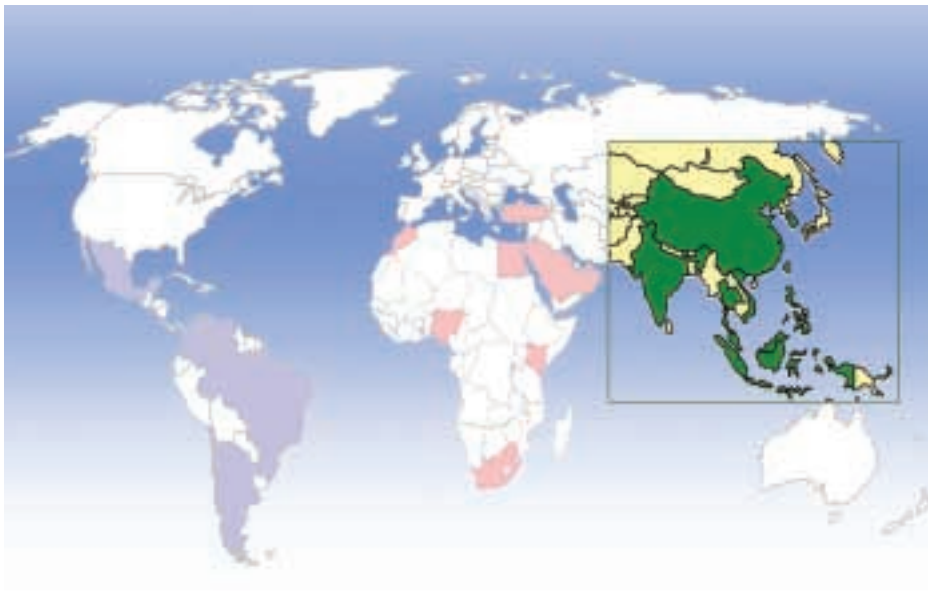
R&D Briefing

Assessing the regulatory environment and its impact on patients' access to new medicines



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South-East Asia and the Western Pacific

CMR International

Institute for Regulatory Science

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South-East Asia and the Western Pacific: Assessing the regulatory environment and its impact on patients' access to new medicines

Highlights from a study among the regulatory agencies in the key emerging markets in the South East Asia and Western Pacific Region and among the companies that operate in those countries.

Key points

The Regulatory Agencies in South East Asia and the Western Pacific share a common goal with the research-based pharmaceutical companies that they regulate. This is to ensure that new medicines become available to patients in a timely and efficient manner, with appropriate safeguards for the public health. The CMR International Institute study aimed to identify the factors that promote best practices among regulatory agencies and to identify barriers to the timely authorisation of safe and effective new medicines, in the region.

Priorities: Authorities identified financial constraints and resource issues as the primary barriers to improving regulatory processes. They are also concerned about companies' internal communications between local affiliate organisations and head offices, especially in dealing with questions raised on applications. A top priority for industry is for improved communications and collaboration between companies and agencies with a view to establishing a more effective and transparent regulatory environment.

Approval times: The time taken for the regulatory review, at national level, is also a primary concern identified by companies that are seeking to make new medicines available in the region. The regional median time for approval of a new medicine is approximately one year but there are considerable differences between countries.

Timing of the CPP: An integral part of the review is the availability of a Certificate of a Pharmaceutical Product (CPP) verifying the authorisation of the product by another recognised authority. The requirement for a CPP to be available prior to filing a marketing application, rather than accepting the CPP at a later stage in the review process can delay the start of the regulatory process by up to two years, while registration is obtained elsewhere.

Transparency is high on the list of important factors that engender confidence and help to create a favourable regulatory environment for making new medicines available. The authorities of the region are, however, very varied in their attitude to openness and transparency in providing information on their regulatory processes and maintaining communications with industry.

Harmonisation: Companies have reported that the guidelines being used by regulatory agencies in the region are not fully harmonised with international guidelines of ICH and WHO. There is a tendency for countries to 'adapt' guidelines rather than 'adopt' them, unchanged. Such divergence could act as a deterrent when applying for authorisation, if companies feel that alternative testing may be expected.

IP protection: Adequate and enforceable protection of intellectual property (IP) rights is a cornerstone for current and future investment in new medicines. Although all the countries in the study have IP legislation there is a strong indication, in some countries, that adequate enforcement of the laws has not been achieved.

The way forward: The study indicated that the way forward for the region is through developing further a constructive dialogue between agencies and pharmaceutical companies on reducing the regulatory impediments to making new medicines available.

