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ORIGINAL RESEARCH ARTICLE

The Saudi Food and Drug Authority: Shaping the Regulatory Environment in the Gulf Region

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Abstract
Objective This study sought to assess the current regulatory review process in Saudi Arabia, identify the key milestones, evaluate the measures used for Good Review Practices (GRevP) and to suggest opportunities for an enhanced regulatory review of medicines.
Methods A questionnaire completed by the Saudi Food and Drug Authority (SFDA) was divided into three parts: Organisation of the Agency, Key Milestones and Timelines and GRevP.
Results Currently the SFDA carries out a full assessment for the review of all major applications, although they currently lack the expertise to evaluate the preclinical portion of the product file. A Certificate of Pharmaceutical Product (CPP) is required at the time of registration and a pricing agreement internally must be developed before authorisation. Applications may have to wait 2–6 months before review, although priority products are taken out of the queuing system. The median review times for new active substances from submission to approval were 340 working days (2011) and 372 working days (2013); however, the target time was 290 working days. Standard operating procedures (SOPs), review templates and an electronic submission tracking system are in place, but the GRevP framework is still evolving.
Conclusion Based on the available resources and capabilities, the SFDA is unable currently to meet its overall target timelines, partly due to the sponsor's time in responding to agency questions. Therefore, it either needs to increase its resources or to implement a risk stratification system based on the Singapore model, which takes into account reviews by reference agencies. The SFDA is encouraged to develop GRevP guidelines to ensure the quality of the review.

Key Points

Currently, the Saudi Food and Drug Administration (SFDA) carries out a full assessment for the review of all national as well as Gulf Cooperation Council centralised applications and, based on the available resources and capabilities, the agency is currently unable to meet its target timelines.

The SFDA could consider an alternative risk stratification assessment model based on the Singapore system, which takes into account the reviews by reference agencies, or alternatively increase the amount of available resources to meet the target timelines.

Standard operating procedures, review templates and an electronic submission tracking system are all in place at the SFDA; however, good review practice guidelines have to be further developed and implemented and the SFDA encouraged to develop these guidelines to ensure the quality of the review.

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1 Introduction

Patients' access to new medicines is affected by several factors, which include regulatory requirements for drug approvals. Currently, the time from drug discovery to submission can take an average of 10–12 years and costs in excess of two billion US dollars [1]. Regulatory authorities, which are required to expedite drug approval and to speed up patients' access to new medicines, are also required to review the products appropriately and to ensure their quality, safety and efficacy [2, 3]. This dichotomy is considered as one of the major challenges facing regulatory authorities today.

Good review practice is one of the key factors that affects the assessment process and eventually the final regulatory decision [2, 4] and many international regulatory authorities have developed guidelines for Good Review Practices (GRevP) to ensure consistency, predictability, transparency, clarity, and efficiency while meeting target timelines. There are several elements of GRevP, which include the availability of standard operating procedures (SOPs), the application of quality management principles, communication with stakeholders, and appropriate training programmes for the reviewers [5]. Evaluating the performance of a regulatory authority on a continuous basis is considered crucial to improve patients' access and to ensure the quality, safety and efficacy of new medicines. Thus, this review was the first to be carried out to evaluate the performance of the Saudi Food and Drug Authority (SFDA) since it was established in 2009 and to identify areas for improvement while maintaining the quality of the regulatory review.

1.1 Saudi Arabia and the Gulf Cooperation Council for Arab States

The Kingdom of Saudi Arabia is considered one of the highest income economies in the Middle East [6]. Government expenditure on health in Saudi Arabia is significant and accounted for more than 6 % [47 billion Saudi riyal (SR); US$13 billion] of the total government expenditure in 2012. It is predicted that the total healthcare budget will rise to SR181 billion (US$48 billion) by 2017 [7]. In addition, the pharmaceutical market in Saudi Arabia is considered one of the most rapidly growing markets globally and the most important market in the Middle East and North Africa (MENA) region. In 2010, the pharmaceutical expenditure per capita was SR500 and the total pharmaceutical expenditure was SR13.5 billion (US$3.6 billion), which accounted for 2 % of the gross domestic product and contributed 18 % of the total healthcare expenditure [8].

The SFDA is the regulatory body in Saudi Arabia responsible for monitoring and regulating food, pharmaceutical products and medical devices. It acquired the responsibilities from the Ministry of Health with regard to pharmaceutical regulation in 2009. The Kingdom of Saudi Arabia has been a member of the Gulf Cooperation Council (GCC) for Arab States since its establishment in 1981. This council involves Kuwait, Bahrain, Qatar, United Arab Emirates and Oman in addition to Saudi Arabia. The objective behind the establishment of this council is to cooperate in different fields and to have similar political and economic directives. Furthermore, the council supports developing unified policies, regulations and laws among the member states [9].

One of the regional initiatives towards harmonisation is the centralised procedure for pharmaceutical product registration within the GCC. The centralised registration procedure was recommended by the Health Ministers Council in the GCC in 1976; however, there was no detailed description as to how this procedure would be implemented until the Kingdom of Bahrain submitted a proposal in 1997 to formulate a Central Registration Committee to oversee pharmaceutical companies and their product registration in the GCC. The main objectives of this process are to ensure that pharmaceutical companies are applying good manufacturing practices and to evaluate and unify regulations related to the export of pharmaceutical products [10].

