 (ALPEN Capital, 2010). The six states decided to formulate standardised regulations through their joint efforts to control the access of medicines into the Gulf Region. In 1998, the GCC Drug Registration System (GCC-DR) was established as a result of the GCC vision three decades ago. At the same time, the six GCC governments took steps to harmonise their regulatory procedures and a set of guidelines and policies were produced.

Several challenges faced the GCC health authorities to successfully operate the new GCC-DR system. Therefore, they have encountered the need for regulatory reforms during the last 10 years, in order to improve their individual systems and to unify their procedures to achieve improved patients' access to high quality medicines throughout the region. These two factors placed the GCC States in a position where establishing a strategic plan is considered critical for them to achieve their goals.

OBJECTIVES

This chapter has three main objectives, namely to,

1. Identify where the seven GCC authorities stand at the present time by recognising their values, strengths, weaknesses, opportunities and threats.
2. Evaluate where the seven GCC authorities want to be in the future by identifying their vision and mission statements, goals, objectives, and driving forces for change.
3. Assess the GCC regulatory authorities' abilities to achieve a standardised regional regulatory system in line with the resources and capabilities of the member states.

There is no perfect strategic planning model for any organisation. Each organisation ends up developing its own approach to strategic planning, often by selecting a model and modifying it (McNamara, 2006). This is what makes GCC harmonisation hard to design and /or implement before conducting a full evaluation of each of the seven authorities' strategies. From this, the resulting commonality can be enhanced while the resulting differences minimised. This approach is more flexible and effective than creating a new harmonisation strategy, which can place the authorities under a considerable pressure which may destabilise the entire regional regulatory environment. A stable environment is a critical factor for the success of any strategic plan.

METHODS

Participants

The senior personnel from each of the seven authorities were selected to participate in the study (Table 7.1) because strategy and strategic issues usually are the responsibility of such individuals. The seven GCC regulatory authorities responded when asked to participate in this study (100% response rate). The questionnaire was sent out in early September 2008 and completed by November 2008 (Appendix B).

Data collection

The seven GCC regulatory authorities were approached with data provision requests. Prior to sending out the questionnaire, in September 2008, each authority was individually contacted to identify the most appropriate person to receive the questionnaire and to ascertain the likelihood of their participation in the study.

To facilitate the self-completion process, detailed instructions were included in the final version of the questionnaire.

Table 7.1 General Information on the seven Gulf Cooperation Council (GCC) regulatory authorities

Country	Authority	Date of Establishment	Number of reviewers	Budget in US$
Bahrain	Directorate of Pharmacy and Drug Control	1979	7	NA
Kuwait	Pharmaceutical and Herbal Medicines Registration and Control Administration	1967	15	3M
Oman	General Directorate of Pharmaceutical Affairs	1976	22	NA
Qatar	Directorate of Pharmacy and Drug Control	NA	3	NA
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	2003	40	134M
UAE	Registration and Drug Control Department	1980's	12	2.5M
Yemen	Directorate General Supreme Board for Drugs & Medical Appliances	1971	10	3M

NA: Not Available

A glossary with definitions of technical terms and a concise background section were also included in the document. Complete contact details were provided in case any participant required further clarification. Following the dispatch of the study pack, the authorities were followed up in order to ensure timely completion of the questionnaires. All seven regulatory authorities completed the questionnaires, with the last one being received in November 2008. A confidential procedure was used for the collection of data with information coded and aggregated on receipt in order to prevent the identification of individual authorities. Subsequently, all the GCC authorities agreed to be identified in the final report. The participants were given the choice to submit their data either on paper or electronically. The use of an electronic questionnaire eliminated the need for additional data handling steps (such as

interpreting handwriting) and improved the quality of the data. Apart from the responses from the seven GCC questionnaires, data were obtained from a literature review that provided further clarification about the concept of strategy formulation and aided in the creation of a new proposed GCC harmonised strategy.

Piloting the Questionnaire

Even experts in questionnaire design find it difficult to produce the right questionnaire on their first attempt (Van Teijlingen and Hundley, 2001). Therefore, it is vital to pilot the questionnaire to ensure its practicality and appropriateness for the participating authorities. The idea is to test the questions on two selected GCC regulatory authorities (Kuwait and UAE) to refine the questionnaire to reveal any unanticipated problems with the questions' wording or instructions. It also helps to ensure that the respondents understand the question and that these questions are going to yield useful answers (Van Teijlingen and Hundley, 2001). The pilot respondents from the two authorities were asked for feedback with regards to the length of time required for completing the questionnaire, the ease of understanding the questions and instructions, the attractiveness and clarity of the layout and any other comments (Huxham, 2005). After the pilot study, the questionnaire was found to be ideal for the region and was, therefore, distributed to the remaining five authorities for completion.

Data processing and analyses

Thorough checks and editing of the questionnaire responses were carried out to ensure the quality of the data while missing data, incomplete answers and contradictory responses were queried with the respondents and the results were audited by an independent person to ensure further accuracy of the data. Finally, conclusions from the analyses were drawn based on patterns of similarities and differences between the member states.

Identifying the sequence of the strategic planning stages

In order to establish a clear model for a harmonised strategic plan for the GCC regulatory authorities, it was necessary to define the sequence of activities to be followed. There were different options identified from the literature for the sequence and an appropriate one was chosen for this study. In general, an organisation needs to know exactly where it stands, and then determine where it wants to go and how it will get there (Kristoffersen, 2009). Strategic planning is a creative process and the

fresh insight arrived at one stage might easily alter the decision made at a previous stage. Inevitably the process moves forward and backward several times before arriving at the final set of decisions (Zarkesh, 2008).

Since the seven GCC States have well-established regulatory authorities with robust historical activities, it was hard to imagine a future independent of the past. Therefore, it was more appropriate to carry out the situational analysis (internal and external analyses) before deciding about a realistic approach for the GCC regulatory authority's directions and future harmonised regulatory strategic plans.

RESULTS

Stating the current position

Organisational values

Organisational values are defined as the collective principles and ideals that guide the thoughts and actions of individuals within an organisation. This study examined the ideas, beliefs, perceptions, and attitudes of individuals in the GCC authorities that collectively act as the motivating factors to shape the existing state of the art within each authority. The analysis of the GCC authorities' core values were based on the sense that employees and managers make of what they do (Rekom et al., 2006). Without such "sense-making" approach, management will have a hard time implementing a strategy that is compatible with their organisational values (Pant and Lachman, 1998).

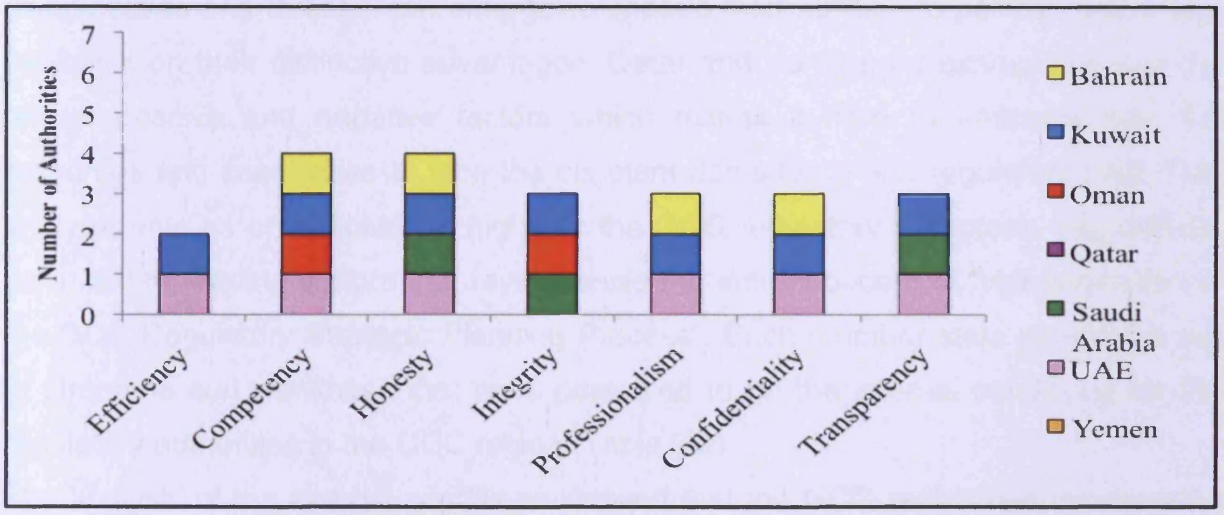
The GCC States have expressed collective values, principles and ideals, which guide their actions for better regulatory services. Twenty-Eight values were stated by the seven GCC States but no one value was common to all authorities. However, seven values were found to be the most prevalent, namely, efficacy, competency, honesty, integrity, professionalism, confidentiality and transparency (Figure 7.1)

The assessment of core values provided critical information necessary to examine the current organisational philosophies and processes and determined congruence within the existing behaviours and practices (Seevers, 2000). As an initial step in the strategic planning process, a value audit provided the basis for the decision-making process with regards to the current and future direction of the GCC authorities.

Regulatory internal and external analysis

The initial steps in the strategic planning process is to address the questions "Where are we?" and "What do we have to work with?"(Yielder and Burns, 1999). Examination of the history and changing environment (both internal and external) of an organisation allows the analysis of the current positions of the GCC authorities to be identified. In this study, each authority was found to have a vision statement, a mission statement, goals and objectives. However, it would be meaningless to establish a harmonised future vision without identifying the present strategic resources and capabilities available in the GCC Region.

Figure 7.1 Common Gulf Cooperation Council (GCC) organisational values



Answering the question of what we have to work with involves consideration of the internal and external environment of each GCC regulatory authority. Such analysis of the strategic environment is called the SWOT analysis and it was carried out in this study to identify the Strengths, Weaknesses, Opportunities and Threats (SWOT) in the seven GCC regulatory systems.

These elements of the SWOT analysis are described as follows (LeDoux *et al.*, 2005),

- Strengths and opportunities are positive factors that support current strategies and improved performance.
- Weaknesses and threats impede performance and suggest risks in the current strategies.
- Strengths and weaknesses indicate internal conditions.
- Opportunities and threats indicate external conditions.

Therefore, analysing the strengths, weaknesses opportunities and threats in each GCC authority yields necessary facts to consider when developing the GCC harmonised vision. Each authority has a set of SWOT items that correlate to its position in the GCC regional regulatory environment. Some authorities stated more positive factors (strengths and opportunities) than other authorities depending on their current perceptions about their own distinctive advantages such as Bahrain, Kuwait, Oman, Saudi Arabia and UAE, where they mentioned numerous strengths and opportunities that currently play a vital role in their respective strategies and improved performances.

However, the more positive factors these authorities have, the more risk factors (weaknesses and threats) can emerge to impede their abilities to perform better and capitalise on their distinctive advantages. Qatar and Yemen, for example, stated the fewest positive and negative factors which makes it hard to embrace their full resources and capabilities to face the constant demands of the regulatory field. This analysis acts as an indicator to highlight the GCC regulatory resources, capabilities, risks and motivating factors that revolutionise the entire concept of "Harmonisation of the GCC Regulatory Strategic Planning Process". Each member state provided a set of strengths and weakness that were perceived to be the internal conditions for the regulatory authorities in the GCC region (Table 7.2).

The analysis of the internal conditions showed that the GCC region has experienced staff and the required regulatory structure with appropriate legislations, processes and regulations in place supported by an active cooperation between the authorities. However, the experience gained by the staff was obtained from working in the authorities for a long period of time, but it is not able to create experts in new or existing regulatory practices. Therefore, the GCC is lacking the required experts that could enhance its capabilities to advance its system. They also lack the proper training and education programs to create the required skills and expertise in many fundamental regulatory areas.

On the other hand, the seven GCC States provided a set of opportunities and threats as external conditions that may have an impact on the authorities' performance. The analysis of the external conditions demonstrated that the GCC authorities have significant potential to improve their regulatory practices by utilising the opportunity of collaborating with regional and international regulatory agencies.

Table 7.2 Analysis of the internal conditions within the Gulf Cooperation Council (GCC) regulatory authorities

Country	Strengths	Weaknesses
Bahrain	Ministry of health support Well trained and experienced staff Active cooperation with other GCC authorities Long experienced system	Lack of training in certain areas Lack of experts in some specialties Low budget Shortage of staff
Kuwait	Reputable authority in the GCC Region Long Experience in the field Caring, experienced staff Influential at the government healthcare level	Lack of IT infrastructure Limited resources Limited QA measures Dependent authority (not self-sufficient)
Oman	Long-term professional experience Good legislations Transparency and honesty Team decision-making	Shortage of personnel Lack of training in certain areas
Qatar	Experienced system fulfilling local needs	Shortage of experts
Saudi Arabia	Existing regulatory processes Technical skill set of management	Inconsistent regulations for technology transfer Lack of approval systems to a variety of drugs Lack of adverse event monitoring system Long approval process Pricing disconnected from market demands Weak public education
UAE	Good experts Guidelines available Electronic system available	Shortage of staff Old Laws Dependent Department (not self-sufficient)
Yemen	Equipped central QC lab Appropriate financial resources Independency	Weak legislations Lack of political support Lack of human resources Absence of transparent procedures Absence of priorities Lack of coordination and integration

Furthermore, the GCC authorities seek to employ the emerging technologies to improve their drug approval processes such as the electronic submission of the Common Technical Documents (e-CTD). However, the authorities are faced with high staff turnovers, which affect the balance of experienced personnel required to maintain the standard level of their practices. An additional problem was the constant danger of an increasing number of substandard and counterfeit drugs from all around the world which combined with the limited resources and capabilities in the region challenges the authorities' ability to deal with this issue (Table 7.3).

Table 7.3 Analysis of the external conditions within the Gulf Cooperation Council (GCC) regulatory authorities

Country	Opportunities	Threats
Bahrain	Independent authority Expand through GCC cooperative efforts Approval of new organisational chart.	Poor funding Loss of staff Open market Increasing number of generic medicines Increasing herbal medicines
Kuwait	Better relations with competent agencies Use of emerging technologies Diversify into various regulatory practices Hiring qualified expert reviewers	Manual work delays regulatory approvals Increasing workload and industry pressure Increasing external complaints Bureaucracy
Oman	Collaborating competent authorities (e.g. WHO)	Shortage of experts Lack of resources
Qatar	Establishing a website to increase efficiency.	Loss of staff
Saudi Arabia	Consolidation of individual functions Limited number of importers Presence of key players in Saudi Arabia	Emergence of new drug classes (biologics) Emergence of new technologies Lack of control over dispensing drugs higher incidence of metabolic diseases and cancer
UAE	Good communication New laws are welcomed New strategic plans are welcomed	Local organisations available (Abu Dhabi, Dubai)
Yemen	Not available	Not available

The overall SWOT analysis that emerged from the review of the GCC's internal and external regulatory environment demonstrated the commonly shared needs of the seven GCC regulatory authorities (Table 7.4).

Table 7.4 Overall SWOT analysis for the Gulf Cooperation Council (GCC) regulatory authorities

Strengths	Weaknesses
Experienced technical staff Well established authorities Existing legislations and regulations Active cooperation between the authorities	Shortage of experts Lack of training and educational programs
Opportunities	**Threats**
Working in collaboration with regional and international agencies Emerging technologies seeking new modern drug approval processes	High staff turnover Increased number of substandard and counterfeit medicines

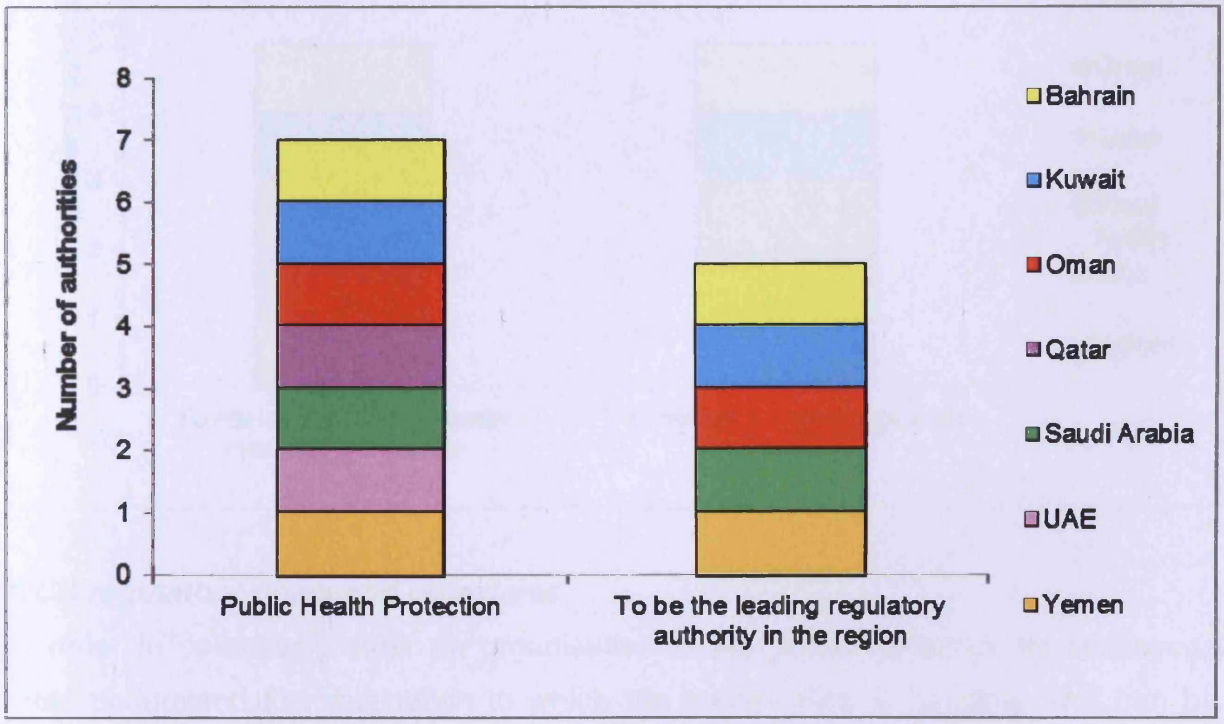
Setting Strategic Direction

The next step in the strategic planning process is deciding "Where do we want to be?" As the articulated vision stems from the existing values and environmental status of GCC authorities, it is essential that this step involves all individuals and processes that play a role in achieving the vision. The vision is then translated into a mission statement: a broad, comprehensive statement of the purpose of the authority. After stating the vision and mission statements, it is rational to articulate the organisational goals (Schilder, 1997). These goals are the desired long-range conditions that indicate the intended future direction of the GCC regulatory authorities. Goals can only be achieved by means of accomplishing strategic objectives that summarise the tasks and activities that must be undertaken to achieve a strategic goal (Yielder and Burns, 1999). Finally, it is crucial to understand the driving forces that motivate the GCC regulatory authorities to carry out the desired changes to achieve their future goals. Therefore, this study examined the main factors for setting the strategic direction of the GCC regulatory authorities, namely, the vision statement, mission statement, goals, objectives, and driving forces for change.

Vision statements

The vision statement is a concise statement of what the organisation wants to be at the end of the planning cycle (LeDoux et al., 2005). A well-articulated strategic vision creates enthusiasm for an improved performance by all members of an organisation. Strategic visions usually have time horizons of five years or more unless the organisation is new or the environmental conditions (e.g. political, financial, economical) are unpredictable or unstable that it is difficult to see that far into the future with any degree of confidence (Zarkesh, 2008). Therefore, after analysing the GCC regulatory environment, it is important to assess where each GCC authority wants to be in five years' time based on their existing resources and capabilities. This was achieved by evaluating the common aspects shared by the seven GCC vision statements. Two major aspects were mostly shared by the GCC regulatory authorities, namely, to protect the public health and to become the leading regulatory authority in the region (Figure 7.2). These shared aspects can be valuable in establishing benchmarks or blueprints for the future of the GCC harmonised regulatory strategic plan.

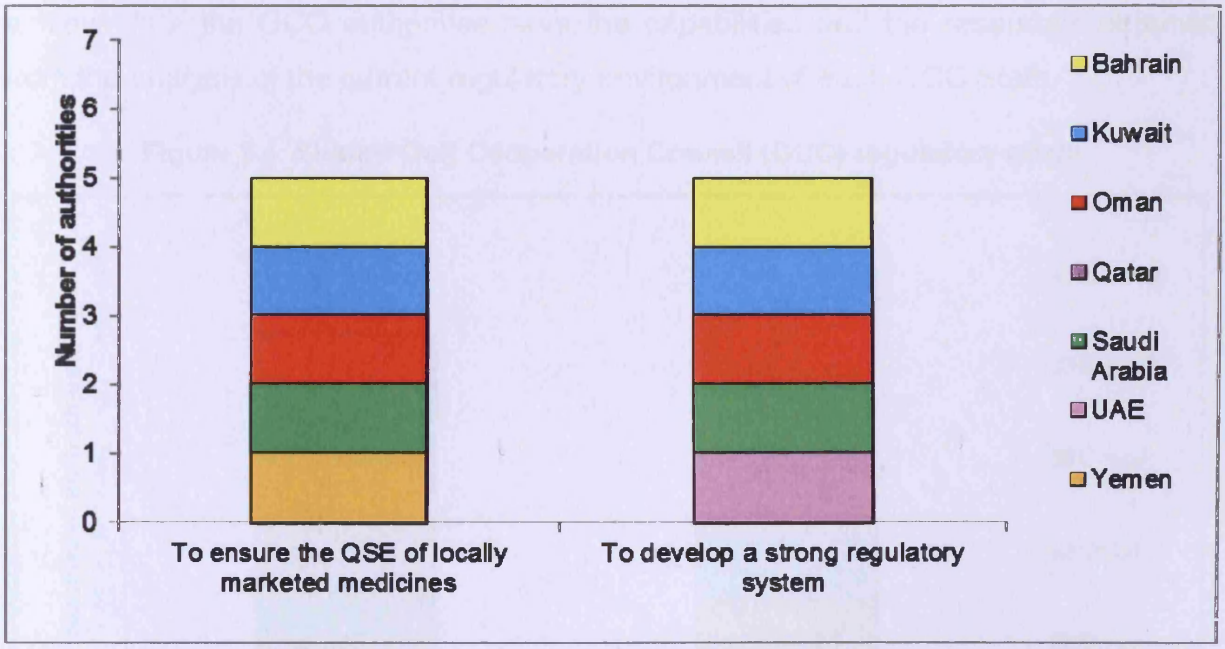
Figure 7.2 Shared aspects between the seven Gulf Cooperation Council (GCC) vision statements



Mission statements

The mission describes the approach the organisation will take to achieve its vision (Yielder and Burns, 1999). It basically defines the purpose of the organisation's existence which inspires the managers to achieve their long-term vision, and helps channel organisational efforts and strategic initiatives (Zarkesh, 2008). A mission should address the opportunities and needs that an organisation exists to address, what the organisation is doing to address these needs, and the principles and values that guide the work within the organisation (Radtke, 1998). Therefore, it is crucial to highlight the purpose for the existence of the seven GCC regulatory authorities and two major purposes were extracted that were shared by the seven GCC authorities, namely to ensure quality, safety, and efficacy of the locally marketed medicines and to develop strong regulatory systems (Figure 7.3).

