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# Evaluation of the Gulf Cooperation Council Centralized Procedure: The Way Forward

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**Abstract**

The aim of the study was to evaluate the Gulf Cooperation Council (GCC) centralized regulatory review process. Regulatory review times—including submission and application dates for new active substances (NASs) and existing active substances (EASs) using a standardized template for the period of 2006 to 2010—were collected directly from the GCC office located in Riyadh, Saudi Arabia. A total of 413 products (96 NASs and 317 EASs) were approved during the period, with an overall significant increase in the EASs ($P < .001$). The median approval times increased from 107 calendar days in 2006 to 265 in 2010 ($P < .001$). The lowest approval time was for EASs submitted by the Gulf companies (134 days) and the longest for NASs submitted by international companies (346 days) ($P < .001$). These data were also analyzed according to therapeutic classes and dosage forms. The results also showed that the lowest number ($n = 16$) approved during the period was in 2010, and this was due to a major regulatory change implementing the International Conference on Harmonisation product stability guideline for the region. The findings indicate that the delay and the wide range in approval times could be reduced by utilizing a standard assessment template for product review and the implementation of a clock stop system for company responses to questions from the GCC central registration committee. Furthermore, using information technology tools would speed up the registration process rather than the manual exchange of product registration files between the executive office and the member states.

**Keywords**

regulatory review, Gulf Cooperation Council central registration, pharmaceutical companies, product approval time, key milestones

## Introduction

Since the establishment of the Gulf Cooperation Council (GCC) in 1981, the Gulf states have experienced major challenges in the regulatory environment similar to those seen around the world.[1] The timeliness with which regulatory authorities approve new medicines for marketing affects health care professionals, the pharmaceutical industry, and patients.[2] Thus, an unnecessarily long approval process delays access to new medicines that may improve patients' health status. Variation in the availability of medicines in different countries has been studied since the early 1970s,[3] and some marked differences have been found.

The Gulf Centralised Committee for Drug Registration (GCC-DR) was formed in May 1999 and included Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates with Yemen (joining in 2003). The GCC-DR consists of 2 representatives from each member state, and the main role of the committee is to register pharmaceutical companies and their products through the joint coordination of scientific safety, efficacy, and quality of medicinal products. During the period and since its establishment (1999-2010), the GCC centralized system received 1824 medicinal product applications and approved 1165 medicines.

It seems that regulatory approval times are influenced by the type of assessment carried out by different authorities. Al-Essa[1] identified 3 models of assessment and the extent of the scientific review in the GCC authorities—namely, the verification review, the abridged review, and the full review (see Table 1). Some GCC countries use more than one assessment

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**Table 1.** Models of assessment and the extent of the scientific review in the Gulf Cooperation Council authorities.

| | Bahrain | Kuwait | Oman | Qatar | Saudi Arabia | UAE | Yemen |
|---|---|---|---|---|---|---|---|
| Type of review model: | | | | | | | |
| I: Verification review | ✓ | ✓ | | | | | ✓ |
| II: Abridged review | ✓ | | ✓ | ✓ | | ✓ | |
| III: Full review | | | | | ✓ | ✓ | |
| Similarity to locally registered product: | | | | | | | |
| Fully identical | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Mostly identical | | | ✓ | | | | |
| Closely similar | | | | | | | |
| Extent of scientific review: | | | | | | | |
| 1. CMC data | | | | | | | |
| Detailed review | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | NA |
| Reviewed when necessary | | | ✓ | | | | |
| 2. Nonclinical data | | | | | | | |
| Detailed | | | | | ✓ | ✓ | ✓ |
| Reviewed when necessary | ✓ | ✓ | ✓ | ✓ | | ✓ | |
| 3. Clinical data | | | | | | | |
| Detailed | | | | | ✓ | ✓ | ✓ |
| Reviewed when necessary | ✓ | ✓ | ✓ | ✓ | | ✓ | |
| Addition information obtained from | | | | | | | |
| Other agencies' internal review reports | ✓ | | | ✓ | | | ✓ |
| Reports available on the Internet | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| General Internet search | ✓ | ✓ | ✓ | ✓ | | ✓ | |

Pharmaceutical companies experience a number of difficulties that can delay registration in the Middle East. These include requirements by most local authorities for both a certificate of pharmaceutical product from the source country and a registration of manufacturer prior to a marketing authorization application. The findings of an international survey suggest that these requirements result in a delay of 6 to 10 months on average.[4] The length of the review process depends on the type of products being registered and the requirements of the approval process, with different countries imposing different registration requirements on the manufacturers.[5] CMC, chemistry and manufacturing control; NA, not available; UAE, United Arab Emirates.

review model, depending on the type of product and/or its regulatory status with other authorities.

