Trends in the Regulatory Landscape for the Approval of New Medicines in Asia

To address the complex challenges in the global regulatory environment and the growing demand for patient access to new medicines, regulatory agencies in Asia are actively engaging in regulatory-strengthening and capacity-building initiatives including the use of priority pathways, reliance in the prior reviews of trusted authorities and work sharing to facilitate better utilisation of resources.

This R&D Briefing focuses on the trends observed for 8 countries in the Asia region for 166 new active substances approved from 2009-2017*. The briefing explores converging review times, joint regional submissions and the positive effects of regulatory reform in China.

*See page 6 for methodology

Briefing Highlights

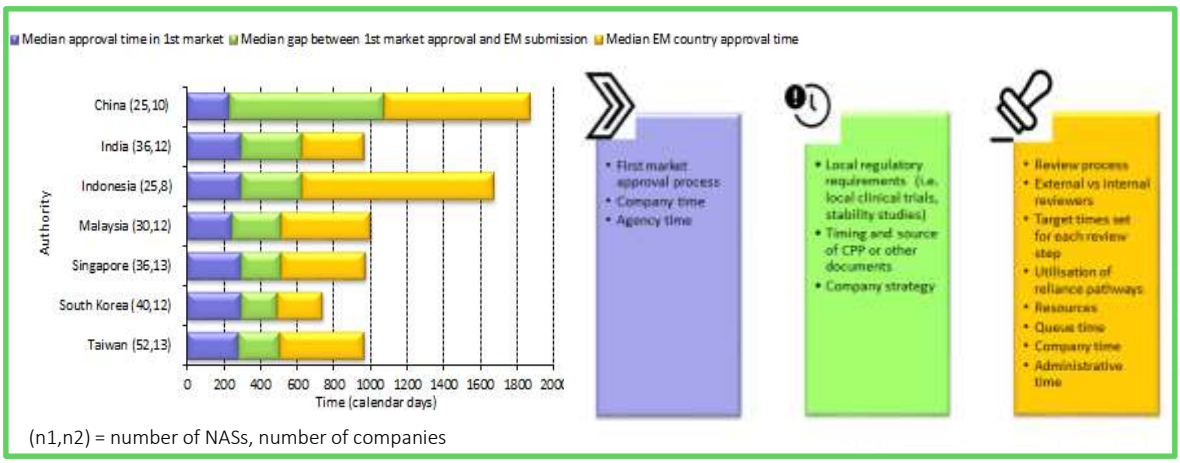
- From 2008-2017 average review times in India, Taiwan, Singapore, South Korea and Malaysia converged to an average between 400-500 calendar days; this average increased slightly in 2017.
- From 2015-2017 median review time was longest in Indonesia (1057 days) and China (800 days).
- From 2009-2017 there was minimal variability in regulatory review times in Malaysia, Singapore, South Korea and Taiwan and review timing in South Korea was consistently under 1 year.
- Government-mandated 2015 regulatory review improvements in China have resulted in 133 new drugs being approved through a new priority review route and an application backlog decrease from 22,000 to 3,440.
- A number of countries and regions have developed facilitated regulatory review pathways. These reliance pathways are in place in Indonesia, Malaysia, Singapore and Thailand. China, Taiwan and Vietnam conduct priority review. Rolling submissions and conditional approval is possible in South Korea. These facilitated pathways contribute to a shortening of regulatory review times and increased regulatory efficiency.

Regulatory review processes and timelines

The time to regulatory approval of new active substance (NAS) in Asia can be measured by three distinct time points:

1. **time of approval in the first market**, which generally is a first-wave market (USA or Europe);
2. **the submission gap**, (time between first-market approval and submission to a particular authority);
3. **marketing authorisation (MA) time** (time between submission and approval, which includes company and agency time). These time points are influenced by a number of factors, one of which is the regulatory landscape within different jurisdictions (Figure 1).

Figure 1: Overall median roll out time to Asian countries for NASs approved 2015-2017 and factors influencing their roll out.