Figure 7.3 Shared reasons for the existence of the Gulf Cooperation Council (GCC) regulatory authorities



GCC regulatory goals and objectives

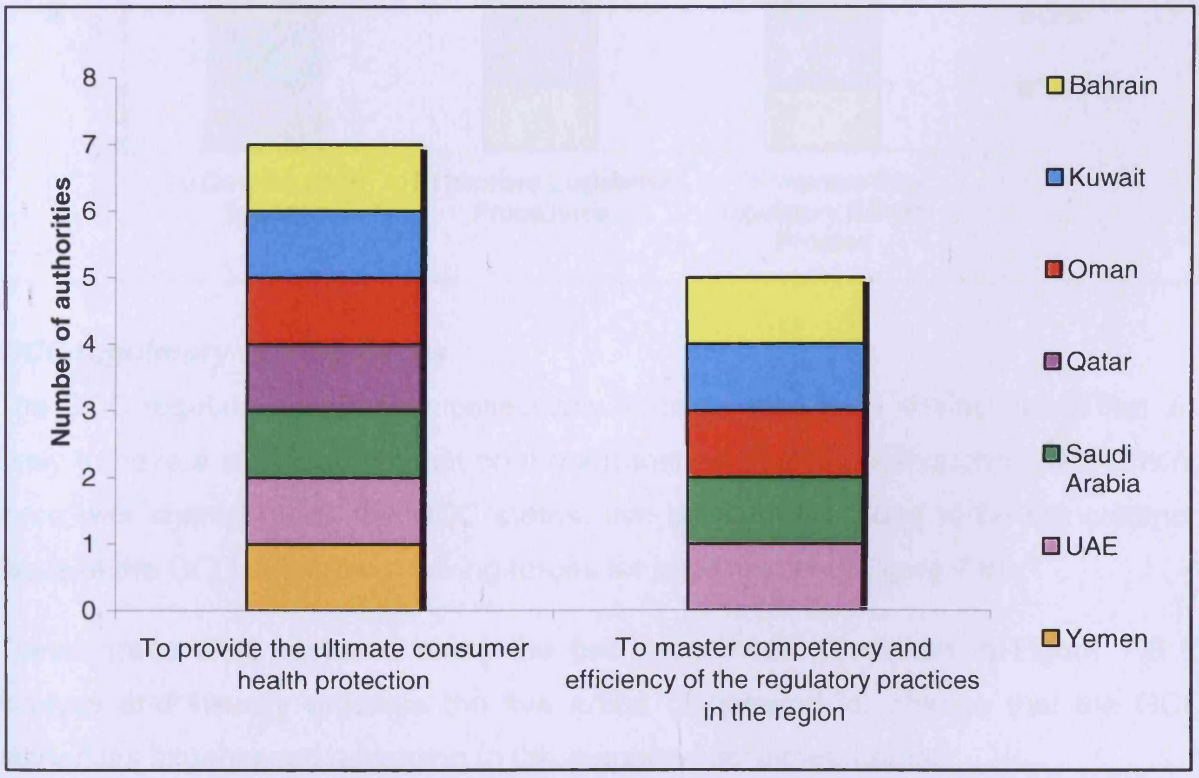
In order to collectively steer an organisation in the proper direction, its employees must understand the destination to which the organisation is heading. This can be achieved and communicated by setting the organisation's goals and objectives in conjunction with its mission. This results in organising the goals and deciding their

appropriateness to the organisation's vision and mission statements which should be in line with the current capabilities and needs of the organisation.

What often happens, however, is that the management who set the mission and determine the goals may not carry out an adequate job of analysing the present situation to ensure that the appropriate goals are selected and communicated and may not carry out an appropriate job of adequately communicating the mission, goals and objectives to the organisation. Failure to do this results in improper decision-making and, eventually, a failed strategy.

Therefore, this study assessed GCC regulatory authorities' goals and objectives that support their mission and vision statements. Various visionary goals were stated by the GCC authorities, and two were most commonly shared between the seven states, namely, to provide the ultimate consumer health protection and to master competency and efficiency of the regulatory practices in the region. By looking at the GCC common goals, it can be clearly established that these coincide with the common aspects of the GCC vision statements (Figure 7.4). This means that these goals are achievable if the GCC authorities have the capabilities and the resources obtained from the analysis of the current regulatory environment of each GCC State.

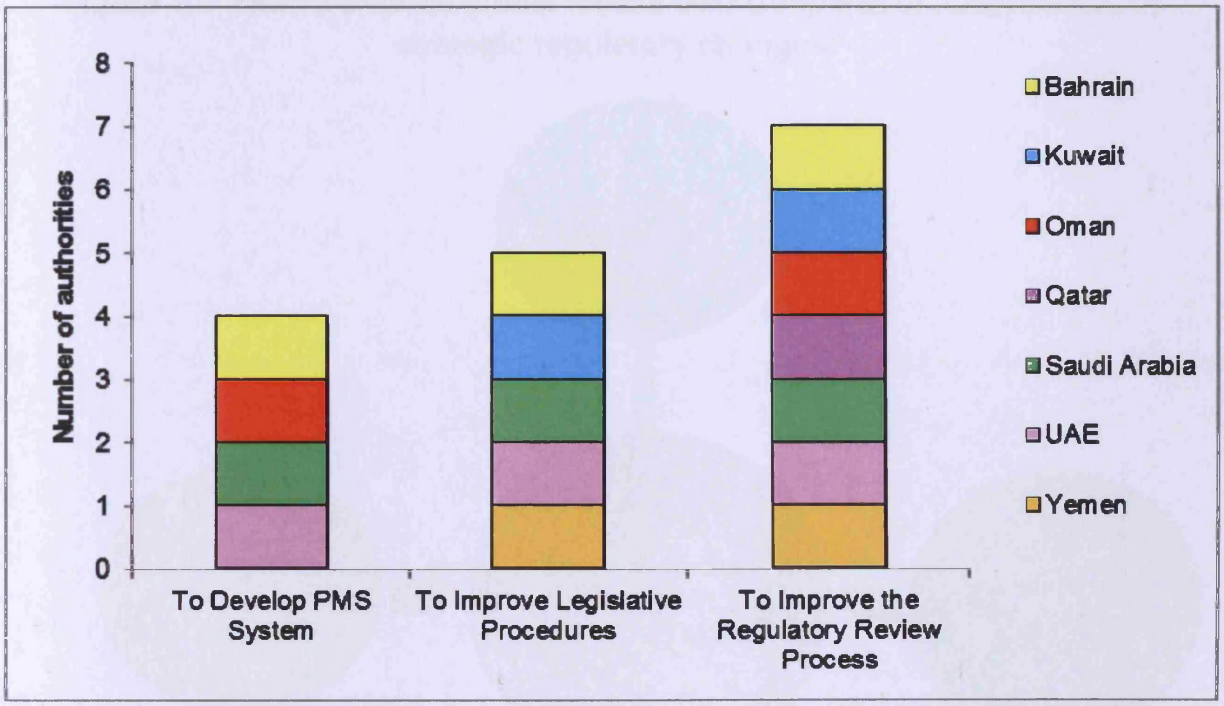
Figure 7.4 Shared Gulf Cooperation Council (GCC) regulatory goals



A variety of other goals were also mentioned such as unifying health policies, improving regulatory practices and enhancing administrative and technical capabilities, but the above two shared goals were found to be mostly linked to the authorities' vision and mission statements.

The GCC authorities have also specified their measureable steps towards achieving their desired goals. After analysing the sets of objectives provided by the Gulf States, the three most commonly shared objectives have been extracted from the responses obtained from the GCC authorities, namely to develop a PMS system, to improve the legislative procedures and to improve the regulatory review process (Figure 7.5).

Figure 7.5 Shared objectives of the seven Gulf Cooperation Council (GCC) regulatory authorities



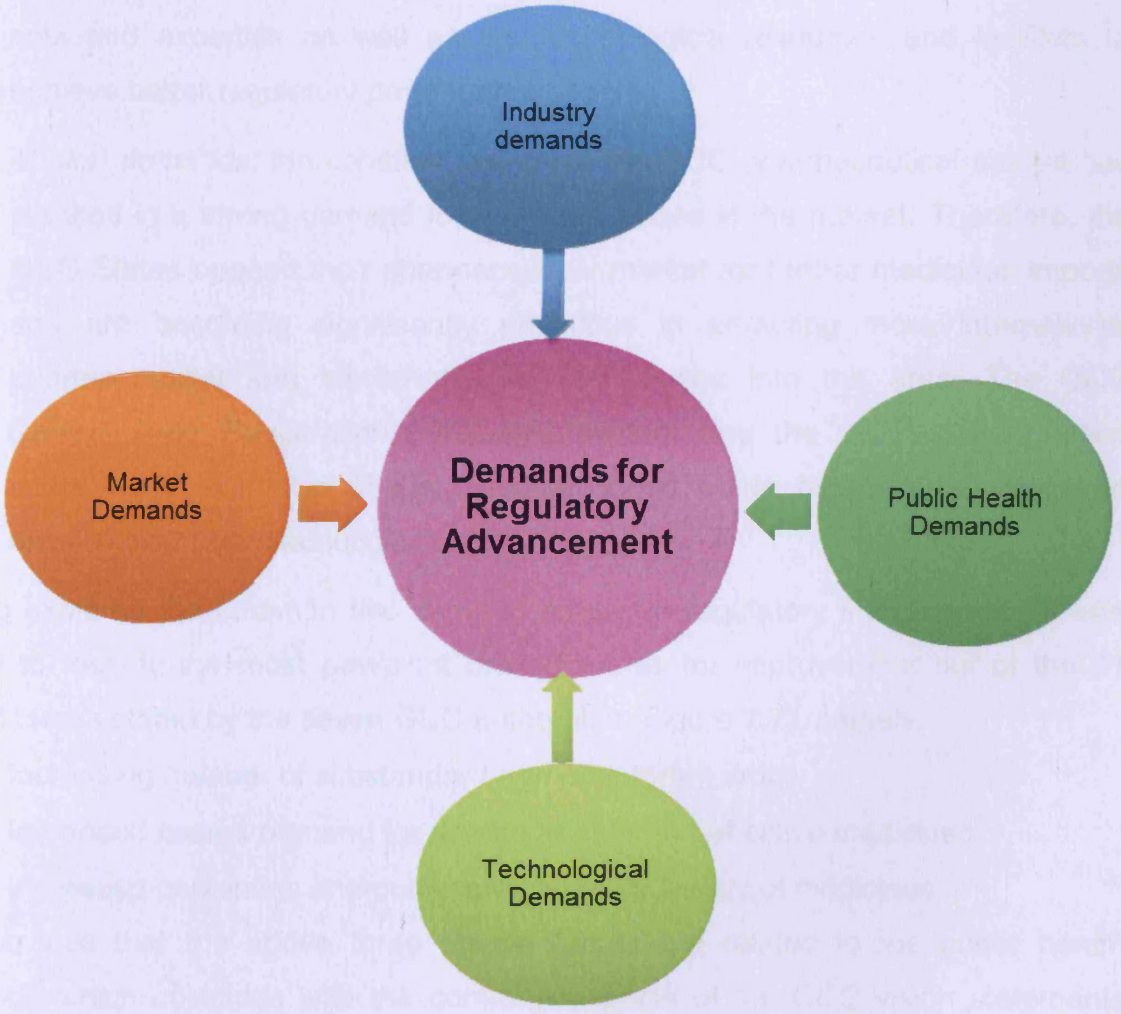
GCC regulatory driving forces

The GCC regulatory authorities collectively stated a total of 21 driving forces that are likely to have a significant impact on the authorities by 2015. Although no one driving force was shared by all the GCC states, five areas were found to be the common focus of the GCC authorities' driving forces for improvement (Figure 7.6).

These areas were revealed using the five-force model illustrated in Figure 7.6 to analyse and visually organise the five areas of demand for change that the GCC authorities experienced according to the respondents' views, namely,

1. *Demands for regulatory advancement:* this is considered the centre of the GCC authorities' focus and are, therefore, constantly facing the demands to expand and improve their regulatory services to cope with the speed of the regulatory advancement.
2. *Industry demands:* the GCC authorities are faced with the increasing number of pharmaceutical companies 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 authorisation of pharmaceutical products without affecting the quality of the new medicines.

Figure 7.6 The Five-Force model for the Gulf Cooperation Council (GCC) strategic regulatory changes



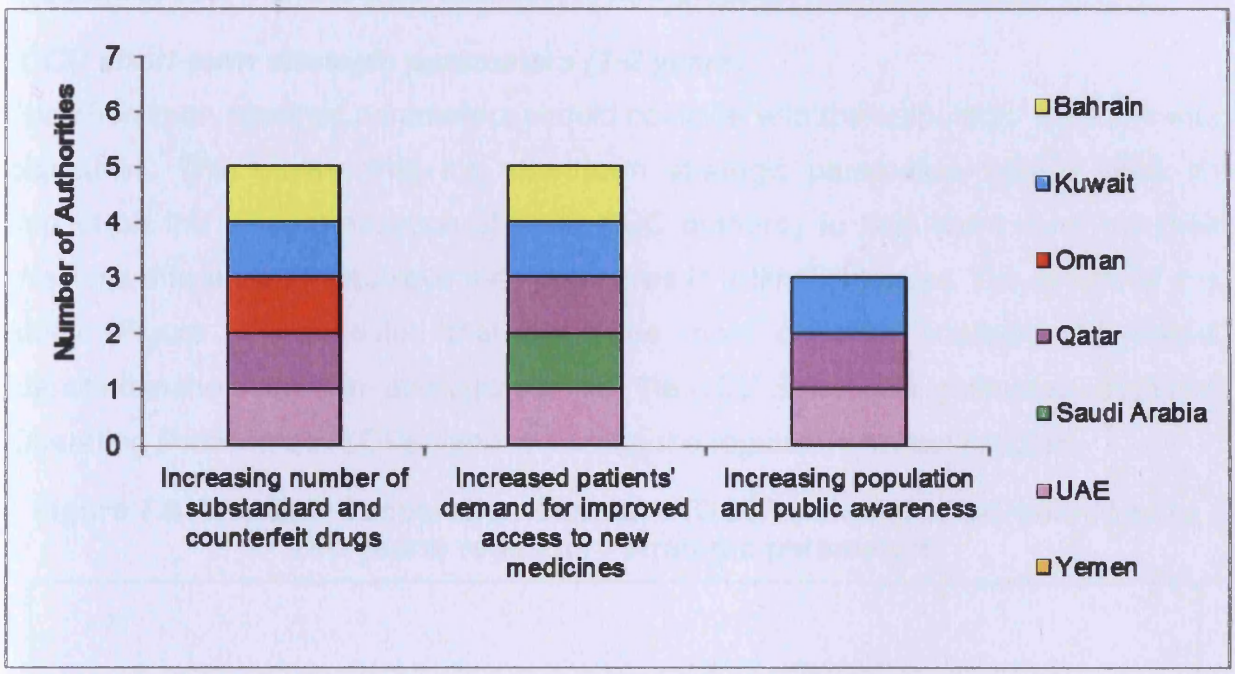
3. *Public health demands:* medicines should be safe, efficacious and of the desired quality to be available to patients at the national level. Therefore, the public health demands that the GCC authorities become sufficiently capable to combat low standard and counterfeit medicines as well as to effectively monitor the post-marketing surveillance of pharmaceutical products available in the local market. Furthermore, the authorities have the responsibility of providing national patients with innovative and high quality medicines to treat life threatening diseases or chronic illnesses and to prioritise the assessment of medically urgent medicines.
4. *Technological demands:* to cope with the latest developments in the regulatory field and to be in line with the highly competent regulatory authorities, the GCC authorities realise their need to be sufficiently resourced and capable of providing advanced regulatory services through acquiring the appropriate skill sets and expertise as well as the technological resources and facilities to achieve better regulatory performance.
5. *Market demands:* the constant growth of the GCC pharmaceutical market has resulted in a strong demand for more medicines in the market. Therefore, the GCC States opened their pharmaceutical market for further medicines imports and are becoming significantly ambitious in attracting more international pharmaceutical and biotechnological companies into the area. The GCC Central Drug Registration (GCC-DR) system and the GCC custom union policies are examples of the potential efforts made by the GCC States to expand their pharmaceutical market.

Having explored the common five demand areas for regulatory improvement, it was crucial to identify the most prevalent driving forces for improvement out of the 21 driving forces stated by the seven GCC authorities (Figure 7.7), namely,

- Increasing number of substandard and counterfeit drugs
- Increased patient demand for access to safe and effective medicines
- Increased population and public awareness of safety of medicines

It is obvious that the above three driving forces are related to the public health demands which coincides with the common aspects of the GCC vision statements described earlier.

Figure 7.7 The three most prevalent driving forces for change in the Gulf Cooperation Council (GCC) regulatory authorities



Strategy Development

After identifying all the elements to set the strategic direction and clarify where the GCC authorities are heading in the future, it is now critical to explore what they are doing to achieve their visions, missions, goals and objectives.

Strategy development is where the various findings from the external and internal analysis are placed in a context along with the mission and goals of the GCC authorities in order to determine the best course of action for success. The GCC authorities have their own strategies which were identified in this study. Each strategy shapes the authority's own identity and, therefore, in order to achieve a harmonised GCC strategy, it was crucial to analyse the common strategic parameters in the GCC short-term (one to two years) and long-term (three to five years) plans. These common parameters can be juxtaposed with the outcomes of the situational analysis and the GCC strategic direction to create a harmonised action plan for the GCC regulatory authorities. Information provided from the five-force analysis is a key to understanding the authorities' efforts to determine what needs to be done differently to achieve the desired vision.

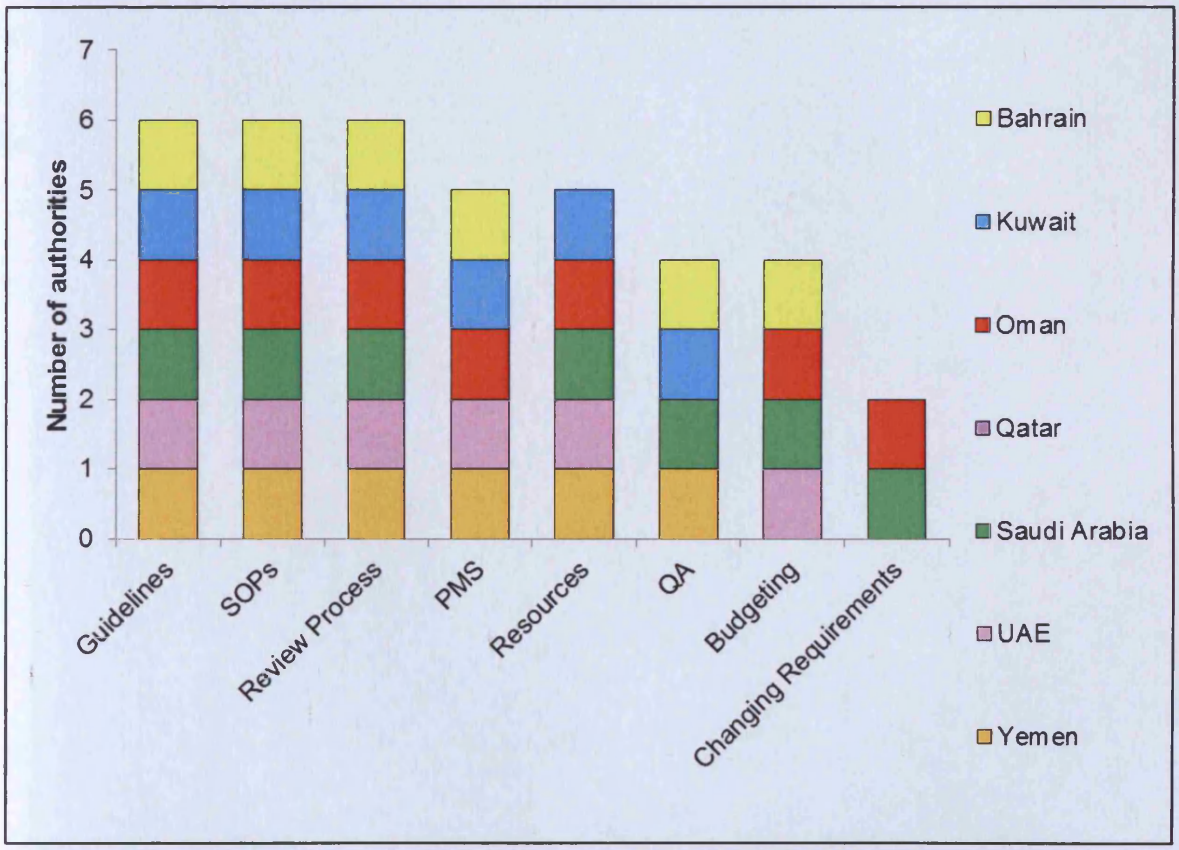
In this study, eight strategic parameters were evaluated through the assessment of the short-term and the long-term strategic plans within the seven GCC regulatory

authorities and these were guidelines, SOPs, changing requirements, quality assurance, post-marketing surveillance, review process, resources and budgeting.

GCC short-term strategic parameters (1-2 years)

The short-term strategic parameters should coincide with the authorities' missions and objectives. This means that the short-term strategic parameters should have an impact on the present situation of each GCC authority to help them carry out their missions efficiently and achieve their objectives in a timely manner. The results of this study (Figure 7.8) revealed that the three most common strategic parameters identified in the short-term strategic plans of the GCC States are: guidelines, Standard Operating Procedures (SOPs), and improving the regulatory review process.

Figure 7.8 The Gulf Cooperation Council's (GCC's) shared short-term (one to two years) regulatory strategic parameters



These parameters coincide with the shared reasons that structured the mission statements of the seven GCC regulatory authorities (to ensure the quality, safety and efficacy of the locally marketed medicines and to develop a strong regulatory system).

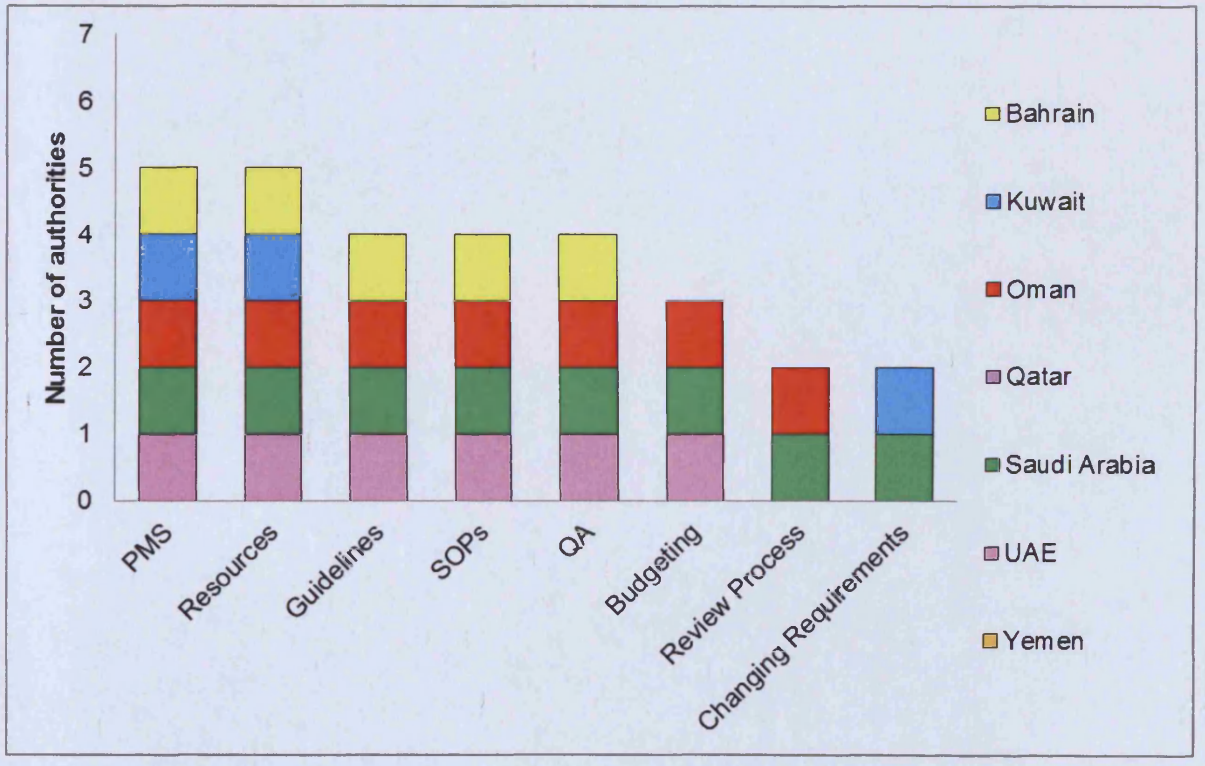
Developing standard GCC guidelines and SOPs are important to build quality into the regulatory review process and will ultimately ensure the approval of quality, safe and

effective medicines. Furthermore, the GCC standards guidelines and SOPs are essential to build the fundamental basis for a strong GCC regulatory system. The three strategic parameters also correspond to the objectives of the GCC authorities, namely, to develop a Post-Marketing Surveillance (PMS) system, to improve the legislative procedures, and to improve the review process. Developing standard guidelines and SOPs for the GCC region are essential to develop the basic foundation for a PMS system and to improve the regulatory review process and the legislative procedures. Therefore, the mission statements, the objectives and the short-term strategic parameters are correlated which suggests the possibility for the successful development and implementation of the short-term strategic plans.