The Ministers of Health approved a two-phase approach for the implementation of the centralised registration procedure proposed by the Executive Office of the GCC Ministers of Health in 1999. Phase one (1999–2001) involved the registration of pharmaceutical companies and products with priority being given to locally manufactured products in the GCC. Phase two involved the assessment of the whole process and system. The Centralized Registration Committee of the GCC started with two meetings and increased to four meetings annually as the number of applications increased. In addition, two meetings are conducted to cover registration policies and updating regulatory guidelines.

The centralised procedure has helped to adapt unified guidelines such as GCC stability guidelines and bioequivalence guidelines and has also enabled the simultaneous registration of products in all member states. However, although 130 products were approved by the Gulf Cooperation Council Drug Review (GCC-DR) in 2009, this number was dramatically reduced to 16 products the following year. The median approval time for new active substances (NASs) together with existing active substances increased from 180 working days in 2009 to 265 days in 2010 as a result of adopting these new guidelines. In addition, the SFDA started to evaluate all

products being assessed by the GCC-DR, which subsequently increased the overall review times as well as utilising resources that in turn influenced the national review times of the SFDA.

1.2 Study Rationale

This study aimed to evaluate the assessment process within the SFDA and identify areas for improvement that would enhance the SFDA decision-making process. This is the first study to evaluate the SFDA performance since it took over the responsibility for pharmaceutical regulation in 2009. The study, however, does not include the transition period from 2009 until 2010 but focuses on 2011 to 2013.

The SFDA is the only member state in the Gulf Region which carries out a full review for all products (except for non-clinical data). The other member states either carry out an abridged or verification review, apart from the United Arab Emirates which conducts a full review for biological and biotechnology products. In addition, the SFDA reviews all applications submitted for the centralised registration procedure, regardless of those member states that have been designated to carry out the review.

2 Objectives

The main objectives of this study were to

- assess the current regulatory review process in Saudi Arabia;
- identify the key milestones, timelines and stages of the review;
- evaluate the measures used to ensure consistency, transparency, timeliness and predictability in the review process;
- suggest opportunities for enhanced regulatory practices in Saudi Arabia through an understanding of the quality of the SFDA decision-making processes;
- identify how to improve patients' access to high-quality new medicines.

3 Methods

3.1 Study Participants

The study was facilitated by the Director of Product Licensing and the Executive Licensing Director of the Saudi Food and Drug Authority, who are responsible for setting and implementing policies, procedures, and guidelines for the regulatory review system in collaboration with other departments within SFDA.

3.2 Data Collection Process

A questionnaire was designed by the Centre for Innovation in Regulatory Science (CIRS) to be completed by the SFDA to determine the details of the regulatory review process in Saudi Arabia. This was based on a questionnaire that had been previously used to evaluate the regulatory environment in the APEC region [11]. The questionnaire was divided into three parts.

Part I, *Organisation of the Agency*, provides details of the agency's structure, organisation and resources. It also explores review model(s) for the scientific assessment of medicines to determine if the data were assessed in detail by the agency or if they relied on the results of assessments and reviews that are carried out elsewhere.

Part II, *Key Milestones and Timelines in the Registration of Medicines*, used a standard process map and milestones developed by CIRS through the study of procedures of mature regulatory agencies as well as those of the emerging pharmaceutical markets. This allowed for the description of the SFDA regulatory processes and for the standardisation of the definitions of those processes. The standardisation facilitated the collection of important information and allowed the data to be illustrated in a common format to simplify comparisons among regulatory agencies.

Part III, *Good Review Practices* (*GRevP*): *Building quality into the assessment and registration processes*, examined the activities that contribute to the quality of the decision-making process and those measures that have been adopted to improve consistency, transparency, timeliness and predictability in the regulatory review.

This questionnaire had been developed for previous use in the analysis of the regulatory environment in several emerging pharmaceutical markets [11]. It enabled the determination of the congruence with SFDA core practices and ensured the appropriate identification of the essential details and the collection of complete data. Data were collected on applications for NASs that had not previously been approved by the authority. After the questionnaire had been completed, the data were input into a standard Microsoft Word document for auditing, correction and comment by the authority's participants.

4 Results

4.1 Part I: Organisation of the Agency

Before 2004, the regulation of medicines was administered by a department within the Ministry of Health. The SFDA was established by Ministerial Decree in 2004 to bring the regulation of food and medical products under one

independent agency and the procedures for the review and authorisation of medicines have been under the direction of the SFDA since 2009, although there was a transition period until 2010.

The SFDA performs marketing authorisations, post-marketing surveillance, laboratory analysis of samples, clinical trial authorisations and regulates the advertising and pricing of medicines. Although the SFDA law states that one of its financial resources is the licensing fees from the sponsors, the SFDA is not able to directly utilise this contribution as the fees are transferred to the Ministry of Finance, which in turn provides the SFDA with their annual budget.

The Drug Sector of the SFDA, which regulates medicines for human and veterinary use, currently has a staff of 421. At present, 76 staff members are assigned to the review of marketing applications. This includes 65 pharmacists, 8 other scientists, 3 project managers and 4 statisticians. Two physicians are on the staff for the purpose of clinical trial approvals only.