Background

The emerging markets, especially those in the newly industrialising countries, are becoming increasingly important to pharmaceutical companies in their global development and marketing strategies. Traditionally, the focus has been on drug development, regulation and sales in the three major markets of the EU, USA and Japan and many studies have been carried out on these regions. In 2004, however, CMR International initiated a major study that looked beyond these three regions and examined, in particular, the regulatory environment for making new medicines available in the major markets in the 'rest of the world'.

The countries included in this survey (Box 1) all have national procedures for the regulation of medicines. These are at different stages of development but they share a common goal with the longer-established agencies and with the pharmaceutical companies that they regulate. This is to ensure that new medicines become available to patients in a timely and efficient manner, with appropriate safeguards for the public health.

With this goal in mind, the CMR International study set out to identify the factors that promote best practices among regulatory agencies and to identify barriers to the timely authorisation of safe and effective new medicines.

Survey of the South East Asia and the Western Pacific Region

The eleven countries that were included in the study for SE Asia and the Western Pacific are extremely diverse, ranging from China, with a population of 1306 million to Singapore with 4.4 million inhabitants. Traditional and herbal medicines have an important role in the medical practices and culture of the region but the pharmaceutical markets also support a full range of established 'western-style' medicines and their generic equivalents. This study, however, focused on the regulatory procedures for authorising innovative new medicines and making them available to patients.

Data were collected from nine multinational pharmaceutical companies that are actively involved in registering new medicines in the region and enhancing currently marketed medicines through major line extensions (use of the product in new indications, patient populations or disease states). Information was also collected through a survey and from face-to-face interviews with the regulatory authorities in the countries in the study, with the exception of China and Vietnam.

The topics covered in the survey are shown in Box 2. Both companies and agencies were asked to provide specific data, where relevant, but they were also given the opportunity to record their perceptions and views on the current regulatory environment.

The three regions in the study

South East Asia and Western Pacific

China
Hong Kong
India
Indonesia
Malaysia
Philippines
Singapore
South Korea
Taiwan
Thailand
Vietnam

Middle East and Africa

Bahrain
Egypt
Jordan
Kenya
Kuwait
Morocco
Nigeria
Oman
Saudi Arabia
South Africa
Turkey
United Arab Emirates

Latin America

Argentina
Brazil
Chile
Colombia
Costa Rica
Mexico
Venezuela

Box 1

Box 2

Topics covered in the CMR International Study: Regulatory Authority and Company questionnaires

Authority overview and performance
Type of agency, its current and future 'mission' and objectives, data on review timelines;

Relevance of regulatory status in other countries
Recognition of the regulatory status in other countries and use of the WHO model Certificate of a Pharmaceutical Product (CPP);

Transparency of the process
Willingness of agencies to provide advice and information on review procedures, including consultation on guidelines;

Application Procedures and Data Requirements
Type of procedures, use of expert committees and outside experts, acceptance of internationally harmonised guidelines for format and content of applications;

Clinical Trials
Regulatory requirements for local clinical trials and companies' experience of official procedures for conducting trials in the country;

Policy and Perceptions
Official policies and the industry perception of policies relating to the grounds for granting and refusing authorisations, the influence of price on decisions and the extent to which intellectual property protection is implemented.

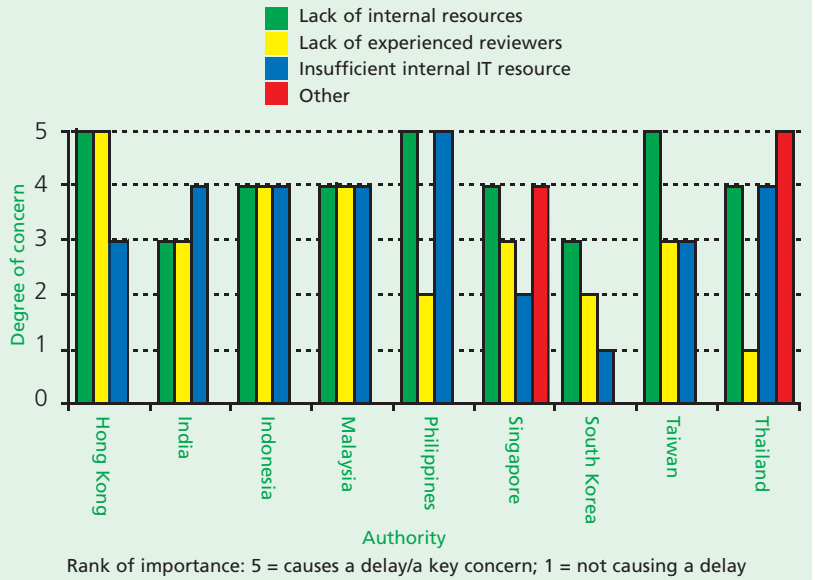
The final section of the questionnaire also asked both companies and regulatory authorities for their views on major hurdles and key success factors for making new medicines available to patients, with a minimum of delay.

