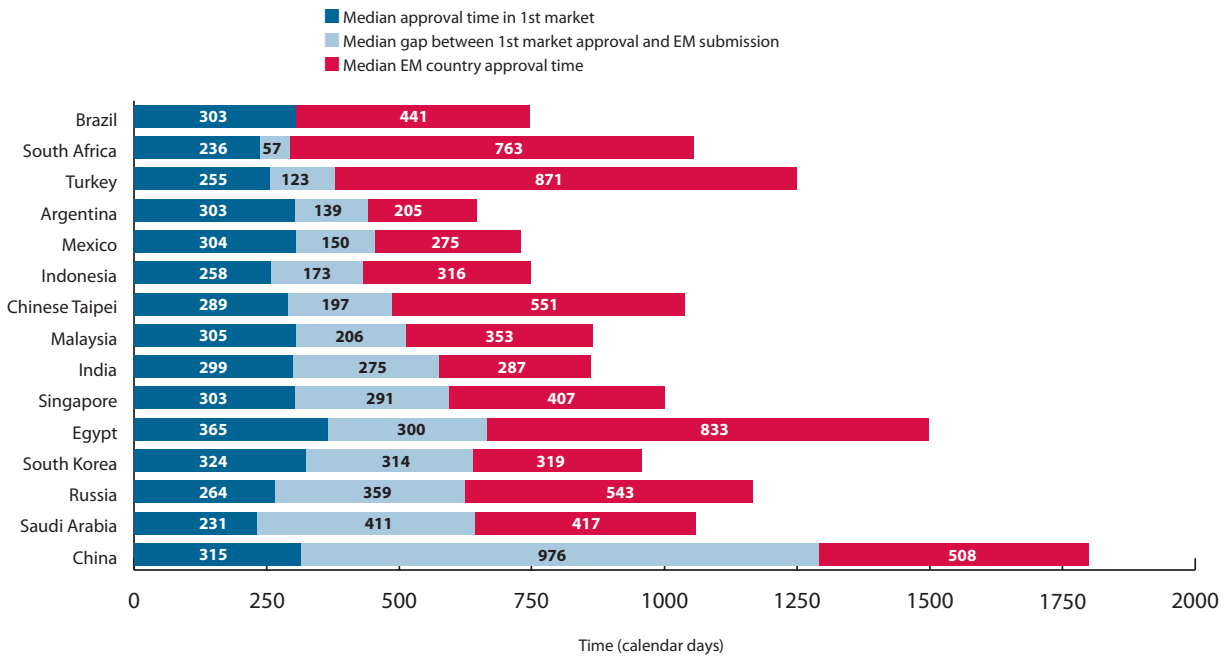
CHARACTERISING THE INFLUENCERS OF SUBMISSION LAG TIME FOR MEDICINES IN THE EMERGING MARKETS

ANALYSIS OF SHORT AND LONG LAG TIME FACTORS



Median roll out time to emerging market countries for new active substances approved 2006-2010

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Lag Time (the light blue bar representing time from which a product has been granted market authorisation in its first market to the time that its application is submitted for review by an authority) in the Emerging Markets varies widely and can have a major impact on the availability of new medicines to patients in these countries. Numerous factors affect the Lag Time in an Emerging Market, including the local regulatory and legal environment, company strategies, and factors related to the nature of the disease and the therapeutic alternatives. This report summarises research conducted by CIRS to assess the factors that influence short and long Lag Times to these developing jurisdictions.

R&D BRIEFING 51

CIRS Centre for Innovation in Regulatory Science

Abbreviations and Definitions

Applications vs Products: The term "Applications" is used when showing data across countries as one product may have an MAA submitted to more than one country (see MAA below)

Biological: A substance isolated from animal tissues; eg, vaccines, hormones and antigens; or plant alkaloids

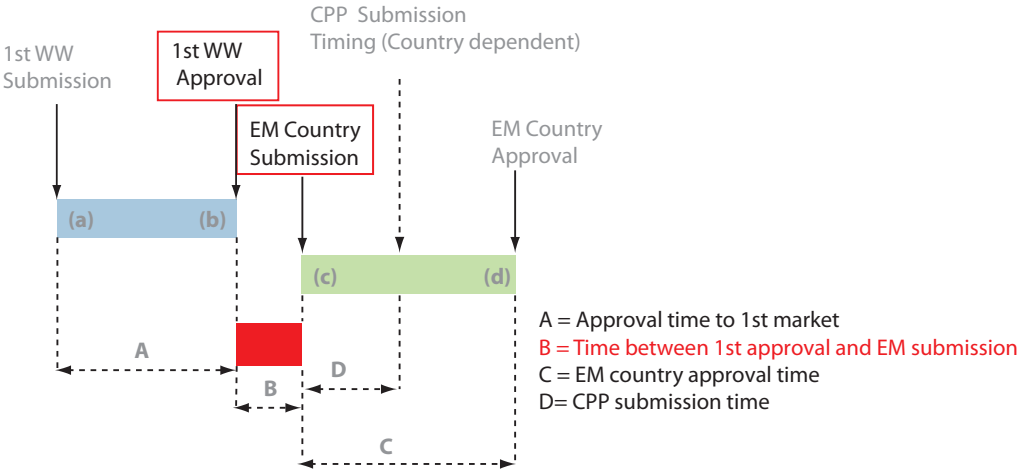
Biotech entity: Product produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals, or plants

Chemical: An entity produced by chemical synthesis.

CPP (Certificate of Pharmaceutical Product): is a certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product

EMaRReT Database (Emerging Markets Regulatory Review Times): A unique collection of company-based information on worldwide regulatory activity managed by CIRS

Lag Time: As defined by CIRS, that time period in calendar days from the first world approval to the time that the product is submitted for regulatory review in another country (period "B" in figure below).