4.1.1 Model of Assessment in Saudi Arabia

McAuslane and colleagues [11] identified three types of assessments practiced by regulatory agencies: the verification review (type 1); an abridged review (type 2); and a full review (type 3). The verification assessment avoids duplicating the assessment of a new product that is identical to one that has been approved elsewhere. The elements of a verification assessment within the Singapore model include the recognition of an authorisation by two or more reference or benchmark agencies and a verification process to validate the status of the product and to ensure that the product for local marketing conforms to the authorised product. An abridged assessment also conserves resources by not reassessing the full scientific supporting data but rather focuses on aspects that must be evaluated specifically for the local environment. Product registration by one reference or benchmark agency is a prerequisite of an abridged review within the Singapore system. An abridged assessment is carried out in relation to the use of the product under local conditions. For a full assessment, the regulatory 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. A full, independent review of quality, preclinical (safety), and clinical (efficacy) data is carried out. Information on registrations elsewhere (if any) are taken into consideration, but are not a prerequisite to filing or for authorisation. In practice in some countries using type 3 assessment, prior authorisation is a legal requirement before local authorisation could be finalised, but filing the application and the review is not delayed.

Saudi Arabia conducts a full assessment in the review of all major applications (NASs and major line extensions). Two variations on type 3 assessment are possible at the SFDA. For products evaluated under type 3A, information on prior registration elsewhere may still be a prerequisite to final authorisation, whilst the review of products under type 3B is considered 'self standing'.

4.1.2 Data Requirements and Assessment

The Certificate of Pharmaceutical Product (CPP) is required for registration in Saudi Arabia, although other evidence such as an electronic CPP or publication on an official regulatory website can be accepted as alternative to a CPP. Under certain circumstances, based on the importance of the product, a CPP may not be required at the time of application. The product assessed in the CPP or in the alternative evidence must be identical to the product submitted to the SFDA.

Full clinical and efficacy data are required for the application and the SFDA performs a complete assessment of these data and issues a report. Although preclinical data are required for application, the SFDA currently lacks the expertise to evaluate these data and only assesses the quality and the clinical portions of the product file. However, the preclinical data are required for potential evaluation in the event of a post-approval safety incident.

The SFDA performs structured benefit–risk assessments from their point of view. The clinical opinions of the agency always take into account national disease patterns and unmet medical need and sometimes take into account differences in medical culture or practice, although sufficient data on these criteria are not supplied in all applications. The SFDA clinical opinions, however, do not incorporate the consideration of ethnic factors.

The agency always attempts to obtain additional data from other agencies' internal assessment reports and publicly available reports such as the European Public Assessment Reports (EPARs). The SFDA sometimes attempts to obtain additional data from general internet searches and other resources such as local epidemiology studies.

The recognised reference agencies for Saudi Arabia are the European Medicines Agency, the UK Medicines and Healthcare Products Regulatory Agency, the US Food and Drug Administration, France's Agence de Sécurité Nationale pour les Médicaments et Produits de Santé, Australia's Therapeutic Goods Administration, Health Canada and Swissmedic. The SFDA takes into account the evaluations of product information leaflets and summaries of product characteristics issued by these reference agencies.

4.2 Part II: Saudi Arabia Regulatory Review Process

A map of the review process in Saudi Arabia is examined and described in detail in Fig. 1. It is a simplified representation of the main steps in the review of NASs and applications. The map represents the review and authorisation of a product that is approved on the first cycle. However, it does not include the steps that follow the refusal of an application such as hearings or appeals. The procedures for the review and authorisation of medicines are performed within the Drug Sector of the SFDA.

A CPP that has been legalised by an Embassy or Consulate is required at the time of application. With the approval of the SFDA Executive Licensing Department, submissions without CPPs can be accepted if they are accompanied with a commitment to submit the legalised copy before final authorisation. An incomplete submission is held as pending and a request for the missing data is sent to the applicant. There is a 90-day limit for responses to these requests, but the SFDA has accepted responses that exceed the time limit. The target scientific assessment time does not include the time for sponsors to respond to the assessors' questions.

4.2.1 Queue Time

In practice, applications have to wait 2–6 months after validation before being picked up for review, even though the target time is currently 2–8 weeks. However, priority products, that is, medicines designated as either intended for the treatment of serious or life-threatening conditions or those that demonstrate the potential to address unmet medical needs or that are on the SFDA exempted list, are taken out of the queuing system and given a priority review. The Agency regards the backlog of applications as a