Priorities for the Region's Authorities

The Authorities were asked to identify and prioritise the key difficulties that they face, which can cause delays to the timely authorisation of new medicines and their access to patients. Clearly, many agencies feel that they are unable to fulfil their obligations to the public because of limitations and resource constraints that need to be addressed at a higher administrative or political level. Whilst these internal factors are not within the scope of industry to remedy, there were also external factors where changes in company practices could lead to improvements.

Figure 1

Authorities' perception of the internal factors that cause delay to the timely access of patients to new medicines



Rank of importance: 5 = causes a delay/a key concern; 1 = not causing a delay

Internal factors

Figure 1 presents the internal factors that authorities cite as reasons that can cause delay to the regulatory process. Lack of resources is viewed by agencies as the major factor, or jointly the most important factor, by all countries.

Lack of experienced reviewers and insufficient IT resource are also regarded as important factors.

Without adequate funding authorities cannot establish an efficient infra-structure, with appropriate IT facilities and it is difficult to attract and retain well qualified, experienced staff. These are seen as the main contributing factors to delays in the regulatory process which, in turn, impede the timely access for patients to new medicines.

External factors

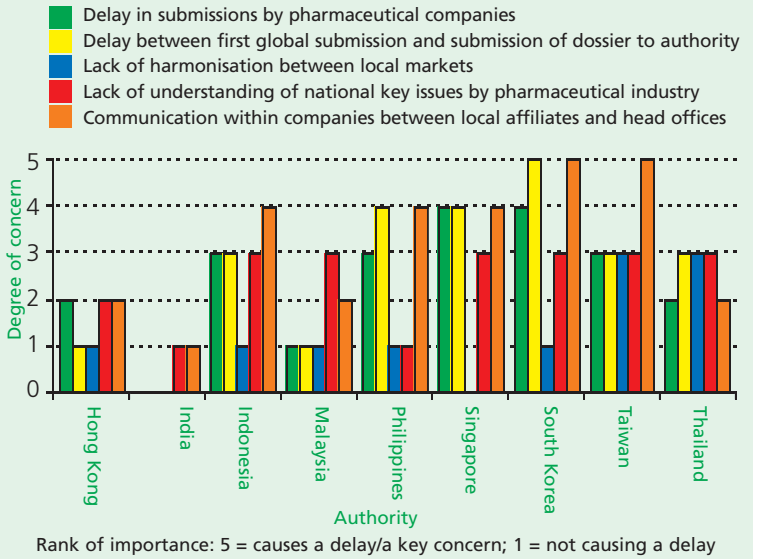
The analysis in Figure 2 presents the authorities' perception of the external factors that have a negative impact on the efficiency of their operations.

In many authorities' view, a lack of communication within companies, i.e., between local affiliates and head offices, is seen as a key factor. It is believed that this may reflect instances where there has been a misinterpretation of information by the local organisation when reporting back to the company headquarters regarding questions on submissions.

Delay between first global submission and submission of the dossier to the local authority is also perceived as important when considering delays in patients' access to medicines from an authorities' perspective. This is discussed further in relation to the timing of the CPP.

Figure 2

Authorities' perception of the external factors that cause delay to the timely access of patients to new medicines



Rank of importance: 5 = causes a delay/a key concern; 1 = not causing a delay

Companies' perspective

Patients' access to new therapies may be delayed if companies are discouraged from doing business in the region by the perception that there are regulatory hurdles that make product authorisation slow or unduly burdensome. Companies were therefore asked to identify their major causes of concern when applying to register medicines in the region.

Figure 3

Major cause of concern that may prevent or delay patient access to new medicines: Company data

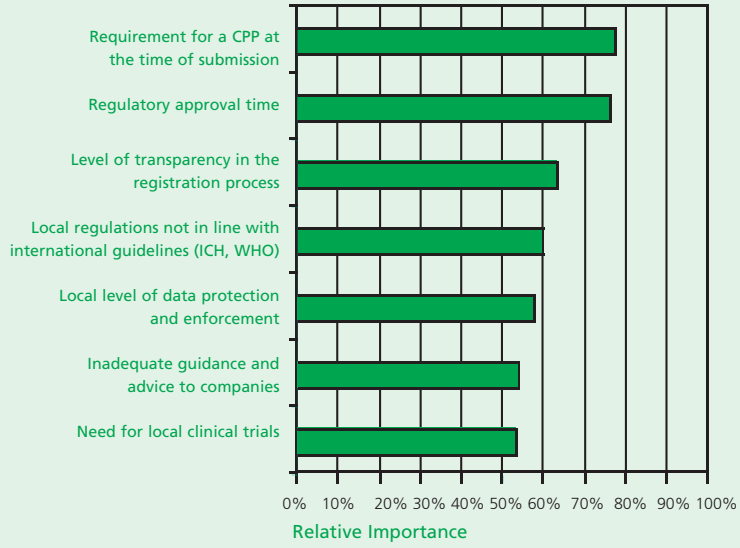


Figure 3 summarises the company response highlighting the items of greatest concern.

