

ASIA UPDATE KEY ISSUES IN THE REGISTRATION OF PHARMACEUTICALS

Key messages

- Pharmaceutical companies are increasingly involving the emerging markets of Asia in global clinical development plans; more companies are including clinical data generated in Asia as pivotal submissions.
- The industry goal of simultaneous submissions in the Asian region is becoming more of a reality for pharmaceutical companies.
- A commonly identified barrier to registration in Asian markets is the requirement for a Certificate of Pharmaceutical Product (CPP) from the source country at the time of dossier submission. The requirement for CPPs to be legalised also poses a significant barrier to registration in Asia.

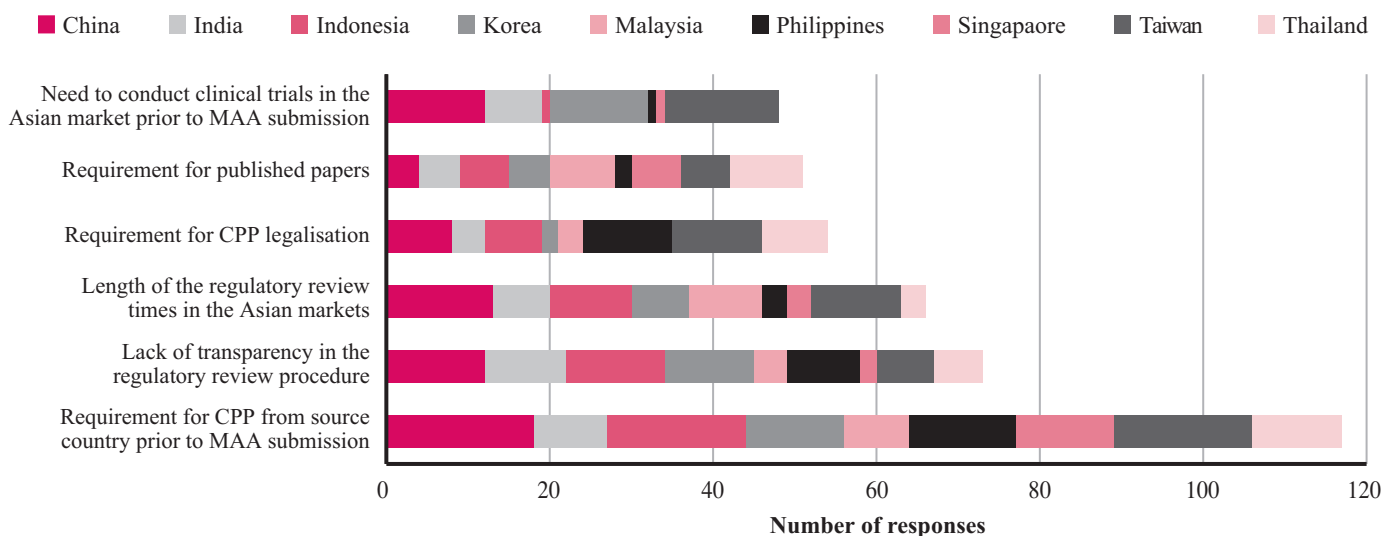
Perspective

The emerging markets of Asia offer considerable potential for growth in the pharmaceutical sector despite the economic instability of recent years. The Asian pharmaceutical market is predicted to grow at an annual rate of more than 10% over the next few years,¹ ensuring that the region remains attractive to the pharmaceutical industry.

Together with opportunities, there are barriers to be overcome before medicines are registered in this region. In 1998, CMR International conducted a survey of the pharmaceutical industry in order to identify the key barriers to the registration of new medicines in Asia, and to explore company strategies for development and registration in the region.²

This survey has been repeated in order to capture recent changes in the environment for registration in Asia and to identify current barriers to registration. The present survey focuses on nine key Asian emerging markets: China, India, Indonesia, South Korea, Malaysia, the Philippines, Singapore, Taiwan and Thailand. Aggregated results from 24 international pharmaceutical companies are presented in this R&D briefing.

