

R&D Briefing

Kingdom of Saudi Arabia: Factors affecting the timelines for the authorisation and availability of medicinal products



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A study of

Factors affecting the timelines for the authorisation and availability of medicinal products in the Kingdom of Saudi Arabia

Key points	1
Background	2
Methodology for the study	2
Review process and milestones	3
Approval times	4
Review 'milestones'	6
Factors affecting review times	8
The analytical testing stage	9
Summary	9
Further analysis	9
Institute Regulations Advisory Board	back cover

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Research International
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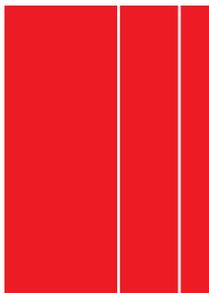
Key points



This unique study is the first in-depth analysis of the trends and changes in the regulatory approval times for medicines in the Kingdom of Saudi Arabia. Not only have the overall approval times been benchmarked for the years 1998 to 2003 but the times that products take to pass through the different stages in the review process have also been studied. This methodology, which identifies key 'milestones' in the review process for the purpose of calculating performance metrics, has allowed strengths and weaknesses of the regulatory procedure to be identified.



The data shows a steady decrease in the median approval times, by year of approval. This indicates that changes that have been introduced into the review procedures during the period of the study have had a beneficial effect on efficiency. These changes include reorganisation of the management structure and the increased use of information technology (IT).



The overall approval time varies considerably according to the location of the company submitting the application. Products from local companies have the fastest approval times, followed by companies in other Gulf Cooperation Council (GCC) States and Arab, non-Gulf countries, with products from International companies having the longest approval times.

The performance metrics for the different stages in the review process show that the scientific review is carried out relatively rapidly and accounts for only a small proportion of the total approval time, in most cases.



The study also highlights the fact that the analytical testing stage of the review process is the major rate-limiting step. The time taken to request samples and carry out analyses (including the time for companies to respond to questions) accounts for more than 50% of the total approval time for most products. This procedure is carried out sequentially rather than in parallel with other review activities and the outcome of the analyses show that the only problems detected are of a minor nature and the incidence is less than 1.5% of samples tested.

This report has been abstracted from the doctoral thesis being prepared by Hajed Hashan, who is studying for a PhD with the Welsh School of Pharmacy, University of Wales, Cardiff. Mr Hashan is on sabbatical from the Saudi Arabia Ministry of Health where he held the post of Director of Regulatory Affairs.



Background



There are many factors that have an impact on patients' access to new medicines, of which the regulatory procedures for product authorisation are often the most significant. Unnecessarily lengthy and onerous review procedures not only cause delays in providing valuable new medicines to health professionals and their patients, but can also act as a deterrent to international companies seeking new markets for their products.

Other factors that impact patient access include policy issues relating to the selection of medicines, the logistics of distribution and supply and financial constraints. The study summarised here, however, focuses on the regulatory review process and timelines for the approval of medicines. Performance metrics for the years 1998 to 2003 have been collected and analysed in order to identify trends and changes in timelines and to assess the factors that have an impact on regulatory review times.

The study is part of a wider review of regulatory procedures in Gulf Cooperation Council (GCC) States and examines the regulatory procedures in the Kingdom of Saudi Arabia (KSA).

The Review Process and Milestones

Key players in the process

The Registration Section of the Saudi Arabian Ministry Health:
The Regulatory Authority for KSA

Scientific Committee: made up of outside experts and specialists from the Ministry of Health

Central Laboratory for Analysis of Drugs and Food (CLAF): responsible for the analysis of samples of all products prior to authorisation

Registration Committee: takes the final decision on the authorisation and pricing of products

Health Minister: a Ministerial Decree is issued following authorisation after which the Registration Certificate is granted

The review procedures for KSA are outlined in *Figure 1*. For the purpose of this report, the procedure has been divided into four main stages:

- Validation and queue;
- Scientific assessment;
- Analysis of samples; and
- Collection of pricing data.