GCC long-term strategic parameters (3-5years)

The long-term strategic parameters stated by the GCC authorities was found to coincide with the GCC shared visionary aspects and goals of the GCC regulatory authorities. The results of this study (shown in Figure 7.9) indicate that the two most commonly identified long-term strategic parameters are PMS and resources.

Figure 7.9 The Gulf Cooperation Council's (GCC's) shared long-term (three to five years) regulatory strategic parameters

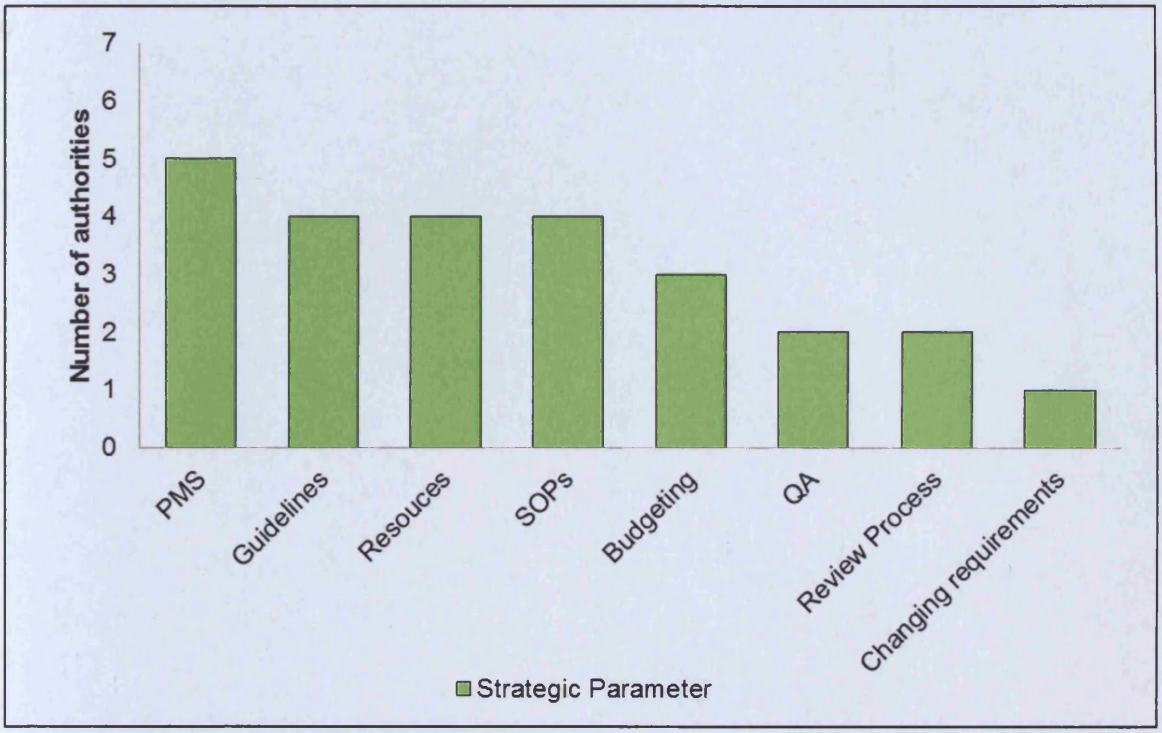


These correspond to the shared aspects of the seven vision statements (to protect the public health and to be the leading regulatory authorities in the region), as well as the two common goals (to provide the ultimate consumer health protection and to master the competency and efficiency of the regulatory practices in the region). PMS is a common long-term strategic parameter that stems from the GCC authorities' responsibilities to protect the public health from harmful effects of medicines after they are approved for marketing. The provision of sufficient resources is also important to master the competency and efficiency of regulatory practices and to ultimately become a leading authority in the region. This requires the availability of qualified and trained experts, advanced drug approval technologies, sufficient funding and work facilities to improve the performance of the GCC regulatory authorities.

Strategic parameters identified in both short-term and long-term strategic plans in the seven GCC regulatory authorities

This study was carried out to develop a common ground for a standardised regulatory system for the seven GCC authorities. It is crucial to examine the parameters identified in both the short-term and long-term strategic plans of the seven GCC authorities. The study revealed that four strategic parameters were identified (Figure 7.10), namely, the guidelines, SOPs, PMS, and resources. This means that to develop a successful harmonisation of the GCC regulatory strategic plans, the authorities should develop standardised GCC guidelines and SOPs. They should provide sufficient resources to support efficient and effective regulatory services such as qualified and trained experts and technological facilities that improve the quality of the GCC regulatory performance. The authorities are also concerned about the status of the medicines after they are approved for marketing in the region and they realise the importance of setting up guidelines and SOPs and providing sufficient resources to support the development and implementation of an efficient PMS system for the GCC Region. The GCC authorities are initiating actions with regards to the establishment of PMS activities in the region through requesting the submission of PMS reports as part of the safety data section of the registration dossier for the GCC-DR approval.

Figure 7.10 Shared strategic parameters identified in the short-term and the long-term strategic plans of the Gulf Cooperation Council (GCC) regulatory authorities



Overview of the GCC strategic planning profile

This section provides a general view of the strategic planning profile of the GCC regulatory authorities obtained from the analysis of the individual systems and the resulting shared aspects of the strategic planning processes between the seven GCC States. The analysis of the internal and external environment revealed that the GCC authorities have well-established regulatory systems which is a common strength in all the GCC States. However, they lack the qualified expertise and the proper training and continuing education programmes for their employees (Table 7.5).

The GCC authorities have the opportunity to work in collaboration with each other as well as with regional and international competent regulatory agencies to improve the performance and to seek new drug approval processes using modern technologies. These opportunities can minimise the staff turnover and can help the authorities combat the problem of substandard and counterfeit drugs entering the local market (Table 7.5).

Table 7.5 Overview of the situational perspectives shared by the seven Gulf Cooperation Council (GCC) regulatory authorities

Strategic Component	Measure	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Strengths	Experienced technical staff	✓	✓	✓	×	✓	✓	×
	Well established regulatory system	✓	✓	✓	✓	✓	✓	✓
	Good existing legislations, guidelines and processes	✓	×	✓	×	✓	✓	×
	Active cooperation with other authorities	✓	✓	✓	×	✓	×	×
Weaknesses	Shortage of experts	✓	✓	✓	✓	×	✓	×
	Lack of training and education programmes	✓	✓	✓	✓	×	×	×
Opportunities	Working in collaboration with regional and international regulatory agencies	✓	✓	✓	×	✓	✓	×
	Emerging technologies seeking new modern drug approval processes	✓	✓	×	×	✓	✓	×
Threats	High staff turnover	✓	✓	✓	✓	×	×	×
	Increased number of substandard drugs with limited resources	✓	✓	✓	✓	×	✓	×

After understanding the authorities' resources, capabilities and opportunities for improvement, their strategic directions were assessed to understand where they want to be positioned in the future (Table 7.6).

The analysis of all the components of the strategic direction (vision statement, mission statement, goals, objectives and driving forces for change) revealed that the GCC authorities aim to protect the public health from the harmful effects of medicines and, therefore, their existing mission is to develop a strong regulatory systems and to master the competency and efficiency of the regulatory practices to ensure that the locally market medicines are of the desired quality, safety and efficacy standards.

However, to accomplish their mission, the authorities have the objectives of improving their legislative procedures and their regulatory review processes as well as developing strong PMS systems. These objectives coincide with the shared aspects of the seven GCC vision statements.

Table 7.6 Overview of the directional perspectives shared by the seven Gulf Cooperation Council (GCC) authorities

Strategy component	Common Elements	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Vision	Public health protection	✓	✓	✓	✓	✓	✓	✓
	To be the leading regulatory authority in the region.	✓	✓	✓	×	✓	×	✓
Mission	To ensure QSE of locally marketed medicines	✓	✓	✓	×	✓	×	✓
	To develop a strong regulatory authority	✓	✓	✓	×	✓	✓	×
Goals	To provide the ultimate consumer health protection	✓	✓	✓	✓	✓	✓	✓
	To master competency and efficiency of the regulatory practices in the region	✓	✓	✓	×	✓	✓	×
Objectives	To develop s PMS system	✓	✓	✓	×	✓	✓	×
	To improve legislative procedures	✓	✓	×	×	✓	✓	✓
	To improve the regulatory review process	✓	✓	✓	✓	✓	✓	✓

Finally, the analysis of the short-term and long-term strategic plans revealed that the GCC authorities share four main strategic parameters identified in their overall strategic plans. These are the guidelines, SOPs, PMS and resources (Table 7.7).

Table 7.7 Overview of the strategic planning perspectives shared by the seven Gulf Cooperation Council (GCC) regulatory authorities

Component	Parameters	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE	Yemen
Short-term	Guidelines	✓	✓	✓	×	✓	✓	✓
	SOPs	✓	×	✓	×	✓	✓	✓
	Changing requirements	×	✓	✓	×	✓	×	×
	QA	✓	×	×	×	✓	×	✓
	PMS	✓	×	✓	×	✓	✓	✓
	Improving the review process	✓	×	✓	×	✓	✓	✓
	Resources	×	×	✓	×	✓	✓	✓
	Budgeting	✓	✓	✓	×	✓	✓	×
Long-term	Guidelines	✓	×	✓	×	✓	✓	×
	SOPs	✓	×	✓	×	✓	✓	×
	Changing requirements	×	✓	×	×	✓	×	×
	QA	✓	×	✓	×	✓	✓	×
	PMS	✓	✓	✓	×	✓	✓	×
	Improving the review process	×	×	✓	×	✓	×	×
	Resources	✓	✓	✓	×	✓	✓	×
	Budgeting	×	×	✓	×	✓	✓	×

The identification of the common strategic parameters expressed a strong turning point for the seven GCC authorities towards achieving a harmonised regulatory strategic plan that is applicable in the region. Setting up proper guidelines, SOPs and resources for the PMS, review process and other regulatory practices can be a potential opportunity for the development and implementation of a harmonised action plan that produces successful outcomes for the GCC authorities.

DISCUSSION

Harmonisation of strategic plans is critical for the future of the GCC regulatory authorities. It has been of interest to the GCC regulatory senior managers since the establishment of the European Centralised Procedure. The GCC authorities decided to collaborate their efforts to face the regulatory challenges together. However, prior to commencing the process of strategic planning, the concept of strategy should be

clarified. A precise (5P's) definition of strategy was given by Mintzberg (1987) which is described in the context of the GCC regulatory systems as follows,

- Strategy is a plan: it is a direction or a course of action for the future of the GCC regulatory authorities.
- Strategy is a pattern: it demonstrates consistency in the performance of the GCC regulatory authorities.
- Strategy is a position: it is the place within the environment where the authorities can seek out resources and opportunities from their surroundings
- Strategy is a perspective: it is the fundamental way of performing within the authorities according to their internal capabilities
- Strategy is a ploy: a specific "manoeuvre" intended to overcome any regulatory challenges.

The GCC strategies should fulfil the above 5P's criteria to be successful. However, planning includes several activities or steps in the process. Different people often have different ways of presenting a strategy for an organisation which is considered the fingerprint of a successful strategic manager. There is no "perfect way" to conduct a strategic planning process but the basic fundamental components are common in all strategic plans.

The order of the strategic planning activities in this study was based on the fact that the GCC authorities are well-established organisations with long historical backgrounds that gave distinctive identities to the seven authorities. These individual identities cannot be neglected when establishing a new harmonised vision for the region and for this vision to be reachable it has to be formulated within the context of the existing status of the regulatory systems. Furthermore, the shared values and beliefs of the GCC authorities were also critical for this study because they determine the parameters or boundaries for setting the strategic options. The study revealed that seven values were found to be the most prevalent in the GCC region, namely, efficiency, competency, honesty, integrity, professionalism, confidentiality, and transparency. The GCC strategic options are bound by these beliefs and, therefore, it is an important start for a successful mapping for the GCC harmonised strategic plan. Then, it was reasonable to perform some sort of scan, or review, of the present status of the individual authorities within the regulatory environment by looking at their strengths, weaknesses, opportunities and threats (SWOT analysis). The SWOT

analysis revealed several organisational needs and capabilities that were explored in the comparative study of the regulatory review processes and the measures used to achieve quality in the review processes in the GCC States (Chapter 5 and Chapter 6).

The first positive factor was the active cooperation with other authorities which was stated by four out of seven authorities (Bahrain, Kuwait, Oman and Saudi Arabia) as a strength. This cooperation is actively seen in the joint review performed by the GCC regulatory authorities for the GCC Central Drug Registration (GCC-DR) system. Joint review was a quality measure addressed in detail in Chapter six which explored the strong cooperation between the seven states as an effective monitoring system to ensure consistency and clarity of the review process.

The second positive factor was the opportunity to work in collaboration with regional and international agencies. This was an opportunistic view shared by five out of seven authorities (Bahrain, Kuwait, Oman, Saudi Arabia and UAE) which corresponds with the collaborative activities that exist in five authorities (Bahrain, Oman, Qatar, Saudi Arabia and UAE) and explored in Chapter six to provide training and continuing education for the assessors. These collaborative efforts are essential to build the assessors' knowledge and skills in the area of dossier assessment. However, training should be formalised and emphasised to achieve the desired quality outcomes. The downside of not enforcing the training programmes was perceived as a weakness by the GCC States because it is an critical element to achieve quality in the regulatory practices.

The third positive factor shared by four GCC authorities (Bahrain, Kuwait, Saudi Arabia and UAE) was the opportunity for advancement by utilising new technologies for the drug approval process such as the electronic submission of the common technical document (e-CTD) which has been introduced in the Saudi Food and Drug Authority (SFDA). All the positive factors are considered critical to overcome the threats that concern the GCC authorities such as the high staff turnover and the increased flood of counterfeit and substandard drug into the GCC market.

The next phase of the strategic planning process is setting the strategic direction. It is now possible to come to a conclusion about what the GCC States must do as a result of the major issues and opportunities facing them. This conclusion includes the ultimate strategic goals they should achieve. The objectives underpinning the goals

should be Specific, Measurable, Achievable, Realistic and Timely (SMART) (Bell, 2004). The goals should coincide with the vision statement while the objectives should be able to achieve the missions of the GCC authorities. The results showed that the four components of the strategic planning process were closely linked to each other and, therefore, they can be achieved with success. Furthermore, the authorities demonstrated the major demand areas that drive them towards improving their practices and the results showed that the three most prevalent driving forces (the increasing number of counterfeit medicines, the increasing patients' demand for improved access to medicines and the growing public awareness as well as the size of the population in the each country) revolved around the public health demand as the major driving force for better regulatory services in the region. Standardising the GCC vision and mission statements helps the GCC authorities to focus their efforts onto the area of protecting the public health underpinning the GCC harmonised regulatory strategy.

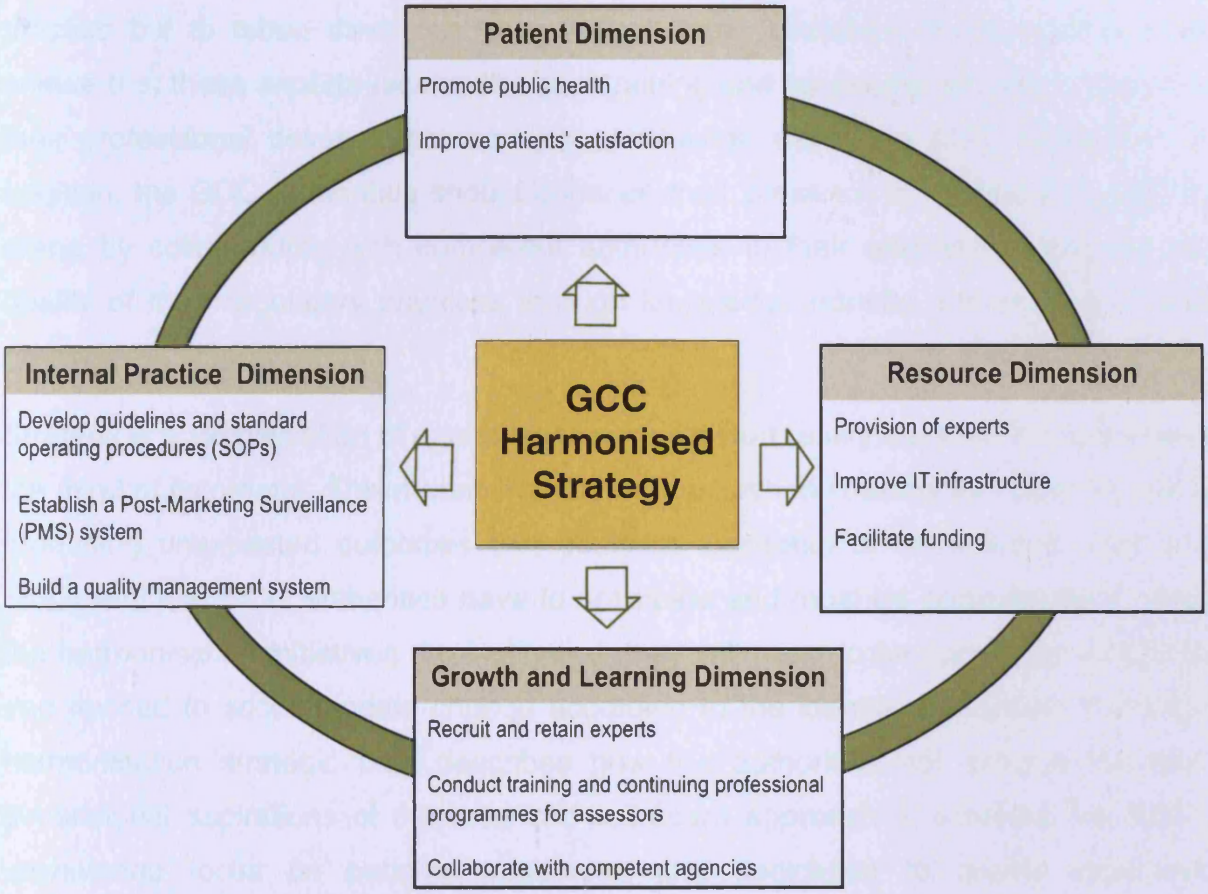
Balanced-Scorecard Framework for the GCC Harmonisation strategy

After using the five force model to analyse the competitive capacities of the GCC authorities, it is reasonable to generate a framework for the harmonised GCC strategic plan using the balanced scorecard approach. The balanced scorecard is a performance measurement methodology for organisations to track the progress in achieving their strategic goals. In order for the GCC authorities to implement a successful harmonisation strategy, they need to create a balance in their performance between four strategic dimensions (Figure 7.11), namely,

- Patient dimension; this is a patient-focused organisational performance.
- Resource dimension; this focuses on organisational performance associated with the availability of resources.
- Internal practice dimension; this measures the internal practices and system processes of efficiency and effectiveness.
- Growth and learning dimension; this measures the progress towards achieving the attraction, development and retention of staff

The idea is to develop two or three measurements for each dimension that can be directly linked to the shared aspects of the GCC strategic vision and goals.

Figure 7.11 Balanced Scorecard framework for the Gulf Cooperation Council (GCC) harmonised strategic planning process



Template was adopted from: www.bscdesigner.com

Patient's dimension is the most critical strategic dimension in this study as the aim of any regulatory authority is to protect the patient from harmful effect of medicines and to make safe and effective medicines available to patients in a timely manner. However, to achieve this, the GCC authorities must ensure the availability of appropriate financial, technological, human and other tangible resources (e.g. computers, books and work facilities) to achieve the required performance level.

Furthermore, the GCC authorities need to pay attention to their internal practices which can have a significant impact on the quality of their regulatory practices such as developing guidelines and Standard Operating Procedures (SOPs), establishing efficient and effective Post-Marketing Surveillance (PMS) and Quality Assurance (QA) systems.

Finally, the authorities should always ensure that their technical staff are updated with the latest developments in the regulatory field. Recruitment of experts is an essential practice but to retain them can be a difficult task. Therefore, the authorities must ensure that these experts receive the best training and continuing education to ensure their professional development and job satisfaction within the GCC authorities. In addition, the GCC authorities should enhance their presence in the global regulatory arena by collaborating with competent authorities in their attempts to improve the quality of their regulatory practices through knowledge transfer and sharing of best practices.

Strategy is a simplification of a process that may distort reality because it only exists in the mind of its creator. This means that the harmonisation strategy can face the risk of producing unexpected outcomes that could be desirable or undesirable. This is a probability that GCC authorities have to anticipate and must be prepared for it. Once the harmonisation initiatives are instigated, they will need to be constantly monitored and revised to accommodate change according to the identified priorities. The GCC harmonisation strategic plan describes how the authorities will achieve the four-dimensional aspirations of the balanced-scorecard approach. It confirms the GCC's unwavering focus on patients, resources and dedication to quality measures. Consolidating redundant systems and eliminating unnecessary processes in each GCC authority are the first step towards the desired goals.

In this study, eight strategic parameters were explored and associated with the GCC strategic objectives (Guidelines, SOPs, changing requirements, quality assurance, PMS, improving the review process, resources and budgeting). Four out of the eight parameters were identified in both short-term and long-term strategic plans of the GCC States. These are: guidelines, SOPs, PMS and resources. By examining the standardised GCC aims, a direct correlation can be observed between the GCC standard aims and their common strategic parameters. Setting up standardised guidelines and SOPs for the pharmacovigilance system and regulatory review processes is the fundamental responsibility of the GCC authorities. These also require the provision of adequate human and technological resources as well as setting up the appropriate infrastructure to build strong and competent regulatory systems in the GCC Region.