MAA: Market Approval Application. The dossier that is submitted for review by a regulatory agency

NAS (New Active Substance): The active ingredient that is intended to furnish pharmacological activity or other direct effect to a pharmaceutical product. This may be a chemical, biopharmaceutical or radiopharmaceutical substance that is or is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.

TA: Therapeutic Area, as defined by the Anatomical Therapeutic Chemical (ATC) Classification System (ATC code)

Key Points

- This study has been conducted using the CIRS EMaRReT database, which tracks new medicines and line extensions in 15 Emerging Markets (Argentina, Brazil, Mexico, South Africa, Egypt, Russia, Turkey, China, India, Indonesia, Malaysia, Saudi Arabia, Singapore, South Korea and Chinese Taipei) to determine Lag Time from first world approval to submission in these countries.
- 896 applications for New Active Substances (NASs) submitted between January 2000 and December 2010 were evaluated to gain an understanding of the factors that influence multinational pharmaceutical company strategies for introducing new medicines into Emerging Markets countries as well as to characterise the factors that enhance or hinder submissions to Emerging Market countries such as country-specific issues, product characteristics, and safety considerations. The study also surveyed companies to determine why some of their products have short drug lags while others have long Lag Times.
- The vast majority of the 896 applications (78%) were submitted to EM countries with a short Lag Time of less than 2 years. Lag Times of 6 years or more represented approximately 7% of submissions.
- To the extent that the country's regulatory system permits, 19% of the applications to the Emerging Markets were submitted before marketing approval was granted in the first market.
- Country-specific influences were identified: applications were made to Brazil much earlier than other countries; in China, Russia and India, more than 10%-16% of their applications had Lag Times of 6 years or more.
- Factors such as the judicious timing of CPP submission and company use of internal resources to "fast-track" a product shorten Lag Times.
- The type of product did not seem to influence the time taken to submit a new medicine after first approval, although therapy area did have some influence, particularly with regard to some applications for anti-cancer/ immunomodulators and nervous system products.
- Several factors contribute to longer Lag Times for products entering a second market, including the prevalence of the target disease in the market, specific product-related characteristics, local medical practices and standards of care, and the regulatory, political and legal environment in the Emerging Market. Further, local requirements for clinical trials and the place of the country in the company's overall global strategy contribute to Lag Times.
- This analysis indicates that once innovative pharmaceutical manufacturers obtain marketing approval in one market, they generally promptly seek marketing approval in other markets. This suggests that market incentives drive company efforts to enter Emerging Markets early. However, factors that may be difficult to control may slow a second-market introduction, and need to be addressed in the context of incentivising global medicines development.
- The regulatory requirements in Emerging Markets and the industry's response to these are constantly evolving, either placing barriers or facilitating the speedy access to new medicines. In order to monitor the effects of these factors, CIRS will continue to analyse the ongoing EMaRReT database to inform best practice in global medicines development.

Background

Multinational pharmaceutical companies integrate world-wide medicine discovery, research, regulatory and distribution plans into a product's overall development programme. While most products are initially introduced into commerce in the major developed markets (i.e., United States, Europe, Japan), all companies, due to the increasing importance, create plans that include making these products available in the developing or "Emerging Markets".

The Emerging Markets have diverse and often less predictable regulatory schema than mature jurisdictions and many factors influence the rollout of new medicines to these populations; these include:

- **Internal (company) factors:** Related to a company's strategy, operations and goals.
- **External (local) factors:** Related to the environment in the target country.
- **Overlapping factors:** Where the company may be able to work alongside the regulatory agency to facilitate a speedy submission process.

Consequently, each innovator pharmaceutical company weighs a variety of factors to determine their strategy for bringing new medicines to a particular Emerging Market economy.

Drug lag is an issue for both companies and countries and understanding the factors that influence how and when the MAA for a new medicine is submitted to a particular jurisdiction and what the factors are that speed or delay this process provides insights into factors that affect the time required for new medicines to reach patients in these important new economies.

Since 2004, CIRS (formerly the CMR International Institute for Regulatory Science) has been working in association with the industry and agencies on an Emerging Markets Programme designed to develop a greater understanding of the regulatory aspirations, barriers, and priorities that impact the submission, review and availability of new medicines in countries outside the ICH-affiliated regions. (Patel et al 2010)

CIRS has identified several consistent key steps in the process of worldwide medicine regulatory submissions. These are illustrated in the Definitions. This study analysed "Lag Time", defined by CIRS as the time in calendar days between a medicine's first approval (in any country) to the date of the compound's MAA submission to one of the 15 defined Emerging Market countries. Gaining an appreciation for the influencers of this "Lag Time" can provide the basis for a methodical analysis of the most expedient manner to effect product introductions, while providing a basis for discussions on the pertinent issues of return on investment, regulatory efficiency, intellectual property protection, and most importantly, timely patient access to medicines.

The overall objectives of this study were to:

- Determine Lag Time from first world approval to submission in an Emerging Market for a cohort of recent NASs
- Gain an understanding of the factors that influence multinational pharmaceutical company strategies for introducing new medicines into Emerging Markets countries
- Characterise the factors that enhance or hinder submissions to Emerging Market countries
- Understand the regulatory and country-specific issues, product characteristics, regulatory considerations and other underlying business factors that accelerate or delay MAA submissions in the Emerging Markets

The research described in this report does not address the influence of payer decisions on the time in which a medicines becomes available to patients in these jurisdictions, often referred to as the "4th hurdle" to patient access (following the successful demonstration of adequate proof of a product's quality, safety and efficacy to a regulatory body). This topic is the subject of additional research being conducted by CIRS.