The verification model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorized by one or more recognized reference agencies elsewhere. The abridged review model also conserves resources by not reassessing scientific supporting data that have been reviewed and accepted elsewhere, but it does include an "abridged" independent review of the product in terms of its use under local conditions. In the third type of review (full review), 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, preclinical, clinical) for a major application.

In the verification model, which is applied in Bahrain, Kuwait, and Yemen, the local agency recognizes the scientific review and authorization decision made by one or more reference agencies in which it has confidence. Evidence of the review and its outcome is provided by the certificate of a pharmaceutical product or its equivalent. The extent of the technical supporting information required in the submission (eg, pharmaceutical quality/chemistry and manufacturing control data) is determined by the individual agency. This review consists primarily of a "checklist" to ensure that the administrative and legal requirements have been met and that an assessment of the medicine has been carried out in relation to, for example, risk-benefit, risk management, and local medical practice and infrastructure.

However, the abridged model is also applied in Bahrain for biotech and biological products and in Oman, Qatar, and United Arab Emirates (UAE) for all products.[4,5] The agency receives a summary of the technical data (the equivalent of module 2 of the International Conference on Harmonisation Common Technical Document[6]) but may ask for additional details to be supplied in the course of the assessment. This model normally relies on the product having been authorized by a reference regulatory agency before the authorization is granted, but the initial application need not necessarily be delayed until the formal certificate of a pharmaceutical product is available, and this leads to a shorter approval time. The challenge for carrying out an abridged review is that the regulatory agency requires the appropriate experts to be available internally with appropriate competencies and training, which may include partnering with other agencies. The availability of evaluation reports from the reference agency is also a key factor.

After receiving the file, the executive board identifies 2 member states alphabetically to review the files and provide their recommendations to the GCC-DR. However, for the remaining member states, the opportunity to review the files is optional. The registration of the company is based on the recommendation of the inspection team. If the company has been recommended to be registered, the GCC-DR issues the registration certificate; otherwise, the company will be notified accordingly. The inspection team consists of 3 members from 3 member states. The selection of members is carried out on the basis of certain criteria where every member state would have an equal number of visits. Upon completion of the visit, the head of the inspection team prepares a visit report that is signed by other members of the team and then submitted to the GCC-DR, which forwards the registration files of the products to each individual member state for evaluation. As of 2011, samples are sent for analysis in parallel with the registration file to 1 of the 4 laboratories (Saudi Arabia, UAE, Kuwait, and Oman) that are accredited by GCC-DR, and the registration of products is determined on the basis of the analysis reports.

The aim of the study was to evaluate the GCC's centralized regulatory review process. This included reviewing the timelines of new active substances (NASs) and existing active substances (EASs), identifying the opportunities and threats to the process, and proposing strategies that could help policy makers in the GCC enhance the review process.

## Methods

Information on the total number of applications and approvals for the 5-year period from January 2006 to December 2010 were obtained directly from the Executive Board of the Health Ministers' Council for GCC States. This includes NASs, EASs, biological products, and vaccines, together with the application submission and registration dates. The analysis for NASs and EASs covered the total number of registered products and regulatory approval times between 2006 and 2010 for different cohorts of pharmaceutical companies (GCC, non-GCC Arabs, international, and Asian), dosage forms (ie, solids, semisolids, liquids, injections), and therapeutic indications.

### Study Hypotheses

- There was a significant increase in the number of products registered from 2006 to 2010.
- There was a significant increase in the approval time between 2006 and 2010 in the GCC-DR.

### Procedure

A standardized data collection template was designed to enable the structured documentation of all the relevant information (eg, date of submission, date of clock stop and start, date of approval, country of origin, product type, formulation, therapeutic area, dosage form) for all products reviewed and available in the GCC office, and this formed our sampling frame. These data were manually collected from the GCC office in Riyadh, Saudi Arabia, during from summer to autumn 2011. The study received full approval from the GCC central office in Riyadh, Saudi Arabia.