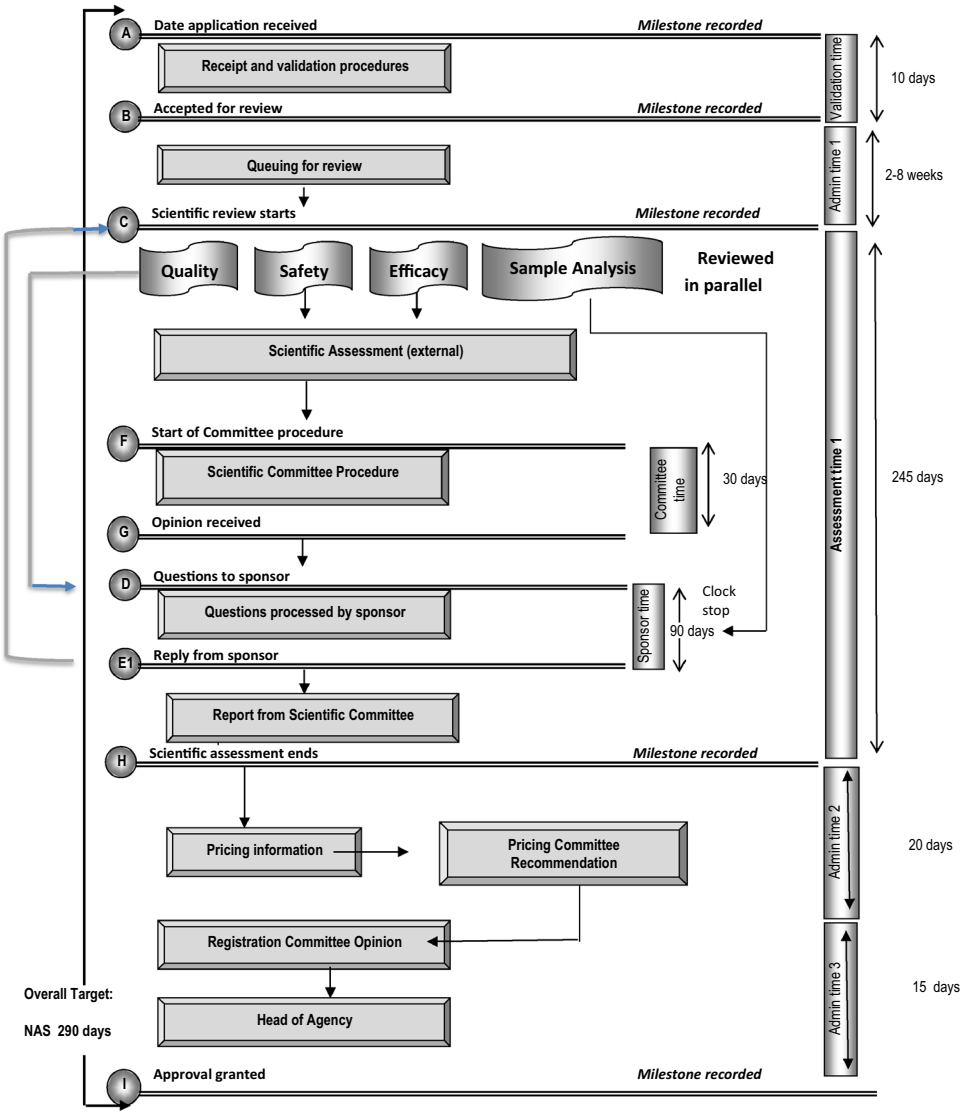

Fig. 1 Regulatory process map for Saudi Arabia. *NAS* new active substance

problem and is addressing the situation by the development of a team from different SFDA departments that has been tasked with determining the causes for the backlog and proposing possible solutions. The scientific data for submissions are separated into two sections for the review: one section reviews quality and the other the safety and efficacy. All data are assessed in parallel and the target time for scientific review is 245 working days, and 290 working days for the overall review.

4.2.2 Scientific Assessment

In the primary scientific evaluation, the application is passed for assessment to the agency staff. Different procedures are carried out in specific SFDA sections or departments, depending on the type of drug, especially if the product is a new chemical entity or biological product. The reviewer must complete a scientific product report form, detailing the trade name, generic name, indication and country of origin. For safety and efficacy assessments, the SFDA technical staff prepare assessment reports that will be reviewed by one of the Scientific Committee members and discussed in a committee meeting. The quality portion of the assessment is completely performed by SFDA staff.

Scientific Committee members are usually given 2 weeks to review the SFDA staff assessment report for efficacy. The committee members do not have a contractual agreement, although they sign a conflict of interest declaration and they are mainly responsible for providing a clinical opinion on individual products and providing advice to the agency staff on specific technical issues.

4.2.3 Questions to Sponsor

Questions for the sponsoring company may arise at any time during the SFDA assessment. Safety and efficacy assessment questions are batched and sent to sponsors separately from the batched questions that relate to the quality assessment. There is a 90-day time limit or clock stop for sponsors to reply to SFDA questions; however, the SFDA has accepted responses that exceed the time limit. The sponsor can meet with internal SFDA staff to discuss questions and queries that arise during the assessment, pre-specifying the points for discussion so that relevant SFDA staff can be invited. There are no restrictions or fees for such meetings.

4.2.4 Expert Committees

An integral part of the SFDA review, the Scientific Committee is consulted after the agency has reviewed and reported on the scientific data for safety and efficacy, although the agency is not mandated to follow the Committee's recommendations. The quality assessment report prepared by internal staff is not submitted to the Scientific Committee. There is no time limit for the Scientific Committee procedure, but the timing is approximately 1 month. After finalising all assessment reports, the application is forwarded to the pricing department to suggest a price for the product based on the pricing guideline and Pricing Committee recommendation.

All assessment reports including the recommendations of the Scientific Committee, Pricing Committee and Inspectors are forwarded to the Registration Committee. Based on the decision of this committee, the approval of the Chief Executive Officer of the SFDA then follows.