Methodology

This study was conducted in two parts:

1. Analyses of the EMaRReT database to determine Lag Times

The EMaRReT database is an ongoing data collection activity coordinated by CIRS. Detailed data regarding the submission of NASs and major line extensions have been collected once yearly from 2004 by CIRS from international research-based pharmaceutical industry participants. Strict confidentiality is maintained with respect to the identity of the individual products. Information described in this report is shown as aggregated summary trend analyses and other presentations that maintain the confidentiality of the data providers. For further details of this methodology see McAuslane et al 2009.

CIRS focuses its data collection activities on the following 15 countries, providing a unique data set across a diverse mix of emerging regions:

Focus Countries				
Argentina	Egypt	Malaysia	Saudi Arabia	Singapore
Brazil	**India**	**Mexico**	South Africa	Chinese Taipei
China	Indonesia	**Russia**	**South Korea**	**Turkey**
Highlighted countries represent BRICK-TM nations				

Data have been provided by 14 multinational pharmaceutical companies,10 of which are in the top 15 as ranked by 2011 global sales, thereby providing a comprehensive picture of recent approaches to global medicines development. The database contains 2399 submissions (based on 802 new molecular entities). CIRS undertakes periodic assessments of the EMaRReT database to identify trends in regulatory activities and to inform improvements in medicines development and regulatory review procedures (McAuslane et al, 2006 and 2009).

In this study, CIRS investigated the EMaRReT database to characterise Lag Times and to understand factors that influence a company's decision and strategy for entering an Emerging Market. These analyses could, therefore, inform broader strategies for the efficient introduction of novel medicines to these countries.

The analyses addressed NAS MAAs submitted during the period of January 2000 to December 2010, which encompassed 896 applications. This time period was selected to reflect a cohort of products that represent recent corporate and regulatory activity, creating a robust, current data set.

Lag Times were organised according to the following cohorts:

- ≤ 0 years
- > 0 – 2 years
- > 2 – 4 years
- > 4 – 6 years
- > 6 years

2. Analyses of factors influencing Lag Times

Potential influencing factors were assessed including the following.

- Country-specific drug lag profiles
- Product type and therapy area
- Timing of CPP submission
- Companies focusing internal resources ("fast-track") on a product

For products with a Lag Time of 4 or less years, CIRS prepared a simple survey; participants were asked to identify for 10 key countries (Brazil, Mexico, South Africa, Russia, Turkey, China, India, Indonesia, South Korea, and Chinese Taipei) what influenced their decision to submit quickly. These included 17 country-, company- and product-specific factors and were tallied by country to understand characteristics that facilitated submissions and shortened Lag Time. Respondents selected the top 5 factors per country and weighted these 1-5 (1 = most important).

In addition, CIRS conducted a separate detailed, confidential sponsor survey, by product, to identify factors that most significantly influenced the delay in MAA submissions for products with a Lag Time of > 5 years and < 12 years. Specifically, CIRS asked each respondent to rank a series of possible reasons for the delay. Topics elicited included:

- Product's special characteristics
- Regional or other regulatory issues (including CPP and related factors)
- Clinical/Safety issues
- Business-related considerations (production capacity, licensing agreements, distribution barriers etc.)
- Other issues and strategic considerations

Results

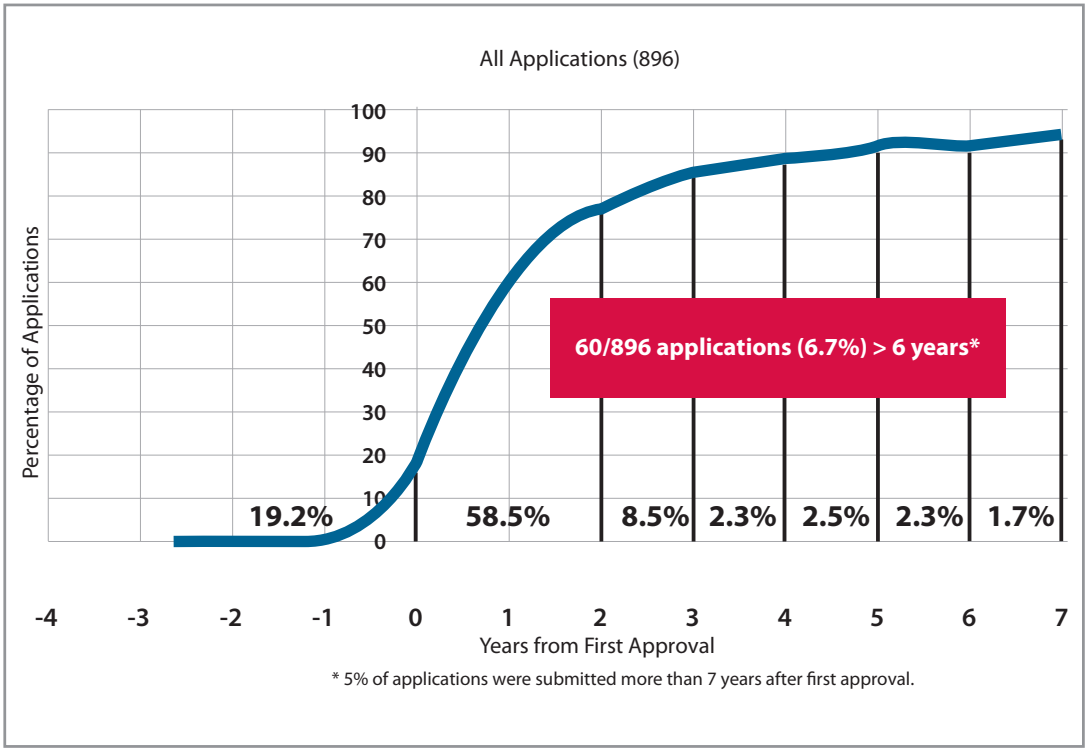
Lag Time

As seen on the first page, median Lag Times (denoted in the bar chart as the light blue bar) varied widely. The shortest Lag Times were in countries where a CPP was not required to be submitted at the same time as the MAA (i.e., Brazil). The longest Lag Time was observed in China, where a significant delay occurs to fulfil regulatory requirements for collecting specific types of manufacturing and local clinical data.