### Statistical Analysis

The data were processed with Excel (Microsoft Corp, Redmond, WA, USA) and SPSS 2010 for Windows (SPSS Inc, Chicago, IL, USA). Nonparametric statistics—namely, Mann-Whitney *U* test and Kruskal-Wallis 1-way analysis of variance (ANOVA)—and linear regression were employed to test the research hypotheses and examine associations between relevant variables. Type 1 error was set at the 5% level.

## Results

Pharmaceutical companies are required to submit 16 samples of their product in addition to 8 copies of the product dossier and 1 original copy, which would remain with the Gulf central registration office. While 2 separate GCC states would be chosen through a computer program alphabetically (according to the countries name) to act as rapporteurs, the other GCC states would keep the dossiers for documentation purposes. The rapporteurs are not chosen because of their expertise in a certain area of regulatory science but to give equal opportunities to all the member states in a systematic manner of selection. Similarly, the reference laboratory chosen to carry out the analysis is based on the equity of the number of dossiers distributed among these laboratories and not on their ability to perform the analysis.

The review process map (Figure 1) indicates the main steps in the review and approval process and identifies the key milestones for monitoring and analyzing timelines. There are basically 5 steps for the regulatory authority in the Gulf central registration system, and some of these steps are critical and constitute a substantial part of the review process. Receipt and validation include the administrative registration (reference number), checks on legal requirements, the status of the company and manufacturer, as well as a ''checklist'' validation of the application content. During the 5-year period of this study (2006-2010), the number of pharmaceutical products (EASs and NASs) for human use successfully registered through the GCC centralized registration procedure was 413,