Figure 1 Major barriers to registration in Asia



Participants were asked to identify which of a list of factors caused them major problems when registering new medicines in Asian markets. This figure shows the six most commonly identified issues. The maximum possible response for any one barrier is 216.

Barriers to registration

The barriers to registering New Active Substances (NASs), as perceived by respondent companies, are displayed in Figure 1. The main barrier to registration in Asia is the requirement for a Certificate of Pharmaceutical Product (CPP) prior to the submission of a Marketing Authorisation Application (MAA). This barrier was identified by between 33% and 75% of companies for each market and was also identified as the main barrier in the previous survey.

Lack of transparency in the review procedure appears to have become more of an issue since the last survey and has been identified by more participants this time. Other identified barriers include the length of review times and the need for CPPs to be legalised by the embassy or consulate of the destination country.

The markets of Asia have considerably different regulatory processes. The effect of this is that barriers identified in some markets are of no relevance to other markets. For instance, the requirement for Plant Master Files is the most commonly identified barrier in Taiwan, but is not a major barrier in other markets.

CPP requirement

The submission of a CPP is a necessary condition of registration in many emerging markets and production of CPPs guarantees that any new medicines have been approved following a thorough review in one of the more experienced agencies.

Regulations regarding CPPs differ between agencies in Asia. In general, at least a CPP from the source country is required, but some authorities require multiple CPPs. The timing of submission of CPPs can differ, although CPPs are usually presented to authorities at the time of MAA submission (Figure 2). For industry, the commonest barrier to registration is the requirement for a CPP from the source country prior to submission and this barrier can cause delays to the availability of new medicines to patients in Asia of up to 10 months.

At present, companies generally provide CPPs before

submission and rarely delay the provision of CPPs until approval (Figure 2), although there is considerable variation in company practice between authorities. Interestingly, since the previous survey, the timing of CPP provision has shifted in Thailand, Korea and Malaysia such that a greater proportion of companies are now able to delay CPP provision until approval (Figure 3). These results indicate that CPP regulations may have become increasingly flexible in some markets in recent years, which could expedite the availability of new medicines to patients.

CPP legalisation

The requirement for CPP legalisation is perceived as the fourth commonest barrier to registration (Figure 1). The CPP scheme was set up by the World Health Organization, whose guidelines indicate that CPP legalisation is an unnecessary step.³ But in general, companies tend to legalise CPPs for many Asian markets (Figure 4). Once again, there is considerable variation in company practices between markets. CPP legalisation is a regular practice in the Philippines and Taiwan, but few companies legalise CPPs for authorities in Korea or Singapore.

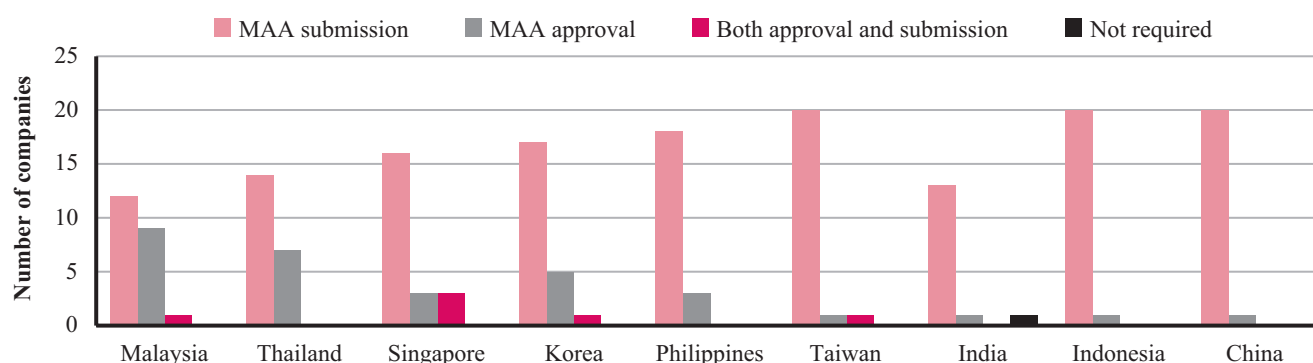
Regulatory approval times

In the previous survey, the length of review times was the second most important barrier to industry, and it is now the third. This suggests that approval times may have improved in some markets. An analysis of approval rates (which gives an indication of approval times) in the region also suggests improvements in some markets.