The Issues

■ **Regulatory Approval times:** The time taken for the authorities in the importing country to review and determine an application is important to companies in planning a launch strategy for a new medicine.

■ **Timing of the CPP:** By definition, a CPP (see below) can only be issued after a new product has been authorised in another country. The need to obtain a CPP before filing an application in the importing country builds an automatic delay into the registration process.

■ **Transparency in the Review Process:** Experience from the ICH regions has shown the value and benefits of an open and transparent relationship between companies and regulatory authorities.

■ **Harmonisation with International Guidelines:** If local regulations for technical data on new medicinal products are not in line with international norms, companies can be deterred from applying for authorisation because of concerns that additional testing might be required.

■ **Intellectual Property and Data Protection:** Adequate and enforceable protection of IP rights is regarded as a cornerstone for current and future investment in new medicines. Deficiencies in such protection that could lead to the availability of pirated products and the disclosure of confidential data are major disincentives to the registration of new products.

■ **Guidance and Advice from the Agency:** This is closely related to the transparency of the system, and reflects the importance attached by companies to being able to interact with the agency and obtain advice on the application procedures and requirements.

■ **Need for local Clinical Trials:** As companies move towards global drug development they are increasingly seeking centres of excellence in the emerging markets where clinical studies can be conducted. Concerns arise, however, where there are requirements for local trials to be conducted as a condition of obtaining authorisation.

Glossary Notes

Certificate of a Pharmaceutical Product (CPP)

Under the WHO Certification Scheme for the Quality of Products moving in International Commerce a regulatory authority that has authorised a medicinal product may be asked to issue a CPP to the authority in an importing country, verifying the regulatory status and confirming that the product complies with standards for Good Manufacturing Practice (GMP).

International Conference on Harmonisation (ICH)

Full title: International Conference on the Harmonisation of Technical Requirement for the Registration of Pharmaceutical Products for Human Use.

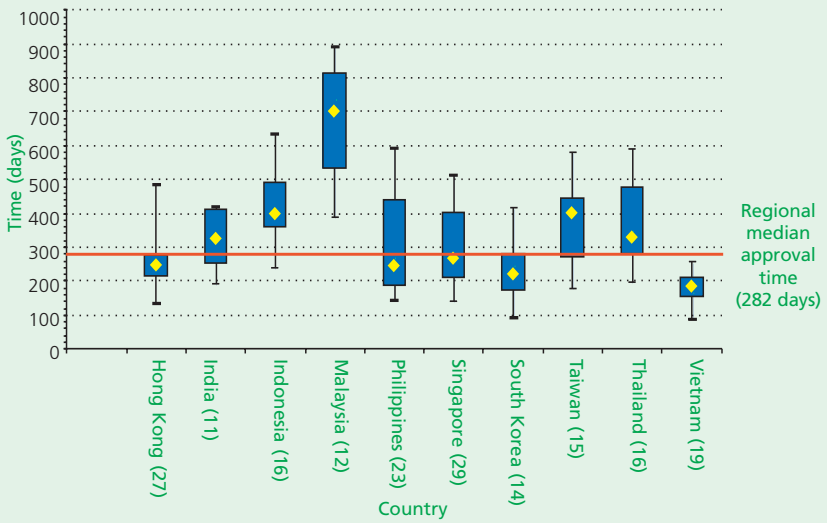
This is a three-region (EU, USA and Japan) six-party (Regulatory Authorities and industry associations) initiative that has agreed over 50 regulatory guidelines for developing new medicinal products ('ICH guidelines').

Regulatory approval times

A knowledge of median approval times and potential variability is important to companies in planning a launch strategy for new medicines in the different countries in the region.

Figure 4

Regulatory approval times for NASs submitted and approved between 2001 and 2003 (calculated from company data)



Data are shown for NASs that were submitted and approved between 1 January 2001 and 31 December 2003.
(n) = number of NAS
Box: 25th and 75th percentiles. Whiskers 5th and 95th percentiles.
Diamond = median

The analysis in Figure 4 presents the median approval times (date of submission to date of marketing approval) for new active substances submitted and approved between 2001 and 2003. On the basis of these data, the regional median is 282 days but regulatory approval times vary quite considerably between countries and, in some cases, within countries. The approval time in Malaysia is exceptionally long for the region, at 727 days, whilst the medians for other countries lie between 150 and 400 days.