SUMMARY

- The GCC States expressed several values and beliefs that were considered as the basic boundaries for their strategic options.
- The seven GCC regulatory authorities have well-established systems with robust historical backgrounds that shape their individual identities in the regional and international regulatory environment.
- The situational analysis of the GCC regulatory authorities revealed general internal and external strategic conditions that determined their resources and capabilities to set a basic common ground for their future strategic directions.
- The seven member states demonstrated several shared features in setting a future harmonised regulatory strategic direction for the GCC Region.
- The shared aspects resulted in the emergence and proposal of a new vision statement, mission statement and standard regulatory aims that were used as the basic component of developing harmonised action plans for the Gulf Region.
- The GCC States are responsible to fulfil several regulatory demands particularly the public health demand for patient access to safe, effective and quality medicines in a timely manner which is the major driving force of the GCC authorities to improve their regulatory systems.
- The seven Gulf States shared common strategic parameters that form the basic building blocks of a harmonised regulatory strategic plan, namely, guidelines, standard operating procedures (SOPs), resources, and post-marketing surveillance (PMS).

CHAPTER 8

General Discussion

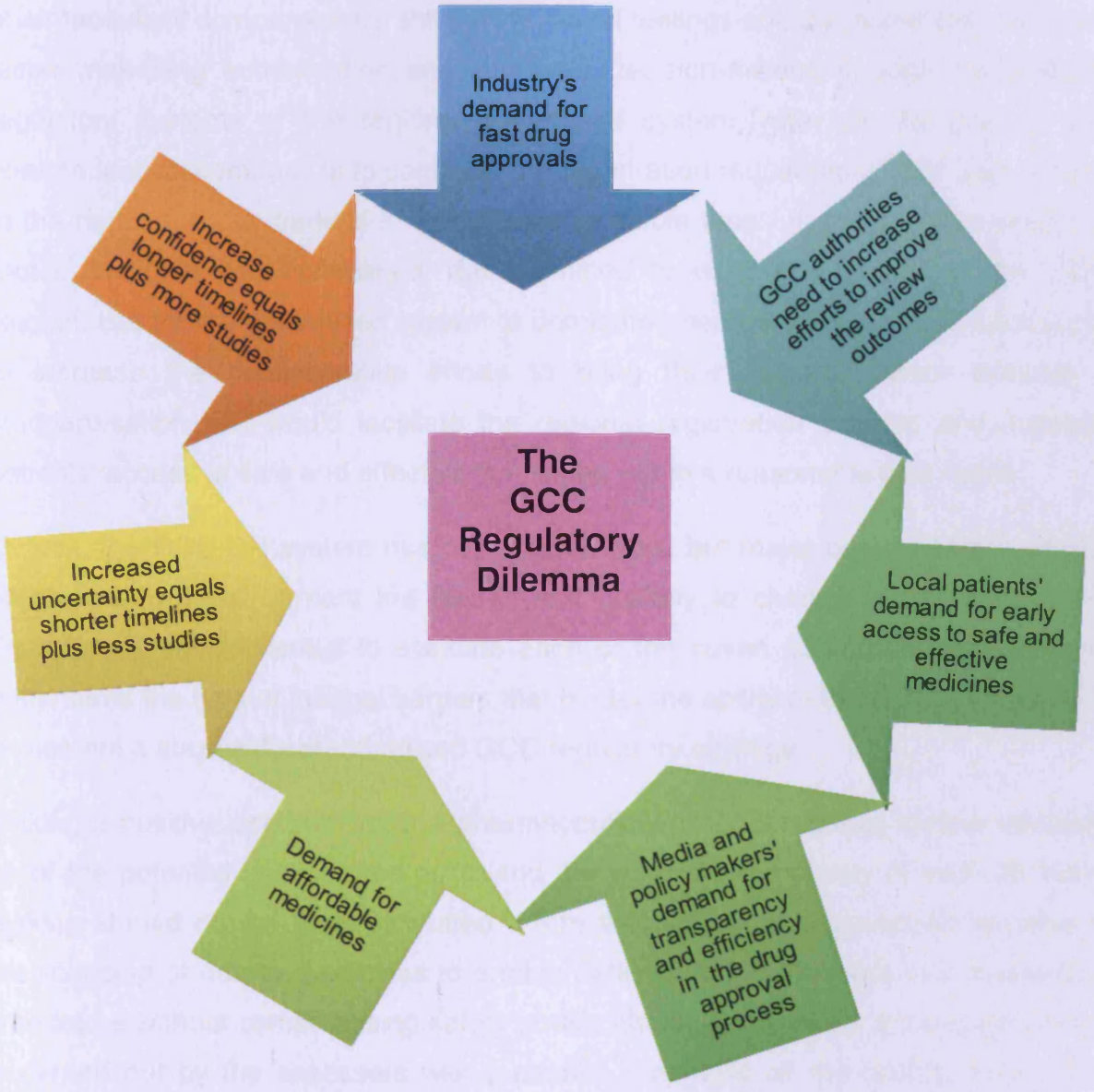
The current dynamics of bringing new medicines to market are being influenced by conflicts between the agendas of regulators and payers (McAuslane et al., 2009). This dilemma has been further complicated by previous high profile drug withdrawals, the increasing need to improve the drug development systems, and the need to avoid exposing patients to unnecessary risks of possibly ineffective treatments (Eichler, 2008). Despite the existence of standards for drug regulation now for at least 50 years, there are still many problems with the safety and efficacy of medicines in both developing and developed countries. The regulators are under pressure from the pharmaceutical industry to approve medicines more quickly by minimising regulatory 'bottlenecks' and to carry out reviews and evaluations of data in the shortest possible time (Hill and Johnson, 2004).

Medicines are not ordinary commodities as patients are not in a position to make appropriate decisions about when to use them. Due to the sophisticated scientific issues related to medicines, medical training alone may not be sufficient to be able to make professional judgement about their safety and efficacy. Similarly, basic training in pharmacy may not be sufficient to make proper judgements about medicines quality, efficacy and safety (American Pharmaceutical Group (APG), 2010). The regulators' dilemma of balancing access to market against the requirements for complete registration data is also reflected in the European Medicines Agency's (EMA) draft roadmap to 2015 (Lonngren, 2010). The EMA's primary focus is on improving core regulatory operations that address the public health needs, facilitate access to new medicines and optimise the use of medicines. Public health interests are the responsibility of all regulatory authorities. However, in practice this means balancing the interests of industry (commercial productivity) and patients' needs (Hashan, 2005). The same challenges caused the emergence of the GCC regulatory dilemma and its impact on patients' access to medicines in the seven Gulf States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) (Figure 8.1).

The GCC regulatory authorities are under pressure to fulfil several responsibilities towards the public, industry, media, politicians, and towards each other. They need to satisfy the industry and public demands by approving effective medicines in a timely manner, to coordinate their efforts to make sure that these medicines are approved quickly without negatively impacting the quality of the assessment process, to ensure

that these medicines are not overpriced and to respond to media and policy makers with maximum transparency about why certain medicines are approved or rejected.

Figure 8.1 The Gulf Cooperation Council (GCC) Regulatory Dilemma



Historically, 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. This system was initiated after the European Centralised Procedure had succeeded in overcoming numerous challenges and had earned the trust of both European (EU) member states and the pharmaceutical industry since its inception in 1995.

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 the GCC-DR cannot implement a compulsory system until the required level of standardisation in the regulatory review systems has been reached. However, pharmaceutical companies are still having mixed feelings about whether they can gain faster marketing authorisation and improved decision-making through the national regulatory systems or the regional centralised 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. 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 a standardisation that would facilitate the regional registration process and maintain patients' access to safe and effective medicines within a reasonable time frame.

Overall, the GCC-DR system has had a good start, but major barriers still lie ahead and some of these barriers are built-in and unlikely to change in the near future. Therefore, it was essential to evaluate each of the seven authorities individually to understand the type of internal barriers that hinder the ability of the GCC authorities to implement a successful standardised GCC regulatory strategy.

Making a positive decision about a pharmaceutical product requires careful weighing up of the potential benefits and risks, and the scientific complexity of such decision-making should not be underestimated. 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. 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 and 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 (Rägo and Santoso, 2008). Therefore, the GCC States need to strengthen their national regulatory authorities to ensure that the manufacturing, marketing and use of medicines are

regulated effectively. In broad terms, the mission of the national authorities is to protect and promote public health (Rägo and Santoso, 2008). While this may sound logical in theory, the differences in interpretation are considerable between regulatory authorities in the GCC region.

The purpose of this research has been to evaluate the regulatory environment 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 Kuwait in order to develop an appropriate model for the evaluation of other GCC countries in the region. Trends in patients' access to New Active Substances (NASs) and Existing Active Substances (EASs) in the government and private sectors over the period from 2006 to 2009 in Kuwait was analysed in chapter four. The similarities and differences of the regulatory review process between the seven GCC authorities was the focus of chapter five while chapter six compared the elements of quality used in each of the seven authorities to optimise the decision-making outcomes and improve the quality of the review process. Finally, the regulatory strategic planning processes in each of the seven GCC authorities were examined in chapter seven to identify the common strategic parameters that can be used to establish a harmonised regulatory strategic planning process for the GCC Region.

The study began by thoroughly examining the Kuwait Drug and Food Control (KDFC) authority as an example of a medium-sized regulatory authority in the Gulf Region to gain an insight into certain aspects and gaps that may have been overlooked when conducting the comparative study on the member states. Furthermore, the previous study conducted on the GCC Region by Hashan (2005) examined the Saudi General Directorate of Medical Licensing and Pharmaceutical Affairs, which was the regulatory body controlling the licensing of medicinal products under the autonomy of the Ministry of Health until 2008. The new Saudi Food and Drug Authority (SFDA) is an independent stand-alone authority which was established to perform high standard, sophisticated and specialised regulatory practices in Saudi Arabia. Therefore, it was neither possible to follow-up the progress of the previous research nor to use SFDA to represent the majority of the medium sized and less developed authorities in the Region.

One of the most distinctive practices undertaken by the KDFC is the existence of two separate departments for the pricing and registration of pharmaceutical products. The two departments have run in parallel to register and price a medicinal product since June 2009, while they were running sequentially by registering the product and then pricing it after granting the registration approval before 2009. This improved practice may have an impact on the speed of the registration process and the timely access to new medicines. It is a similar, but less sophisticated, system to the Canadian pricing mechanism. Health Canada has an independent Medicines Prices Review Board which was created to ensure that the new medicines are not overpriced. The board issues an annual report to the parliament through the Minister of Health on drug price trends of all medicines, cost drivers and drug utilisation plans in Canada (Health Canada, 2006). The Kuwait pricing department has a simple role of performing a comparative price analyses with regional regulatory authorities, particularly UAE, to determine the price of a medicine to be marketed in Kuwait. With the population growth and the increasing lifestyle diseases (e.g. cardiovascular diseases and diabetes), it is essential to undertake cost-effective analysis as part of the price review process in Kuwait and the other GCC States and this is a common deficiency in the entire GCC Region.

Another important aspect that needs to be highlighted in Kuwaiti 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 recognised regulatory authorities. If not, it is critical to consider a thorough and more specialised 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 authorised by at least two reference authorities (EMA, US FDA, Health Canada and MHRA) (Health Science Authority (HSA), 2011), except for biological and biotechnology products. This is similar to the Bahraini and UAE models of review. Bahrain carries out a verification review for all types of products registered in countries with competent authorities and an abridged review for biological and biotechnology products. UAE conducts an abridged review for all types of applications approved by recognised authorities and a full review for applications not approved elsewhere. Saudi Arabia performs a full review on all types of application while Oman performs an abridged

review for all products and Yemen, Qatar and Kuwait uses a verification review for all products. It must be noted that all the GCC regulatory authorities require the submission of the Certificate of Pharmaceutical Product at some point during the registration process as this is the most important requirement for successful completion of the approval process in the seven member states. The GCC countries 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 such as biological and biotechnology products.

Furthermore, this research project explored areas of similarities and differences that enable the achievement of a successful standardisation of the regulatory review process in the Gulf Region. An extensive amount of work has been carried out over the last decade with several emerging markets such as in Southeast Asia and Western Pacific, Middle East and Africa, Latin America, and Central and Eastern Europe (Walker et al., 2005a; Walker et al., 2005b; Walker et al., 2005c). But a thorough examination of the GCC review process and the quality measure used to improve the quality of the assessment procedures have only been carried out by Hashan (2005). However, several changes have occurred since 2005 such as the transition of the Saudi regulatory authority from the Ministry of Health to the independent SFDA, the accession of Yemen as a new member in the GCC Council for Health Ministers and the GCC Central Registration Committee and the structural and managerial changes that occurred in the UAE regulatory authority in 2008. These may have had an impact on the speed of patients' access to new medicines. The impact could be positive if it involved a transition to a more developed, specialised and independent regulatory system like in SFDA, or it could be negative if it involved managerial changes that include personnel of less experience and/or skills than the previous ones. This is a critical issue that can influence the quality of decision-making in any regulatory authority.

Patients' access time to NASs and EASs in the private and government sectors was examined in Kuwait. It was not possible to carry out a comparative assessment between approval times of medicines in the seven Gulf States due to the lack of electronic tracking systems that allow retrospective analysis of the approval times to be made in each GCC authority. However, being part of the key regulatory team in the KDFC, the author was able to collect data on the registration and pricing times from

the archived documents in Kuwait for the period 2006 to 2009. The findings showed that median patients' access time to NASs in Kuwait ranged from 11 to 26 months over the period from 2006 to 2009, while for EASs it was between 14 to 28 months. This was not too different from the WHO (2004) published data on the marketing authorisation time for industrial countries over the period from 1993 to 2001.

WHO (2004) also published marketing authorisation approval times for other developing countries. However, the limited data obtained suggested that the average approval times for the pharmaceutical products are often faster that in developed countries with the largest pharmaceutical market share. In particular, Costa Rica has approval times approaching 1.5 months. These short approval times were similar to those which occurred in Kuwait in 2008 where the most efficient practices were being in place evidenced by the shortest median time for patients' access to NASs (5.5 months) and EASs (6 months) throughout the four-year study period.

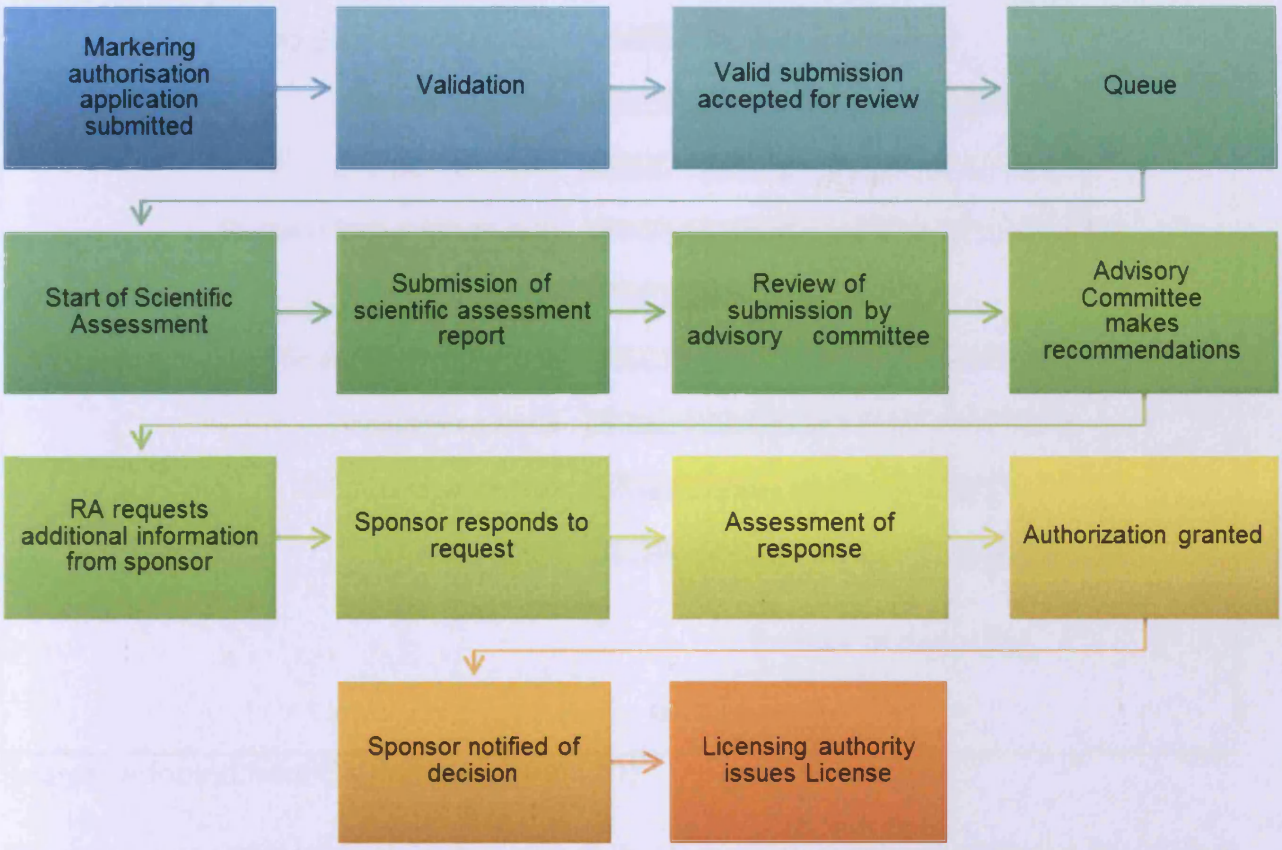
In providing an insight into the approval timelines in Kuwait as an example of a medium sized regulatory authority in the GCC Region, it was reasonable to examine the common milestones and stages of the review processes conducted in each Gulf State. These milestones can provide an idea about the steps involved in the GCC review process which may have an impact on the overall approval time.

Regulatory review milestones were previously evaluated in mature agencies to understand the reasons behind their differences in the review times (CMR Briefing 11, 1997). Eleven authorities were invited, namely Australia, Canada, European Union (EU), France, Germany, Italy, Japan, Netherlands, Sweden, UK and USA and nine participated in the study. The assessment was based on the 'Generic' regulatory review process suggested by CMR (1997) for the eleven authorities to identify which of the steps were relevant to their own procedures (Figure 8.2).

The study showed that the date of submission was the only milestone recorded by the nine authorities. Likewise, the seven GCC authorities also record the submission dates. The quality, safety and efficacy sections of the dossiers are assessed in the nine authorities, while even though they are required to be well organised in three sections (quality, safety and efficacy) for submission to five GCC authorities, most of the Gulf States perform nonclinical and clinical assessment only when there is a query

that needs to be examined. However, six GCC authorities perform extensive pharmaceutical quality assessment on all applications.

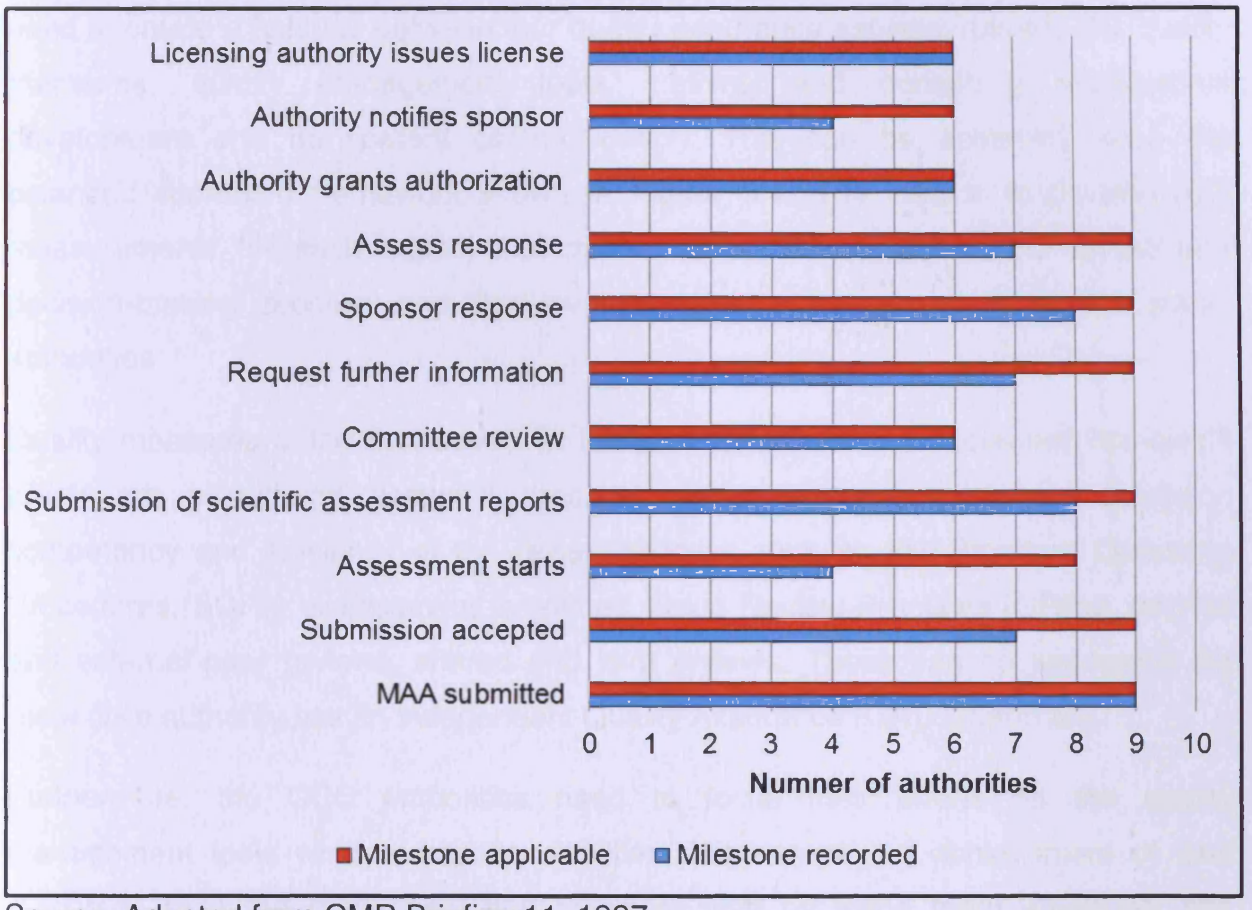
Figure 8.2 The 'Generic' regulatory review process



Source: adopted from CMR briefing 11, 1997

In general, when the review process was evaluated for the regulatory authorities in mature markets (CMR Briefing 11, 1997), it was possible to obtain information about the applicable milestones in each authority and to gain an insight into the time taken for each milestone to be completed in each authority (Figure 8.3). This is not applicable in the GCC States simply because the electronic handling and tracking of review times does not exist in the majority of the GCC States which makes it hard to perform comparisons between review times for the Gulf States. Therefore, the authorities were asked to provide their target times to complete each milestones in the review process. However, although these target times can provide a rough estimate of what the authorities are hoping to achieve in terms of the speed of the patients' access to new medicines, they may not reflect the true situation.

Figure 8.3 Milestones recorded by nine mature authorities



Source: Adopted from CMR Briefing 11, 1997

The other important aspect in this research study is the activities carried out in the GCC authorities pertaining to the quality as it applies to regulatory submission and procedures, rather than the more conventional association with the quality assurance of the medicines themselves (Cone and McAuslane, 2006). This is a very critical aspect of the regulatory approval process because the goal of any management in any competent authority is to meet the obligations placed on them by the government and to meet the expectations of stakeholders (industry and public), for safe and effective medicines to be made available to patients. In order to achieve this, quality measures should be built into the regulatory review process as well as to the submitted dossier (Smith, 2001). This study is particularly important for the GCC regulatory systems because the limited data available on the review timelines does not imply a low review performance level as this can be better determined by examining the quality management tools being used to achieve an acceptable performance outcome in each authority.

In order for the GCC authorities to build quality into their regulatory practices, they need to create a balance between four quality assurance aspects, namely, the quality measures, quality management tools, training and continuing professional development and transparent communication. This can be achieved using the balanced scorecard framework shown in Figure 8.4. The idea is to develop four measurements for each aspect that directly affect the quality of the review and decision-making process and the level of performance in each of the seven authorities.