Since January 1998, China has approved 35% of NASs submitted by respondent companies, whereas Singapore has approved 81%. The variation in approval rates between authorities in Asia is clearly quite substantial, particularly when compared with approval rates in major Latin American markets which are universally above 74%.⁴ Only the Philippines, Thailand and Singapore have comparable approval rates.

Encouragingly for industry and patients, approval rates appear to have improved in some markets since the previous

Figure 2 Timing of the requirement for a Certificate of Pharmaceutical Product



Respondents indicated whether they had generally supplied a CPP at the time of MAA submission, MAA approval or whether a CPP was generally not required. In most cases, CPPs were provided at the time of MAA submission.

Submission strategies

survey, particularly in Singapore, and no market has demonstrated a substantial decline in approval rates. Approval times may therefore be getting faster in the region, but this can only be definitively explored by measuring approval times for individual compounds.

Clinical development

The need to conduct clinical trials before MAA submission is, for some markets, one of the key barriers to registration. Over 80% of respondents have received requests to conduct local clinical trials by one or more of the Asian markets. The majority of these requests came from authorities in China, Taiwan, Korea and India. Although these markets requested some trials prior to MAA submission, most requests were for trials to be carried out before approval.

In addition to performing clinical trials because of regulatory requirements, 29% of respondents include clinical data collected in Asia as pivotal evidence for submissions to ICH regions. In the previous survey only 18% of companies collected pivotal data in non-ICH Asian markets. The change suggests that companies are increasingly including the emerging markets of Asia in their multinational clinical development plans.

Most companies would ideally submit MAAs simultaneously in all the major markets of Asia (Figure 5). Only 29% of respondent companies are currently able to do this, although this is an improvement compared with the previous survey in which only 14% of respondents were submitting simultaneously in markets within the region.

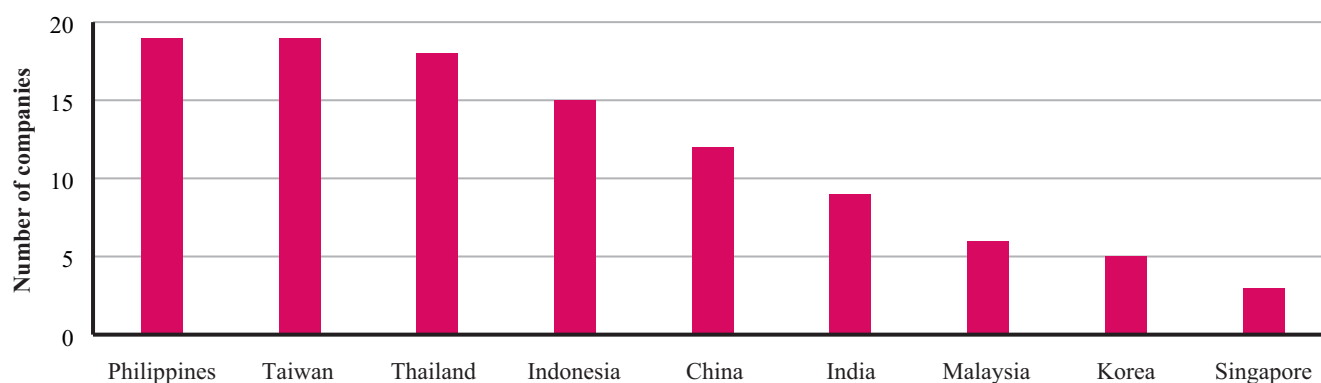
This change may be an indication of successful harmonisation initiatives within Asia. The Association of Southeast Asian Nations (ASEAN) has an active Product Working Group on Pharmaceuticals which looks at various harmonisation issues. Also, regional meetings organised by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) regularly focus on harmonisation within Asia. Furthermore, some countries have adopted International Conference on Harmonisation (ICH) Guidelines even though they are not officially part of the ICH initiative. These efforts must be maintained in order for regional harmonisation to be achieved.