Five 'milestones' delineating these stages have been defined starting with the date of submission and ending with the date of the decision by the Registration Committee

Methodology for the study

Data have been collected for all products that were approved by the KSA Ministry of Health in the years 1998 to 2003, inclusive. Metrics have been calculated for the total approval times and for the time intervals between the five major regulatory milestones shown in *Figure 1*.

Sources of information

The data have been compiled from the following information sources:

- Registration Section of the Saudi Arabian Ministry of Health
- Original documents from the Registration Committees including the registration application form from the pharmaceutical companies
- Scientific Committee Reports
- Analytical result report issued by the CLADF*
- Registration and pricing decisions from the Registration Committee

Further information was obtained from the CMR International Marketed Medicines Database (IMMED) and sources in the public domain.

*Central Laboratory for Analysis of Drugs and Food

Products included in the study

- New molecular entities (NME)
- Biological/biotech compounds
- Generics
- Biologicals (blood products, IV fluids)
- Combination products
- Antigens
- Vaccines
- Line extensions
- Products submitted via the Gulf central registration process



Review Process and Milestones

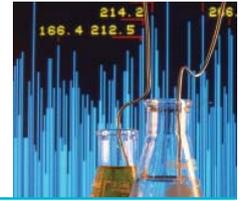
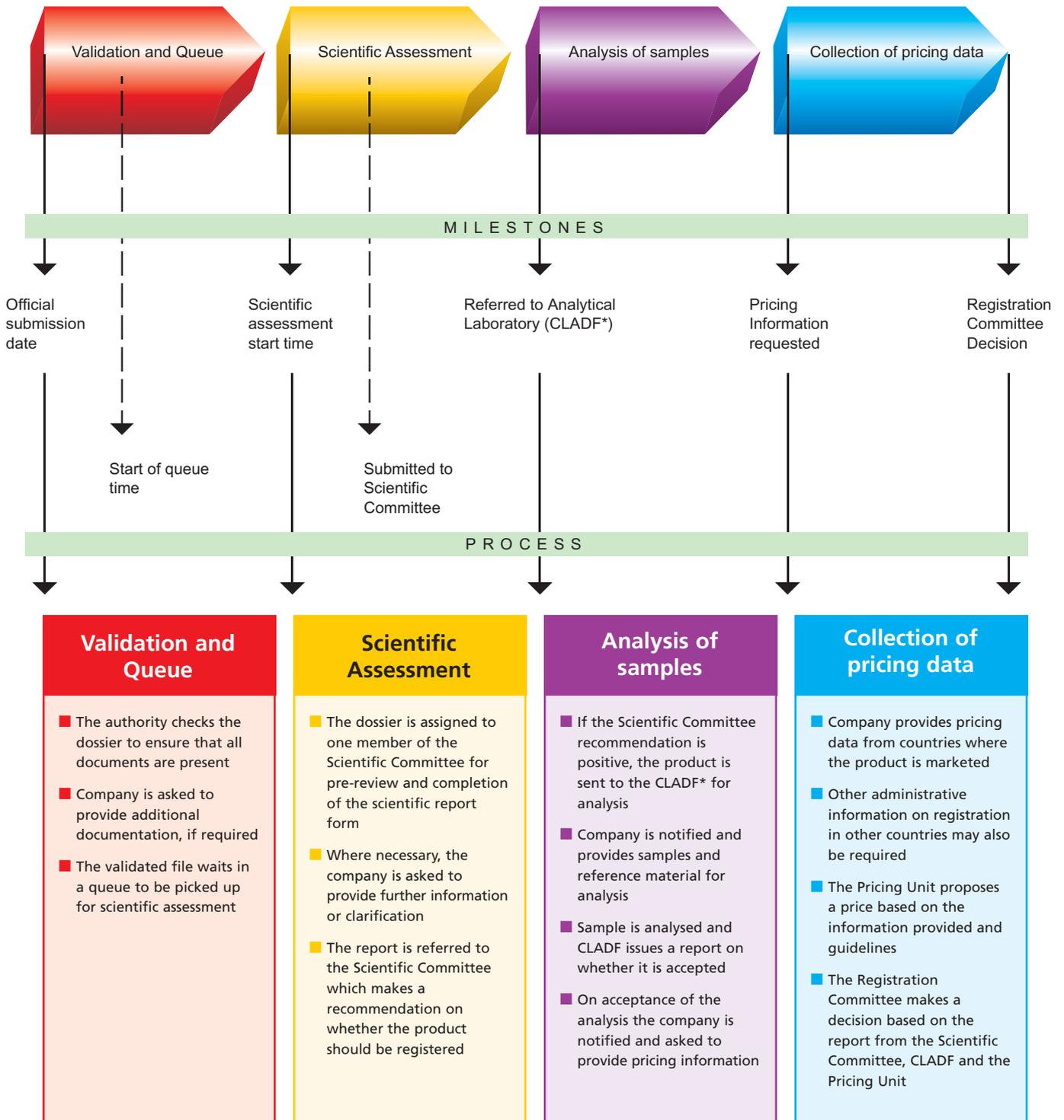