(n1,n2) = number of NASs, number of companies

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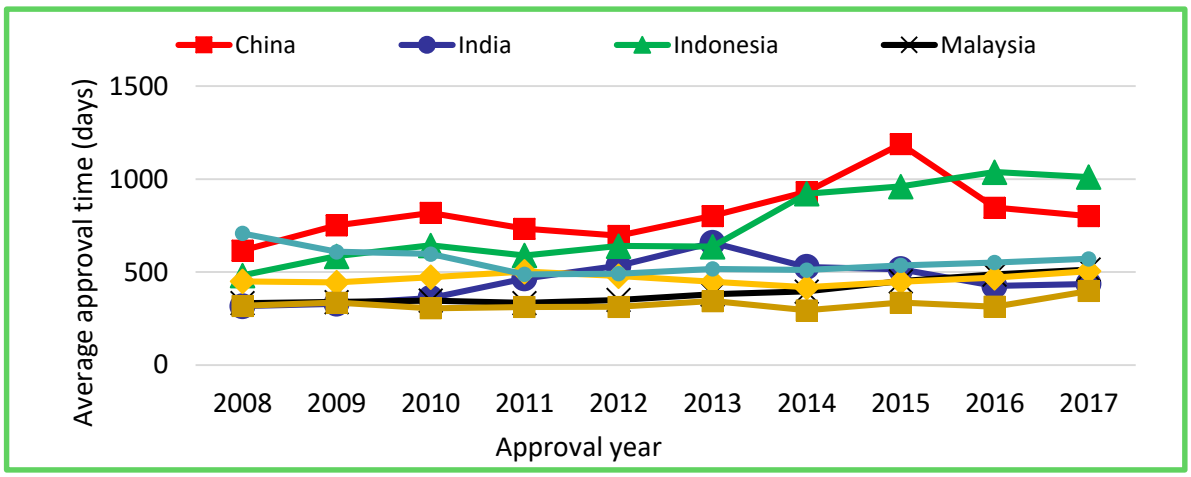
Trends and predictability in the review

Approval time trends over the last decade*

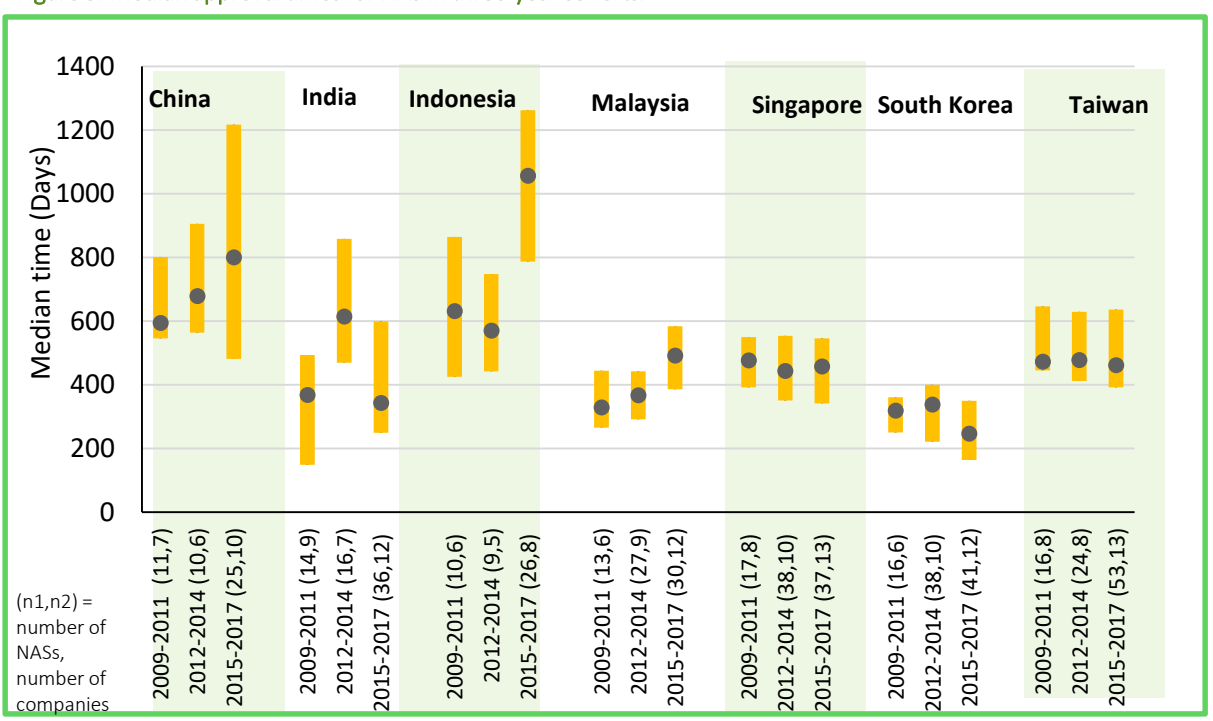
Over the last decade, regulatory agencies in Asia have undergone many changes to streamline their MA process. Figure 2 shows the **three-year moving average** of the time required for NAS approvals. From 2008-2017, the approval times for India, Taiwan, Singapore, South Korea and Malaysia converged to an average between 400-500 calendar days; this timing increased slightly in 2017. When looking at timelines to approve medicines from a global perspective, the 2018 median times to approve medicines in the first market ranged from 214 days (US FDA) to 519 days (SwissMedic). *CIRS R&D Briefing 70* However, it is important to note that regulatory review times include agency time, impacted by issues such as domestic regulatory policies, resourcing and lack of infrastructure and company time, affected by such factors as response time to questions and supply of requested documentation.