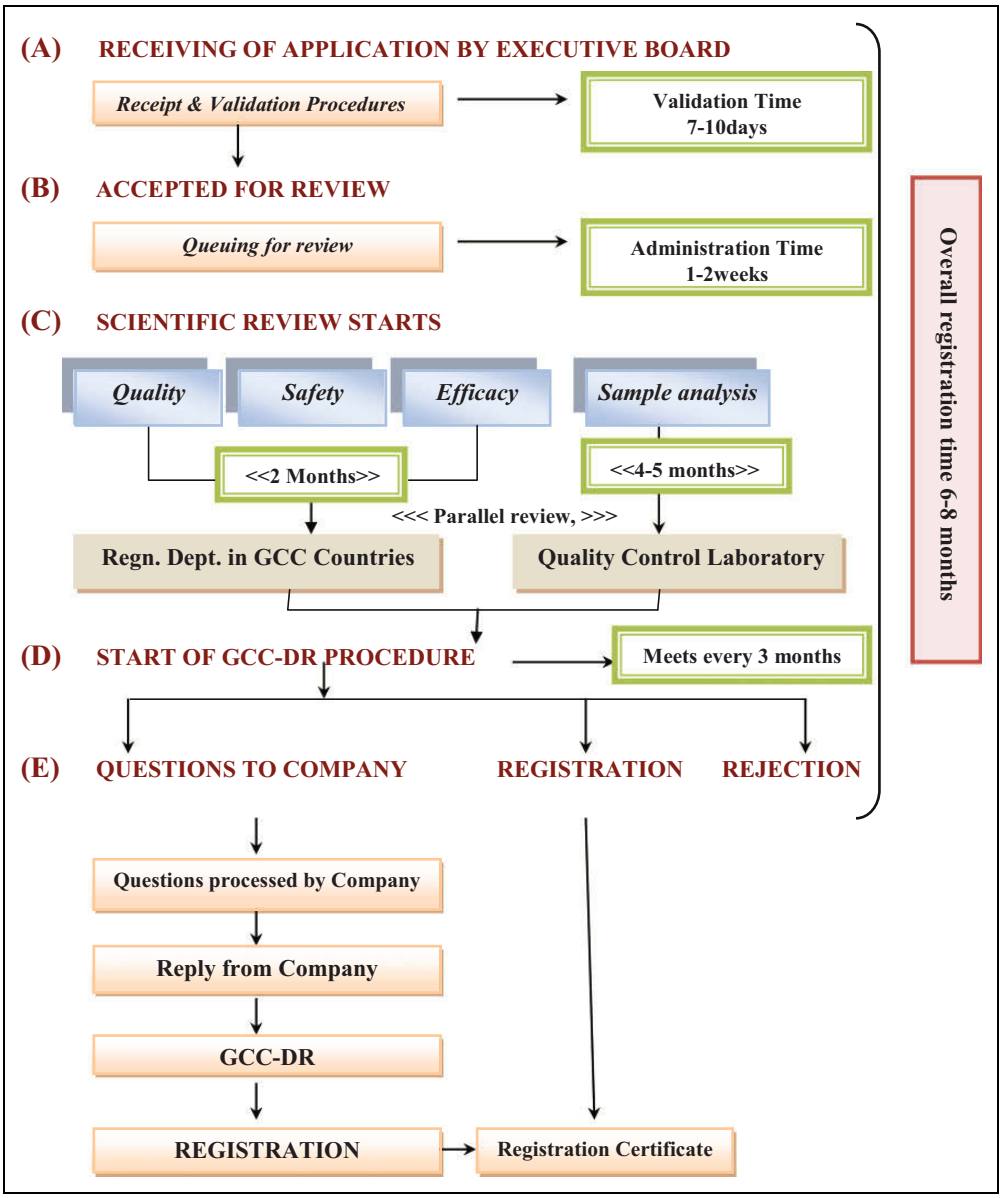


**Figure 1.** Process map for Gulf Cooperation Council centralized registration.

and the median approval time measured from 107 days in 2006 to 265 days in 2010.

## *Total Number EASs and NASs Approved*

The highest number of products approved was in the year 2009 (n = 130) and the lowest number in 2006 (n = 60) (Figure 2). There was a substantial drop in 2010, with only 16 products registered, which was due to the fact that the pharmaceutical companies failed to comply with the new GCC guidelines for stability testing of active pharmaceutical ingredients and finished pharmaceutical products. The GCC countries come under climatic zone III and IVa (hot and dry, hot and humid) and the new guideline, which was implemented in 2009, replaced the long-term testing condition of 25°C ± 2°C / 60% ± 5% relative humidity for climatic zone III and IV with 30°C ± 2°C / 65% ± 5% relative humidity. The results showed an overall significant increase ($P < .001$) in the total number of registered pharmaceutical products between 2006 and 2009.

## *Comparisons of the Number of Products Approved According to the Manufacturer's Origin*

Of the 413 products approved, 96 were NASs and 317 EASs. There was a similar number of EASs registered centrally in 2007 and 2009 (n = 85, 27%), followed by 2008 (n = 76, 24%), 2006 (n = 56, 18%), and 2010 (n = 15, 5%). Statistical analysis, based on a simple linear regression analysis, showed

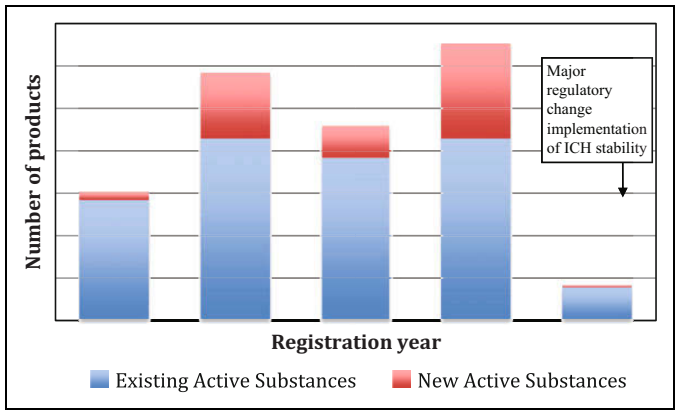


**Figure 2.** Approved pharmaceutical products (existing active substances and new active substances) in the Gulf centralized procedure, 2006-2010.

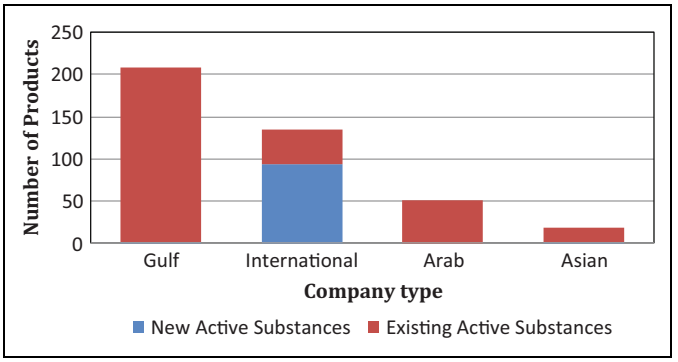


**Figure 3.** Approved pharmaceutical products (existing active substances and new active substances) for Gulf Cooperation Council (GCC) international, Arab, non-GCC, and Asian companies, 2006-2010.

that the increase in the number of registered EASs over time was statistically significant ($P < .001$). The highest number of NASs was registered in 2009 (n = 44), while the lowest was in 2010 (n = 1). Out of the 96 NASs, 93 products (97%) were submitted by international companies. By individual regions, 208 (50%) products were identified as being approved from the Gulf, 51 (12%) from Arab non-GCC companies, 19 (5%) from Asian companies, and 135 (33%) from international companies (Figure 3).