Figure 1





Approval Times

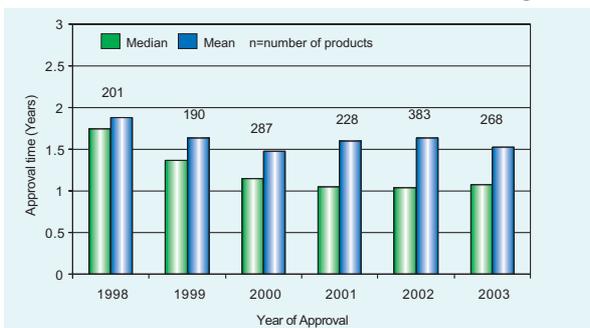
Data have been collected for a total of 1713 products that were successfully registered in KSA in the years 1998-2003. Approval times have been calculated for the 1557 products for which both submission and approval dates are available. These products have been classified according to source of manufacture and divided into four groups:

- **Local:** Saudi Arabian companies or local subsidiaries of international companies
- **Gulf:** Companies located in the other Gulf Cooperation Council (GCC) states (Bahrain, Kuwait, Oman, Qatar and the United Arab Emirates)
- **Arab, non-Gulf:** Companies situated in the Middle East, excluding the Gulf States
- **International:** Research-based or generic companies in the rest of the World (predominantly Europe, USA, and Japan)

Number and classification of products included in the study								Table 1
Company Type	Number of companies	Number of products by year						Total
		1998	1999	2000	2001	2002	2003	
Local	10	53	60	123	87	125	75	523
Gulf	4	9	31	26	16	44	21	147
Arab, non-Gulf	23	36	12	18	22	59	50	197
International	104	103	87	120	103	155	122	690
Total	141	201	190	287	228	383	268	1557

Approval time for all products 1998-2003

Figure 2



The approval time for a product is measured from the first review milestone (official submission date) to the last (decision by Registration Committee).

The mean and median approval times have been calculated for the products approved in each of the six years of the study (a total of 1713 products).

The results are given in *Figure 2* which shows that the median decreased from 1.7 years in 1998 becoming steady at about 1 year from 2001.

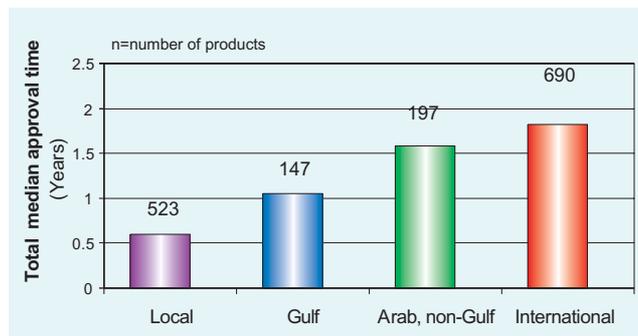
Variation in median approval times (1998-2003) according to source

Figure 3

One of the hypotheses to be tested in the study was the perception that approval times varied according to the source of the products, with priority being given to the review of products produced locally.

In *Figure 3* the mean approval times for all products authorised 1998-2003 are compared and this trend is clearly identified, although the type of product from the different sources may also have an influence.