Quality measures is the first aspect in the proposed balanced scorecard framework which are considered essential practices for ensuring consistency, accuracy, competency and efficiency of the review process such as the Standard Operating Procedures (SOPs), assessment templates, Good Review Practices (GRPs), internal and external peer reviews, shared and joint reviews. These can be secured if the respective authority has an independent Quality Assurance (QA) department.

Furthermore, the GCC authorities need to focus their efforts on the quality management tools which comprise activities that ensure the achievement of best outcomes from the managerial and technical staff by using them effectively and efficiently. These activities include reviewing stakeholders' and assessors' feedback, providing feedback to the pharmaceutical companies on the submitted dossier, carrying out internal and external audits and establishing an electronic tracking system for monitoring the approval process in each of the seven authorities.

Training and continuing professional development (CPD) programmes involve engagement of experts to work with the authorities' staff to improve the quality of their assessment through knowledge and skill transfer. These programmes are critical for the advancement of the GCC regulatory systems because they motivate the employees to be more efficient, increase their capacity to adopt new technologies and methods, reduce staff turnover and enhance creativity and innovation. This can be achieved by conducting formal training programmes for assessors, providing placements and secondments to competent authorities, attending external courses and post-graduate programmes and carrying out in-house and/or on-the-job training.

Figure 8.4 Balanced scorecard framework for the types of quality measures and activities included in the study on the GCC regulatory authorities

Template adopted from: www.bscdesigner.com

Finally, transparent communication is an important aspect for building quality into the GCC regulatory systems. Effective communication ensures knowledge transfer, saves time and expenses for information transfer, enhances the relationship between the sponsor and the authority, increases the employees' confidence and job satisfaction, and prevents confusion and misunderstanding of the delivered message regarding sensitive issues. Transparency builds trust between the two parties through sharing knowledge, continuous follow-up, consistency and predictability of outcomes. These can be achieved by providing pre-submission advice and increasing the level of information made available to the public. Furthermore, post-approval discussion

between the sponsor and the authority is a critical practice to improve the quality of the review process and the submitted dossier which will enhance the level of trust between the two organisations. It is also useful to build trust in the authority's technical staff by allowing them to take part in the communication process and provide their valuable inputs for the pre-submission and post-approval discussions with the sponsor. This improves the assessors' knowledge and skills in handling a quality review more efficiently and effectively. Therefore, details of the technical staff involved in the review process should be provided to sponsors.

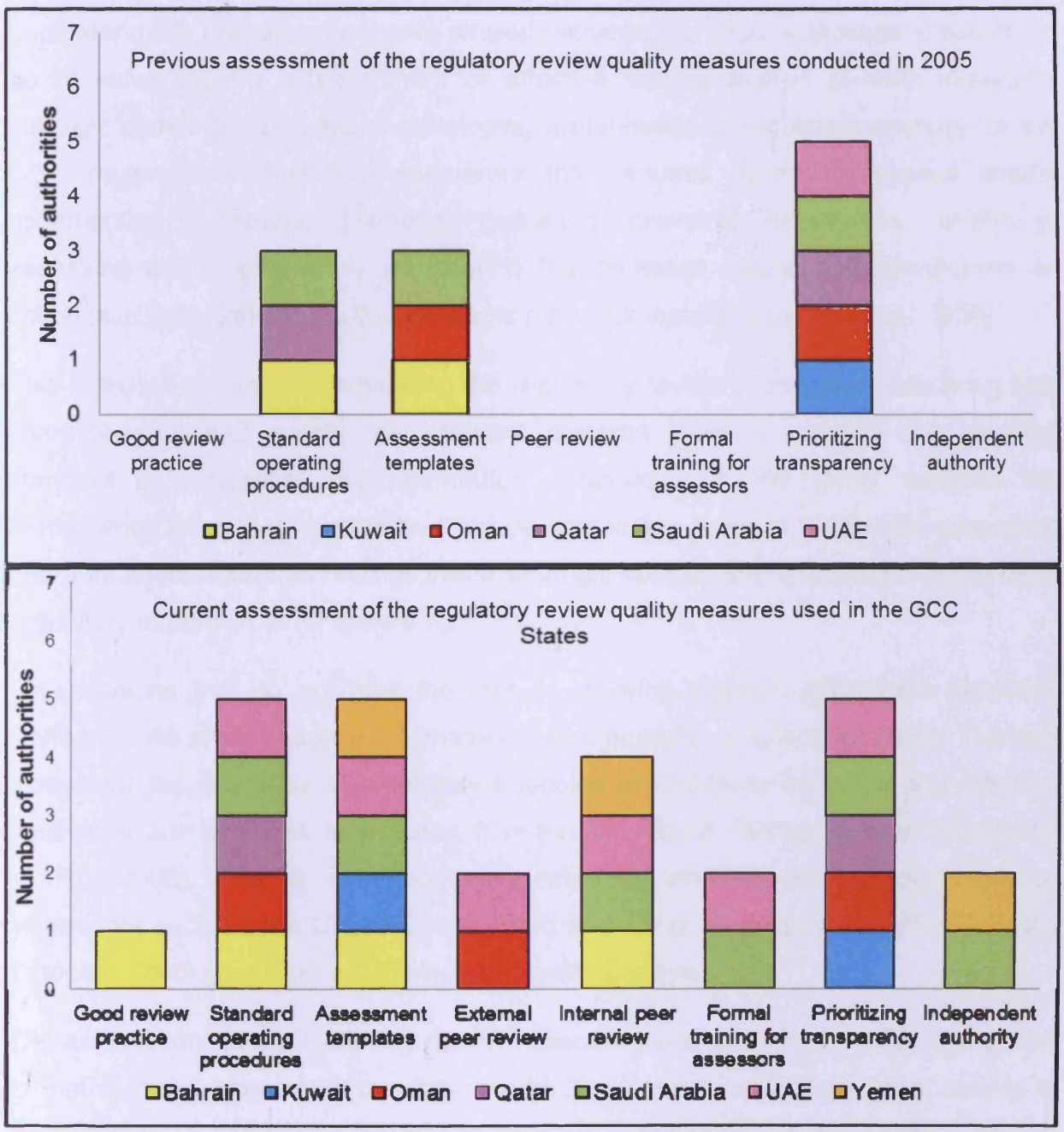
The previously conducted study by Hashan (2005) revealed numerous gaps in the quality management systems in place. Several quality measures did not exist in most of the GCC authorities and even the ones which did exist in a few of them were used differently. This made the comparison between the seven GCC authorities rather difficult to achieve. Furthermore, the quality building was a fairly new approach which was never encountered by any Gulf State before. Therefore, addressing areas for improvement in the quality of the review process rather than approval timelines was an eye catching concept, yet it was hard to be fully understood by the GCC regulators.

This study follows on the progress of the previous research on building quality into the GCC regulatory review process. The added value that this study presents is that regulators are now more familiar with the quality measures and are more able to highlight important areas of quality that are currently in place, and which may have evolved since the last research project.

The most important quality measures that showed a significant change since the last GCC Study are illustrated in Figure 8.5. The figure shows the outcomes of the last study as opposed to the outcomes generated from this study. The progress is evidenced in the increasing number of authorities adopting quality measures to improve their regulatory review practices (Figure 8.5).

It is now important to take the key outcomes generated from the research and apply them in the context of the standardised strategic planning process to identify the starting points that need to be addressed to build a GCC regulatory strategy which aims at standardising the regulatory review process in the Gulf Region.

Figure 8.5 A progress of the quality measures adopted by the GCC regulatory authorities since 2005



Regulatory strategy is an end-product of regulatory intelligence. Great ideas and good intentions cannot by themselves lead to a successful project (Iyer et al., 2004). Essential elements of the standardisation process include strategy formulation and implementation. The goal of regulatory intelligence is to proactively understand the regulatory environment, current trends, available resources, applicable and adoptable factors, and the values and missions that govern a successful standardisation of the regulatory strategies in the GCC Region. Therefore, a thorough investigation of the

review systems, quality measures used to improve the assessment procedures and the strategic planning processes in the seven Gulf States was carried out to understand the critical components shared between the GCC authorities which could be of value for the establishment of effective standardisation of their regulatory strategic plans. The process of developing a standardised regulatory strategy for the GCC region is a multi-step endeavour that requires identifying shared needs, ascertaining resources, planning, gathering pertinent information, analysing, assessing and appropriately interpreting the gathered information, developing an action plan, and drafting the final strategic report for distribution (Iyer et al., 2008).

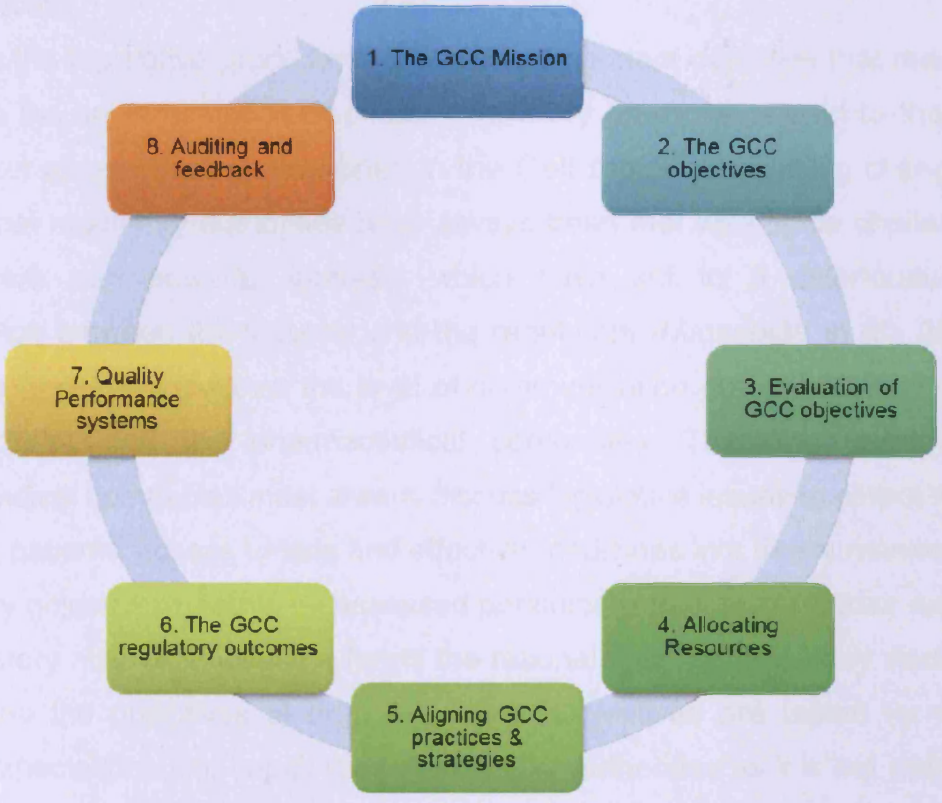
This research focused on evaluating the regulatory review processes, assessing their characteristics and quality management systems used to achieve the required standard of outcomes. The information obtained from this study revealed the fundamental gaps that need to be filled by developing a set of systematic processes that puts all the research findings into a strategic context that shapes the future GCC regulatory strategic plan (Figure 8.6).

Organisations that do not take the time to develop mission statements are often ineffective. An organisation with a mission has a purpose, a reason for being. The sole reason for the existence of regulatory agencies is to ensure that safe and effective medicines are available to patients (Center for African Refugees and Immigrants (CARI), 2008). This is commonly suggested in international agencies' mission statements such as the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), and Health Canada.

The assessment of the GCC regulatory missions revealed that their roles are similar to that of major agencies around the world. They aim to ensure patients' access to quality, safe and effective medicines and to develop strong regulatory systems. However, this study showed that 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 fulfil the regulatory needs. The GCC States recognize the importance of resources, both human and financial, for the development of strong regulatory systems. The lack of resources can be compensated to some extent by effective collaboration among countries and information sharing (WHO Drug Information, 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 remain a challenge for the development of a robust drug regulatory system.

Figure 8.6 The GCC roadmap to successful standardisation of the regulatory systems



The GCC regulatory objectives describe the expected regional accomplishments during the short-term period of one to two years which should be consistent with their mission. This study revealed that the GCC authorities are focused on accomplishing objectives in areas where they mostly lack the necessary resources and capabilities. The post-marketing surveillance (PMS) system is an area of concern in most of the Gulf States because it is not fully established. This requires the development of proper guidelines, standard operating procedures (SOPs) and effective legislation. The PMS system is a new regulatory system that needs the appropriate infrastructure, human resources, information technology (IT) facilities, educational programmes and quality assurance tools.

Another shared objective in the GCC region was to improve the regulatory review process. This objective can be directly linked to the GCC mission of ensuring the availability of safe and effective medicines in the region which can only be

accomplished by incorporating the quality measures discussed in chapter six such as establishing a standardised GCC quality policy, SOPs, assessment templates and good review practice (GRP) guidelines. Furthermore, communication should be improved between the seven authorities to facilitate exchange of best practices and knowledge between the authorities and the industry to improve the quality of the GCC review process.

Improving the legislative procedures is another important objective that may have an impact on the implementation of critical regulatory practices related to the pre- and post-market assessment of medicines in the Gulf region. Legislative changes in the international regulatory authorities have always been met with fierce challenges from stakeholders with powerful interests which have led to a deterioration in the relationships between the industry and the regulators (Matsebula et al., 2005). This has had a negative impact on the level of communication and transparency between the authorities and the pharmaceutical companies. Therefore, authorities and pharmaceutical companies must always discuss legislative issues to pinpoint areas for improving patients' access to safe and effective medicines in a timely manner.

Regulatory objectives need to be assessed periodically to determine their relevance to the regulatory mission because it forms the rationale for the regulatory decisions and must define the objectives of drug regulation. Objectives are tested for relevancy, realistic expectations and capabilities of the GCC authorities as it is not reasonable to apply objectives that cannot be achieved by less resourceful authorities. This is accomplished by periodically reviewing the Strengths, Weaknesses, Opportunities and Threats (SWOTs) within each of the seven GCC authorities to ensure that the stated regional objectives are reasonable for each member state. Furthermore, quality management tools should be utilised to evaluate how well these objectives are accomplished by enhancing feedback activities between the assessors, stakeholders and the regulators and by carrying out internal and external quality audits to obtain a full comprehensive understanding of the quality of the review outcomes and the level of the regulatory performance in each authority. Regulatory outcomes are statements that describe what the regulatory reviewers are expected to know and/or achieve in relation to the GCC mission and objectives. If they achieve the expected outcomes, it is anticipated that they will be able to accomplish the long-term vision and goals of the GCC regulatory system. However, to ensure the employee's ability to achieve the expected outcome, training and continuing professional development (CPD)

programmes must be implemented. As science, technology and medical practices evolve, it would be inappropriate and unethical for a reviewer unfamiliar with the current science and technology to be assessing an application and making judgements on matters outside their area of expertise. It is also necessary to evaluate staff competence by assessing reviewers under examination conditions to ensure that they have the appropriate skills and are updated with the developments in their area.

Performance management is an essential tool that provides the means to improve organisational performance by linking and aligning individuals, teams and organisational needs and objectives. It also provides the means to recognise areas of best practice and to manage underperformance (Martinez, 2000). Performance management involves systematic, regular and a stringent assessment of the internal resources and capabilities within each regulatory authority. Any accomplishments and improvements in the review practices are clearly described, quantified and assessed for effectiveness on a regular and systematic basis.

The performance of authorities is of great importance to all stakeholders. Public and political pressures along with formal complaint procedures from the pharmaceutical companies have increased the GCC authorities' attention to quality, benchmarking and performance management. However, the GCC States are still lacking quality assurance approaches whose existence will undoubtedly facilitate the introduction of performance management for the following reasons (Martinez, 2000):

- In the quality assurance programmes, staff are familiar with the setting and monitoring of review targets
- There is normally a person leading the quality assurance process whose role will have many similarities with that of the steering and implementing performance management.
- Quality assurance provides a structured means for the evaluation of the regulatory services.

Therefore, setting-up a quality assurance unit/department in each GCC authority is an essential element to accomplish the required level of the regulatory review performance outcomes.

Resources are one of the common strategic parameters identified in the short- and long-term strategic plans of the GCC States. In strategic planning, resource allocation is a plan for using the available resources, for example human resources, particularly

in the short-term plans, to achieve future goals. This proposed resource allocation plan has two parts shown in Figure 8.7 (Capatina and Cristea, 2009), namely,

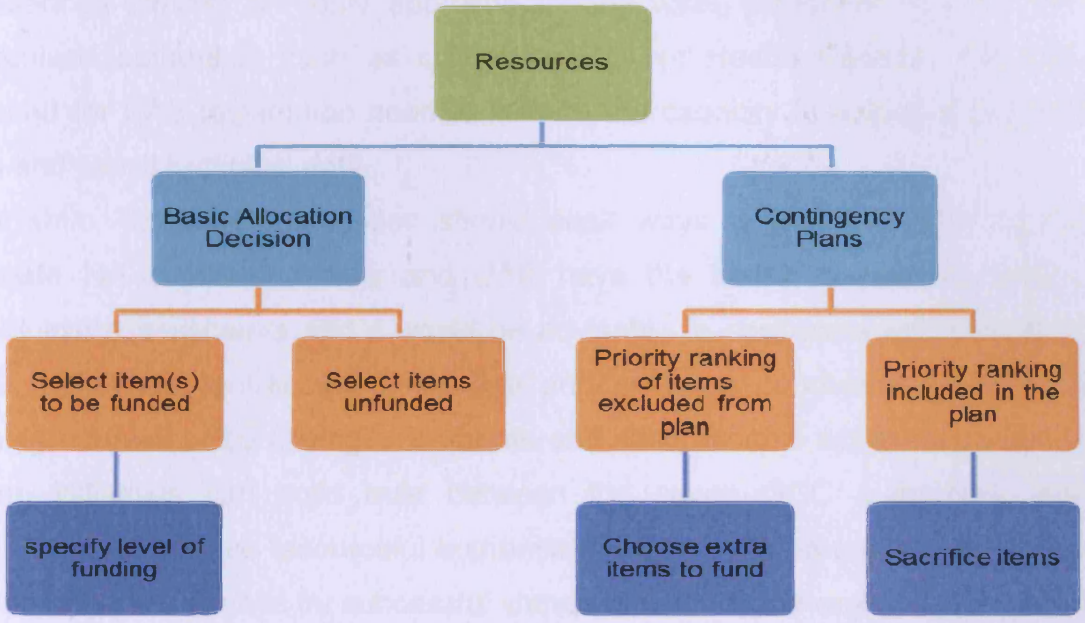
1. *The basic allocation decisions*: These involve essential items to fund in the plan, the level of funding they should receive and which to leave unfunded. For example, salaries of the authority's staff and the remuneration of the GCC central registration committee members are basic fundamental items that must be funded, while for example there is no need to plan the funding of department renovations every year.
2. *Contingency plans:* these consist of two plans, namely,
   a. The priority ranking of items excluded from the resource allocation plan, showing which items to fund if more resources should become available. An example would be to hire full-time IT experts to monitor the use of IT facilities efficiently and effectively, or to send more employees for external courses, post-graduate degrees or placements and secondments in competent authorities if there are more resources available.
   b. The priority ranking of items included in the resource allocation plan, shows which items should be sacrificed if total funding must be reduced. For example, it is possible to sacrifice having in-house training if an efficient on-the-job training is conducted or vice versa; or chemists, physicians or biostatisticians can be sacrificed if the reviewing pharmacists receive proper training in the scientific assessment of the registration dossier.

A shortage of qualified personnel and high turnover rate of employees was cited as a major problem facing the GCC authorities in the SWOT analysis. The authorities continuously recruit personnel with the relevant qualifications but they still require experience to become effective regulators (Matsebula et al., 2005).

Several factors could be involved in the staff turnover problem within the GCC regulatory authorities. Poor remuneration may have an impact on the speed of the registration process of pharmaceutical products because assessors are not motivated to improve their performance. Although the GCC authorities are aware of such problem, they are limited with their abilities to solve it because all payments and remunerations are government by their national treasuries. In addition, staff are paid according to established salary bands for the entire government sector. Saudi Arabia

may stand out in this case, having an independent, stand-alone, authority with the largest budget in the region (134million US$).

Figure 8.7 The proposed Gulf Cooperation Council (GCC) regulatory resource allocation plan



This budget includes salaries, remuneration, continuing education programmes and post-graduate studies for the assessors. In South Africa, most of the staff who left the Medicines Control Council (MCC)/ Medicines Regulatory Affairs (MRA) between 1997 and 2002 moved to the industry due to the inability of the authority to retain skilled staff as a result of salary discrepancies between the public and the private sector (Matsebula et al., 2005). Another problem is observed from the staff members who work for the industry for few years, move to the regulatory authorities, and then return to the industry at a higher level than when they left. This situation is more common with the foreign and non-GCC Arab employees. In the US FDA, one of the best resourced authorities in the world, many senior regulators with a background in the industry, are likely to be more sympathetic towards the industry's demands (Abraham, 2002).

Retaining and recruiting the right calibre of staff is critical to ensure that regulators stay ahead of industry. The desperate lack of capacity and high levels of staff turnover are issues that might be addressed by rewarding staff appropriately and structuring suitable career paths for them. An important strategy might be to re-foster and

enhance the organisational values that focus on the protection and advancement of public health, rather than merely responding to industry's demands.

Furthermore, it is highly recommended that this problem be handled by training internal reviewers specifically to review existing active substances (EASs). New Active Substances (NASs) are only approved if they were authorised in countries with recognised authorities such as US FDA, EMA or Health Canada. The expertise required for EAS registration need to include the capacity to assess bioequivalence data and possibly clinical data.

Meanwhile, the GCC authorities should seek ways to increase their capacity to evaluate NASs. Saudi Arabia and UAE have the ability to perform clinical and nonclinical assessments and it would be advisable to cooperate with the rest of the GCC authorities to transfer knowledge and skills by conducting workshops and training courses or by having placements and secondments within these authorities. These initiatives can build trust between the seven GCC authorities, establish confidence in the less resourceful authorities, improve staff morale and performance and increase the chance for successful standardisation in the region. In addition to the scientific capacity, the GCC authorities must have effective systems for tracking application assessment processes and decision-making. These systems require the appropriate use of information technology (IT). IT personnel and facilities are limited in most of the GCC States but even if these IT facilities were available, the reviewers do not necessarily have the skills to use them.

In terms of financial resources, it would be worthwhile to assess the impact of different budget structures on performance across the authorities. Government support in the form of budget is the method of financing employed in most of the GCC States. Only Saudi Arabia and Yemen are self-financed by fees. 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). Governments should be fully committed to financially support the GCC authorities and should prioritise funding of the regulatory review process. Without such support improvements in the technological and scientific skills and facilities will remain a significant limiting factor in the quality of the review process.

Understanding the alignment between review practices and strategies promotes efficient and effective performance outcomes. Practices and strategies are "two sides of the same coin" and one cannot work without the other. Practices need strategies to

be performed with precision, consistency and efficiency, while strategies need practices that transfer theoretical concepts to an operational context.

Guidelines were one of the most common strategic parameters addressed in this research. They are generally important for good review practice, good laboratory practice, and good manufacturing practice for pharmaceutical products. They are derived from a systematic review of the literature and are designed to act as a vehicle to improve patient-centered outcomes and reduce variation in the assessment practice (Royal College of Nursing, 2006). They are formal strategies that provide a theoretical framework from which the GCC authorities can develop and monitor the effectiveness of their quality assurance systems. They also help to build public and industrial confidence in the GCC regulatory systems.