Of the 317 EASs registered in the Gulf central registration between 2006 and 2010 by individual regions, 206 (65%) products were identified as being approved from the Gulf, 51 (16%) from Arab non-GCC companies, 18 (6%) from Asian companies, and 42 (13%) from international companies.

## Total Approval Time for EASs and NASs

The total approval time for the period studied (2006-2010) includes all the 413 EASs and NASs from different companies

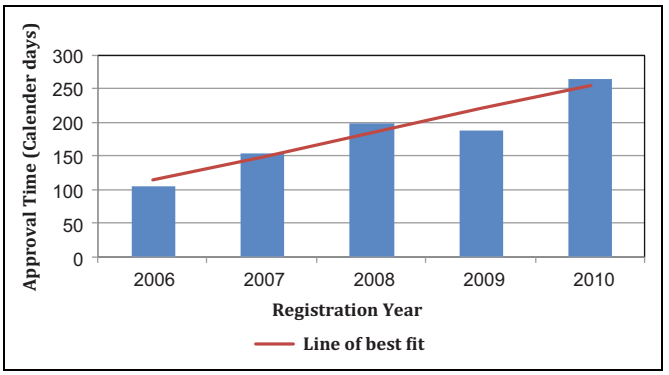


**Figure 4.** Median approval time for all pharmaceutical products (existing active substances and new active substances) in the Gulf centralized procedure, 2006-2010.

(Figure 4). During the 5 years, the median approval time ranged from 107 days in 2006 to 265 days in 2010. There was a significant increase in the median approval time between 2006 and 2010, which was due to several factors, including the limited number of meetings by the GCC-DR. This was in spite of the fact that the 7 member states met 4 to 5 times a year to discuss the product review reports, as well as there being a steady increase in the number of applications. Another reason for the delay in registration was the assessment review process, where there is a lack of a standard evaluation template for product assessment, which leads to an increase in the correspondence with the GCC requesting additional information from the sponsor. Statistical analysis based on the nonparametric test (Kruskal-Wallis test, 1-way ANOVA) over the 5-year period showed a significant increase in the approval time for pharmaceutical products ($P < .001$) (Figure 4).

The median time for the 317 EASs to be approved in the Gulf centralized procedure increased from 114 days in 2006 to 265 days in 2010. Statistical analysis according to the nonparametric test (Kruskal-Wallis test, 1-way ANOVA) across the 5-year period showed that this was statistically significant ($P < .05$).

## Comparisons of the Approval Time

### Origin of the Manufacturer

The median approval time for EASs varied for different cohorts of companies based on location with the shortest approval time for Gulf company products (134 days) and the longest for those from international companies (346 days). The shortest approval time for Gulf company products was due to the waiver of analysis requirements. A product is waived from analysis if it is registered in any 1 of the 4 GCC countries (Oman, Saudi Arabia, United Arab Emirates, or Kuwait) where the quality control laboratory for these states has the accreditation from the GCC. The median approval time for

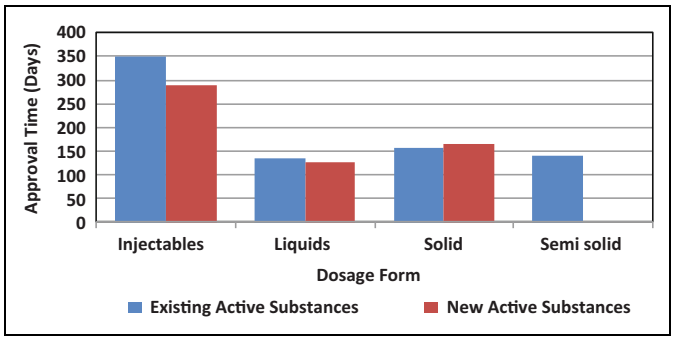


**Figure 5.** Median approval time for different dosage forms for existing active substances and new active substances in the Gulf centralized procedure, 2006-2010.