When the Lag Time for the cohort of applications made during the period 2007-8 was compared by country for that of 2009-10, it was noteworthy that with the exception of Argentina, all countries where comparative data were available for a consistent cohort of companies showed a decrease in submission Lag Times (Data on File, CIRS).

Of the 896 applications, 78% were filed within 2 years of the innovator manufacturer receiving marketing approval in the first market (Figure 1). It is important to note that in 19% of applications analysed in this study, the Lag Time was a negative number. This occurred when a product's MAA was submitted to an Emerging Market before it received its first world approval. The reasons for these short (accelerated) Lag Times are discussed later in this report.

Figure 1. Distribution of Lag Times for all Emerging Market countries combined.



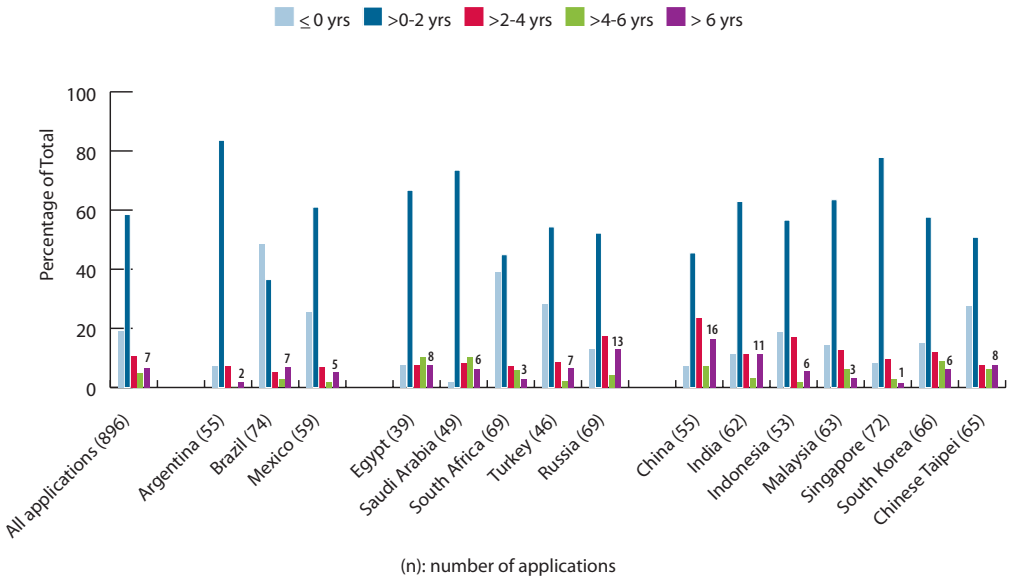
A small yet potentially important number of applications had Lag Times of 5 years or more. These represented approximately 7% of the total database. There was no indication that these were clustered in only selected countries (Table 1).

Table 1. Distribution of products with Lag Times of 5 years or greater.

Time Period	Number of Products	Number of Countries
5-6 years	**15**	**11**
6-7 years	**14**	**12**
7-8 years	**7**	**7**
8-9 years	**6**	**4**
9-10 years	**5**	**2**
10-11 years	**3**	**3**
11-12 years	**0**	**0**
> 12 years	**13**	**12**

When compared across countries, Lag Times of >0 to 2 years were most commonly observed. For China, Russia and India, a higher percentage was noted for products in which Lag Times was >6 years (Figure 2).

Figure 2. Distribution of Lag Time for all applications 2000-2010 (N=896)



Influence of Product Type and Therapeutic Area

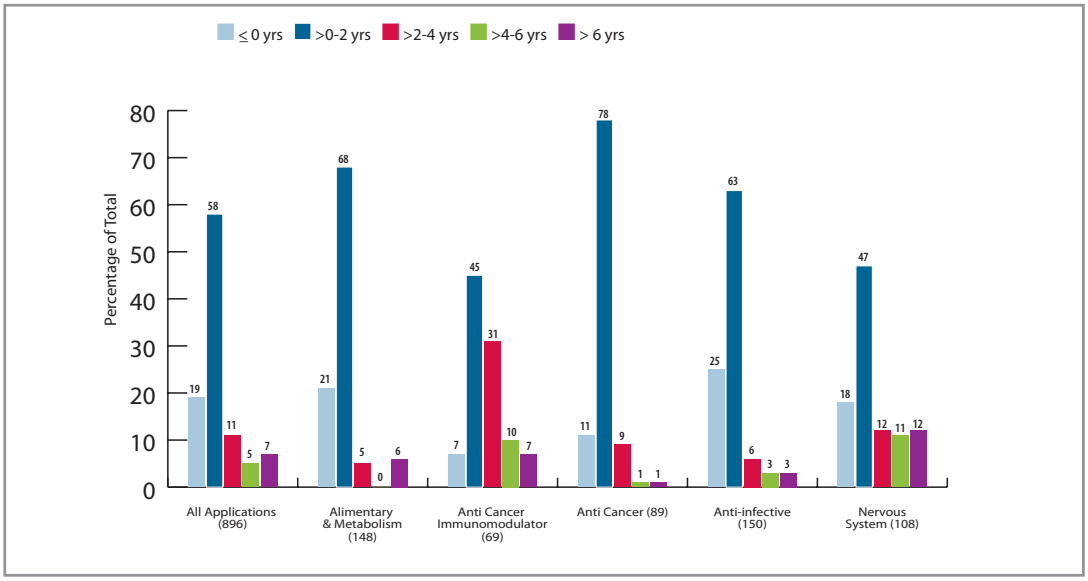
All applications were tagged for product type and therapeutic category.