Figure 2: Three-year moving average approval times for NAS approved 2008-2017.



Understanding process predictability

Figure 3: Median approval times for NAS in three-year cohorts.

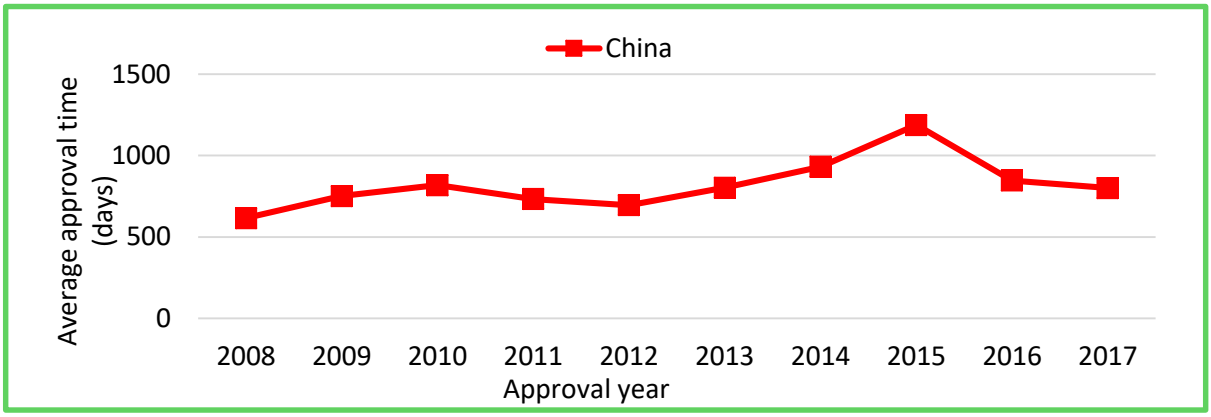


The variability of approval time around the median is one measure of the predictability of an agency's regulatory review process. The narrower the variability, the more predictable the process; however, variability may be influenced by different types of review pathways. Malaysia, Singapore, South Korea and Taiwan have shown the least variability over the past nine years, showing that their approval process is relatively predictable, with South Korea also having median approval times under one year over the nine-year period. This contrasts with China, Indonesia and India, where regulatory approval times have considerable variability.

* Figures 2 and Figure 3 use different analysis and year-range data set; therefore, these should not be used for direct comparison. Figure 2 shows the approval time as a three-year moving average and Figure 3 shows approval times in median and percentiles, using a 3-year cohort.