The Registration Committee is composed of external experts representing governmental healthcare providers and internal staff representing the departments involved in the assessment process. This committee is legally responsible for setting national pharmaceutical policy and for making the appropriate decision to approve, reject or withdraw a marketing authorisation application based on the recommendation of the scientific review reports and for approving the suggested price for products that are authorised. Sponsors are not informed of a positive scientific opinion before the authorisation is issued.

In addition to the assessment of scientific data on quality, safety and efficacy, the decision to grant or refuse an application depends on the internal pricing agreement and product labelling information as determined during the assessment. Authorisation is not dependent on sample analysis. If the registration committee decides to register the product and the decision is approved by the CEO, the company will be notified that the committee approved the marketing authorisation of the product with the price and how the SFDA arrived at that price, whether it was based on a reference price in another country, the price of similar products or it was based on the pricing rules for generics if it is a generic product. In the notification letter, the company will be asked to pay the registration fee (SR1000) within 30 days if they accept the approved price. If the company is not satisfied with the approved price or the decision was a refusal to grant the marketing authorisation to the product, they have the right to submit an appeal request against the decision within 60 calendar days. The company should pay the appeal fee and submit a formal appeal letter along with the scientific justification supporting the appeal. Target timelines for the SFDA review process can be seen in Table 1.

Most of the approved NASs (87 %) are sponsored by international companies, with local companies responsible for 13 %. The number of approved products from local companies and international companies from 2011 through 2013 is shown in Fig. 2. The highest numbers of approved products for international and local companies were 43 and 6 products, respectively, in 2013. From 2011 through 2013,

Table 1 Target times for SFDA review procedures

Process	Target
Validation	10 working days
Scientific assessment	245 working days
Sponsor response time	90 working days
Expert Committee(s)	30 working days
Authorisation procedure	<1 month
Overall review time	NASs: 290 working days

NASs new active substances, *SFDA* Saudi Food and Drug Authority

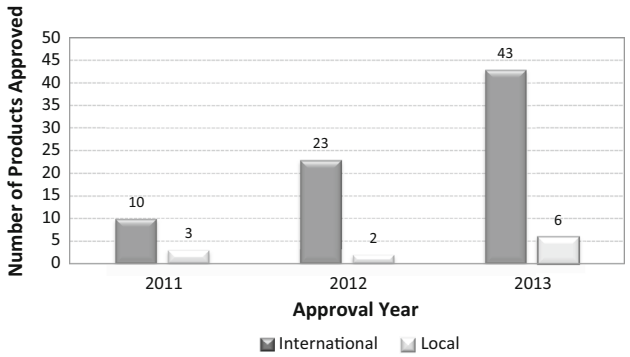

Fig. 2 Number of approved new active substances from local and international companies (2011–2013)

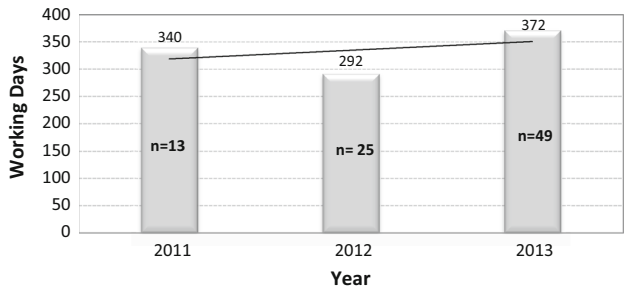

Fig. 3 Median approval timelines for new active substances (new molecular entities and biologicals) 2011–2013

the median approval time for the 11 products sponsored by local companies was 372 working days and 340 for those 76 products sponsored by international companies.

The highest number of NASs were approved in 2013 (49), with a median approval time of 372 working days. In 2011, 13 NASs were approved, with a median approval time of 340 working days, which is comparable to the median approval time in 2013. The fastest median approval time in 2011–2013 (292 working days) was achieved in 2012 in the approval of 25 NASs (Fig. 3).

Figure 4 shows the distribution of approval times for NASs between 2011 and 2013. The scientific assessment time was reduced from 247 working days in 2011 to 192

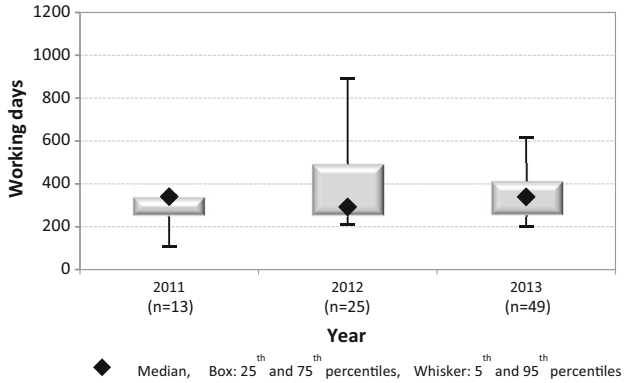

Fig. 4 Distribution of approval times for new active substances between 2011 and 2013

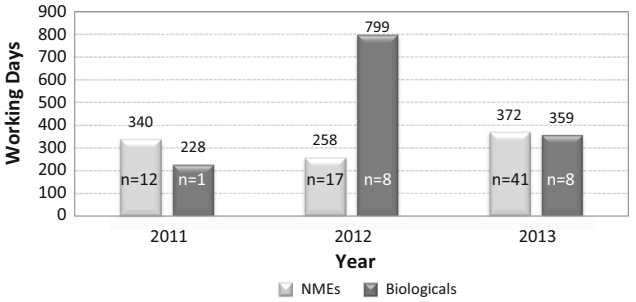

Fig. 5 Median approval time for new molecular entities (NMEs) compared with biologicals (2011–2013)

working days in 2013, which represents almost two thirds of the total approval time. The sponsor's median response time ranged from 92 working days in 2011 to 101 days in 2013. The median assessment time for NASs was within the performance target timing from 2011 through 2013 and overall assessment times that exceed target timing therefore appear to be due to the time sponsors take to respond to questions.