No noticeable change in Lag Time distribution based on the product type being submitted (chemical, biological, or biotech) was identified for this cohort of applications.

However the therapeutic category of the product appears to influence Lag Time particularly for anti-cancer/immunomodulators and nervous system applications which show a different profile and proportion of products that take longer than for medicines in other therapeutic categories. More than

50% of anti-cancer/immunomodulators were filed within two years after the first market approval, and 17% were filed within 4 years after approval in the first market. (Figure 3). Similarly, for applications for medicines to treat nervous system disorders, more than 12% of such applications were filed more than 6 years after first market approval. There were insufficient data in this study to determine a cause for these differences.

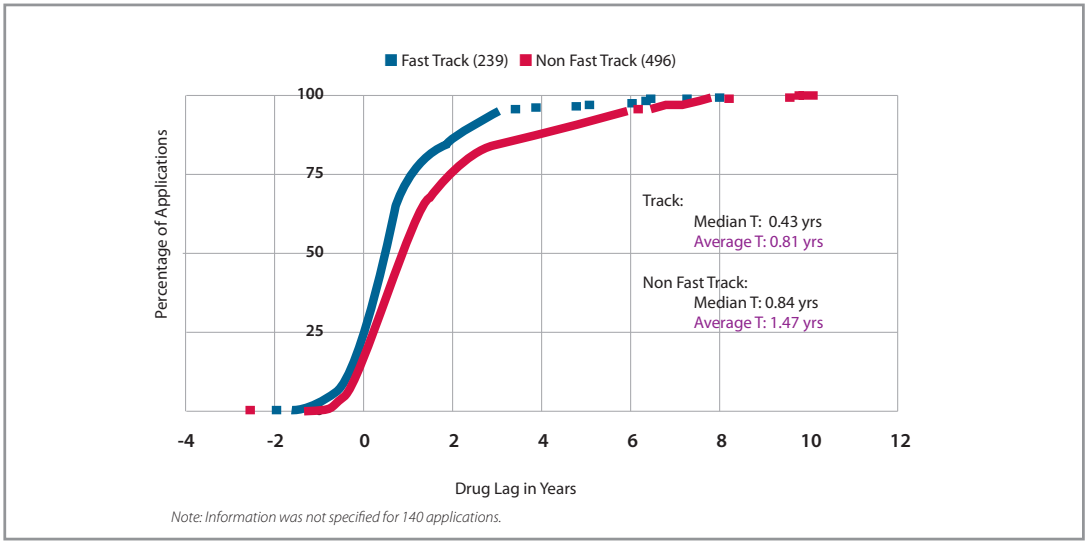
Figure 3. Lag Time distributions varied by therapeutic area



Role of the Fast-Track and CPP

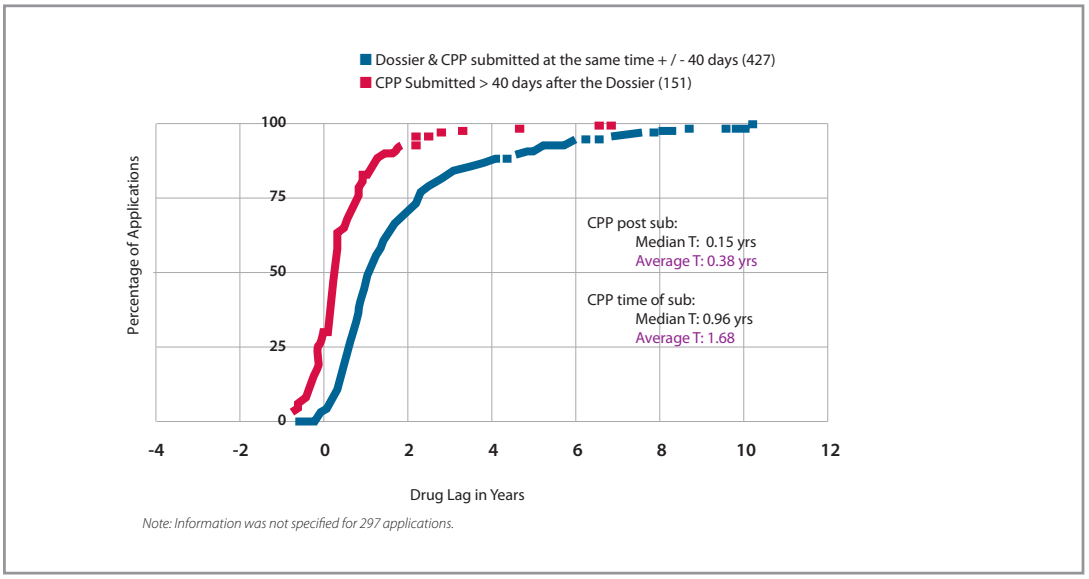
An important influence on reducing Lag Time was played by the effort placed behind a particular product by the company. CIRS asks companies to note whether a particular product was the target of a specific enhanced development/marketing commitment for a specific country. We term this the company's "Fast-Track" effort (not to be confused with the strict terminology of a regulatory Fast Track submission). As can be seen in Figure 4, by year one, 75% of Fast-Tracked applications had been submitted to Emerging Market countries; non-Fast-Tracked products had a median Lag Time twice as long. Overall the median Lag Time was 0.43 yrs for Fast-Track versus 0.84 yrs for non-Fast-Track. As expected, and unsurprisingly, when companies place resources behind a product, its Lag Time is shortened.