Figure 3 Percentage of CPPs provided at approval: 1998 survey vs 2001 survey



To compare results of the previous survey with those of the current survey, the percent of companies that provided CPPs at approval was calculated from both sets of results.

Figure 4 Provision of legalised Certificates of Pharmaceutical Product



Respondents were asked if they generally supplied legalised CPPs to each authority.

The future

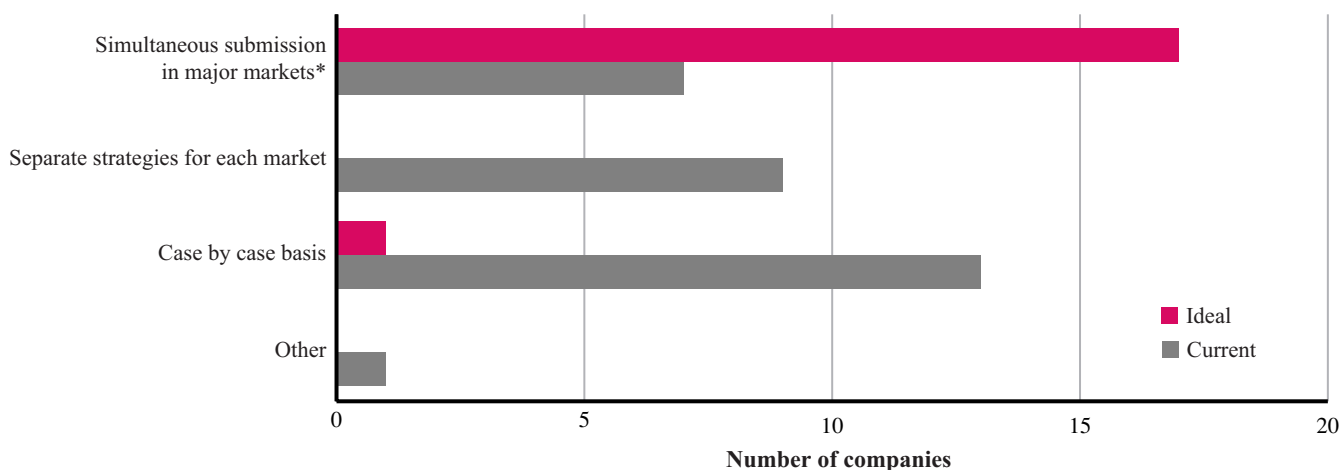
At present, there are a number of barriers to the timely and successful registration of new medicines in the non-ICH markets of Asia. These barriers can potentially delay patient access to new medicines.

Encouragingly, the regulatory environment in some Asian markets has improved over the past few years. There are indications that companies are increasingly incorporating the region into core development plans, that harmonisation efforts have improved the industry's ability to submit simultaneously in Asian markets, and that in some markets, the regulatory environment has become more flexible in terms of the timing of CPP provision. This is welcome news for patients in the region who should benefit from improved access to the newest and most innovative medicines available.

Conclusions

- With continuing dialogue and cooperation between industry and regulatory authorities, supported by groups such as ASEAN, IFPMA and CMR International, the environment for the registration of pharmaceuticals in Asia should continue to improve, thus enabling faster patient access to new medicines.
- Regulatory authorities can improve patient access to medicines by reducing the restrictions relating to the provision of CPPs. This could include a reassessment of requirements concerning the timing of CPP provision and the legalisation of CPPs.

Figure 5 *Submission strategies in Asia*



*Major markets commonly identified: China, Korea, Taiwan

Companies were asked to identify their ideal submission strategy for the markets of Asia, and also their current submission strategy. Currently, the most popular strategy is to make submissions on a case by case basis. Some companies identified more than one of the listed strategies as 'current'.



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