These differences have been analysed further in *Figures 4-7*.





Approval Times



In Figures 3-7 the median (■) and mean (■) approval times have been calculated, by year, according to the source of the products. The numbers of products approved in each year are indicated above the respective bars

Figure 4



Figure 5



The approval time for products from local companies has remained relatively constant over time.

These are consistently lower than for products from other sources suggesting that priority is given to the review of products from local sources, although other factors, such as the type of product, may also have an influence.

The sizeable decrease in approval time between 1998 and 1999 is seen only for products from Gulf companies and might be attributed to a change in priority in reviewing GCC products. Subsequent increases may be attributed to the establishment of new Gulf companies who were not familiar with regulatory requirements for KSA.

Figure 6

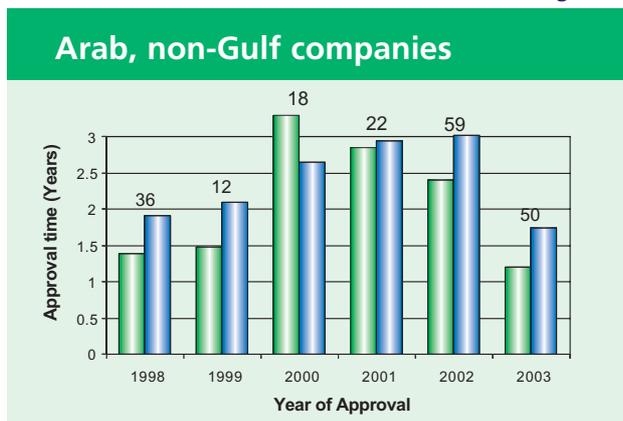
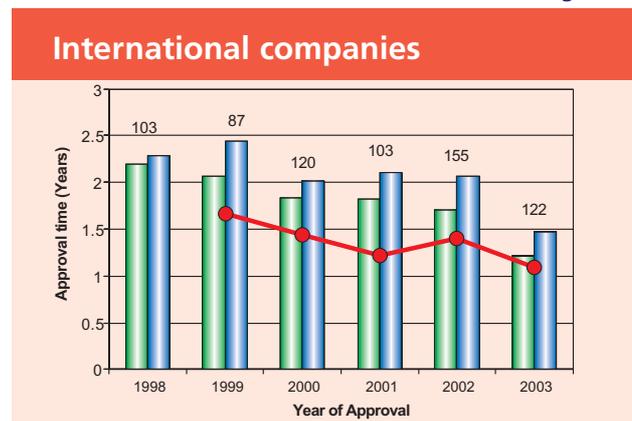


Figure 7



The change in approval times, by year, for Arab, non-Gulf companies does not reflect the overall downward trend observed in Figure 2. On closer examination, however, it has been found that the approval of a cohort of 26 products reviewed between 2000 and 2002 was considerably delayed because of regulatory differences between KSA requirements and the country of origin, including the absence of registration in a reference country, in some cases.

For products from International companies, there has been a downward trend in the median approval time over the years, which is particularly marked in 2003. The higher mean values, resulting from products with exceptionally long approval times are seen because some products that were approved in the years covered by the study were submitted as early as 1994. These have been seriously delayed in the system for a variety of reasons. A further analysis was therefore undertaken excluding products submitted before 1998 and the revised mean values are shown by the red line on the chart (●—●).



Review 'milestones'



Although the overall approval times are an important indicator of the performance of a regulatory agency, they provide little insight into the way in which products move through the review 'pipeline' and do not identify the points of strength and weakness in the process. For this reason further analyses have been carried out to measure the time taken for the stages between the process 'milestones' identified earlier (pages 2-3).

For the purpose of the comparisons, times between milestones are calculated as medians and are given in calendar days. It should be noted that products are only included in these analyses if both the start and end dates for the stage in the review are known.

Figure 8 gives the overall analysis for all the products in the study, divided according to the source company and measured for the total six years of the study.

Figures 9-12, shown opposite, provide a similar breakdown for each type of company, showing the way in which the time between milestones has changed over the years.