Figure 4. Lag Time analysis based on company resources applied to applications where the drug lag is 12 years or less (n = 875).



The time at which a CPP is required from an applicant during the MAA submission process also has a dramatic effect on Lag Time. Of the 875 applications, 578 had information regarding CPP timing; for 151 of these applications, the CPP was submitted >40 days after the dossier had been submitted but prior to receiving regulatory approval. Median Lag Time for dossiers submitted to countries where the CPP can be delivered 40 days or more after the dossier submission was 0.15 years compared to 0.96 years in the other CPP-dependent countries (Figure 5).

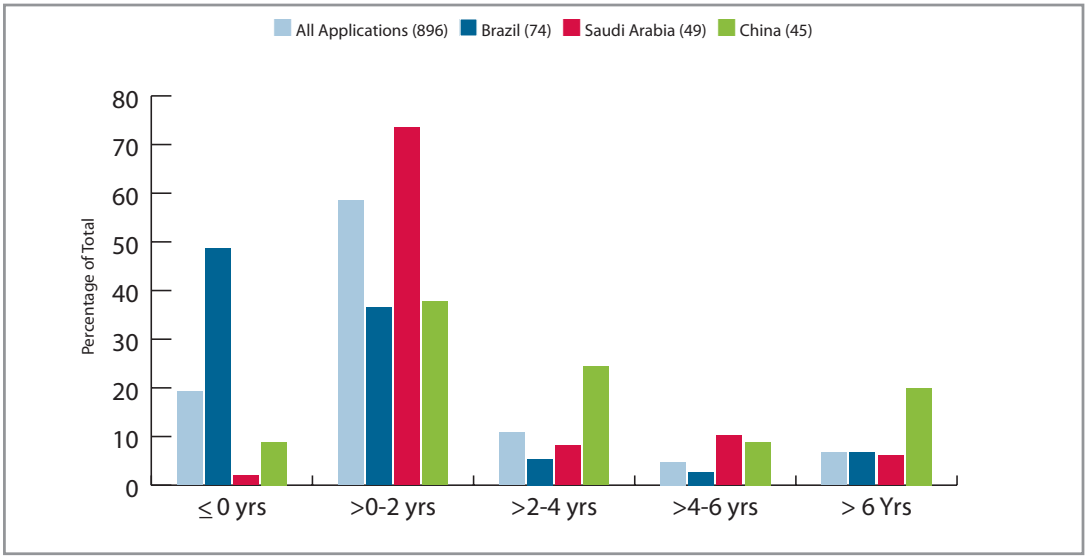
Figure 5. Lag Time analysis based on timing of CPP submission where the drug lag is 12 years or less (n = 875.).



Country-Specific Lag Time Distribution Analyses

CIRS investigated Lag Time distributions for all 15 countries and compared these results with the overall database. The following countries have been highlighted here because they are examples of how the role of regulatory requirements within these jurisdictions can been seen to shorten or lengthen the Lag Time for many products. A comparison of the distribution of these applications by country is shown in Figure 6.

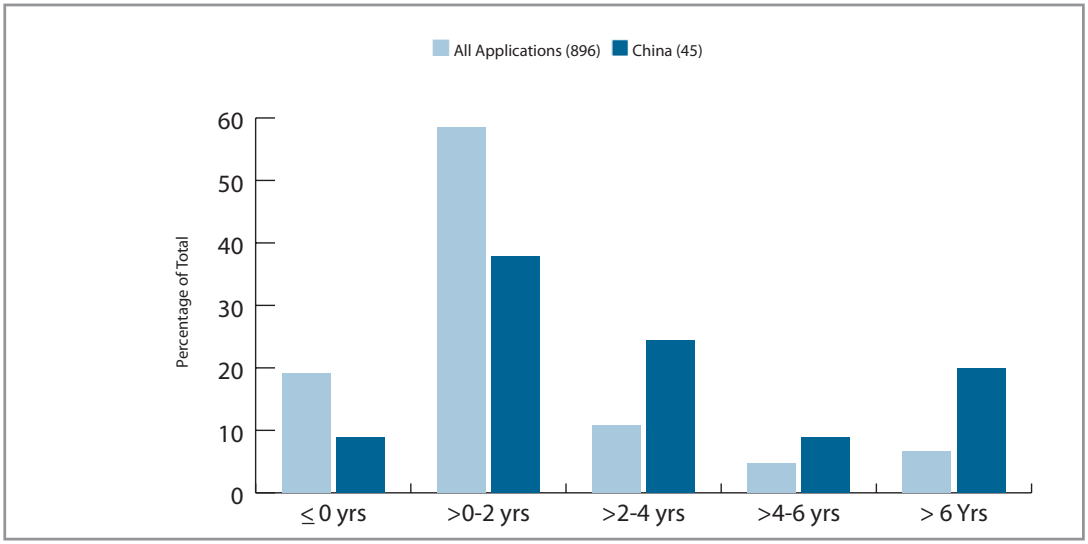
Figure 6. Comparison of Lag Time across Brazil, Saudia Arabia and China.