It should be noted that India, Indonesia and Singapore have different regulatory procedures and priorities according, for example, to the source, regulatory status and medical importance of the product, which are not distinguished in these data.

When looking at the overall time for product approval in the region, however, account also needs to be taken of the time at which the review process can start, relative to authorisation in the ICH regions. As noted, this is largely influenced by CPP requirements.

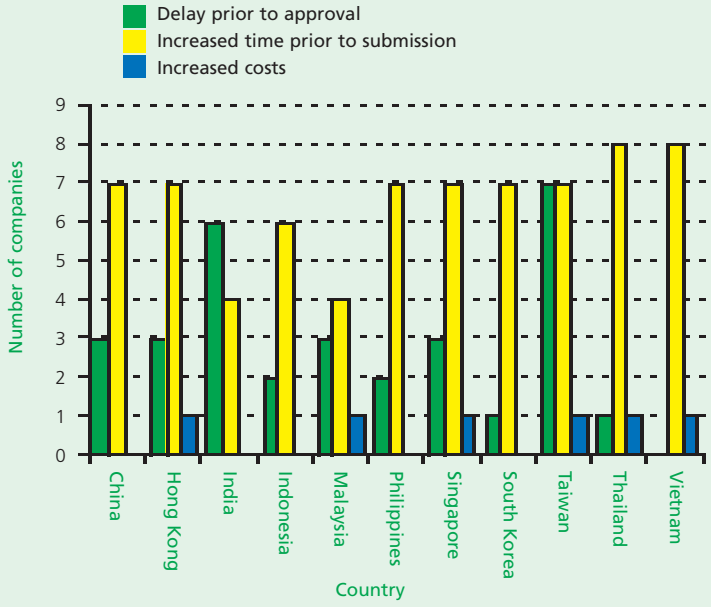
Certificate of a Pharmaceutical Product (CPP)

Certification that a product has been duly registered by an authority that is regarded as a 'reference' agency should be of great advantage when applying for a marketing authorisation in another country.

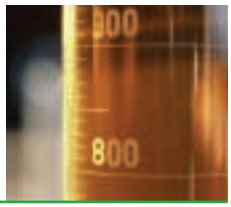
However, when companies were asked whether the CPP was an issue in the region they indicated clearly that it was a cause for concern in all the countries in the study. Figure 5 gives the results of a question asking for views on the ways in which the certification scheme was impeding, rather than expediting, the authorisation of new medicines.

Figure 5

Companies' perception of CPP requirements as an issue



Certificate of a Pharmaceutical Product



The issues from a company perspective

■ Timing of the CPP: Whether the Certificate must be made available:

> At the time of making an application in the importing country while authorisation is obtained elsewhere*; or
> After the application is filed but before authorisation, in which case applications can be filed in the emerging markets within the same time-frame for registration in the ICH regions.

■ Authentication of the CPP: Some agencies in importing countries require certificates to be authenticated by their embassy or consulate in the country where the certificate is issued. Companies consider that authentication by the regulatory agency issuing the certificate (as recommended in WHO Guidelines for the Certification Scheme) should suffice.

■ Source of the Certificate: A strict requirement that the certificate must be issued by the regulatory authority in the country from which the product is actually exported can create problems when manufacture is outsourced to a country where the product may not be registered for marketing.

Companies believe that a CPP from a reference list of regulatory authorities should suffice along with confirmation that the product is manufactured under GMP conditions.

*CMR International data indicates that the median time for obtaining an authorisation through, for example FDA or EMEA is 400-500 days. Requiring a CPP before accepting an application can, therefore, delay the start of the review process by some two years.

Authorities requirements for CPPs

The analysis in Figure 6 shows the authorities' position on the stage at which they require a CPP to be submitted. Two countries, India and Thailand have indicated that, although CPPs are, officially, required at the time of application there can be flexibility, provided the certificate is available prior to approval. Malaysia is recorded as 'any other time' since the requirements vary between generics and new active substances but CPPs are required at the time of submission for the latter.