The median approval time for the one biological product approved in 2011 was less than for new molecular entities (NMEs), whereas in 2013 the approval times for both types of products were similar (Fig. 5). However, in 2012 the median approval time for biological products (8) was 799 working days compared with 258 working days for NMEs. Figure 6 shows the distribution of approval times for NMEs and biological products from 2011 to 2013.

The most commonly approved products by therapeutic class were

(a) anti-infectives for systemic use (17 products);
(b) antineoplastic and immunomodulating agents (16 products);

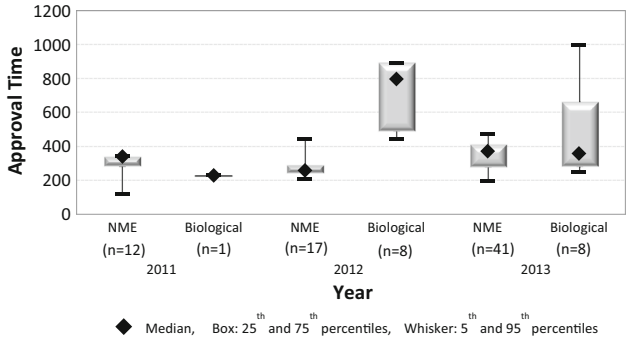

Fig. 6 Distribution of approval times for new molecular entities (NMEs) and biological products (2011–2013)

(c) blood substitutes and perfusion solution (14 products);
(d) cardiovascular system (10 products);
(e) alimentary tract and metabolism (10 products);

while the lowest number of approved products by therapeutic class were for systemic hormonal preparations and dermatological products.

The median approval time by therapeutic class is very similar for the most commonly approved classes from anti-infectives for systemic use (357 working days) to anti-neoplastics and immunomodulating agents (339 working days) and cardiovascular system products (340 working days).

4.3 Part III: Good Review Practices (GRevP)—Building Quality into the Assessment and Registration Processes

4.3.1 General Measures Used to Achieve Quality

Although the SFDA does not currently have an internal quality policy, defined as "overall intentions and direction of the organisation related to quality, as formally expressed by top management", it is the intention of the agency to develop such a policy in the future. Currently, there are no SFDA guidelines for GRevP, which are defined as "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." However, GRevP has been implemented informally in the SFDA to some extent, based on the practices of other agencies such as the EMA and US FDA as well as on international standards. In addition, there are SOPs for the assessment process and a standard format and template for assessment reports as well as a lexicon and comment databank to ensure consistency of expression in those reports.

The existing SFDA GRevP framework is still evolving and could be improved but there is a lack of implementation of GRevP and utilisation by staff has not yet reached the expected levels. Along with issues related to high turnover at the SFDA, this lack of use may be because specific GRevP guidelines are required to show the importance of GRevP to reviewers and because the staff require additional training to understand and learn about this topic.

SOPs were defined for this study as "written documents that describe in detail the official procedures to be followed for a specific operation." SOPs are currently implemented at the SFDA for the guidance of scientific assessors, for completing assessment templates and for other procedures in the regulatory review process. However, there are no SOPs for the Advisory Committee that is consulted during the review process, but this is being considered.

Assessment templates, which set out the content and format of written reports on scientific reviews, are currently used in the review of NASs at the SFDA. The SFDA quality assessment templates are based on the World Health Organization (WHO) template, whilst the templates to assess safety and efficacy are internal SFDA templates. Elements included in the SFDA assessment template are drug substance; drug product; comments on the label; toxicology (for some reviews); regulatory background, or the product's worldwide status among regulatory agencies; clinical pharmacology; clinical efficacy; clinical safety; and benefit–risk assessment. However, the assessment template for safety and efficacy is being reviewed in respect of the importance now bestowed on benefit–risk assessment, as there would be value in implementing a structured standardised framework and documenting system as used by other regulatory authorities [12].

The 17-member Scientific Committee meets once weekly to review all major applications and the assessment reports are prepared by internal reviewers. These assessment reports can also be shared with the GCC regulatory authorities on request. The reports are not published on the website nor do sponsors receive a copy. An external peer review procedure is currently used for safety and efficacy assessments of all products at the SFDA and all reports are discussed in the safety and efficacy review team meeting. The final report is also reviewed by one of the Scientific Committee members and findings are discussed in the Scientific Committee meeting. In addition, an internal peer review is carried out for quality assessment.