China: The Chinese drug regulation process differs from that in many other countries in that MAAs for all imported medicines (subject to waivers) are required to include data from local clinical trials. This means that there are two distinct stages to the drug registration process in China – first the applicant seeks permission to conduct the necessary local clinical trials (referred to as the CTA), and then the applicant submits their new drug application (NDA), which includes the local clinical trial data.

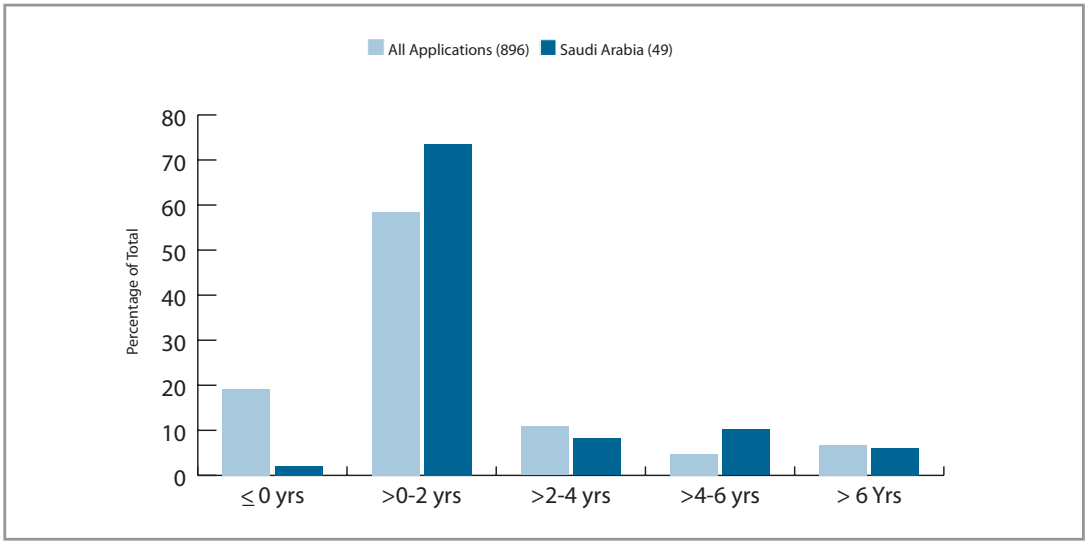
As shown in Figure 7, approximately 20% of applications were submitted to China with a lag Time of 6 years or more. The median Lag Time for submissions to China during the period of 2006-2010 was 976 calendar days.

Figure 7. A comparison of Lag Time distributions for Chinese applications (n=45) vs all applications.



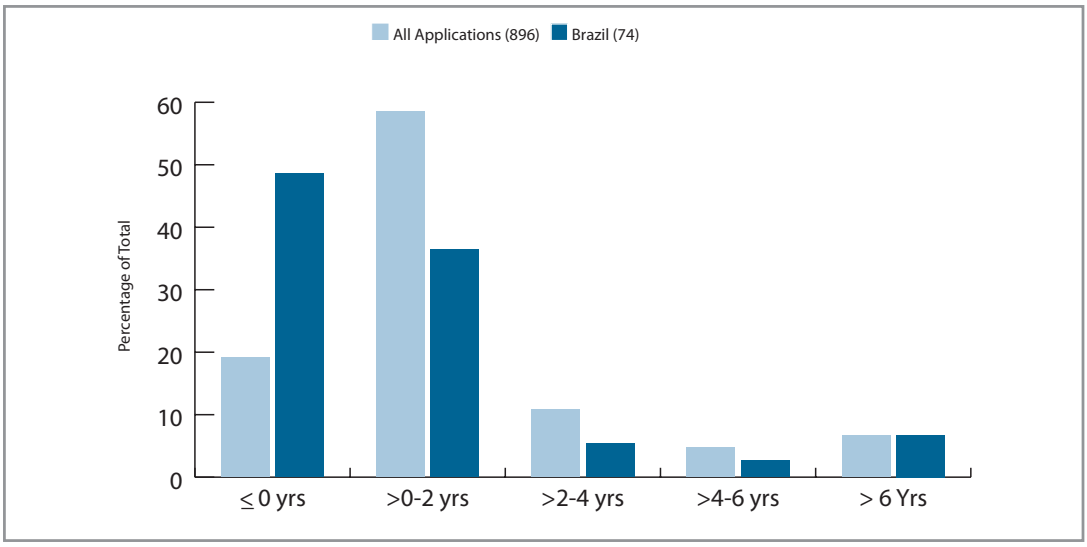
Saudi Arabia: A shift to longer Lag Times is observed in this country due to specific regulatory requirements that delay many submissions. These unique requirements include the need for the product to have had one year of marketed experience in another jurisdiction; a requirement for reference prices; and the requirement that the CPP be available at the time of submission. Of the 49 products assessed for this country, 37 had a Lag Time of 2 years or less, while 5 (10%) had lag times of 5 years or more.

Figure 8. A comparison of Lag Time distributions for Saudi Arabian applications vs all applications.



Brazil: The regulatory submission process in Brazil is characterised by the fact that a CPP is not required to be available at the time the MAA is submitted for review. There can be significant administrative delays in receiving CPPs from the index jurisdictions; therefore, these delays do not impact Lag Time in Brazil. Rather, many companies submit their MAA prior to approval from the first country and therefore, many products in the database have a zero or negative Lag Time for this country (Figure 9).

Figure 9. A comparison of Lag Time distributions for MAAs to Brazil vs all applications



Company Survey of Factors that Influence Lag Times

Short Lag Times (<5 years): Multinational research-based companies participating in the EMaRReT programme were asked to complete a country-specific questionnaire identifying factors that contribute to short Lag Times for products submitted to those countries. Of these companies, 8/14 (57%) responded to the survey. While all of the 15 factors described in the survey played a role in at least one country, the most common factors for shortened Lag Time based on company scores were as follows (Table 2).