Figure 8



Observations

- The overall picture is of a review procedure where the scientific assessment is relatively efficient, with median times of 35 days for locally manufactured products and 72, 55 and 63 respectively for Gulf, Arab, non-Gulf and International companies
- The delay while the application queues for assessment can be as long as the scientific review time. Local company applications are picked up within a median time of 29 days while the delay for other applications is between 57 and 63 days. This reinforces the earlier observation that priority is actively given to applications from local sources.
- The longest time, for all types of companies, is clearly the period during which the application is referred to the CLADF which collects samples and other data and carries out analyses. The median for international companies was as high as 288 days and even for products from local companies a delay of 115 days was incurred.
- The time required for companies to comply with final-stage requirements is also sizeable, particularly in the case of international and Gulf companies. This is primarily comparative pricing in other countries but may include other administrative information. The relative speed with which local companies are able to provide this information may reflect proximity to the regulatory agency and familiarity with the requirements.



Review 'milestones'



Figures 9-12 show the way in which the time between the review 'milestones' has changed over the years, for each type of company. (When comparing the data it should be noted that different scales have been used on the x-axes of the charts).

Figure 9

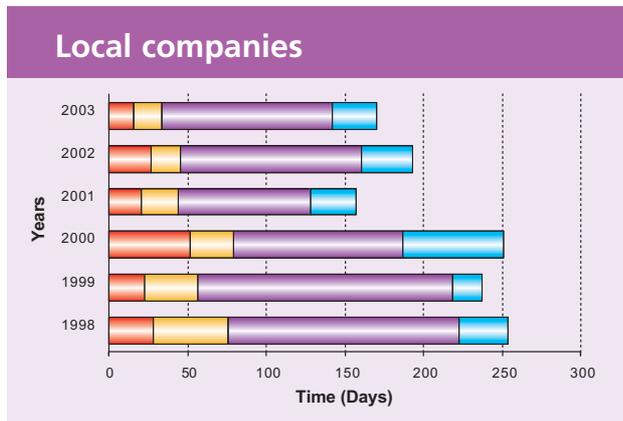
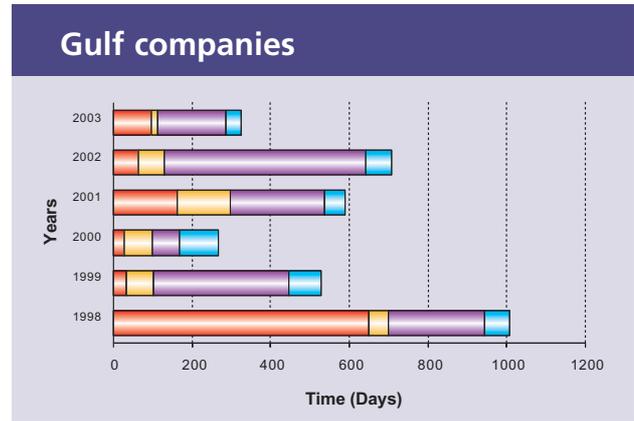


Figure 10



The time taken for the analytical testing stage clearly dominates the picture for local companies. The downward trend seen in 2000 and 2001 was mainly due to priority being given by CLADF to local companies. With the reduction in queue and scientific review times, however, the percentage of the overall time that is taken up by the analytical testing stage is almost unchanged: 68% in 1998 and 63% in 2003.

The breakdown of median time for each stage in the process, over the years, shows a more complex pattern for the Gulf companies. The exceptionally long queue time for 1998 and the sizeable reduction in 1999 and 2000 reflect a change in policy under which applications from Gulf companies were given the same queuing priority as local applications.

The slightly increased queue time for 2002 can probably be explained by the increased number of local products that year (125) – see table 1.

With the exception of 1998, the delay caused by analysis of samples is the dominant feature and even in the most-improved year, 2003, the analytical time accounts for over 50% of the total time for all sections.