Procedural guidelines provide detailed information to regulators and reviewers about the way in which strategies are implemented and provide a useful reference point for those who need to know about the practical aspects of carrying out the assessment procedures. The most successful standardisation strategies experienced (e.g. EMA) have been based on firstly developing common guidelines for dossier assessments and then ensuring that legislation is enacted to support these assessments (Hill and Johnson, 2004). In addition, the importance of making sure that there are sufficient resources in terms of time and money for meetings and negotiations to achieve common outcomes cannot be overstated.

In the majority of GCC States, most reviewers believe they assess the full dossier and the authorities have confidence in the outcomes of their reviews. However, when the authorities were presented with the type and definition of assessment models being conducted in other parts of the world, they recognised their position in terms of the extent of the scientific assessment being carried out in each of the seven authorities. Most of the authorities carry out a verification or an abridged review; both of which conserve resources and save duplication of review efforts made by reference agencies. However, abridged reviews involve detailed assessment of certain product issues to ensure its applicability to the local condition such as gender and or ethnicity studies. Only two authorities conduct full reviews (Saudi Arabia and UAE). Therefore, it is critical to consider conducting training courses and/or placement programs in these countries to allow the transfer of skills and knowledge to the other authorities and facilitate the achievement of a successful standardisation in the region.

Peer review is another quality measure that needs to be addressed in the region. Some authorities allow re-evaluation of the assessment reports made by internal reviewers to aid better decision-making. However, it is recommended to consider the need for experts in specific fields to review relevant parts of the registration dossiers. In the 'Center of Drug Evaluation and Research' (CDER), all applications are reviewed by physicians, chemists, microbiologists, toxicologists or statisticians (US FDA, 2010a).

The registration of medicines in the Gulf States is influenced by its authorisation in other countries with developed regulatory systems, particularly the US FDA and/or EMA. New Active Substances (NASs) which are not approved in reference authorities cannot be registered in any Gulf State. Existing Active Substances (EASs) which are not registered elsewhere will only be accepted for review if the NAS comparator is registered and marketed in the GCC region, if the bioequivalence data are provided and if they are registered in countries with competent authority systems. Furthermore, the GCC States lack the experience or the expertise to fully evaluate NASs and they are dependent on approvals from other reference authorities. Therefore, the seven GCC authorities require the submission of the CPP as an evidence of registration from a competent authority for all pharmaceutical products.

Finally, joint reviews are another form of dossier assessment that is conducted in the region. It is an idea that was taken from the EMA where separate assessments of the registration dossier are conducted by several authorities which contribute to the final assessment of the individual reports during the committee meeting where the final decision is made by agreement between the member states. However, joint reviews are not conducted at a national level, although some GCC States occasionally rely on approval in Kuwait, Saudi Arabia and/or UAE; or they may request information from international authorities such as the World Health Organisation (WHO) or US FDA. The GCC authorities recognise the importance of conducting joint reviews to reduce the workload and to share knowledge and best practices that will ultimately increase confidence in their regulatory systems.

Auditing is the process used to interpret the quality of the review process conducted by each of the seven GCC authorities and the impact of the reports and assessment templates on the quality of the decision-making process. Feedback is a critical measure to create and maintain a systematic quality assurance system. When successfully implemented, all elements of quality assurance process interact

efficiently with one another. Several GCC authorities conduct internal auditing but only one authority (Oman) conducts external auditing to assess the quality of the review process. External audits can provide an unbiased and independent feedback on the review practices and assessment reports. Furthermore, external auditors can provide feedback on areas that may be overlooked by the internal auditors which can improve the quality of the review process.

In general, Saudi Food and Drug Authority (SFDA) has been able to stand out in terms of having clear strategies, extensive and focused budget, as well as the drive and the attitude towards advancing the regulatory system in Saudi Arabia. These strategies and practices, however, may not necessarily be a way forward for the other six GCC States as they are still in the early stages of their development.

Benefits of the Harmonisation Strategy

Currently the GCC authorities face a number of challenges; however, an effective regulatory review process in each of the member states underpinned by appropriate quality measures for decision-making and a standardised strategy leading to an effective centralized procedure would have several important benefits. These would include:

- Pharmaceutical companies would only need to compile one dossier for the region as a result of the standardisation of the regulatory requirements.
- An improvement in the quality of the review as an outcome of the appropriate use of the resources, expertise and shared best practices.
- A degree of flexibility on the part of the individual member states as well as a greater consistency in their regulatory outcomes.
- Patients' access to safe and effective medicines within a reasonable time frame to all seven GCC States.
- The improvement in communication and cooperation between the seven GCC authorities which would enable them to position themselves as a major player in the global regulatory environment.

Study Limitations

- One of the main limitations of the Kuwait benchmarking study was the lack of an electronic tracking system which prevented the availability of data prior to 2006 and limited the trend analysis to a period of four years although ideally it would have

been desirable to review the last decade. However, the impact was minimal because a complete data set was obtained for the number and types of pharmaceutical products (NASs and EASs) in both the private and government sectors and included registration and pricing review times, which enabled a detailed comparative study over the period 2006 to 2009.

- The study of the approval timelines in Kuwait (Chapter 4) is a quantitative analysis conducted in a relatively short period of time (2006-2009) and, therefore, it was difficult to draw conclusions from trends. However, the study provided an overview of the challenges facing the Kuwaiti Authority's approval process over the four-year period.
- The studies on the regulatory review process, quality of decision-making and strategic planning process (Chapter five, six and seven) are qualitative. They provided unstructured information that was collected via the people's perspectives, views, experiences, feelings, insights and behaviours and, therefore, they are difficult to replicate. However, the studies are original and are an excellent starting point for the GCC authorities to standardise quality measures, review practices and regulatory strategies to achieve the required level of harmonisation in the GCC region.
- For any questionnaire to be practical and to secure a high response rate necessitates it being of a reasonable length. This prevented the possibility of evaluating certain areas in greater depth. However, this study covered the majority of relevant topics and was the first endeavour to pinpoint areas of practice that can be used to achieve the required level of standardisation in the GCC review process.
- As a questionnaire was used to evaluate the regulatory review processes and the quality measures in the GCC authorities, a number of technical terms such as "validation stage" and "scientific assessment stage" may have led to a misunderstanding or misinterpretations in the questions posed. This issue could have been enhanced by the language barriers and the diverging abilities of respondents in understanding, interpreting and communicating in the English language. The limitation, however, was mitigated by the inclusion of a glossary to guide the study participants with such terms in order to ensure consistency in their understanding.In view of the special relationship between the author and the Heads of the regulatory authorities in the GCC States, being a former member of the GCC Central Registration Committee and a key regulator in the Kuwait regulatory authority, who took the commitment and responsibility to collect data, there is considerable confidence in the information that has been provided in the thesis.

Recommendations

Seven recommendations were produced as a result of this study, namely,

- Adoption of a standardised assessment template
- Provision of specialized training and continuing professional development programmes including secondment to competent reference authorities
- Development of an electronic tracking system that will enable continuous monitoring of review times
- Adoption of parallel assessment of sample analysis and pricing with the scientific assessment to improve patients' access time
- Engagement of external quality audits by accredited external certification bodies
- Improvement of transparency in order to increase the confidence in their review practices
- Provision of resources and the establishment of regulatory guidelines as the starting point for an effective and harmonised regulatory strategic plan for the GCC region.

Future Work

In view of the fact that the topics addressed in this research project are likely to remain key issues for the foreseeable future, it would be valuable and beneficial to use the same study instruments for future work in this area.

In the light of the GCC Central Drug Registration (GCC-DR) system, the seven regulatory authorities have had a long experience in cooperating in the review process of the centrally register pharmaceutical products in the Gulf region. However, the system faced many obstacles particularly with regards to the authorities' concerns of losing their sovereignty. They were also apprehensive about the possibility of changing their entire procedures and practices more than their neighbouring authorities in the region. These concerns may have disappeared with time and therefore, it is essential to have a future study that will examine the views of the seven GCC authorities about the current status of the GCC-DR system and its impact on their individual systems.

Furthermore, pharmaceutical companies were also sceptical about the GCC-DR system and whether it would improve the review process and the approval timelines in

the GCC region ten years ago. They are still wondering whether it is faster to register a pharmaceutical product through the national or the centralized procedure. However, the industry's view is evolving about the efficiency of the GCC-DR system as opposed to the national systems. 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 marketing authorisation for their products in each Gulf State is an essential project that should be considered in future studies.

In addition, the GCC-DR has been registering medicines in the Gulf Region for over ten years. Therefore, it is valuable to perform an assessment of the GCC-DR timelines and the number of registered product since its inception in 1999 and it is important to conduct a comparative study between the GCC-DR approval timelines and the national approval timelines to complete the picture for both the individual authorities and the pharmaceutical companies. The authorities will then have a view of the importance of their individual roles and the efficiency of the GCC-DR system and the pharmaceutical companies will be able to make better judgement when they decide to submit the product for central or national registration.

The pricing process is an integral part of the overall approval process of medicines in each of the seven GCC regulatory authorities but it has not been analysed extensively in this research. Therefore, it should be addressed in future work in order to make recommendations for further improvements.

It is clear that the aims and objectives of this study have been achieved and the findings have demonstrated the potential added value of a harmonised strategic planning process for the GCC Region. The research underpinning this thesis found differences in the Gulf States in most areas including structures, procedures, quality measures and strategic parameters which determined the degree of standardisation the can be achieved. It is hoped that the findings of this study will enable a greater standardisation in the requirements, performance, procedures and guidelines in the GCC States leading to one strong regulatory body that facilitates an effective drug approval process for the region. This may contribute to similar initiatives in other regions of the world.

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APPENDIX A

Questionnaire (1): Regulatory Review Process in The Gulf cooperation council (GCC) States

Review of key milestones, target times and quality of decision-making in the assessment and registration process

CONFIDENTIAL

Regulatory Review Process in GCC States

Review of key milestones, target times and quality of decision-making in the assessment and registration process

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CMR International

Institute for Regulatory Science

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Welsh School of Pharmacy
Cardiff University

The Welsh School of Pharmacy is one of twenty four UK schools of pharmacy and the only one in Wales. For over 80 years, the School has cultivated a strong tradition of innovative pharmaceutical education, scientific research and latterly, continuing education to pharmacy practitioners.
Judged by nationally recognised standards, the School is the top UK school of pharmacy. Our research has received a 5A (Excellent) ranking in the 2001 RAE (Research Assessment Exercise) and we were awarded an excellent for the quality of our teaching and learning in the last TQA (Teaching Quality Assessment) (http://www.cardiff.ac.uk/phrmy/newsandevents/news/guardian-rates-cardiff-as-top-for-pharmacy-teaching.html)

The Research Fellow

This study is performed by Reem Al-Essa, formerly the Drug Registration and Release Superintendent at Kuwait Drug and Food Control Agency, as part of her PhD research program with Cardiff University-Welsh School of Pharmacy, in collaboration with CMR International Institute for Regulatory Science. The study aims at assessing the regulatory review processes, review milestone and approval timelines in the regulatory agencies in all GCC states. An evaluation of how each GCC country is building quality into the review process and the measures undertaken by each authority to ensure that the optimal quality review will be the main target for this study.

CONFIDENTIALITY STATEMENT

All data will be kept strictly confidential and the data set for each agency will be reviewed and approved by each member state before it is shared with the other GCC state. The final report will initially be presented as anonymised data (i.e. GCC states will not be identified). Only after an agreement has been reached by the member states for the results to be identified, will the report be prepared.

REGULATORY REVIEW PROCESS IN GCC MARKET

Review of key milestones, target times and quality of decision-making in the assessment and registration process

BACKGROUND

This questionnaire represents the second Phase of the CMR GCC market Programme which is studying the regulation of new medicines in the GCC market and looking at the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines, that can have an impact on their availability to patients.

The first phase was initiated by Dr. Hajed Hashan (KSA) in 2006 to assess the current regulatory environment in 6 GCC states (KSA, Kuwait, Bahrain, Oman, Qatar, UAE) using comparative data, at the country and regional level, in order to identify the key issues for improving review practices and making new medicines available in an efficient and timely manner. Some of these, for example the timing and use of the Certificate of a Pharmaceutical Product (CPP) and the length of the review process were analysed in more detail in these 6 states countries. This study highlighted the need to understand more about the different steps in the review process and the way in which these affect the overall timeline. GCC regulatory authorities also showed an interest in having a greater understanding of how agencies are building quality into the review process.

The current second phase of the study is being carried out among the regulatory agencies in seven GCC regulatory authorities: ***KSA, Kuwait, Bahrain, Oman, Qatar, UAE and Yemen.***

Through this study, CMR International Institute for Regulatory Science in collaboration with Cardiff University, Welsh School of Pharmacy proposes to map the key milestones and associated activities, for each agency and to determine the quality measures employed by the agencies in their different procedures.

OBJECTIVES

The objectives are to:

- Identify the key milestones and target times for each authority and the main activities between milestones.
- Identify the model(s) of the review which is being undertaken by each of the agencies.
- Identify opportunities for the exchange of better practices amongst the regulatory authorities.
- Assess how agencies are building quality into the assessment and registration processes.

OUTPUT

Participating agencies will receive a report from which they can compare their regulatory procedures with those of peer agencies across the region. This will include an analysis of where time is spent in the review process with the opportunity to identify where time is lost.

The outcome will allow an analysis of the quality measures that are, or are not, in place for a certain type of review. It will provide a baseline for subsequent comparative studies across agencies to establish best practices.

ABOUT THE QUESTIONNAIRE

The attached questionnaire is divided into two sections:

Part I: Key milestones in the registration of medicines, which explores the review and approval process for new active substances (NAS) and existing active substances (EAS).

Part II: Building quality into the assessment and registration process which looks at the activities that contribute to the quality of the decision-making process and measures adopted to improve consistency, transparency, timeliness and competency in the review processes.

The **Introduction** to the questionnaire asks the Authority to provide current information on its structure, organisation and resources. It also explores ***review model(s)*** for the scientific assessment in terms of the extent to which data is assessed in detail by the agency rather than relying on the results of assessments and reviews carried out elsewhere. The questionnaire is intended to be used as the basis for a face-to-face interview between Agency staff and Reem Al-Essa.

FOCUS OF THE STUDY

The study is intended, primarily, to document procedures and practices that relate to medicines that are the subject of **major** applications, i.e., new active substances and existing active substances.

New Active Substance (NAS)

A new chemical, biological or pharmaceutical active substance includes:

a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;

an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;

a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;
a radiopharmaceutical substance which is radionucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide has not been previously authorised.

Existing Active Substance (EAS)

An existing chemical, biological or pharmaceutical active substance includes:

a chemical, biological or radiopharmaceutical substance previously authorised as a medicinal product;

an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product with the same properties with regard to safety and efficacy to that chemical substance previously authorised;

a biological substance previously authorised as a medicinal product, which has the same molecular structure, nature of the source material or manufacturing process;
a radiopharmaceutical substance which is radionucleotide, or a ligand previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide which has been previously authorised.

Major Line Extension

A major line extension is a modification to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug deliver system.

INTRODUCTION

1. INFORMATION ON THE REGULATORY AUTHORITY

As background to the discussions about your agency, its practices and procedures it would be helpful to have the following basic information on its structure and the way it is established:

Title of the Agency/Division responsible for the regulation of medicinal products for human use

If this is part of a parent agency with a wider remit (e.g., Food and Drugs) please give the title:

Scope and remit

1.1 Please indicate the scope of responsibility of the Agency:

Medicinal products for human use	☐ YES	☐ NO
Medicinal products for veterinary use	☐ YES	☐ NO
Medical devices and *in vitro* diagnostics	☐ YES	☐ NO

1.2Indicate the main activities that are covered by the agency

- ☐ Marketing authorisations/Product licences
- ☐ Clinical trial authorisations
- ☐ Post-marketing surveillance
- ☐ Regulation of advertising
- ☐ Laboratory analysis of samples
- ☐ Price regulation
- ☐ Other

Type of agency

1.3 Indicate which of the following best describes this agency

- ☐ Autonomous agency, independent from the Health Ministry administration
- ☐ Operates within the administrative structure of the Health Ministry

ate of establishment of the current agency ☐

Size of agency

Please note that the following questions refer to the regulation of **medicinal products for human use.**

1.4 Please provide information on staff numbers

- Total staff in the agency ☐
- Number of reviewers for applications for marketing authorisations/ product licences ☐

*1.5 Please indicate the professional background and numbers of the **technical** agency staff assigr to the review and assessment of medicinal products*

	Employed as assessors	*Number*
• Physicians	☐ YES ☐ NO	
• Pharmacists	☐ YES ☐ NO	
• Other scientists	☐ YES ☐ NO	

Fee structure

1.6 Are fees charged to sponsors for the review and assessment of applications for medicinal products for human use? ☐ **YES** ☐ **NO**

If **YES**, please provide the following information:

Marketing application fee for	***Local currency***	***US$***
☐ New Active substance		
☐ Established ingredient – proprietary product		
☐ Existing Active substance		
☐ Major line extension		
☐ Variations		
☐ Other		

Budget

Please indicate whether the following data ☐ are in the **public domain** *or*

☐ Should be treated as **confidential**

1.7Please provide the following information on the agency budget for the regulation of medicinal products for human use

	Local currency	***US$***
☐ Total annual budget		
Year for which data are given		

If the budget is sub-divided according to different activities, please specify

	% of total budg
☐ Clinical trial authorisations	
☐ Marketing authorisations	
☐ Pharmacovigilance	
☐ Other post-marketing controls	
☐ Other activities (specify)	

Sources of funding

1.8 Please provide the following information in relation to the way the agency is funded

Funded entirely by the government	☐ **YES** ☐ **NO**
Self-funded entirely from fees	☐ **YES** ☐ **NO**
Partially funded from different sources (please giv proportions of total budget)	____% Government ____% Fees ____% Other (specify)

Additional documentation

To assist CMR International to better understand your organisation please provide copies of any ***organisation charts*** *that show the structure of the agency and its relationship to other regulatory bodies, e.g., medical device agency. It would also be very useful to have copies of any background papers that describe the* ***functions***, ***remit*** *and* ***mission*** *of the agency.*

2. TYPE OF DATA ASSESSMENT

Three basic types of scientific review have been identified as a result of discussions with regulatory agencies and presentations at the CMR International Institute Workshop on *The Emerging Markets: Regulatory issues and the impact on patients' access to medicines,* Geneva, Switzerland, March 2006. Many agencies apply a different level of data assessment to different applications, according to the type of product and/or its regulatory status with other agencies. The data assessment models for scientific review are described in section 2.1 below and further questions are set out in 2.2 to analyse the types of scientific review in more detail.

2.1 Please indicate by checking the boxes below, which descriptions fit the model(s) used by your agency in the assessment of major applications i.e., new active substances (NASs) and major line extensions as described on page 2.

Data Assessment Type 1

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 authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency 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 authorisation(s)

TYPE 1	☐ Not used	☐ Used for all major applications
	☐ Used for selected applications (please specify)	

Data Assessment Type 2

This model also 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 pharmaceutical (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 recognised agency elsewhere is a pre-requisite before the local authorisation 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.

TYPE 2	☐ Not used	☐ Used for all major applications
	☐ Used for selected applications (please specify)	

Data Assessment Type 3

In this model the agency 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 3 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 authorised by a reference agency before the local authorisation can be finalised.

TYPE 3	☐ Not used	☐ Used for all major applications
	☐ Used under the following conditions (please specify)	

If your agency has recognised 'reference agencies' (as in Types 1 and 2) please provide the list:

2.2 Data requirements and assessment

Regulatory Status:	**Authorised in one or more reference countries**	**Authorised elsewhere but not in a reference country**	**Not authorised elsewhere at the time of application**	**Priority/fast track products**
Evidence of authorisation by other authorities				
Requirements for a CPP as part of the review	☐ with application ☐ before authorisation ☐ not essential	☐ with application ☐ before authorisation ☐ not essential	☐ before local authorisation ☐ not essential	☐ with application ☐ before authorisation ☐ not essential
Other documentation from the authorising agencies accepted as evidence of registration	☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence	☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence	☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence	☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence
Other evidence accepted				
Verification of identity between the authorised product and the local application				
The following are checked:	Information must be: *Identical Closely similar*	Information must be: *Identical Closely similar*	**Not applicable**	Information must be: *Identical Closely similar*
Dosage form	☐ ☐	☐ ☐		☐ ☐
Strength	☐ ☐	☐ ☐		☐ ☐
Ingredients	☐ ☐	☐ ☐		☐ ☐
Indications and dose	☐ ☐	☐ ☐		☐ ☐
Warnings and precaution	☐ ☐	☐ ☐		☐ ☐
Product label	☐ ☐	☐ ☐		☐ ☐
Other (specify)				
Scientific data required to support the application (Reference is made below to sections of the ICH Common Technical Document (CTD) as an example of the level of detail but does not imply that the CTD in necessarily accepted)				

Regulatory Status:	**Authorised in one or more reference countries**	**Authorised elsewhere but not in a reference country**	**Not authorised elsewhere at the time of application**	**Priority/fast track products**
Pharmaceutical quality/CMC	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)
Scientific data required to support the application (continued)				
Nonclinical data	☐ Written summary (2.4) ☐ Tabulated data (2.5) ☐ Full data (Module 4)	☐ Written summary (2.4) ☐ Tabulated data (2.5) ☐ Full data (Module 4)	☐ Written summary (2.4) ☐ Tabulated data (2.5) ☐ Full data (Module 4)	☐ Written summary (2.4) ☐ Tabulated data (2.5) ☐ Full data (Module 4)
Clinical data	☐ Written summary (2.5) ☐ Tabulated data (2.6) ☐ Full data (Module 5)	☐ Written summary (2.5) ☐ Tabulated data (2.6) ☐ Full data (Module 5)	☐ Written summary (2.5) ☐ Tabulated data (2.6) ☐ Full data (Module 5)	☐ Written summary (2.5) ☐ Tabulated data (2.6) ☐ Full data (Module 5)
Extent of Scientific Review				
Quality/CMC data	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report
Comment				
Non-clinical data	☐ Only examined if there is a query	☐ Only examined if there is a query	☐ 'Check list' review for completeness of data	☐ Only examined if there is a query

Regulatory Status:	**Authorised in one or more reference countries**	**Authorised elsewhere but not in a reference country**	**Not authorised elsewhere at the time of application**	**Priority/fast track products**
	☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report	☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report	☐ Detailed assessment and evaluation report	☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report
Comment				
Clinical data	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. bridging studies) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. bridging studies) ☐ Detailed assessment and evaluation report	☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. bridging studies) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. bridging studies) ☐ Detailed assessment and evaluation report
Comment				

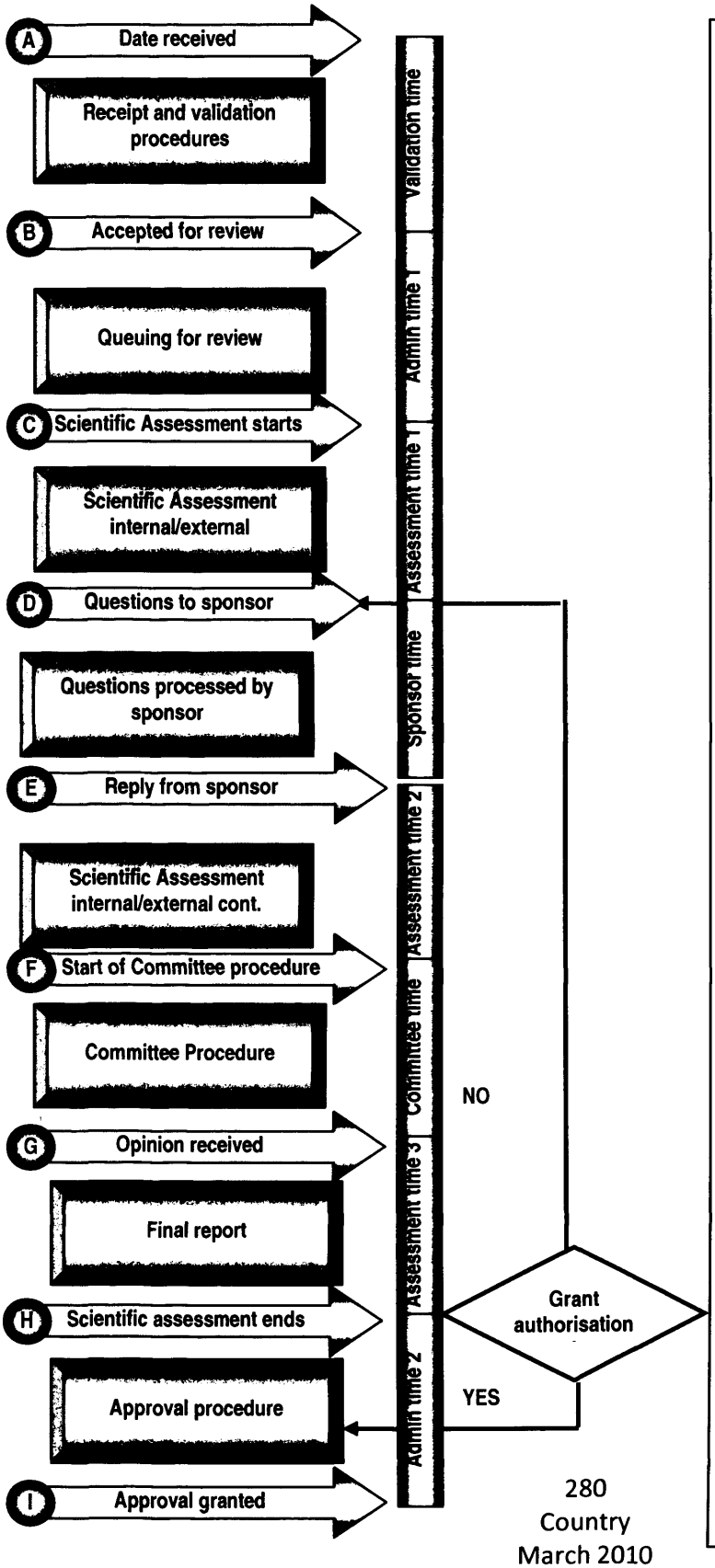
Additional information, not in the application

The agency tries to obtain	Information is sought: *Never* *sometimes* *always*	Information is sought: *Never* *sometimes* *always*	Information is sought: *Never* *sometimes* *always*	Information is sought: *Never* *sometimes* *always*
Other agencies' internal assessment reports	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Reports available on the Internet (e.g., EPARS)	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
General Internet search	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Other data (specify	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐

PART I - KEY MILESTONES IN THE REGISTRATION OF MEDICINES

REVIEW PROCESS MAP AND MILESTONES

This part of the questionnaire is based on the General Model below giving a process map and milestones that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process for monitoring and analysing timelines.