4.3.2 Quality Management

The SFDA identified the three most important reasons for the introduction of quality measures at the agency as the need to be more efficient, to minimise errors, and to ensure

consistency. Accordingly, the authority has created a dedicated four-person department for the ad hoc assessment and assurance of quality in the assessment and registration process for new medicines and this section reports to the Vice President for Drug Affairs.

To bring about continuous improvement in the assessment and authorisation process, the SFDA reviews assessors' feedback and also analyses stakeholders' opinions through complaints, meetings or workshops and takes necessary actions to address any issues that are raised. The agency also uses an internal tracking system to monitor consistency, timeliness, efficiency, and accuracy and since 2013 has carried out internal quality audits such as self-assessment, using the findings to improve the system. Finally, external quality audits are performed by an accredited certification body to improve the system and the SFDA has obtained an International Standardization Organization (ISO) certificate.

4.3.3 Quality in the Review and Assessment Process

Official guidelines to assist industry in the registration of medicinal products are available in English on the SFDA website. Pre-application scientific advice is also available to applicants although there is no policy to monitor the quality of the advice. There is also no clear SFDA policy for meeting with applicants before or during the assessment, but some formal contact such as meetings and some informal contact via telephone or email is possible before assessment. During the assessment, extensive formal contact including scheduled meetings and informal contact with regulatory affairs staff rather than reviewers is possible. Although applicants may formally request meetings with the reviewers, they are not provided with direct contact information for the staff.

4.3.4 Shared and Joint Reviews

Shared or joint reviews are undertaken when products are submitted through the Gulf Central Registration Procedure and bilateral and multilateral information-sharing agreements are in place. For the GCC centralised procedure, the SFDA jointly reviews the assessment reports with other GCC member states through the GCC Centralized Registration Office. Although the centralised registration guideline states that each application will be reviewed by two member states, the SFDA insists on reviewing all applications to ensure that the products are meeting SFDA standards. However, this extra commitment has created an additional workload for SFDA reviewers and has therefore had an impact on national submission review times. The GCC registration committee meets four times annually and at each meeting, in addition to reviewing the companies' responses to questions on previous submissions, registration renewals and variations, reviewers discuss all new applications. The SFDA has enacted formal measures to ensure consistent quality during the GCC review by adapting SFDA guidelines, most of which are based on ICH guidelines, for use during these meetings. Whilst up until 2013 different assessment templates were utilised by the various Gulf States, since the beginning of 2014 there has been an agreement for standardisation and the SFDA assessment template has been implemented.

These joint reviews have influenced the way in which the authority conducts reviews in general. The SFDA does not specifically benefit from joint reviews with other states, as SFDA reviewers are well trained and possess a qualified scientific background when compared with reviewers in other member states. Moreover, centralised procedures affect the approval time for applications submitted nationally as SFDA reviewers must focus on finalising GCC submissions before each meeting rather than reviewing national submissions.

4.3.5 Training

Training and continuing education are an element of building quality into the SFDA registration process. The agency currently has formal training programmes for assessors and training is carried out through multiple methods including orientation, on-the-job training, the use of external educational speakers invited to the authority, the sponsorship of post-graduate degrees and participation in external courses, internal workshops and conferences, advanced drug regulatory affairs training, WHO pre-qualification and the European Directorate for the Quality of Medicine training.

The agency does not currently collaborate with other agencies in the training of assessors and there are no formal examinations or requirements for the completion of training courses.

4.3.6 Transparency of the Review Process

For the purpose of this study, transparency was defined as "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." The SFDA assigns medium priority to transparency. In addition to SFDA regulations, the agency identified political will, press and media attention and the need to provide assurances regarding public safeguards as the top three incentives for assigning resources to activities that enhance the openness of the regulatory system. Although the registered drug list and information regarding product withdrawals and warnings regarding herbal

medicines are posted on the agency website, the SFDA does not publish Registration Committee decisions. Companies are able to follow the progress of their applications through an electronic tracking system that identifies the status of product reviews and records the terms of granted authorisations. Information on applications is also stored in a searchable archive and companies are provided detailed reasons for the rejection of applications for registration.

5 Discussion

The pharmaceutical market in Saudi Arabia is considered one of the most rapidly growing markets globally and the most important market in the MENA region. Furthermore, the regulatory authority in Saudi Arabia is the most developed regulatory authority in the region, as it has adapted the best international practices and guidelines and has provided its staff with scientific qualifications to carry out their functions appropriately by sending many of them abroad to obtain scientific degrees in various fields. In addition, the SFDA has developed electronic registration and clearance systems which are used at the ports of entry to enable the SFDA to perform its functions effectively.

However, there some challenges encountered by the regulatory authority in Saudi Arabia. One of these is the centralised registration procedure which affects the approval times of national submissions. The lack of expertise and the high turnover of the staff are considered another barrier facing the SFDA. In addition, the SFDA has yet to develop agreements with international regulatory authorities to establish 'On Job Training' (OJT) programmes for SFDA staff to learn how functions and activities are performed in these authorities and eventually to apply what has been learned in the SFDA.

This study, which examined the pattern of total regulatory approval times in Saudi Arabia between 2011 and 2013 for NCEs and biological products, determined that the number of NAS applications received between 2011 and 2013 exceeded the number of applications reviewed in the same period. Therefore, the SFDA should determine, based on the available resources, target times and capabilities, the number of applications it can process annually and identify the total resources required to manage the number of applications it is expected to receive in the future.