Figure 6

	Hong Kong	India	Indonesia	Malaysia	Philippines	Singapore	South Korea	Taiwan	Thailand
CPP to be submitted:									
At the time of application									
After application but prior to approval									
Other timing allowed									
Authentication of CPP:									
Legalisation by national Embassy required									

The issues from an Authority perspective

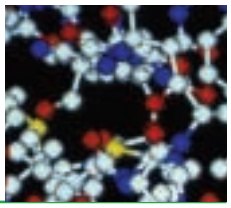
■ Timing of the CPP: The Authority may not wish to commit resources to the processing of an application before it is certain that the product has met the requirements of a major regulatory authority in another country*.

* In practice, this need not be a major concern. CMR International data indicates that over 90% of NMEs that reach the regulatory submission stage will obtain an authorisation from a major regulatory authority (e.g., FDA, EMEA, PMDA).

■ Source of the CPP: Historically, there are political concerns about the export of unauthorised products to developing countries and the regulations do not necessarily take account of current, legitimate sourcing practices among multinational companies.

■ Authentication of the CPP: A differential system would be hard to administer, thus measures that are put in place to guard against forged certificates from unscrupulous traders have to be applied equally to reputable companies.

Transparency

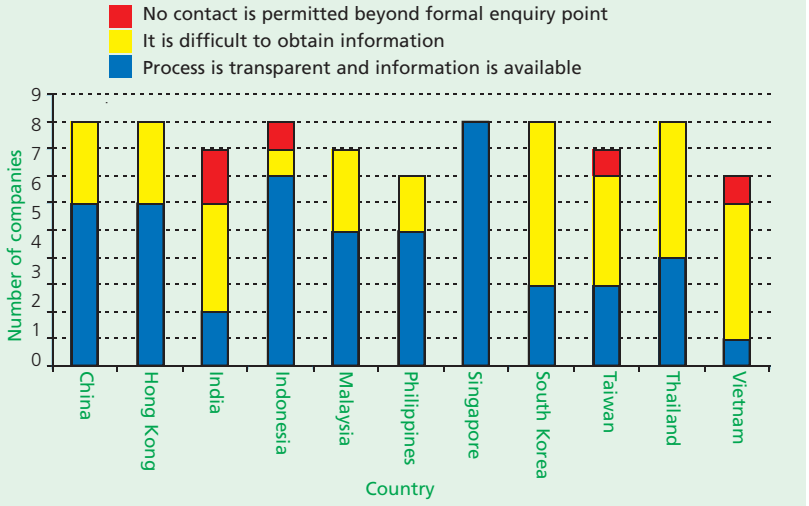


Experience from the ICH regions has shown the value and benefits of an open and transparent relationship between companies and regulatory authorities. The benefits of transparency in the regulatory environment that encourage companies to register new medicines are:

- A 'level playing field' where the rules are clear and the players are treated even-handedly
- The ability to seek and obtain information and advice before and during the review process
- Confidence that industry will be consulted and able to comment on proposals for new laws and guidelines

Figure 7

Companies' experience of feedback from, and contact with, regulatory authorities following submission



Companies' experience

Figure 7 shows the response to a question asking companies for their experience of feedback and contact with authorities following submission.

Companies appear to have a somewhat mixed experience of interactions with individual agencies. At one extreme, however, there is apparent consensus that the Singapore system is transparent with information available to applicants.

The most negative results are reported for India, South Korea, Taiwan, Thailand and Vietnam, with more than half of the companies finding that information is hard to obtain.

Harmonisation

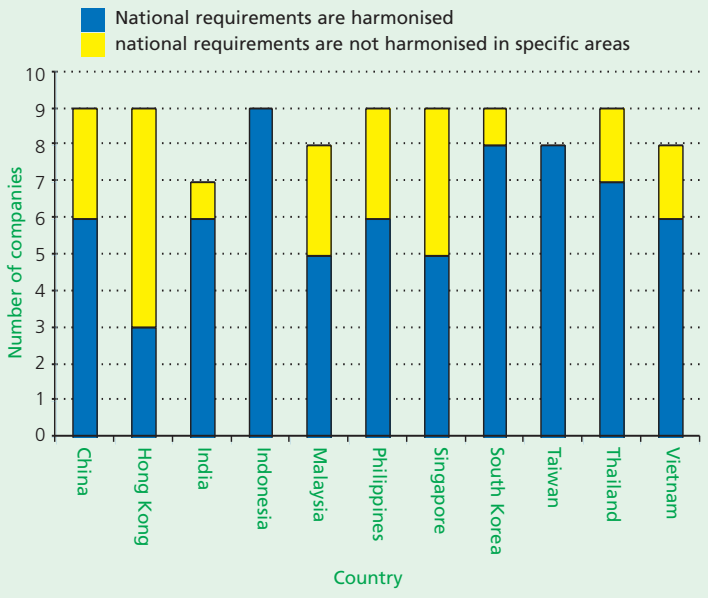
Lack of harmonisation of technical requirements for testing pharmaceutical products can lead to duplication of effort and a waste of valuable resources.