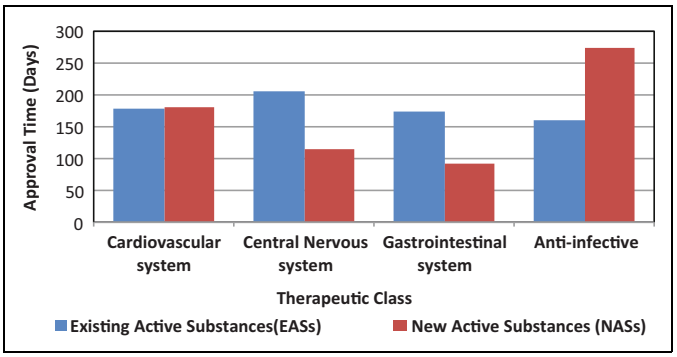


**Figure 6.** Median approval times for different therapeutic classes of existing active substances and new active substances in the Gulf centralized procedure, 2006-2010.

Arab companies was 227 and for Asian companies 332 calendar days. Statistical analysis based on the nonparametric test (Mann-Whitney $U$ test) showed a significant difference in approval time between international companies (median approval time = 346 days) and Gulf companies (median approval time = 134 days) ($P < .001$).

### Registered Products

In 2009, the highest number of NASs was registered (45 products) with a median of 288 days, whereas in 2006, only 4 products were registered (median, 31 days). In 2007, 31 NASs were registered (median, 138 days), while in 2008, 15 products were registered (median, 140 days). However, in 2010, only 1 product was registered with a registration time of 131 days. The results (Kruskal-Wallis test, 1-way ANOVA) showed a highly significant upward trend in the median approval time for NASs between 2006 and 2010 ($P < .001$). This was due to several factors, including the limited number of meetings by the GCC-DR (only 4 or 5 times a year) and a steady increase in the number of registration applications.

### Dosage Forms

From the 317 EASs registered with the Gulf centralized procedure between 2006 and 2010, the lowest number constituted the injectable forms (14%), followed by the semisolid dosage forms (20%) with the highest represented by solid dosage forms (52%). Approval times ranged from 138 days for liquids to 350 days for injectables (Figure 5). In general, when the dosage form is more complex, additional time is needed to approve the product. Special studies and more steps are needed to analyze some products, such as solutions for intravenous infusion, which need additional tests, such as sterility and pyrogen testing.

In terms of dosage forms, of the 96 NASs registered in the Gulf centralized procedure, the lowest number registered was represented by the liquid dosage forms (n = 5) with a median approval time 128 days. The highest number registered was represented by the injectable forms (n = 59) with a median approval time 288 days.

### Therapeutic Class

The therapeutic class of 314 EASs was assessed, and the lowest number was represented by ear, nose, and oropharynx preparations (1 preparation) and the highest number by anti-infective (86 preparations). The analysis of the approval time of EASs registered between 2006 and 2010 involved the 4 largest therapeutic groups—namely, the cardiovascular system, the central nervous system, the gastrointestinal system, and anti-infective.

The range of approval times for EASs analyzed by therapeutic class varied from 206 days for central nervous system products to 162 for anti-infective products (Figure 6). The trend in approval times for EASs from different therapeutic groups was attributed to the GCC-DR assessment requirements, depending on the nature of the products, which may include the need for both clinical and bioequivalent studies and the prolongation of the analytic time.

Ninety-six NASs were approved between 2006 and 2010; the lowest number was represented by the eye, musculoskeletal, and joint disease and respiratory system preparations (1 preparation), whereas the highest number was represented by cardiovascular and nutrition and blood preparations (24 preparations). The median approval times for NASs analyzed by the 4 main therapeutic classes ranged from 274 days for anti-infective products to 92 for gastrointestinal products. The main factor for the variation in the approval time for different therapeutic groups was the nature of the products evaluated.

## Discussion

This study investigated the pattern for regulatory approval times in the Gulf centralized procedure from 2006 to 2010. It also addressed the various factors that may have a positive or negative effect on total approval times. It showed that 413 (EASs

and NASs) were approved in the procedure with the largest number of medicines submitted for review and approved by GCC-DR in 2009. There was a considerable decrease in the number of approved products in 2010 due to pharmaceutical companies failing to comply with the new GCC guideline for stability testing of active pharmaceutical ingredients and finished pharmaceutical products. Thus, the new guideline was a major challenge to most pharmaceutical companies, leading to the rejection of those that failed to meet the new stability study specifications. Other factors influencing the number of approved products in 2010 were that the Saudi Food and Drug Administration began to evaluate all the products in addition to the 2 rapporteurs from the Gulf states designated to review the products. This resulted in a large number of queries raised by the Saudi Food and Drug Administration, which substantially delayed the review process with a significant decrease in the number of products approved in 2010.