Notes

Receipt and validation may include administrative registration (reference number) and checks on legal requirements, status of company, local agent, manufacturer etc. as well as a 'checklist' validation of the application content (e.g., technical sections, CPP status).

Queuing for review: *Administrative time 1* is a measure of the 'backlog' time (if any) while valid applications wait for action to begin.

Scientific Assessment extends from milestone C to milestone H and is a measure of 'review time'. In some systems the 'clock' stops when questions are asked and ***Sponsor time*** (milestone D to milestone E) can be measured and deducted from the agency review time.

Questions to sponsor may be batched and sent at one time or asked throughout the review process, in which case the *Sponsor time* is not easily measured.

In some systems, questions may only be sent to the sponsor after the end of the 'first cycle' scientific assessment (at milestone H).

Committee Procedure: Most review procedures for major applications include a step where the opinion of an expert advisory committee is sought. In this scheme, the Committee procedure is 'nested' within the Scientific Assessment but it may take place after the Agency's scientific assessment is complete.

Second cycle: If the application cannot be granted immediately, on technical grounds, it enters a second review cycle (new data point D: questions to sponsor) and a further scientific assessment is made of the additional data. The Committee Procedure may or may not need to be included in the second and subsequent review cycles.

Approval procedure: The time interval after scientific review (*Admin time 2*) while the formal authorisation is issued may be extended by pricing negotiations and finalisation of analytical and GMP checks.

Approval time is measured from milestone A to milestone.I

Review stages and milestones

This section of the questionnaire is based on the ***General Model*** shown on page 9.

We recognise that not all systems conform to the general model and it would be very helpful if you could provide an outline of the model used by your authority. If this differs according to the **Type of data assessment** (see page 5) please provide information on the different models

When information is given on target or actual times please indicate here whether these are counted in:

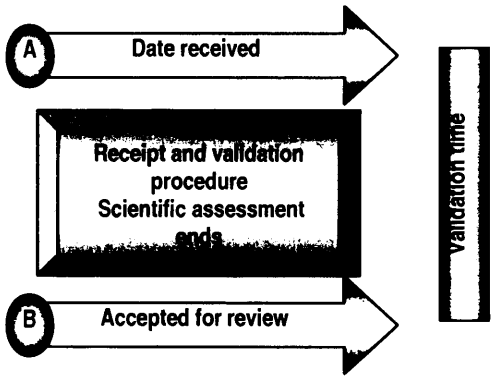
☐ **Calendar days** ☐ **Working days**

When 'milestone' dates are recorded during the review process is the information entered into an electronic tracking/recording system?

☐ **YES,** System in current use ☐ **NO,** System in development (Target date:_____)

☐ **NO,** A manual system will be used for the foreseeable future

3. Receipt and Validation



Pre-submission requirements

3.1. Are there any formal requirements before an application is submitted, for example, notification of intent to submit, assignment of registration code etc.

☐ **NO,** milestone A is the formal start of the application procedure

☐ **YES** (please specify)

Validation

3.2 Is the date of receipt (milestone A) formally recorded? ☐ **YES** ☐ **NO**

3.3 Are the following administrative items checked in the pre-review validation process?

- Legal status of applicant/local agent ☐ **YES** ☐ **NO**
- GMP status of manufacturer ☐ **YES** ☐ **NO**
- Patent/IP status of active ingredient ☐ **YES** ☐ **NO**
- Whether company has paid the correct fee ☐ **YES** ☐ **NO**

Other:

*3.4 For those applications **where prior authorisation elsewhere is essential (see Section 2)** please answer the following questions about the **Certificate of a Pharmaceutical Product*** (CPP)

Is the inclusion of a CPP an absolute requirement before accepting the application as valid?

☐ **YES** ☐ **NO** ☐ For some applications (please specify)

If **YES** must the CPP be legalised by an Embassy or Consulate? ☐ **YES** ☐ **NO**

If **NO**, please indicate which of the following apply

- A CPP must be provided before the authorisation is issued ☐ **YES** ☐ **NO**
- Other evidence of authorisation by other countries is accepted in place of the CPP (e.g., copy of authorisation, Internet reference) ☐ **YES** ☐ **NO**

3.5 Is the application also checked for the following items?

Acceptable format (e.g. ICH CTD or local requirements) ☐ **YES** ☐ **NO**

Correct sections of scientific data (quality, safety, efficacy) ☐ **YES** ☐ **NO**

Other technical items:

3.6 Is the date of acceptance (milestone B) formally recorded? ☐ **YES** ☐ **NO**

3.7 What happens if the application is incomplete?

☐ **Refusal to file:** New application must be made

☐ **File pending:** A request for the missing data is sent to the applicant

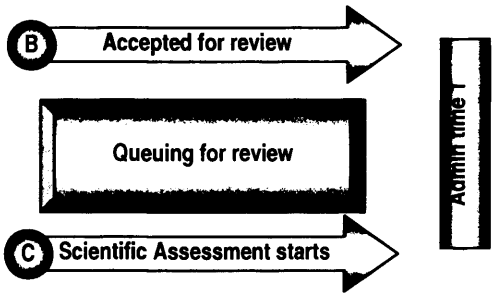
What is the time limit for the applicant to reply?

Notes:

Target time for validation

3.8 Is there a target validation time? ☐ **YES** (specify) ☐ **NO**

4. Queuing/backlog



4.1 Which of the following applies to the queuing system for new applications?

☐ Held in queue after validation (as in the General Model)

☐ Held in queue before validation starts (milestone A)

4.2 What is the current queue time (approximately)?

☐ Less than 2 weeks ☐ 2-8 weeks

☐ 2-6 months ☐ 6 months-1 year

☐ More than 1 year

4.3 Are priority products taken out of turn in the queuing system

☐ **YES,** always

☐ **YES,** sometimes

☐ **NO,** all applications await their turn

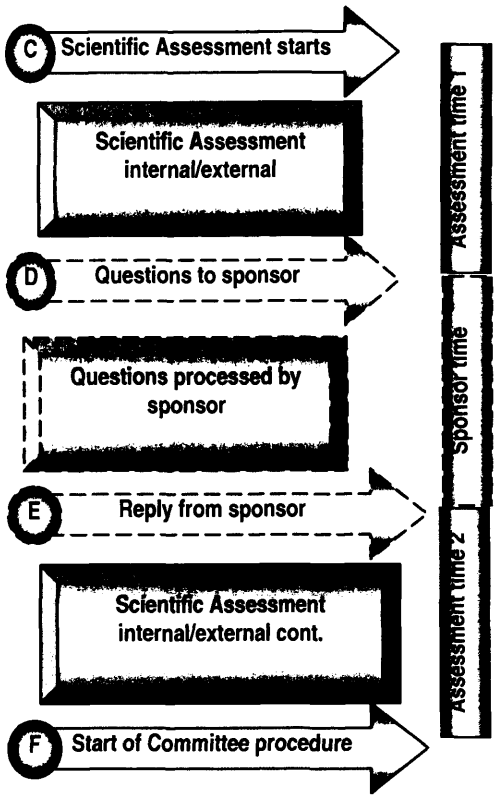
Comment:

4.4 Does the Agency regard the backlog of applications as a problem ☐ **YES** ☐ **NO**

If **YES**, how is this being addressed?

5. Scientific Assessment

5.1 Initiation of scientific review



5.1.1 Is the start of the Scientific Assessment formally recorded (milestone C)? ☐ **YES** ☐ **NO**

5.1.2 Is the scientific data separated into three sections (quality, safety, and efficacy) for review? ☐ **YES** ☐ **NO**

5.1.3 In what order are the different sections assessed:

☐ In parallel ☐ In sequence

If in sequence, please give order

*5.1.4 Who carries out the **primary** scientific assessment?*

☐ Agency technical staff ☐ Sent to outside experts

☐ Different procedure for different sections

Please describe the process:

5.2 Use of outside experts

If outside experts are used for the assessment of scientific data (5.1.4 above) please complete the following:

5.2.1 Number of experts on the agency's list or panel: ☐

5.2.2 Main responsibility:

☐ To provide a detailed assessment report and recommendation

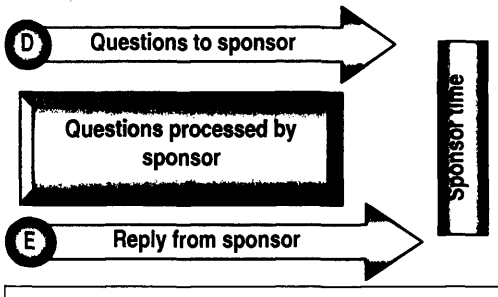
☐ To provide a clinical opinion on the product

☐ To provide advice to the agency staff on specific technical issues

☐ Other (specify)

5.2.3 Is there a contractual agreement on working within deadlines set by the agency? ☐ **YES** ☐ **NO**

5.3 Interaction with the Sponsor



5.3.1 How are questions sent to the Sponsor

☐ as they arise during the assessment ☐ Collected into a single batch

5.3.2 When are batched questions sent to the Sponsor

☐ After the initial assessment but before reporting to the Scientific Committee (as in the General model)

☐ Not until the Scientific Committee has given its advice

☐ Before and after reference to the Scientific Committee

5.3.3 Does the scientific review cease while questions are being processed by the Sponsor ('clock stop') ☐ **YES** ☐ **NO**

5.3 *Interaction with the Sponsor (cont.)*

5.3.4 Can the sponsor time be calculated, i.e., are milestones D and E recorded? ☐ **YES** ☐ **NO**

5.3.5 Is the sponsor given a time limit to reply ☐ **YES** ☐ **NO**

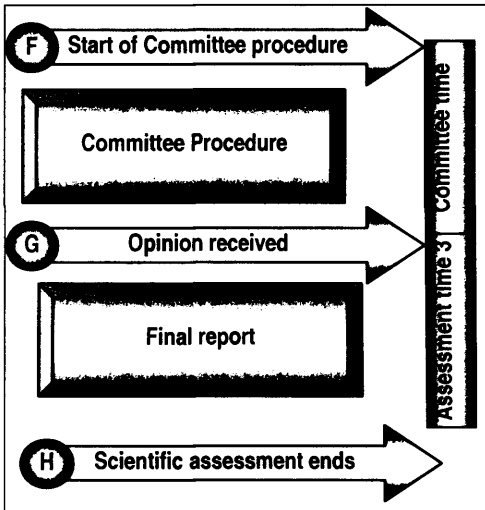
If **Yes**, what time is allowed?

Meetings

5.3.6 Can the Sponsor hold meetings with the agency staff to discuss questions and queries that arise during the assessment ☐ **YES** ☐ **NO**

If **Yes**, what conditions and restrictions (if any) are applied?

5.4 Review by Scientific Committee



5.4.1 Does a Scientific Committee exist for the scientific assessment stage? ☐ **YES** ☐ **NO**

If No, Go to 5.4.8

5.4.2 Is a Committee of Experts (internal and/or external) used in the review process ☐ **YES** ☐ **NO**

*5.4.3 If **Yes**, at which stage in the review?*

- ☐ Responsible for the whole assessment of the dossier from the start of the review
- ☐ Integrated into the agency's own internal/external scientific review procedure
- ☐ Consulted after the agency has reviewed and reported on the scientific data
- ☐ Other (specify)

5.4.4 Are the dates at the start and end of the Committee Review recorded (milestones F and G)? ☐ **YES** ☐ **NO**

5.4.5 Is the agency mandated to follow the Committee recommendation? ☐ **YES** ☐ **NO**

5.4.6 Is there a time limit for the Committee Procedure? ☐ **YES** ☐ **NO**

If **YES**, please give the target

If **NO**, what is the time range (e.g., 1-3 months)

5.4.7 Is there an additional step in the scientific review process, after the Committee has given its opinion? ☐ **YES** ☐ **NO**

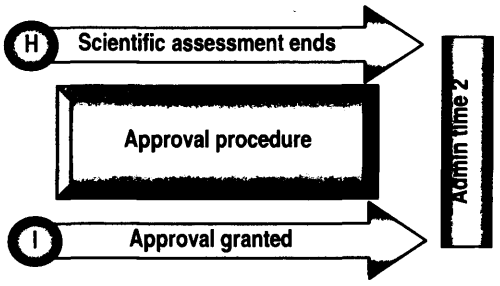
If **YES**, please describe briefly the work carried out at this stage (e.g., final report and agency opinion)

If **NO**, the milestone G will mark the end of the scientific review for the purpose of calculating the review time

Target for scientific review

5.4.8 Is a target time set for the scientific review (milestones C to H)	☐ YES ☐ NO
If **YES** please give target	

6. Decision on the Application



At the end of the Scientific Review (see General Model, page 6) there is normally recommendation that either:

- The product meets the scientific criteria for authorisation (proceed to approval procedure) *or*
- Further data is required before the scientific criteria are met (application enters a **second cycle** at milestone D (questions to Sponsor) *or*
- The application should be refused (not shown in the General Model)

6.1 Responsibility for the authorisation decision

6.1.1 Who makes the decision that a marketing authorisation can be granted?

☐ The Scientific Committee ☐ The Head of the Agency
☐ The Minister of Health
☐ Other (please specify)

6.2 Other Criteria to be met

*6.2.1 Is the issue of the authorisation dependent on a **pricing agreement*** ☐ YES ☐ NO

If **YES**, when are the pricing negotiations started?

☐ At the start of the scientific review ☐ After the end of the scientific review
☐ After granting the registration approval of the medicine.
☐ After the start but before the end of the scientific review

*6.2.2 Is the issue of the authorisation dependent on **sample analysis*** ☐ YES ☐ NO

If **YES**, when is the analytical work started?

☐ In parallel with the scientific review ☐ At the end of the scientific review
☐ After the start but before the end of the scientific review

*6.2.3 Is there a separate negotiation of the **product labelling/ product information** after the scientific opinion is given but before the approval is issued?* ☐ YES ☐ NO

Comments:

6.2.4 Please specify any other legal/administrative matters that must be finalised before the approval can be issued

6.3 Approval procedure

6.3.1 Is the Sponsor informed of a positive scientific opinion at milestone G, i.e., before the authorisation is issued? ☐ **YES** ☐ **NO**
6.3.2 Approximately how long does it take from receiving a positive scientific opinion (at milestone H) to issuing an approval (milestone I) ☐ Less than a month ☐ 1-3 months ☐ 3-6 months ☐ Over 6 months *Comment:*

7. Metrics on the Approval Process for NAS and EAS

It would be very helpful to have the following information on processing times for marketing authorisations that have been received and/or determined in the three years 2007, 2008, 2009.

7.1 Applications received

	Number of applications received in each year			**Current backlog**
Type	**2007**	**2008**	**2009**	
New Active Substance (NAS)				
Existing Active Substance (EAS)				

7.2 Average approval times

	Time from receipt of application to issue of approval		
Type	**2007**	**2008**	**2009**
New Active Substances (NAS)			
Existing Active Substance (EAS)			

7.3 Average launching times

	Time from receipt of application to product launch		
Type	**2007**	**2008**	**2009**
New Active Substances (NAS)			
Existing Active Substance (EAS)			

7.3 Target for approval times

Is a target time set for the overall approval process (milestones A to I) ☐ **YES** ☐ **NO** If **YES** please give target Please comment on the actual review times in relation to the authority's target time

PART II:-BUILDING QUALITY INTO THE ASSESSMENT AND REGISTRATION PROCESS

Quality in the assessment and registration process is important to regulatory authorities as it ensures consistency, transparency, timeliness and competency in the review processes. Regulatory authorities are continuously developing and implementing a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public.

The purpose of this section of the questionnaire is to obtain an insight into the strategies, measures and resources that agencies have in place to develop and maintain quality in their review processes.

8. General Measures used to achieve quality

Please indicate the quality measures currently in place and, where none, plans to introduce such measures in the foreseeable future.

Quality Policy: Overall intentions and direction of an organisation related to quality as formally expressed by top management.	
8.1 Does the Agency have an internal Quality Policy?	☐ **YES** ☐ **NO**
If **NO** are there plans to establish this within the next two years?	☐ **YES** ☐ **NO**
Good Review Practice (GRP): A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports	
8.2 Has the Agency implemented GRP?	☐ **YES** ☐ **NO**
If **YES** please give the title and date of implementation:	
If **NO** are there plans to establish this within the next two years?	☐ **YES** ☐ **NO**
SOPs (Standard Operating Procedures) are written documents that describe in detail the routine procedures to be followed for a specific operation.	
8.3 Are there SOPs for the guidance of scientific assessors	☐ **YES** ☐ **NO**
If **NO** are there plans to establish SOPs within the next two years?	☐ **YES** ☐ **NO**
8.4 Are there SOPs for the advisory committee consulted during the review process	☐ **YES** ☐ **NO** ☐ No Committee
If **NO** are there plans to establish SOPs within the next two years?	☐ **YES** ☐ **NO**
8.5 Are SOPs used for any other procedures in the regulatory review process (e.g., validation)?	☐ **YES** ☐ **NO**
Please specify for the reviewers	
Assessment Templates set out the content and format of written reports on scientific reviews.	
8.6 Are there Assessment Templates for reports on the scientific review of a NAS?	☐ **YES** ☐ **NO**
If **NO** are there plans to establish this within the next two years?	☐ **YES** ☐ **NO**
Peer Review is an additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during assessment of a dossier or at the time of sign-off.	
*8.7 Are **external** peer reviews carried out when a NAS is assessed?*	☐ **YES** ☐ **NO**
If **NO** are there plans to introduce these within the next two years?	☐ **YES** ☐ **NO**
*8.8 Are **internal** peer reviews carried out when a NAS is assessed?*	☐ **YES** ☐ **NO**
If **NO** are there plans to introduce these within the next two years?	☐ **YES** ☐ **NO**
8.9 Are there other general procedures in place to monitor the quality of the review process?	

9. Quality Management

Reasons for introducing quality measures in the authority

*9.1 Please select, from the following list, the **three** most important reasons for the introduction of quality measures*

- ☐ To be more efficient
- ☐ To ensure consistency
- ☐ To achieve stakeholder satisfaction
- ☐ To improve communications in the authority
- ☐ To minimise errors
- ☐ To reduce costs
- ☐ To increase transparency
- ☐ Other (please specify)

Monitoring to improve quality

9.2 Which of the following activities are undertaken by the authority to bring about continuous improvement in the assessment and registration process?

- Reviewing assessors' feedback and taking necessary action ☐ **YES** ☐ **NO**
- Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action ☐ **YES** ☐ **NO**
- Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy) ☐ **YES** ☐ **NO**
- Carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system ☐ **YES** ☐ **NO**
- Having external quality audits by an accredited certification body to improve the system ☐ **YES** ☐ **NO**
- Having a 'post approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments ☐ **YES** ☐ **NO**

Other, please specify

Management responsibility

9.3 Does the authority have a dedicated department for assessing and/or ensuring quality in the assessment and registration process? ☐ **YES** ☐ **NO**

If **YES**, how many staff are involved?

To whom does this section report (e.g. the Chief Executive Officer of the authority)?

If **NO**, is the Authority thinking of setting up such a department? ☐ **YES** ☐ **NO**

10. Quality in the Review and Assessment Process

Improving the quality of applications

10.1 Does the authority have official guidelines to assist industry in the registration of medicinal products? ☐ **YES** ☐ **NO**

If **YES**, how are these guidelines made available? (Please indicate all that apply)

- ☐ Through the authority's website
- ☐ On request
- ☐ Other, please specify
- ☐ Through official publications
- ☐ Through industry associations

Improving quality through interaction with applicants

10.2 Does the authority provide pre-submission scientific advice to applicants ☐ **YES** ☐ **NO**

If **YES** how is the quality of that advice monitored?

10.3 Is the applicant given details of technical staff that can be contacted to discuss an application during review? ☐ **YES** ☐ **NO**

10.4 Please indicate which of the following best describes the level of contact that companies have with agency staff or outside experts during development and during the agency's assessment.

	Development	*Assessment*
Extensive formal contact (including scheduled meetings)	☐	☐
Extensive informal contact (frequent telephone or email contact)	☐	☐
Some formal contact (possibility of meetings)	☐	☐
Some informal contact (possibility of telephone or email contact)	☐	☐
None, or minimal formal contact (rare occurrences of contact, via letter or fax)	☐	☐
None, or minimal informal contact (rare telephone or email contact)	☐	☐

Please comment on general policy for contact with applicants

Committee Procedure

10.5 If your review procedure includes obtaining the advice of a scientific committee of internal and/or external experts (as in Section 5.4) please complete the following:

Name of the Committee

Number of Committee Members

How frequently does the Committee meet?