Companies were asked for their views on the extent to which national requirements, in the region, are harmonised with, or differ from, international (ICH, WHO) guidelines. The results are shown in Figure 8.

Whilst companies support the ASEAN initiatives to promote regional harmonisation this has resulted in ICH guidelines being 'adapted' rather than being 'adopted' unchanged. The divergence of technical guidelines from the international norm could lead to difficulties and delays in registering important new products in the region and act as a deterrent if companies feel that costly additional testing may be demanded.

Figure 8

Harmonisation of national requirements with international (ICH, WHO) guidelines

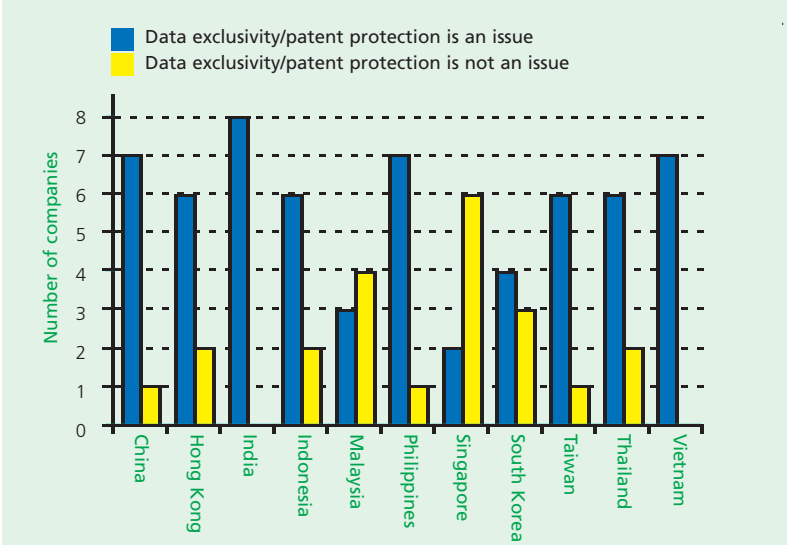


Intellectual Property

Adequate and enforceable protection of intellectual property rights is regarded as a cornerstone for current and future investment in new medicines. Deficiencies in such protection that could lead to the availability of pirated products and the disclosure of confidential data are major disincentives, for companies, to the registration of new products.

Figure 9

Companies' perception of whether data exclusivity or patent protection is an issue of concern



- All the regulatory agencies surveyed reported that data and patent protection, as outlined in the WTO TRIPS agreement had been implemented. Patent protection for pharmaceuticals in India was, however, only implemented in January 2005.
- Companies were asked for their perception of status of IP protection in the region. This was in accordance with 'official' position for most countries although 1/7 and 1/6 companies appeared to believe that there was no legal protection in, respectively, Malaysia and Vietnam.
- Whilst accepting that legal provisions are in force, the large majority of companies indicated that enforcement of the data and patent protection laws remain a major cause of concern (Figure 9). Only in Singapore and Malaysia is IP protection seen as less of an issue.

Demography of the Region

The countries of South East Asia and the Western Pacific that were included in this survey have very diverse characteristics. A snapshot is given in Figure 10 (http://www.cia.gov/cia/publications/factbook)

Figure 10

	China	Hong Kong	India	Indonesia	Malaysia	Philippines	Singapore	South Korea	Taiwan	Thailand	Vietnam
Geography											
Total area (sq. km)	9,596,960	1092	3,287,590	1,919,440	329,750	300,000	692.7	98,480	35,980	514,000	329,560
Land (sq. km)	9,326,410	1042	2,973,190	1,826,440	328,550	298,170	628.7	98,190	32,260	511,770	325,360
Population											
Est. total (millions)	1306.314	6.899	1080.264	241.974	23.953	87.857	4.426	48.423	22.94	65.444	83.536
Median age	32.26	39.4	24.66	26.48	23.92	22.27	36.76	34.51	34.14	30.88	25.51
Life expectancy at birth	72.27	81.39	64.35	69.57	72.24	69.91	81.62	75.82	77.26	71.57	70.61
Economy											
GDP US$	7.262 trillion	234.5 million	3.319 trillion	827.4 billion	229.3 billion	430.6 billion	120.9 billion	925.1 billion	576.2 billion	524.8 billion	227.2 billion
GDP per capita US$	5600	34200	3100	3500	9700	5000	27800	19200	25,300	8100	2700

Future Focus

Specific regulatory hurdles at national level can influence corporate decisions on when – and in some cases whether – to introduce new medicines into new markets, especially where market size is limited.