Figure 11

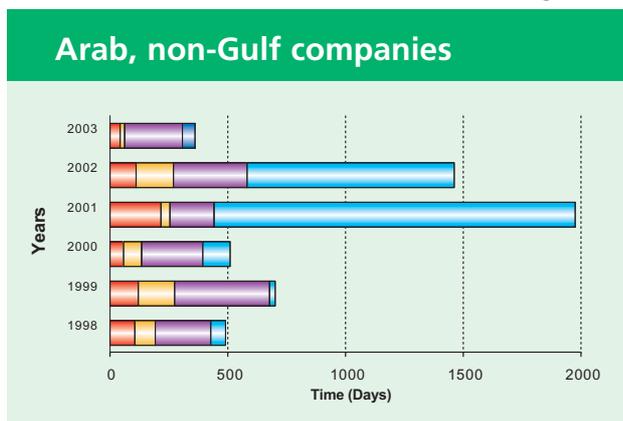


Figure 12



The picture for the Arab, non-Gulf companies is somewhat distorted by the prolonged times in 2001 and 2002 for the last stage in the process in which the company needs to submit final requirements on registration and pricing in other countries to the Registration Committee. This anomaly arose as the result of an exceptional delay in obtaining satisfactory information for 26 products.

The timelines for international companies reinforce the view that the analytical testing stage is the main time-limiting factor in the review and approval process. Although the time taken has improved from the maximum median value of 387 days in 1999 to 258 days in 2003, this still represents 60% of the total time for all sections

Setting this aside, a similar pattern emerges with the analytical testing time dominating the other time periods. In 2003 the analytical time accounts for over 70% of the total time for all sections.

Compared with other industry sectors, the international companies take longer to provide the data on pricing required in the final stages of the review process.



Factors affecting review times

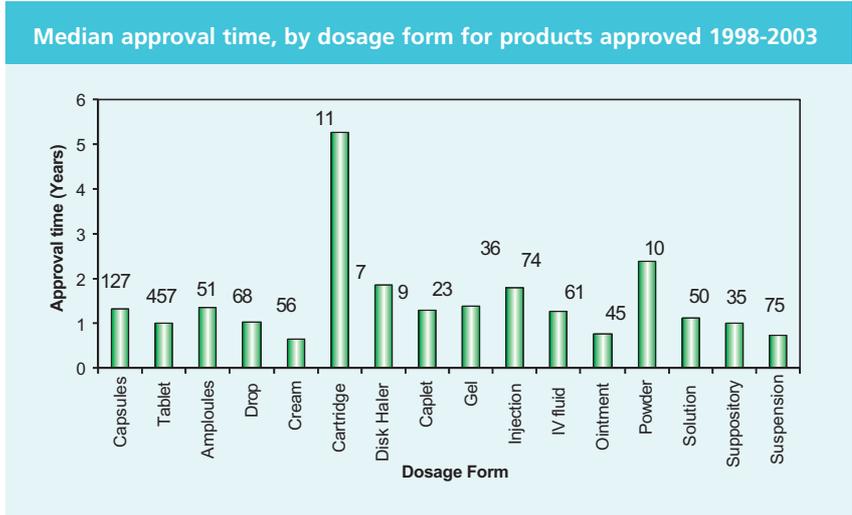


Impact of differences in dosage form

Figure 13

The median approval times for products approved in 1998-2003 were analysed according to the dosage form and the results are given in Figure 13. This shows, not unexpectedly, that the more sophisticated the dosage form the longer the time taken for approval. Hence sterile products and formulations for inhalation show longer approval times than tablets, capsules and topical preparations.

The type of company will also affect the results. For example, cream formulations show the shortest median time and 60% of the 56 products are manufactured by local and gulf companies.