Table 2: Factors that contribute to short Lag Times

Country (number of responses)	Factor 1	Factor 2	Factor 3
Brazil (8)	The size of the country's population and nature of its market made it a target for rapid submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	Other drivers
Mexico (8)	The size of the country's population and nature of its market made it a target for rapid submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	Submission timing is positively influenced by CPP requirements
South Africa (6)	Availability of support from our local affiliate office for the submission facilitates/accelerates the time to submission	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy
Russia (8)	The size of the country's population and nature of its market made it a target for rapid submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry
Turkey (7)	The size of the country's population and nature of its market made it a target for rapid submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry
China (7)	The size of the country's population and nature of its market made it a target for rapid submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry
India (6)	The size of the country's population and nature of its market made it a target for rapid submission	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy
Indonesia (5)	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry	The size of the country's population and nature of its market made it a target for rapid submission	Availability of support from our local affiliate office for the submission facilitates/ accelerates the time to submission
Chinese Taipei (7)	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry	Availability of support from our local affiliate office for the submission facilitates/ accelerates the time to submission	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy
South Korea (7)	Our company strategy is to submit as soon as possible to this country because of its role in our global strategy	The size of the country's population and nature of its market made it a target for rapid submission	Addressing an unmet medical need or offering an important therapeutic innovation within this country is seen as an important driver for entry

Long Lag Times (5 years or more): 8 companies had 54 applications that fell into the Lag Time category of >5 years to < 12 years.

For the purpose of this section of survey, the characteristics of 10 products covering 24 applications and 11 countries were assessed to reflect recent company experience. The factors influencing long Lag Times were found to vary extensively, do not appear to be systematic, and thus are not likely to be reduced by a single overarching approach or mechanism. Based on the aggregated survey results, the most common factors that contributed to long Lag Times were:

Related to company strategy

- The product was not considered by the company to be an internal priority
- Company's perception of the role/value this product in this country
- Availability (or lack thereof) of support from a local affiliate office for the submission

Related to country-specific issues

- This country required local studies/bridging study, which delayed the submission
- Applicant was required to generate additional country-specific clinical data
- This country's place in the Company's overall global marketing and development strategy
- The size of the country's population and nature of its market
- This country's submission requirements were outside the norm/unexpected compared to others which added complexity to the submission process
- Pricing considerations – probability of attaining fair reimbursement once approved

Related to product-specific issues

- Regulatory approval delays in other markets impacted the submission of this product dossier
- Unexpected safety signals from other jurisdictions slowed the submission decision

Observations and Conclusions

This study represents an ongoing comprehensive analysis of the CIRS EMaRReT dataset for the Lag Times for MAA submissions to Emerging Market countries and sought to investigate the factors that underpin these times. While our analyses illustrate that Lag Time exists for most Emerging Market countries, these vary widely; interestingly, when the most recent 2-year cohort (2009-2010 submissions) are compared with the prior 2-year cohort, the Lag Times were found to have decreased in all but one of the countries assessed (Data on File, CIRS).

There are a number of factors that contribute to the long Lag Times for a product to be made ready for review in a second market and these are related to company strategy, to country-specific issues and to product-related issues. The specific contributing factors constitute a diverse set of independent considerations that influence when it becomes feasible for a company to pursue approval of a product in a second market.

Our analyses are based on data from a dynamic, evolving environment. We identified that specific country-related issues, such as their request that local clinical trials be conducted so that these data can be included in the MAA, regulatory delays (in both the subject market and preceding markets), and local business issues affect Lag Time. Some respondents cited regulatory requirements for the longer Lag Times. China requires the conduct of additional clinical investigations of the drug in the local market which can have a significant impact on the Lag Time for that country.

Unfortunately, the different factors that affect Lag Time are not susceptible to a simple formulaic resolution.

The vast majority of products had their MAA filed to an Emerging Country rapidly. Indeed, approximately 78% of applications were filed within 2 years of a first world approval. However, 7% of the applications analysed in this study had Lag Times of 6 years or more. Because these applications correspond to approximately 1 in every 14 submissions to the Emerging Markets, they may represent an important burden on companies, for which delays require an ongoing commitment of time and resources, and for patients, who cannot benefit from the availability of these products in their countries until the

dossier meets local submission requirements and formal approval has been granted by their agency.

Furthermore, we identified a number of legitimate strategic business reasons for why marketing applications may be delayed, including the time required to ramp up local regulatory, marketing and medical presence to submit and support the application, limited resources and support from the local affiliate, the very low prevalence of the target disease in that country and the place of that country in a company's overall global rollout strategy.

These results indicate that most companies strive to submit MAAs for their products quickly (within 2 years of the first world approval); however some products experience noticeable delays (6 years or more) in their submission process. In many cases these delays are due to country-specific clinical or regulatory requirements that are beyond the control of the company or other stakeholders and for which these stakeholders should not be penalised.

The regulatory requirements in Emerging Markets and the industry's response to these are constantly evolving. Agencies implement new requirements that can delay submissions, such as the recently implemented pre-submission GMP inspections in Turkey and the need for local clinical trials in Russia prior to registration. Companies implement global strategies based on factors ranging from market size to local practice of medicine. Such requirements by agencies or changes in company strategy will have a potential influence on the time taken to submit new medicine and for patients to have access to new medicines. CIRS will therefore, continue to analyse the ongoing EMARReT database to inform best practice in global medicines development.

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