Companies were asked to list the areas that each of the authorities might focus on when making changes for the future. The results showed clearly that the priority is for greater collaboration between the authorities and industry. The top six highest-scoring priorities were:

- Greater collaboration between the authority and industry (all eleven countries)
- International harmonisation of regulatory requirements (8 countries)
- Intellectual property protection (7 countries)
- Performance/process improvement
- Greater cooperation with other regulatory authorities
- Development of clinical trial capabilities

The Regulatory Authorities were also asked to look towards the future and identify overall goals in terms of encouraging more local research and clinical development and forging closer links with the pharmaceutical industry. The responses are summarised below.

	Local research and clinical development	Relations with industry
India	Would like to acquire more capacity for new drug development.	Will continue to work closely with industry to provide a flexible working environment.
Indonesia	Plan to focus on local resources, such as raw material (herbal products) and formulation technology. Intends to make improvements in quality (GCP).	Wish to participate in communication and training forums with the industry which focus on regulatory topics.
Malaysia	Aim to provide regulatory direction to promote local R&D bioavailability/bioequivalence, GCP and GLP and studies related to drug utilisation. The number of Ethics Committee/ IRB for the approval of Clinical Trials are to be consolidated.	Seeking partnership with relevant stake holders towards continuous mutual understanding and cooperation.
Philippines	Encourage national companies to conduct local research.	Would welcome workshops with the industry.
Singapore	Aims to ensure that there is no gap in the regulatory infrastructure that hinders the development of clinical research. Plays an important role in the development of Singapore as a centre for biomedical sciences.	Views the pharmaceutical industry as an important partner in ensuring timely access to medicines. Holds regular dialogue sessions with industry to disseminate information and to obtain input.
South Korea	Aiming to improve the clinical trial infra-structure with plans to educate investigators, IRB members and research coordinators.	Prior to changing regulations, the authority will always discuss these changes with the companies.
Taiwan	Promote local research for medicines to treat local diseases. Aim to ensure a GCP environment for clinical development.	Wish to continue to build a transparent relationship with the industry.
Thailand	Wish to support and promote the development of local clinical research in compliance with ICH GCP and to promote Thailand as a centre of excellence in clinical trials.	Aim to enhance the capacity of the local industry to initiate and develop local research.

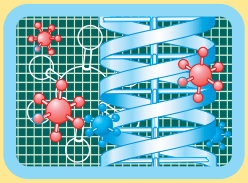
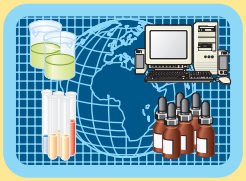
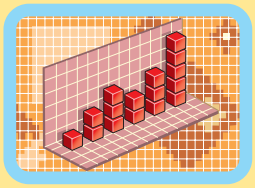
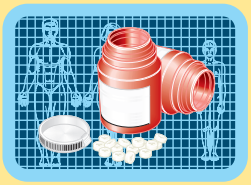
Key Questions for the future

With the aim of developing a regulatory environment that will encourage companies to include the countries of South East Asia at an earlier stage in plans for registering and making new medicines available on a global basis:

- Are there lessons about the benefits of openness and transparency that can be learned from the more communicative authorities in order to influence those that place less emphasis on good communications?
- How can industry and regulatory agencies move forward to identify 'best practice' for harmonised implementation of the WHO Certification Scheme, in order to streamline and expedite procedures for making new medicines available?
- Are regulatory authorities sufficiently aware of the importance of setting, and adhering to, reasonable targets for completing the regulatory review process? Are there similar targets and commitments for company response times when questions are raised by agencies?
- Is there a role for regulatory agencies in encouraging their governments to enforce and police, more rigorously, the laws relating to IP protection in the interests of innovation and transfer of technology?

CMR International Institute for Regulatory Science

Assessing Regulatory Policy and Performance

Regulatory science	Global drug development	Regulatory processes	Patient Access to Medicines
			

2005 Agenda

A New Model for Benefit Risk Assessment	A New Paradigm for Clinical Research	Post-Approval Commitments and Conditional Authorisations	Impact of Regulation on Access in Emerging Markets

Past and future topics

Pharmacogenetics and pharmacogenomics Risk management and benefit-risk assessment Biomarkers and surrogate end-points	Integrated parallel development for the global market Declining submission rates for new medicines Acceptance of foreign data and implementation of the ICH E5 guideline	Performance metrics for regulatory processes Good regulatory practices Critical success factors in regulatory performance	The changing regulatory environment in the emerging markets Early patient access to medicines of therapeutic significance Initiating clinical trials in non-ICH environments

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