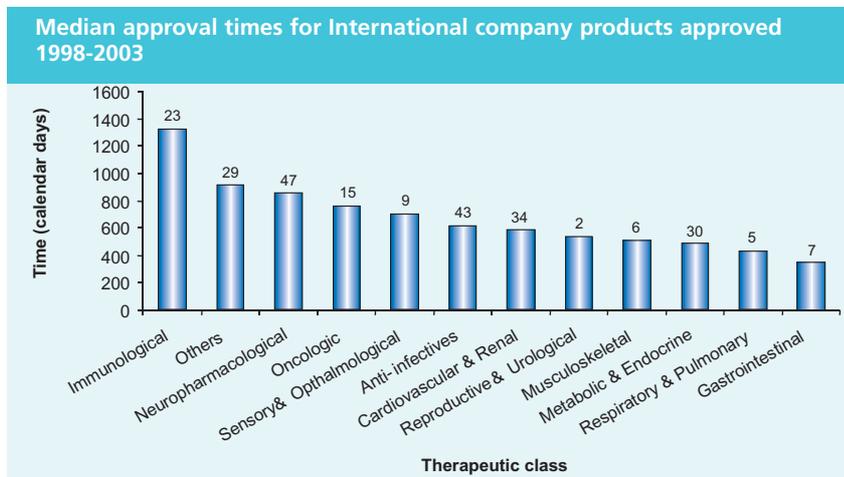


When studied further, in terms of the comparative median times for the different stages in the review of the dosage forms, the following was observed:

- The analytical testing time for disk halers was 965 days whilst the scientific review time was only 47 days.
- By contrast, the scientific review for injection cartridges was 449 days with only 222 days for analysis.
- After the injection cartridges, the dosage forms with the longest scientific assessment time (days) were enemas (102), drops (82.5), capsules (80), and solutions (69).
- Tablets, IV fluids, suppositories, enemas, injection cartridges and gels spent some 200 days in the analytical phase of the review.
- The highest values for the analytical phase were for injections (321 days) caplets (561 days) and disk halers (965 days). The shortest time was for ampoules (45 days). The relatively few products in this group were predominantly anti-cancer agents.

Impact of therapeutic class

Figure 14



Further analyses were carried out on approval times in relation to therapeutic class. The products from International companies approved from 1998 to 2003 were studied and the results shown in Figure 14.

Immunological products had the longest approval time, which is possibly related to considerations of how the products fitted into national vaccination strategies. The longer review times for more specialised products (e.g. neurological and oncological) may also reflect delays in appropriate experts being available for the scientific review.



The analytical testing stage



There are many different factors that may impact the regulatory review of individual products, including the availability of the necessary technical expertise and the ability of companies to respond promptly to requests for additional information. The barriers of culture and language, especially for companies outside the Middle East Region, may also be a factor.

Throughout the study, however, the single recurring factor which most affected review times was the time that products remained in the analytical testing phase which, for the large majority of products accounted for more than 50% of the approval time. As indicated on page 3, the analytical phase does not start until the

scientific assessment has been carried out and the Scientific committee recommends approval. Only at that stage is the company asked to provide samples and testing protocols to the CLADF.

Copies of reports issued by the CLADF from 1999 to 2003 have been studied to ascertain the failure rate and problems found with products referred to the laboratory.

Over 1400 passed through this phase during that period but there were only 19 products that failed and these were for relatively minor reasons (*Table 2*).

Type of company (Number of Products)	Typical reasons for failure	Table 2
Local (3) Gulf (3) Arab, non-Gulf (9) International (4)	<ul style="list-style-type: none"> ■ Capsules: shells not polished, powder adhering to outside, poorly sealed; ■ Specifications: failure to meet dissolution limits, assay outside limits, pH outside limits; ■ Physical characteristics: colour/texture not homogeneous; small particles in creams; ■ Containers and packaging: discolouration inside tube of cream, deposits around bottle openings, packaging not adequately sealed. 	

Summary

- There has been a downward trend in regulatory approval times for products registered in KSA since 1998.
- Factors that have had a positive impact on review times may include managerial reforms and the increased used of information technology.
- The location of the company has a marked effect on approval times with products from local companies apparently being given priority.

- Products from other Gulf companies are the next most rapidly approved followed by Arab, non-Gulf companies with products from International companies taking the longest to register.
- The time taken for the scientific review is relatively short for most products but may vary according to the therapeutic class of the product as a result of the availability of suitable experts to assist the Scientific Committee.