Case Study: the benefits of political will for change

Figure 4. Three-year moving average of approval times for NASs approved in China 2008-2017



Situation

Over the past several years, the Chinese National Medical Products Administration (NMPA) have recognised that their regulatory system was unable to meet the needs of an evolving global industry. A variety of factors were contributing to regulatory inefficiencies including:

- Policy barriers to the consistent implementation of efficient regulatory policies
- A lack of risk-based, scientific regulatory systems and processes
- Low standards for new product registrations
- Low-quality submissions, resulting in multiple rounds of questions to the sponsor
- Staff resources inadequate to meet the influx of dossier submissions
- Lack of internal and external transparency/communication

As a result, there was a heavy backlog of registration applications waiting to be reviewed during the period of 2010-2015, with long, multi-cycle reviews and assessment times for new drugs that were considerably longer than for most major regulatory agencies.

Task and action

In 2015, the General Office of the CPC Central Committee and the General Office of the State Council released Notice No. 42 to address the issues, outlining a series of regulatory improvement initiatives. These included actions to:

- Introduce a priority review system
- Expand the workforce: recruiting a chief scientist, reviewers, project managers, compliance investigators and clinical trial managers

In addition, since October 2016, NMPA has been publishing the review reports and disclosure of review process and progress to applicants.

Results

These initiatives have already resulted in measurable impact. These include:

- The introduction of a priority review pathway to accelerate review has resulted in 133 new drugs being approved through this priority route.
- The number of licensing applications waiting for review and approval dropped from 22,000 to 3,440.
- In 2015-2018, the number of face-to-face meetings grew significantly, from 54 to 322.

Facilitated review pathways

Many agencies have recognised that their market application review times are increasing, which is generally due to insufficient resources. To address this issue, agencies are introducing various approaches to streamline their review pathways and to efficiently use available resources.

One approach is for regulators to work together, which has led to the emergence of new models of regulatory cooperation. A number countries and regions have developed or are developing formal and informal frameworks for cooperation and work sharing, helping to avoid duplication across the partner agencies and facilitating a focus on added-value activities and the efficient use of resources. One such example is the ASEAN Joint Assessment procedure in which the same marketing authorisation application is simultaneously submitted to all participating national regulatory agencies (NRAs). Assessment work is then carried out together by all participating NRAs and a joint assessment report is prepared. At the end of the process, the final decision on the application is taken by each individual NRA through their normal decision-making process based on the joint report and, where applicable, nationally relevant considerations.
The primary purpose of joint assessments is to strengthen the national regulatory authorities' technical capacity and to foster mutual trust and reliance among ASEAN Member States.

An alternative way to achieve cooperation and avoid duplication of work is through the use of a reliance pathway in which the prior regulatory work of trusted regulatory authorities is used by the relying agency, allowing that agency to focus on providing value-added regulatory activities within their jurisdiction and access to high-quality, safe and effective medicines in a timely manner (Table 1).

Table 1. Currently available facilitated regulatory review pathways in Asia.

	Verification route	Abridged route	Priority review	Expedited/ rolling submission	Conditional approval
China					
India					
Indonesia					
Malaysia					
Philippines					
Singapore					
South Korea					
Taiwan					
Thailand					
Vietnam					

Glossary

Verification route: This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency in the importing country is to 'verify' that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorisation(s).

Abridged route: This model also conserves resources by not reassessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions.

Priority review: Regulatory authorities speed the review of certain products to enable faster approval. The review time of an expedited review is substantially shorter than the review time of a standard review. A decision on which product to grant expedited review is normally based on its importance to public health.

Expedited/Rolling submission: Information and data-packages can be submitted and reviewed as they become available even before the official submission date. There is, for example, no need to wait for the availability of the full clinical data before submission of the earlier available pre-clinical data. This allows regulatory agencies to review available data sets as soon as they are available and may allow the shortening of regulatory procedures. Often 'expedited submissions' are referred to as 'rolling submissions'.

Conditional approval: This approach allows for earlier submission and approval with a data set that may be less complete than that of a standard development programme. This approach is usually reserved for products that address a high unmet medical need in a serious or debilitating condition and where the data are nonetheless adequate to demonstrate a positive benefit-risk profile.

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Methodology

The data used for the analyses in this report have been derived from the CIRS Emerging Markets Regulatory Review Times Database, which tracks new medicines and line extensions in 18 emerging markets. The data used for this briefing include those for all new active substances approved between 2009-2017 in the 8 countries in the Latin America region that are included in the database.

Acknowledgements

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