During the 5-year period of this study, the median approval time significantly increased in the GCC region. This was similar to the situation within the centralized procedure for the European Medicines Agency, where over the same period, the median approval time showed a noticeable increase, which was also seen in the standard review for NASs approved by the FDA. In contrast, the median approval time by the Pharmaceuticals Medical Devices Agency in Japan had shown a significant reduction.[7] The change in the GCC region was due to several factors, including the limited number of meetings by the GCC-DR and the increased number of applications for registration. Another factor that delayed the registration was the lack of a standard assessment template for product evaluation, which leads to an increase in the amount of correspondence with the applicant and the request for additional requirements and data. It is recommended to have one standard assessment template, and rather than selecting the reviewing authorities alphabetically, the dossier could be sent to all countries, and all assessments could be combined into one final report on which the final decision in the GCC-DR could be based.

Most GCC local authorities also request pricing information from other markets at the time of marketing authorization application submission. The pricing details are usually required from the country of origin and frequently from neighboring Middle Eastern markets. This barrier to registration could be removed by separating issues of pricing from the regulatory review, which has been designed to evaluate quality, safety, and efficacy.[8–10]

Unfortunately, a clock-stop system is not fully enforced in the Gulf centralized procedure, and this delays the company response to queries from the GCC central registration committee. The implementation of a clock-stop would ensure that a sponsor meets the deadline, and it allows more time for the reviewers to complete the assessment of the submitted data.

The sample analysis stage is an essential part of the review process that affected the overall approval time during the study period. Up to 2010, it was completed after the scientific assessment, as the outcome of the sample analysis affects the final approval decision. However, from 2011, it has been carried out in parallel with the technical and clinical assessment, rather than after the scientific assessment, which therefore avoids influencing the overall registration time, and this has been incorporated into standard operating procedures for the member states.

The queuing process is straightforward and allows appropriate handling of the registration dossiers in an organized manner. However, the lack of regular monitoring of the queue time leads to a backlog. Managing the priority review is another important issue that needs recognition by the GCC-DR and should be dealt with according to set guidelines and standard operating procedures that clearly specify the conditions under which products can be taken out of the queue for such review. Therefore, adequate resources and electronic handling of the queuing process should be provided to support accurate follow-up of the pending dossiers, priority reviews, and fast-track products.

The approval time for pharmaceutical products varied for different cohorts of companies on the basis of their location—for example, the shortest approval time was for the Gulf company products and the longest for international companies. Factors that have a positive effect on the approval time for Gulf companies but have a negative effect on international, Arab non-GCC, and Asian companies include the geographic proximity of the company to the authority, which leads to an effective interaction and, thus, a faster response to any questions asked by the authority. Additionally, most locally manufactured products are generics and do not need much consultation during the scientific review compared to NASs. However, a priority procedure is a common practice in many authorities, and the rapid approval time is due to the GCC states making efforts—particularly, Oman, Saudi Arabia, UAE, and Kuwait—to improve their local manufacturing capabilities and the production capacity for the local population.

It is agreed by many regulatory experts that regionalization is the way forward for regulatory approval.[11,12] The GCC drug approval process was based on the European centralized procedure, which obviously has some major advantages. However, the European centralized procedure appoints a rapporteur and corapporteur that have the relevant expertise, whereas in the Gulf region, the member states are appointed on an arbitrary, alphabetical basis. Again, in the European system, the Committee for Medicinal Products for Human Use meets every month, whereas in the Gulf region, the GCC-DR meets 3 or 4 times a year, which leads to subsequent delays in approvals.

## Conclusions

This study examined for the first time the centralized regulatory review process in the Gulf region. It recommended that if the number of GCC central registration meetings were increased, a clock-stop system implemented, a standard evaluation template for product assessment put in place, and an electronic communication system established with online submission, then this would improve patients' access to medicines. Since this study was completed and the above recommendation made to GCC-DR, three changes have already been implemented namely, evaluations of quality, safety and efficacy are being carried out in parallel with sample analysis, the number of meetings has increased to six per year and the inclusion of a "standardised template" is currently being considered.

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