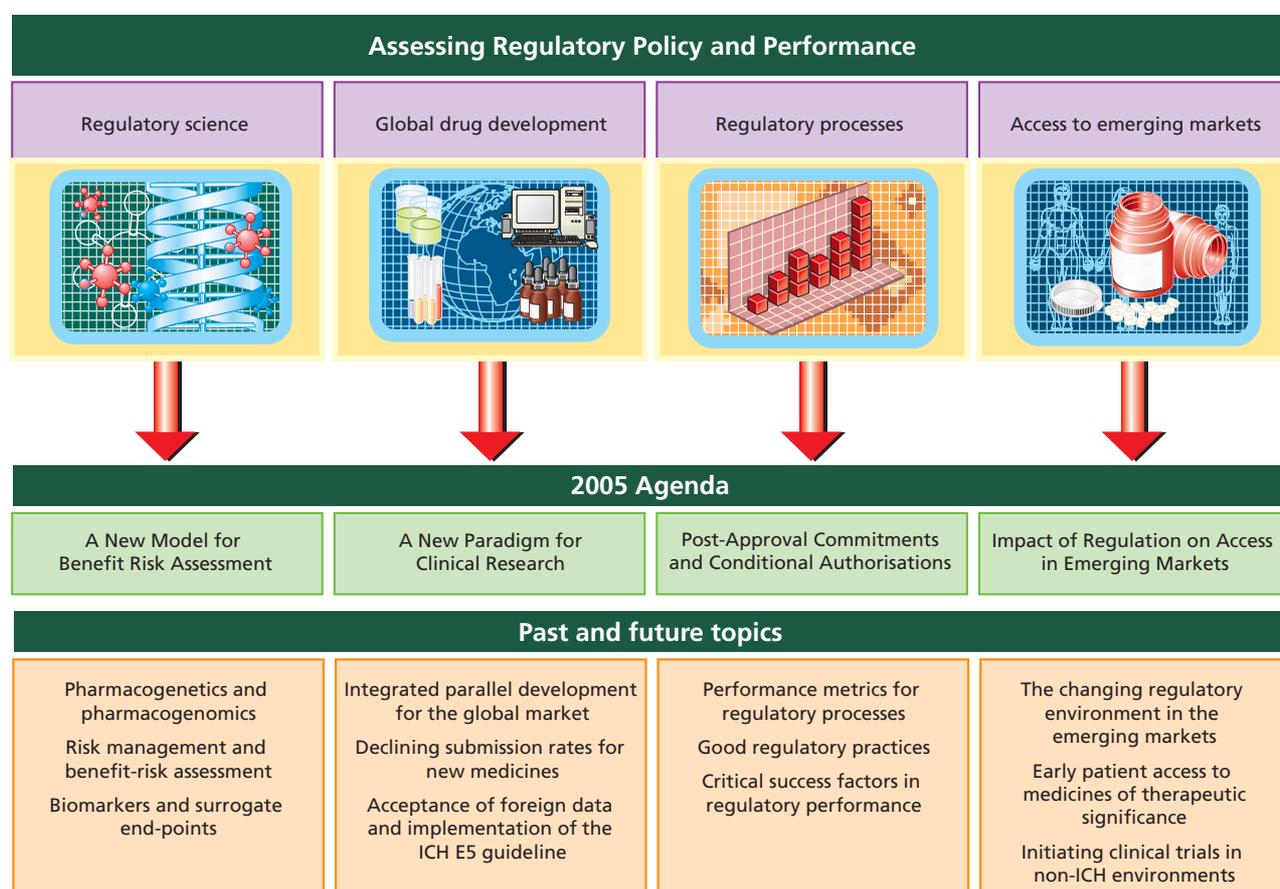
- The rate limiting step in the process is clearly the stage during which the products are sent for analytical testing. This is carried out sequentially and adds over 50% to the overall approval time in the large majority of cases,
- The failure rate of products is low and none of the reasons for failure have serious safety implications.

Further analyses

This study has looked in depth at the time taken for products to move through the four designated stages of the review process but has not differentiated between the time for tasks undertaken by the regulators and the time taken by companies to respond to requests for further information.

A further analysis is currently being undertaken to examine these aspects for the scientific review stage and analytical testing stage.

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