The agency is also encouraged to develop guidelines and regulations to accept and expedite the processing of applications that address a significant medical need. An alternative approach that would enable the SFDA to efficiently review the applications it receives each year is to implement a risk stratification procedure as is carried out within the Health Sciences Authority (HSA) in Singapore. In this system, products that have been approved by two or more reference agencies are evaluated by the verification route described earlier, in which the review is carried out in 60 working days. HSA carries out an abridged review of products that have been reviewed by only one reference agency, with a target time of 180 working days, and only conducts a full review of products that have not been reviewed by any other agencies, with a target time of 270 working days. This approach, which enables the most efficient use of resources, should be carefully considered by all agencies that lack the necessary resources or expertise to perform full reviews of all applications.

The number of products approved by SFDA from local companies and international companies has been increasing each year between 2011 and 2013. Most of the approved NASs were sponsored by the international companies; although local companies do submit NASs, these are typically developed under a license agreement with international companies, which do not have the necessary dedicated research to develop such products. The SFDA has established many regulations that support technology transfer and expertise to encourage international companies to contract with local manufacturers to fully produce their products locally in order to support the development of local manufacturers.

The SFDA only achieved its target times for approvals in 2012, when the median approval time was 292 days, whereas in 2011 and 2013 targets were exceeded by 50 and 82 working days, respectively. One possible solution to this problem is for the Scientific Committee to only review NASs and major line extensions, and internal staff to only review generics. An alternative solution would be to limit GCC-CP review to only NASs and local manufacturers' products, reducing the workload and timeline of national submissions.

The median time for the sponsor to respond to the authority queries varied between 92 and 101 working days during the 3 years, representing one third of the total approval time. While at the same time the scientific assessment time was reduced from 247 working days in 2011 to 192 working days in 2013, representing two thirds of the total approval time. Here there was little difference between the target and the actual median assessment time and little difference between the target response time to questions for companies and the median time for the response.

6 Conclusions

This study has evaluated the regulatory review process by the SFDA for the first time since it took over the responsibility for pharmaceutical regulations from the Ministry of Health in 2009. It has identified the key milestones, timelines and evaluated the measures used for GRevP and suggested opportunities for an enhanced regulatory review.

Currently the SFDA carries out a full assessment for the review of all national as well as GCC centralised applications. However, national applications have to wait 2–6 months before being reviewed, although products meeting medical needs are given priority. SOPs, review templates and an electronic submission tracking system are in place; however, GRevP guidelines have still to be developed and implemented. The findings from the study suggest that the SFDA could consider an alternative risk stratification assessment model based on the Singapore system which takes into account the reviews by reference agencies or alternatively increase the amount of available resources to meet the target timelines.

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References

1. Tufts Center for the Study of Drug Development. Costs to develop and win marketing approval for a new drug is $2.6 billion News release, November 18. 2014. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Accessed 17 Dec 2014.
2. Al-Essa R, Salek S, Walker S. An appraisal of good regulatory review practices in the Gulf Cooperation Council States. Drug Info J. 2012;46:57.
3. Salek S, Mallia-Milanes A, McAuslane N, Walker S. Development and application of Scorecards to assess the quality of a regulatory submission and its review. Drug Info J. 2012;46:73.
4. World Health Organization. Good review practice guidelines for regulatory authorities (draft for comment). 2014. http://www.who.int/biologicals/GRevPGuidelines-RHSC-endorsed-for-WHO_QAS14-576_27022014.pdf. Accessed 17 Dec 2014.
5. Liberti L, McAuslane N, Patel P, Breckenridge A, Eichler HG, Peterson R. Regulatory review: how do agencies ensure the quality of decision making? Clin Pharmacol Ther. 2013;94:305–8.
6. The Saudi economy in figures. 2013. www.mep.gov.sa/themes/GoldenCarpet/index.jsp#1399405095350. Accessed 17 Dec 2014.
7. Hawkins J. Deloitte 2015 health care outlook Middle East. http://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-health-care-outlook-middle-east.pdf. Accessed 16 Mar 2015.
8. Bawazir SA. Saudi Food and Drug Authority. Saudi Arabia pharmaceutical country profile; 2012. http://www.who.int/medicines/areas/coordination/Saudi_ArabiaPSCP_Narrative2012-04-18_Final.pdf. Accessed 17 Dec 2014.
9. The Cooperation Council for the Arab States of the Gulf. http://www.gcc-sg.org/eng/. Accessed 17 Dec 2014.
10. Hashan H. Evaluation of the review process for marketing pharmaceutical products in the Gulf States and its impact on patients' access to medicines. Doctor of Philosophy thesis, 2005. The Welsh School of Pharmacy, University of Wales.
11. McAuslane N, Cone M, Collins J, Walker S. Emerging markets and emerging agencies: a comparative study of how key regulatory agencies in Asia, Latin America, the Middle East and Africa are developing regulatory processes and review models for new medicinal products. Drug Info J. 2009;43:349–59.
12. Walker S, McAuslane N, Liberti L, Leong J, Salek S. A universal framework for the benefit-risk assessment of medicines—is this the way forward? Ther Inn Reg Sci. 2015;49:17–25.