☐ Once a week ☐ Once a Month ☐ Other (specify)

For NAS applications and major line extensions does the Committee review?

☐ All applications ☐ Selected dossiers (specify)

Does the Committee review?

☐ The complete dossier ☐ Assessment reports from the reviewers

Shared and Joint reviews

A ***shared review*** is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A ***joint review*** is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken such as the GCC system.

10.6 Does your authority conduct shared or joint reviews with other regulatory authorities?

☐ **YES** regularly. Please state which authorities ☐ **YES** occasionally. Please state which authorities

☐ **NO** this has never been undertaken

***Shared and Joint reviews** (cont.)*

If **YES** do you have formal measures in place to ensure consistent quality during the review? If **Yes**, please specify	☐ **YES** ☐ **NO**
If **NO**, do you anticipate undertaking such reviews within the next two years?	☐ **YES** ☐ **NO**
10.7 Have these joint reviews influenced the way in which your authority conducts reviews in general? If so, please comment	☐ **YES** ☐ **NO**

11. Training and continuing education as an element of quality

The following questions relate to training and continuing education of assessors working within the authority, including those employed on a full-time basis and those contracted for specific assessments were necessary.

11.1 Do you have a formal training programme for assessors? ☐ **YES** ☐ **NO**

11.2 Which of the following methods are used for training assessors?

- ☐ Induction training
- ☐ On-the-job training
- ☐ In-house courses
- ☐ External speakers invited to the authority
- ☐ Other, please specify
- ☐ External courses
- ☐ Post-graduate degrees
- ☐ Participation in international workshops/ conferences
- ☐ Placements and secondments in other regulatory authorities

11.3 Does your authority collaborate with other agencies in the training of assessors? ☐ **YES** ☐ **NO**

If **Yes**, please give details: WHO, AusAID, World Bank

11.4 Is training tested in examination situations once completed? ☐ **YES** ☐ **NO** ☐ Partly

11.5 Is completion of training courses required for professional advancement? ☐ **YES** ☐ **NO** ☐ Partly

12. Transparency of the review procedure

This section examines 'transparency' in terms of the ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry.

12.1 What priority does your agency assign to being open and transparent in relationships with the public, professions and industry?

☐ High priority ☐ Medium priority ☐ Low priority

Please comment:

12.2 What are the main drivers for establishing transparency? Please indicate the top three incentives for assigning resources to activities that enhance the openness of the regulatory system

- ☐ Political will
- ☐ Press and media attention
- ☐ Need to provide assurances on safety safeguards
- ☐ Other, please specify
- ☐ Public pressure
- ☐ Need to increase confidence in the system
- ☐ Better staff morale and performance

Transparency to the public

The following questions explore the availability of information to the general public on the performance of regulatory authorities

12.3 Please indicate which of the following information items about the assessment and registration of marketing applications is available to the public.

- ☐ Approval of products
- ☐ Approval times
- ☐ Summary of the grounds on which the approval was granted
- ☐ Advisory Committee meeting dates
- ☐ Other, please specify

12.4 How is this information made available

- ☐ Official Journal/periodical publication
- ☐ On request
- ☐ From an official Internet website
- ☐ Other (please specify)

Transparency to companies on application progress

12.5 Are companies able to follow the progress of their own applications?	☐ **YES**	☐ **NO**

If **YES** please indicate the mechanisms available to industry

- ☐ Electronic access to the status of applications
- ☐ E-mail contact
- ☐ Telephone contact
- ☐ Other (please specify)

12.6 Are companies given detailed reasons for rejecting an application for registration?	☐ **YES**	☐ **NO**

Facilities for providing information

12.7 Is there an electronic system for registering and tracking applications	☐ **YES**	☐ **NO**

If **YES** please indicate whether it has the following capabilities

• Tracing applications that are under review and identifying the stage in the process	☐ **YES**	☐ **NO**
• Signalling that target review dates have been exceeded	☐ **YES**	☐ **NO**
• Recording the terms of the authorisation once granted	☐ **YES**	☐ **NO**
• Archiving information on applications in a way that can be searched	☐ **YES**	☐ **NO**
If **NO** are there plans to introduce such a system?	☐ **YES**	☐ **NO**

If so, please give target date for implementation: ____

13. CONCLUDING OBSERVATIONS

The purpose of the following two questions is to try to identify the Agency's own perception of its unique positive qualities and the major impediments it faces in carrying out the review of new medicines and making them available to meet patients' needs.

18.1 List three factors that make a major contribution to the effectiveness and efficiency of your agency's review procedures and decision-making processes for NAS applications
18.2 List three factors that act as barriers to making new medicines available in a timely manner through the regulatory process

Thank you for completing this questionnaire

Please sign and date:

Signature	Position
Name	
Date:	Email:

GLOSSARY AND ABBREVIATIONS

Additional information	Additional data or additional analyses of existing data requested from the sponsor by the regulatory authority during the review process
Advisory Committee	An expert committee that advises the regulatory authority of the safety, quality and efficacy of new medicines for human use
Approval	The approval of a drug product by a regulatory authority, signified by the granting of a marketing authorisation, or the issue of a technical approval letter. However the product may still not be marketable until negotiations for pricing and reimbursement are concluded.
Clinical efficacy	An evaluation based on clinical studies that provide sufficient evidence that the project has a beneficial therapeutic effect or diagnostic value. This is determined by one or more agreed endpoints (such as objective measurements which are validated and accepted to represent appropriate criteria of efficacy i.e. reduced progression or reversal of disease process, improved quality of life and where relevant, reduced mortality for cancer studies, etc).
Clinical summary	Summary of clinical study data that typically includes biopharmaceutic studies and associated analytical methods, clinical pharmacology studies, clinical efficacy, clinical safety, literature references, and synopses of individual studies. Refers to Module 2.7 in CTD format.
Common technical document (CTD) format	Common technical document (CTD) as outlined in the ICH guideline M4 (Organisation of the common technical document for the registration of pharmaceuticals for human use; M4).
CMC	Chemistry, manufacturing and controls. All activities conducted to optimize, scale-up and validate the processes and technologies for transfer to manufacture and all QA, QC and CMC support activities (e.g. CMC project management including CMC contribution to project teams). This includes all drug substance R&D i.e. process research and process development, all drug product R&D i.e. formulation development and process development, all analytical work for drug substance R&D and drug product R&D, clinical supplies and CMC's involvement in the compilation of regulatory documentation.
Good review practice (GRP)	Good review practices are about the process and the documentation of the review process. Good review practices aim to standardise and improve the overall documentation associated with the review, thus ensuring timeliness, predictability, consistency and high quality of reviews and review reports.
ICH	International Conference of Harmonisation
IND	Investigational New Drug

Informal contact	Oral communication between the regulatory authority and sponsor during the review process.
Internal reviewers	Internal reviewers are employees of the Authority
Joint review	The whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.
Marketing Authorisation	Authorisation issued by a regulatory to launch a drug product on the market
Marketing Authorisation Application	Authorisation application submitted to a regulatory authority to launch a drug product on the market to which the application has been submitted.
Milestone	A milestone must involve some form of dated written document to which the regulatory authority can refer. In addition, a milestone must be considered by the regulatory authority to be the point at which one event stops and the next one begins so that the times for events are interdependent.
Major Line Extension	A major line extension is a modification to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.
NAS (New Active Substance)	A new chemical, biological or pharmaceutical active substance includes: a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product; an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised; a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process; a radiopharmaceutical substance which is radionucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide has not been previously authorised.

EAS (Existing Active Substance)	An existing chemical, biological or pharmaceutical active substance includes: a chemical, biological or radiopharmaceutical substance previously authorised as a medicinal product; an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product with the same properties with regard to safety and efficacy to that chemical substance previously authorised; a biological substance previously authorised as a medicinal product, which has the same molecular structure, nature of the source material or manufacturing process; a radiopharmaceutical substance which is radionucleotide, or a ligand previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide which has been previously authorised.
Non-clinical summary	Summary of non-clinical data including: pharmacology, pharmacokinetics and toxicology. Refers to Module 2.6 in CTD format.
Peer review	Peer review means an additional evaluation of an original assessment carried out by an independent person or committee. Peer review can occur either during assessment of a dossier, or at sign-off.
Quality control	Quality control is operational techniques and activities that are used to fulfil requirements for quality. It involves techniques that monitor a process and eliminate causes of unsatisfactory performance at all stages of the quality cycle.
Quality policy	Overall intentions and direction of an organisation related to quality as formally expressed by top management.
Questions to sponsor	The process of asking the sponsor for additional data or additional analyses of existing data. The requests are made by the regulatory authority during the review process.
Scientific assessment	Review of the dossier in terms of safety, quality and efficacy of data submitted.
Shared review	Each authority takes responsibility for assessing a separate part of a dossier.
Sponsor	A company, person, organisation or institution that takes responsibility for initiating, managing or financing a clinical study.
Standard Operating Procedures (SOPs)	Detailed, written instructions to achieve uniformity of the performance of a specific function
Validation of a dossier	The process whereby the authority verifies that all parts of the submitted dossier are present and complete and suitable to be assessed as part of the assessment and registration process.

APPENDIX B

Questionnaire (2): An Evaluation of the Strategic Plans of the Regulatory Agencies in the GCC Region

Respondent's Name: Title:

Agency: Country:

An Evaluation of the Strategic Plans of the Regulatory Agencies in the GCC Region

SURVEY QUESTIONNAIRE

Contact
Reem Al-Essa
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Cardiff University
Welsh School of Pharmacy

Ministry of Health
Kuwait Drug & Food Control

August 2008

Collaborative Team

Kuwait Drug and Food Control

Kuwait Drug and Food Control (KDFC) was established in 1968 under the autonomy of the Ministry of health to ensure the safety of pharmaceutical products, herbal products, veterinary products, medical devices, cosmetics, food supplements and chemical substances as well as to set mandatory standard specifications thereof, whether they are imported or locally manufactured. The control and/or testing activities can be conducted in the KDFC or other agency's laboratories. Moreover, the KDFC is in charge of consumers' awareness on all matters related to food, drug and medical devices and all other products and supplies. (http://www.kufda.org)

CMR International
Institute for Regulatory Science

The CMR International Institute for Regulatory Science is a non-profit division of Thomson Scientific. It works in the regulatory and policy arena and in close association with the research- based pharmaceutical industry and regulatory authorities around the world.
The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme. The institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts. (http://www.cmr.org)

Welsh School of Pharmacy
Cardiff University

The Welsh School of Pharmacy is one of twenty four UK schools of pharmacy and the only one in Wales. For over 80 years, the School has cultivated a strong tradition of innovative pharmaceutical education, scientific research and latterly, continuing education to pharmacy practitioners.
Judged by nationally recognised standards, the School is the top UK school of pharmacy. Our research has received a 5A (Excellent) ranking in the 2001 RAE (Research Assessment Exercise) and we were awarded an excellent for the quality of our teaching and learning in the last TQA (Teaching Quality Assessment)
(http://www.cardiff.ac.uk/phrmy/newsandevents/news/guardian-rates-cardiff-as-top-for-pharmacy-teaching.html)

The Research Fellow

This study is performed by Reem Al-Essa, Drug Registration and Release Superintendent at Kuwait Drug and Food Control Agency, as part of her PhD research program with Cardiff University-Welsh School of Pharmacy, in collaboration with CMR International Institute for Regulatory Science. The study aims at assessing the strategic planning process for the regulatory agencies in all GCC states. An evaluation of how each GCC country is planning for its future drug regulatory control and whether they have prepared and documented both their short-term (1-2years) and/or long-term (3-5years) strategic plans for improving the regulatory system will be the main purpose of this study.

Background

Over the last 10 years, the GCC regulatory agencies have been facing a number of challenges due to the advancement of drug regulatory practices around the world. These advancements have placed the agencies in a position where establishing a strategic plan is considered essential in order to keep pace with the demands of the pharmaceutical market.

This Study proposes to evaluate how each GCC country is planning for its future drug regulatory control and whether they have prepared and documented both their short-term (1-2 years) and/or long-term (3-5 years) strategic plans for improving the regulatory system.

The proposed study will review the drivers for any change that might occur, or have occurred, in the GCC region and will evaluate the future vision of each of the GCC regulatory agencies. The aim is to identify benchmarks which may be used to harmonise the GCC drug regulatory practices in the future.

Objectives

The objectives of this study are to:

- Compare and contrast the strategic plans for any changes in the regulatory systems between the seven GCC states.
- Evaluate the differences underpinning the future strategic plans in the GCC countries.
- Determine the impact and value of understanding strategic plans and their underpinning driving forces in order to shape the future direction of the GCC regulatory systems.

Methodology

The seven GCC regulatory agencies namely (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen) are being invited to participate in this study. Key regulatory personnel in each authority will be asked to participate in a structured interview *(See glossary of terms)*. The study will focus on four areas:

1. The vision statement for each authority

2. Short-term (1-2 years) and long-term (3-5 years) strategic plans

3. Driving forces for any change or improvement

4. Agency's analysis of their Strengths, Weaknesses, Opportunities and Threats (SWOT Analysis).

The structured interview will involve senior personnel within the authority who either have devised or are responsible for the strategic plans of the agency. The followings will be invited to participate:

Participant's name	Title	Agency	Country
Reem Al-Essa	Drug Registration and Release Superintendent	Drug and Food Control - Ministry of Health	Kuwait
Dr. Saleh Bawazir	Vice President of Pharmaceutical Affairs	Saudi Food and Drug Authority	KSA
Dr. Ali Alzawawi	Head of Pharmaceutical Licensing Division- Ministry of Health	Ministry of Health	KSA
Dr. Essa Almansouri	Director of Drug Control Department	Drug Control Department - Ministry of Health	UAE
Dr. Nadia Younis	Head of Registration and Pricing Department	Drug Control Department - Ministry of Health	UAE
Dr. Aysha Alansari	Director Pharmacy Admin.	Drug Control Department - Ministry of Health	Qatar
Dr. Muhammed Alrubaie	Acting Director of Drug Control	Drug Control- Ministry of Health	Oman
Dr. Sawsan Jaffaar	Director of General Pharmaceutical Affairs & Drug Control	Directorate of Pharmaceutical Affairs and Drug Control- Ministry of Health	Oman
Dr. Muhammed Nassir	Director, Pharmacy & Drug Control	Ministry of Health	Bahrain
Dr. Abdulmene'm	Director, General and Supreme Board for Drug and Medical Appliances	General and Supreme Board for Drug and Medical Appliances	Yemen
Dr. Abdalla Abdulkhaleq	Pharmacist, General and Supreme Board for Drug and Medical Appliances	General and Supreme Board for Drug and Medical Appliances	Yemen

Study Output

In view of the importance of improving the regulatory review process and drug approval timelines and of establishing a post-marketing surveillance system in any drug regulatory agency, regulatory studies have focused on assessing these practices with an aim of improving the agencies' performance.

It is hoped that as a result of this study, a hypothesis will be generated that may be of value in helping the agencies to structure and develop their future strategic direction.

Pilot and Full-Scale Study

The Study will be piloted with:

1. Reem Al-Essa, Drug Registration and Release Superintendent, Kuwait Drug and
2. Food Control Authority (KDFC) Control.
3. Dr. Essa Al-Mansouri, Director of Drug Control Department, Ministry of Health
4. Dr. Nadia Younis, Head of Registration and Pricing Department, Drug Control Department, Ministry of Health UAE

The pilot study will be initiated internally in Kuwait and from this experience, the questionnaire will be revised and improved and sent to the targeted respondents in United Arab Emirates (UAE). Comments and suggestions on the study questionnaire, its relevance, layout and wording will also be welcomed from UAE respondents.

In addition, any difficulties encountered will be noted. The feedback will then be taken into consideration in the design of the prospective full-scale study on all GCC states.

Conclusion

It is hoped that this study will be a tool for establishing a baseline for evaluating and comparing the strategic planning process *(see glossary of terms)* and vision statements of the seven GCC regulatory agencies.

Timescale

It is hoped to carry out the pilot study in September 2008. The full study will take place in October 2008 with the aim of providing a draft report in November 2008 which will be sent to all participating GCC states. In the light of the comment received, a presentation will be prepared in December 2008 to be reviewed by all participants before the presentation is made at the Middle East Regulatory Conference in Bahrain on 21st January 2008.

Confidentiality

All data will be kept strictly confidential and the data set for each agency will be reviewed and approved by each member state before it is shared with the other GCC state.

The final report will initially be presented as anonymized data (i.e. GCC states will not be identified). Only after an agreement has been reached by the member state for the results to be identified, will the report be prepared (January 2008).

Glossary of Terms

Strategic Planning
The process by which an organisations, public health or otherwise, envisions its future and develops strategies, goals, objectives, and action plans to achieve that future.

Strategy
An approach taken that will affect the overall direction of the organisation and will establish the organisation's future environment.

Structured Interview
A type of interview in which the candidate is given written questions to answer or problems to resolve at the oral interview site prior to his/her interview. The candidate then presents responses to the questions during the interview.

Vision Statement:
A vision statement outlines what an organisation wants to be. It focuses on tomorrow; it is inspirational; it provides clear decision-making criteria; and it is timeless.

Mission Statement
A mission statement outlines what the organisation is now. It focuses on today; it identifies the critical process (es); and it states the level of performance.

Organisation's Values
Values are the collective principles and ideals which guide the thoughts and actions of an individual or a group of individuals (i.e., an organisation). Values define the character of an organisation – they describe what the organisation stands for.

Goal
A stated aim; something specific the Planning Unit seeks to achieve or bring about in support of its mission. It is a broad statement describing a desired future condition or achievement without being specific about how much and when.

Objectives
An initiative the Planning Unit will take in order to achieve its goal; a measureable step toward the goal. Objectives are action-oriented and measurable. It is a specific statement of a desired short-term condition or achievement; this includes measurable end results to be accomplished by specific teams or individuals within time limits.

SWOT Analysis
SWOT stands for strengths, weaknesses, opportunities and threats. It is a methodology used to aid strategic planning that gained popularity during the 80's. To do a SWOT analysis, consider these:

Strengths: What are your advantages? What do you do well?

Weaknesses: What could be improved? What is done poorly by the company? What are the skills not covered?

Opportunities: What are the current trends?

Threats: What obstacles do you face? What is your competition doing? Are requirements changing? What are the current threats? Do you have resource problems?

The Questionnaire

Part 1: Characteristics of agency and respondent

Organisation
Type □ Autonomous agency, independent from the Health Ministry administration □ Operates within the administrative structure of the Health Ministry
Address
Telephone (including country code)
Fax
Website
Name of person completing this questionnaire
Position
Email Address
Telephone (including country code)
Please provide the following information in relation to the way the agency is funded Funded entirely by the government □ Yes □ No Self-funded entirely from fees □ Yes □ No Partially funded from different sources □ Yes □ No If Yes, Percentage of government funded : ---------- Percentage from fees: ----------

Part 2: Please state the Vision and mission statements and values for the organisation?

2.1 Does your organisation have a Vision statement? □ Yes □ No If Yes, please state your organisation's vision statement:	Definition: A vision statement outlines what an organisation wants to be. It focuses on tomorrow; it is inspirational; it provides clear decision-making criteria; and it is timeless.
Vision statement: 2.2 Is it available in a public domain or a document? □ Yes □ No If yes, please provide	
2.3 Does your organisation have a Mission statement? □ Yes □ No If Yes, please state your organisation's mission statement:	Definition: A mission statement outlines what the organisation is now. It focuses on today; it identifies the critical process (es); and it states the level of performance.
Mission statement: 2.4 Is it available in a public domain or a document? □ Yes □ No If yes, please provide	
2.5 Does your organisation have value(s)? □ Yes □ No If Yes, please state your organisation's Value(s): *(E.g. Integrity, honesty, competency...etc)*	Definition: Values are the collective principles and ideals which guide the thoughts and actions of an individual or a group of individuals (i.e., an organisation). Values define the character of an organisation – they describe what the organisation stands for.
Organisation's values: 2.6 Is it available in a public domain or a document? □ Yes □ No If yes, please provide	

Part 3: Please state the organisation's Goals and objectives

3.1 Does your organisation have Goals? □ Yes □ No If Yes, please state your organisation's goal(s):	A goal is a stated aim; something specific the Planning Unit seeks to achieve or bring about in support of its mission. It is a broad statement describing a desired future condition or achievement without being specific about how much and when.
Organisation's Goal (s): 3.2 Is it available in a public domain or a document? □Yes □No If yes, please provide	
3.3 Does your organisation have Objectives? □ Yes □ No If Yes, please state your organisation's objective(s):	An initiative the Planning Unit will take in order to achieve its goal; a measureable step toward the goal. Objectives are action-oriented and measurable. It is a specific statement of a desired short-term condition or achievement; this includes measurable end results to be accomplished by specific teams or individuals within time limits.
Organisation's Objectives: 3.4 Is it available in a public domain or a document? □ Yes □ No If yes, please provide	

Part 4: Please provide your Agency's analysis of Strengths, Weaknesses, Opportunities, and Threats (SWOT Analysis)

Strengths: *(e.g. long experienced regulatory system)*	Weaknesses: *(e.g. lack of education and training)*
Opportunities: *(e.g. new website for global interaction)*	Threats: *(e.g. loss of staff)*
Is the SWOT analysis available in a public domain or a document? □ Yes □ No If yes, please provide	

Part 5: Agency's short-term (1-2 year) and long-term (3-5 year) strategic plans?

Short-term plans (1-2 years)

Does the agency have short-term plans (1-2 years)

□ Yes □No

If yes, please indicate which of the following factors are considered in your short-term strategic plans and provide statements that indicate your agency's intentions in these areas:

Factor	Statement of intention(s)
□ Guidelines	.....
□ Review process	.....
□ Resources	.....
□ Standard Operating Procedures	.....
□ Changing requirements	.....
□ Post-Marketing Surveillance	.....
□ Quality Assurance	.....
□ Budgeting	.....
□ Other: Please specify (.....)	.....

Long–term plans (3-5 years)

Does the agency have long-term plans (3-5 years)?

□ Yes □No

If yes, please indicate which of the following factors are considered in your long-term strategic plans:

Factor	Statement of intention(s)
□ Guidelines	.....
□ Review process	.....
□ Resources	.....
□ Standard Operating Procedures	.....
□ Changing requirements	.....
□ Post-Marketing Surveillance	.....
□ Quality Assurance	.....
□ Budgeting	.....
□ Other: Please specify (.....)	.....

Part 6: Please describe three major driving forces for change that are likely to have a significant impact on the agency and its work in the next 5 years, such as patients' demand for improved access, increasing population, increasing number of generic medicines....etc

Driving force 1:
Driving force 2:
Driving force 3:
Any Other Comments? □ Yes □ No If Yes, please state your comment briefly:

Part 7: Please provide details on how the strategic plan is documented and approved in the agency?

7.1 Does the agency have an internal system for documenting strategic plans?
□ Yes □ No

If No, are there plans to introduce such system in the next 2 years?
□ Yes □ No

7.2 Does the agency have an internal system for reviewing and approving its strategic plans?
□ Yes □ No

If No, are there plans to introduce such system in the next 2 years?
□ Yes □ No

7.3 Does the agency have an advisory committee for reviewing and generating strategic plans?
□ Yes □ No

If No, are there plans to introduce such committee in the next 2 years?
□ Yes □ No

Part 8: General comments not covered elsewhere in this questionnaire

Name of the respondent:

Position:

Agency:

Signature:

Date: