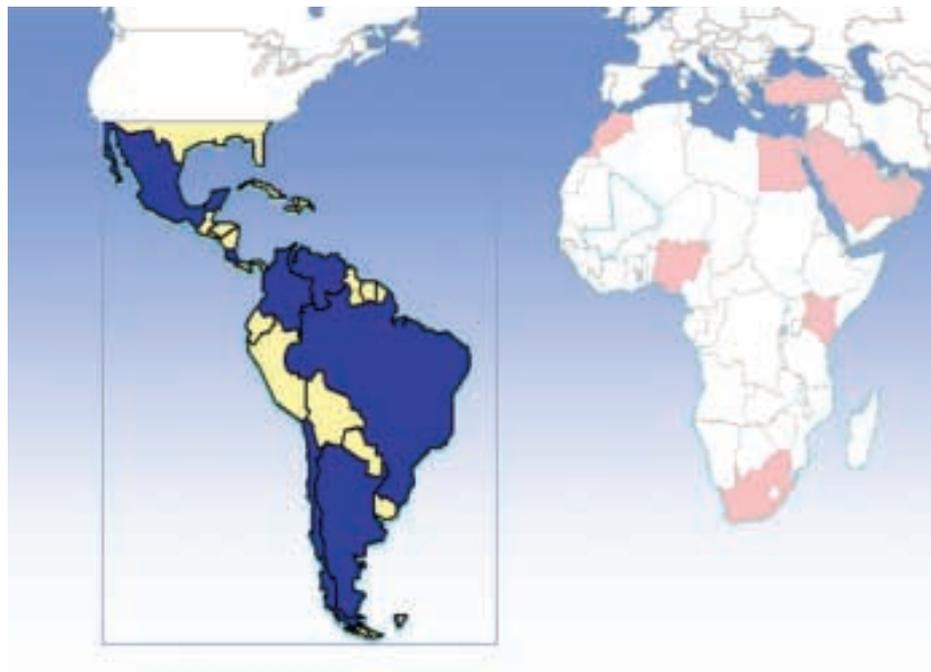


R&D Briefing

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



49

Latin America

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CMR International Institute for Regulatory Science

The CMR International Institute for Regulatory Science has been established as a not-for-profit division of the Centre for Medicines Research International Ltd, in order to continue CMR's work in the regulatory and policy arena and to maintain the well-established links that the Centre has with the pharmaceutical industry and regulatory authorities around the world.

The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts (see back cover).

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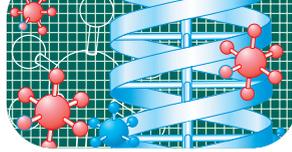
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Latin America: Assessing the regulatory environment and its impact on patients' access to new medicines

Highlights from a study among the regulatory agencies in the key emerging markets in Latin America and among the companies that operate in those countries.

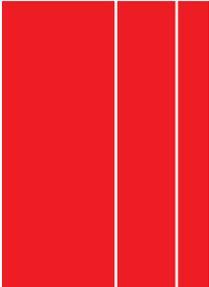
Key points



The Regulatory Agencies in Latin America 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: Whilst lack of resources is a constant cause for concern among most regulatory agencies worldwide, in the Latin American region such 'internal' factors appeared less of a concern than some of the 'external' factors that are perceived as delaying the registration process for new medicines. These include the time lag before companies submit applications for new medicines to national agencies in the region. The industry priorities for the future were focused on four areas: better communication and collaboration between authorities and the industry; improved review processes and procedures; strengthened IP protection; and greater international harmonisation.



Approval times: The regional median time for approval of a new medicine is less than six months although there are considerable differences between countries. Whilst the median is relatively low, companies have nonetheless cited review times as a major issue in the region. The longest approval times are found in Brazil, Chile and Venezuela but in two of these (Brazil and Venezuela) applications can be made at an earlier stage as a CPP (see below) need not be obtained before the application is filed.



Product certification: The requirement for submission of the Certificate of a Pharmaceutical Product (CPP) verifying the authorisation of the product by another recognised authority should facilitate and not impede the approval process, since it provides additional assurances to assist agencies in the importing country. Company data from the study, however, indicated widespread concern about the use of the CPP in the region, related to the time at which it must be submitted.

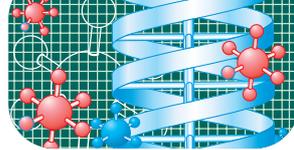
Harmonisation: Although the regulatory agencies in the region, through the Pan-American Health Organization (PAHO), are kept closely in touch with ICH harmonisation, companies have reported that national guidelines are not harmonised with international norms. In particular the ICH Common Technical Document format for applications is not accepted in the region.

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. With the exception of Argentina and Brazil, however, companies have reported concerns about the level of transparency and willingness to communicate during the review process.



IP protection: Adequate and enforceable protection of intellectual property (IP) rights is a cornerstone for current and future investment in new medicines. With the exception of Costa Rica all the countries in the survey have IP legislation, but there remains a serious lack of confidence, on the part of industry, about the effective implementation and enforcement of IP protection in the region.

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 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 Latin American Region

The seven countries that were included in the study in Latin America range from the largest country in the region, Brazil, to one of the smallest, Costa Rica. The countries were selected because of their perceived importance as 'emerging markets', whilst acknowledging the differences in pharmaceutical infrastructure between the countries. Whilst some depend mainly on imports, others (e.g., Brazil and Mexico) have a major national pharmaceutical manufacturing industry. The pharmaceutical markets of Latin America support a full range of medicines both traditional and modern, with widespread use of generics. This study, however, focused on the regulatory procedures for authorising innovative new medicines and making them available to patients. Data were collected from seven 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 Colombia.

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

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.

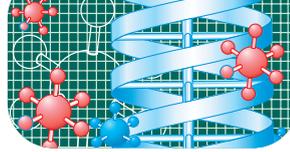
experts, acceptance of internationally harmonised guidelines for format and content of applications;

Clinical Trials

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

Policy and Perceptions

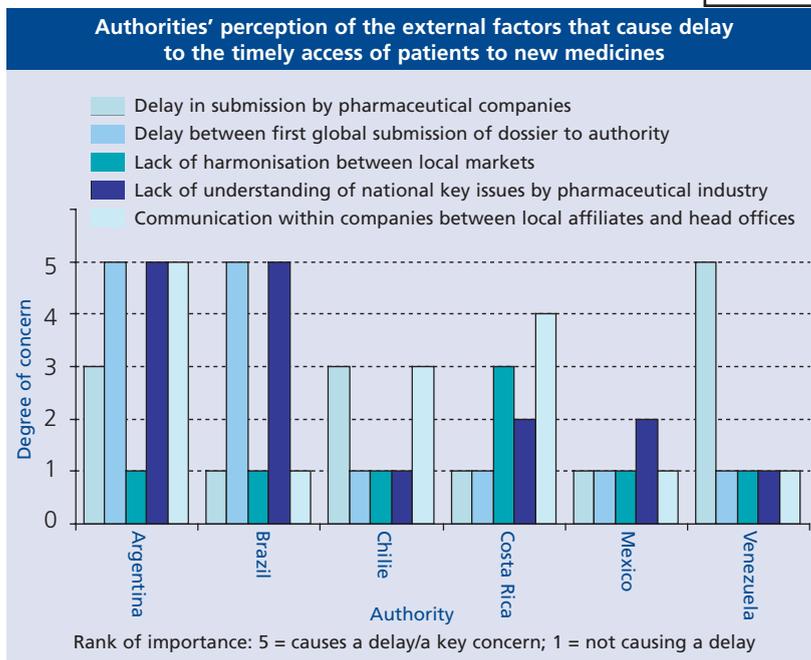
Official policies and the industry perception of policies relating to the grounds for granting and refusing authorisations, the influence of price on decisions and the extent to which intellectual property protection is implemented.



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. Whilst lack of resources is a constant cause for concern among most agencies worldwide, in the Latin American region such 'internal' factors appeared less of a concern than some of the 'external' factors that are perceived as delaying access to medicines.

Figure 1



External factors

When asked to rank the importance of external factors, in relation to the timely review and registration of new medicines, there was a divergence of views between authorities, as shown in Figure 1.

Argentina, Brazil and Venezuela, as well as Chile, to a lesser degree, showed concern about the delay before submissions were made nationally, for products submitted for registration globally. As discussed later, there are policy issues that can delay a company's decision to embark on the authorisation process. One of the regulatory factors, however, is the timing of the CPP.

Argentina and Brazil cited, as a major issue, companies' lack of understanding of national issues and Argentina, Chile and Costa Rica also felt that poor communication between companies' local affiliates and head offices was impeding the regulatory process.

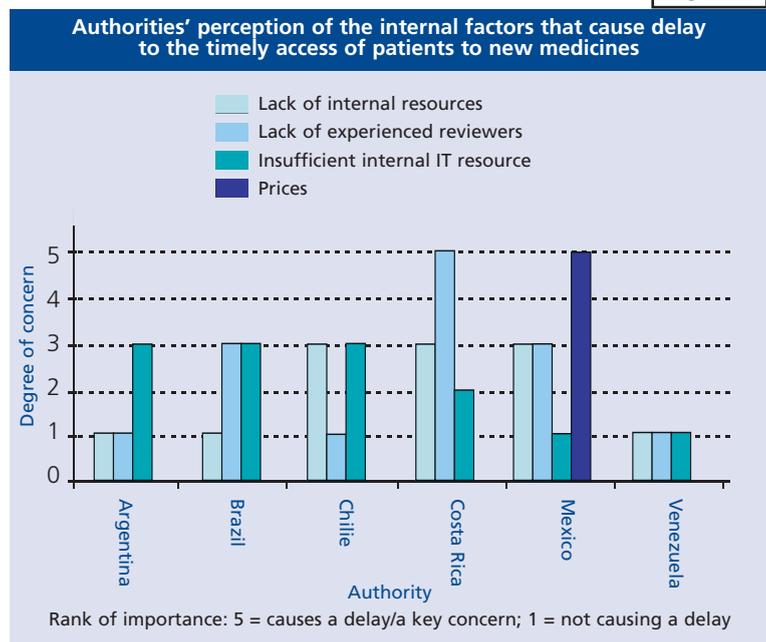
Internal factors

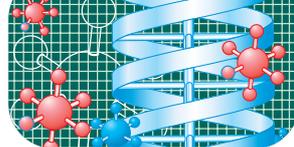
Figure 2 presents the internal factors that authorities cite as reasons that can cause delay to the regulatory process. A lack of internal resources and/or IT resources are cited as impediments to the review process in all countries except Venezuela, although none of the countries in the region saw these factors as a key concern.

Lack of experienced reviewers was highlighted as a major cause of concern in Costa Rica and, to a lesser extent, in Brazil and Mexico.

Mexico also indicated that the high price of medicines was a cause of concern although, elsewhere, the agency indicated that pricing did not form part of the regulatory process.

Figure 2



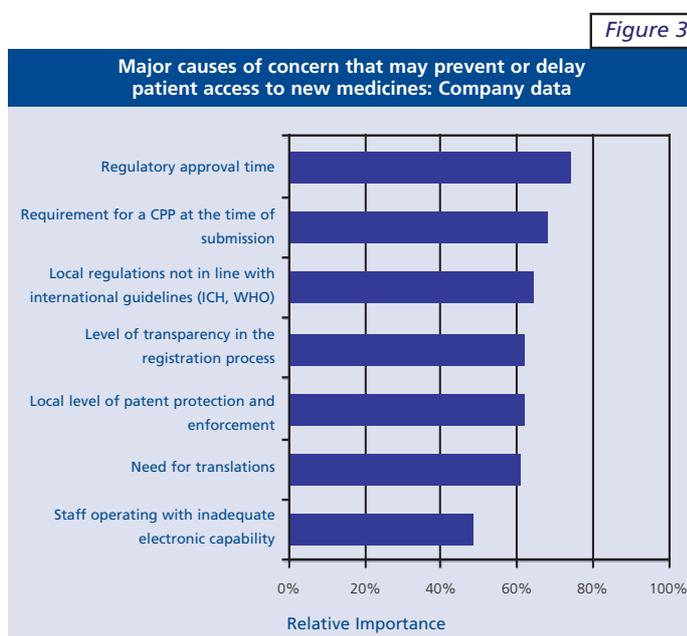


Companies' perspective



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 summarises the company response when asked to identify items of greatest concern



■ **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.

■ **Need for translations:** Requirement for major technical submissions to be translated into the local language can delay the initial filing of an application.

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.

■ **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.

■ **Inadequate electronic capability:** The ability to submit data and communicate electronically is becoming increasingly important in improving the speed and efficiency of interaction between authorities and companies. This is particularly important in relation to tracking the progress of applications and obtaining responses to questions. Companies' concerns are reflected in the responses given by the authorities in Figure 2.

Glossary Notes

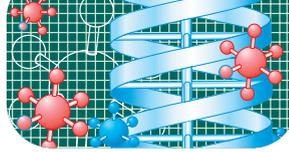
Certificate of a Pharmaceutical Product (CPP)

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.

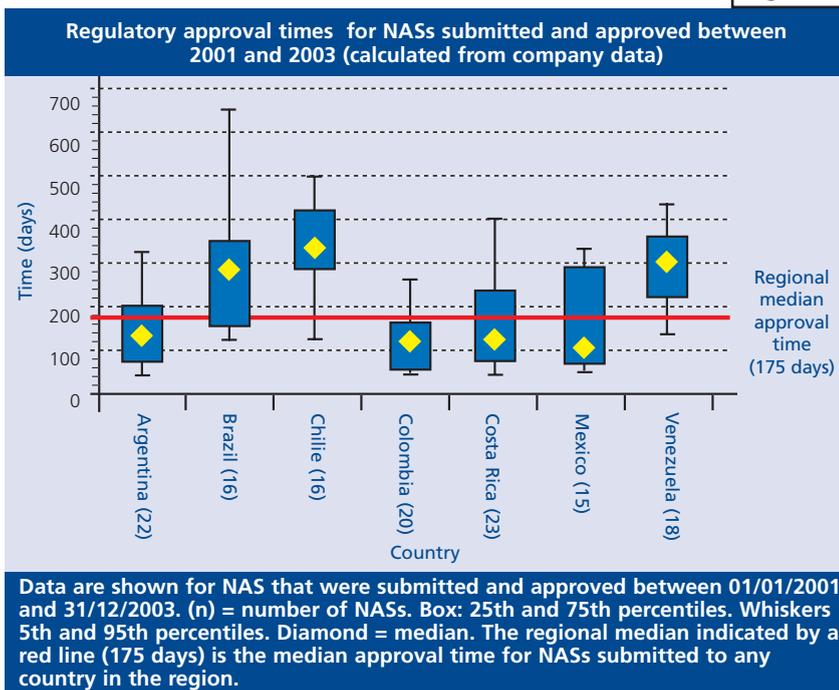
This is a three-region (EU, USA and Japan) six-party (Regulatory Authorities and industry associations) initiative that has agreed over 50 regulatory guidelines for developing new medicinal products ('ICH guidelines').



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



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.

Although companies have cited approval times as a major issue in the region, the overall median time for approval of new medicines is below six months. However, the individual median approval times vary quite considerably between countries and, in some cases, within countries.

The longest review times are found in Brazil, Chile and Venezuela but in two of these (Brazil and Venezuela) a CPP need not be obtained before the application is filed. That is, the initial filing does not have to wait until the authorisation process has been completed by another recognised authority.

In the other countries the prior need for a CPP adds an additional delay, in terms of the time at which new products become available to patients.

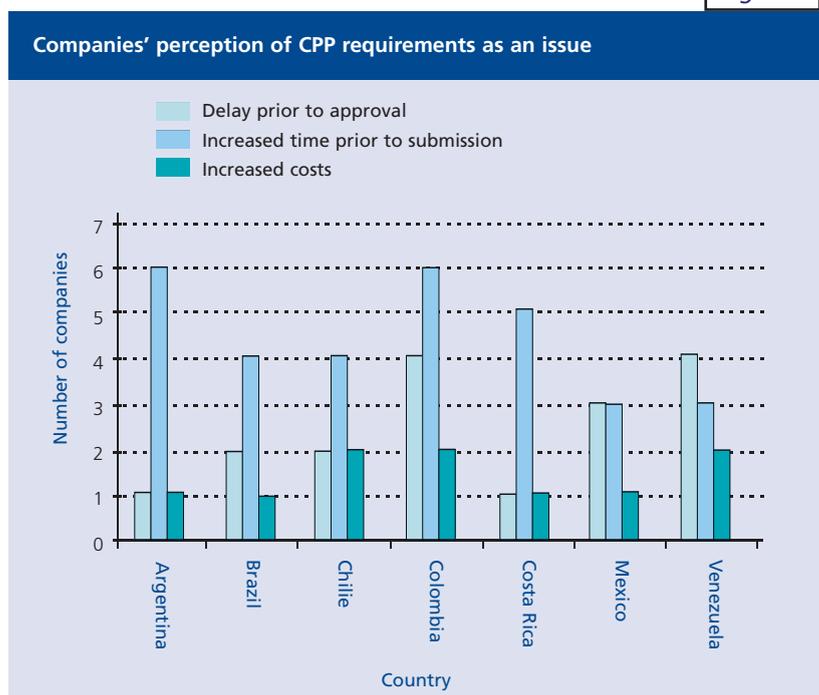
Certificate of a Pharmaceutical Product (CPP)

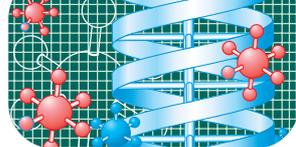
Certification that a product has been duly registered by an authority that is regarded as a 'reference' agency should be of great advantage when applying for a marketing authorisation in another country.

However, when companies were asked whether the CPP was an issue in the region they indicated clearly that it was a cause for concern for the majority of companies in all the countries except Chile.

A further question asked for more detail of the ways the certification scheme appeared to be impeding, rather than expediting the authorisation of new medicines (see Figure 5). Delays before the submission can be filed are seen as a problem across the region, especially in Argentina, Colombia and Costa Rica. It also appears to give rise to some concerns in Brazil and Venezuela although prior submission of a CPP is not a requirement in those countries (see page 6).

Figure 5





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*;
- > 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

Figure 6 shows the authorities' position on the stage at which they require a CPP to be submitted. The majority of countries have an official requirement for the CPP to be submitted at the time of filing an application, however authorities in Brazil and Venezuela state that the CPP can be submitted after the application but are required prior to approval.

All the authorities except Mexico require the CPP to be legalised through the Embassy in the country issuing the certificate. All countries except Venezuela accept a certificate from the country of origin of the product (company headquarters). Venezuela specified that it must be the exporting country.

Figure 6

	Argentina	Brazil	Chile	Costa Rica	Mexico	Venezuela
CPP to be submitted:						
At the time of application	█		█	█	█	
After application but prior to approval		█				█
Authentication of CPP:						
Legalisation by national Embassy required	█	█	█	█		█
Legalisation by regulatory authority accepted					█	

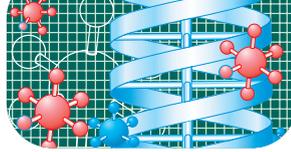
The issues from an Authority perspective

■ **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*.

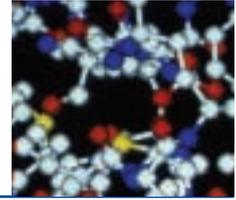
* In practice, this need not be a major concern. CMR International data indicates that over 90% of NMEs that reach the regulatory submission stage will obtain an authorisation from a major regulatory authority (e.g., FDA, EMEA, PMDA).

■ **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.



Harmonisation

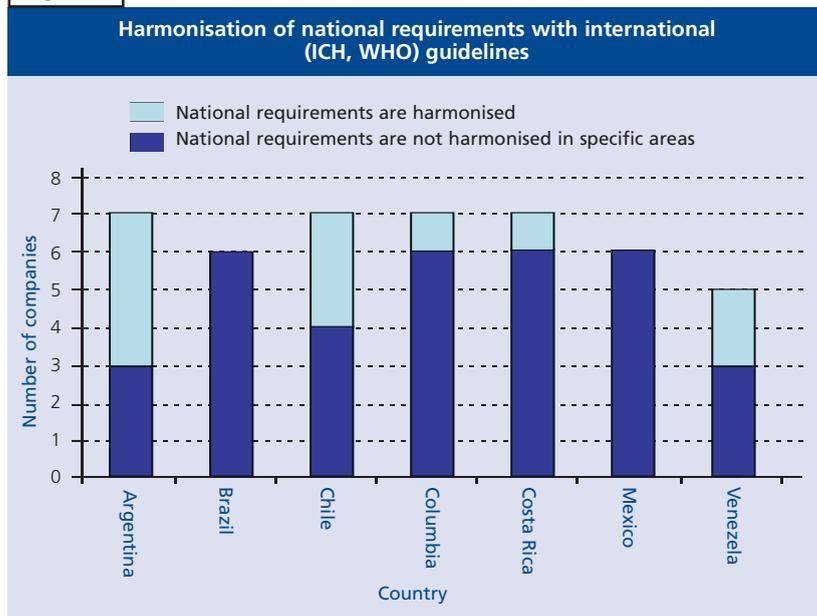


Lack of harmonisation of technical requirements for testing pharmaceutical products can lead to duplication of effort and a waste of valuable resources. This may act as a deterrent to the registration of new medicines if companies feel that costly additional testing may be demanded.

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 7, indicating that industry has concerns about harmonisation, across the region.

All the agencies in the survey participate in the pharmaceutical programmes of the Pan-American Health Organization/WHO Regional Office for the Americas (PAHO/AMRO), which includes the Pan American Network for Drug Regulatory Harmonization (PANDRA). Although the authorities are represented on the ICH Global Cooperation Group (GCG), only Argentina officially accepts use of the ICH Common Technical Document (CTD) format for NAS applications. A few companies have, however, reported that they have used the format in Chile, Colombia, Costa Rica and Venezuela.

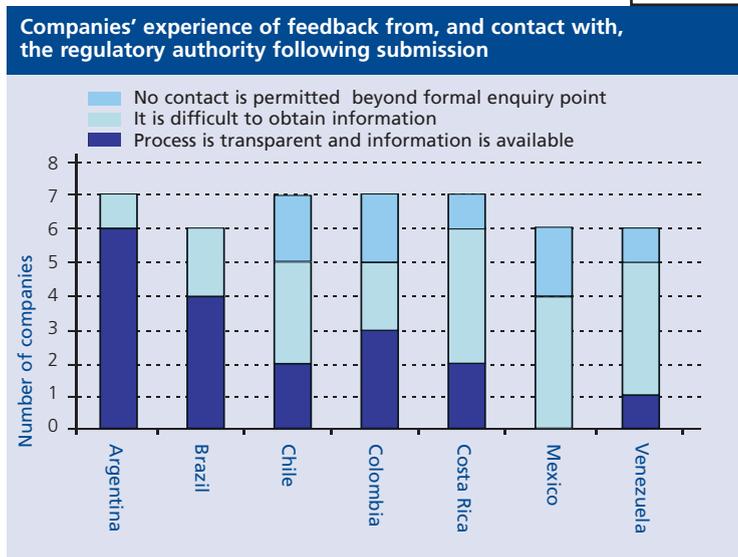
Figure 7



Transparency

Experience from the ICH regions has shown the value and benefits of an open and transparent relationship between companies and regulatory authorities.

Figure 8



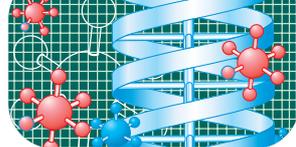
The benefits of transparency in the regulatory environment that encourage companies to register new medicines are:

- 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.

Companies' experience

Figure 8 shows the response to a question asking companies for their experience of feedback and contact with authorities following submission.

With the exception of Argentina and Brazil, the regional picture suggests that companies, in their interaction with the agencies, have experienced a lack of transparency and willingness to communicate during the review process. The most negative results are reported for Venezuela and Mexico.

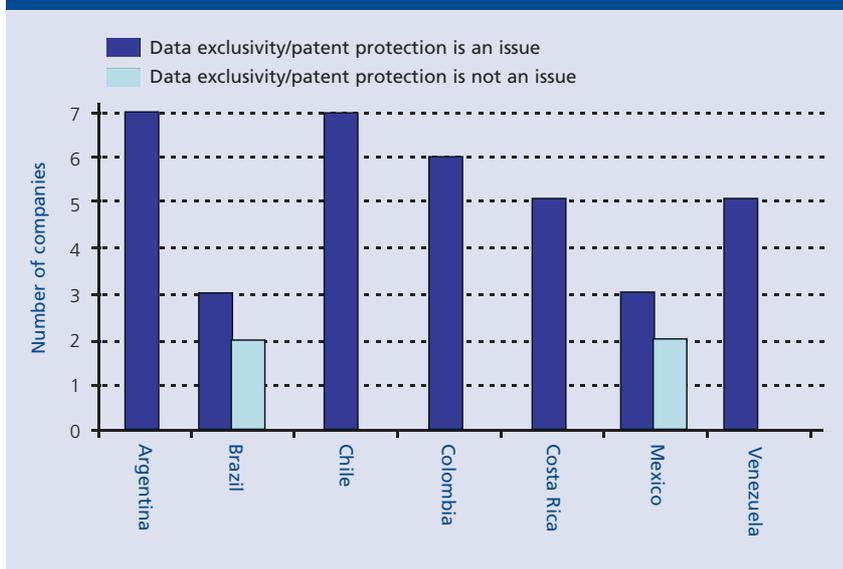


Intellectual Property

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



The authorities in Argentina, Brazil, Chile and Venezuela reported that data and patent protection, as outlined in the WTO TRIPS agreement had been implemented. The Mexican authority indicated that they have data and patent protection to meet local requirements. There is no patent protection for pharmaceuticals in Costa Rica, however new guidelines are scheduled for 2005.

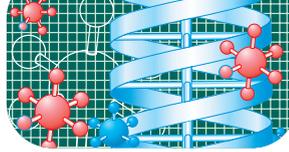
Whilst acknowledging that legal provisions are in force in most countries in the survey, the majority of companies still regard the enforcement of data and patent protection as a major cause of concern in the region (Figure 9). The only exceptions were two companies in Brazil and in Mexico that did not regard IP protection as a problem in the local market.

Demography of the Region

The countries in this study make up a significant part of the Central and Southern America. Although there are common cultural characteristics, they have very diverse demographic characteristics, as illustrated in the 'snapshot' in figure 10. (<http://www.cia.gov/cia/publications/factbook>)

Figure 10

	Argentina	Brazil	Chile	Colombia	Costa Rica	Mexico	Venezuela
Geography							
Total area (sq. km)	2,766,890	8,511,965	756,950	1,138,910	51,100	1,972,550	912,050
Land boundaries (km)	9665	14691	6171	6004	639	4353	4993
Coast line (km)	4989	7491	6435	3208	1290	9330	2800
Population							
Est. total (millions)	39,537,943	186,112,794	15,980,912	42,954,279	4,016,173	106,202,903	25,375,281
Median age	29.42	27.81	30.07	26.04	26.03	24.93	25.6
Life expectancy at birth	75.91	71.69	76.58	71.72	76.84	75.19	74.31
Economy							
GDP US \$ billion	483.5	1492	169.1	281.1	37.97	1006	145.2
GDP per capita US\$	12400	8100	10700	6600	9600	9600	5800



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. There was no single item that emerged a company priority in all countries but the common ‘theme’ for the region is that industry would like to see future improvements in:

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

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. Not all authorities responded but the replies received are summarised below.

Authority	Future Priorities
Argentina	Encouraging local research and local clinical development are a high priority and the agency is working towards close links with the pharmaceutical industry.
Brazil	The authority would like to encourage local clinical development and work towards closer links with the pharmaceutical industry. In order to ensure quality, agency staff will be required to take a federal examination.
Chile	The authority would like to promote local research and local clinical development. The IT infrastructure is being upgraded with the objective to make the process more dynamic and transparent.
Mexico	The authority is also planning to make major changes to the regulations including those involving R&D and pricing. Priorities also include facilitating local clinical trials and encouraging local research.

Key Questions for the future

What steps can be taken at country and regional level to engage both regulators and industry in meaningful discussions on medium- to long-term improvements in regulatory procedures, with the aim of developing a regulatory environment that will encourage companies to include the countries of Latin America at an earlier stage in plans for registering and making new medicines available on a global basis?

■ Are companies justified in criticising review times in the region? Better information on agency’s target times, the extent to which these are met and the time taken by companies to respond to questions might help provide a more balanced picture.

■ Are there opportunities for authorities in the region to discuss, with industry, any scientific concerns about the implementation of ICH guidelines in order to ensure that divergences do not impede the timely registration of NASs developed for the global market?

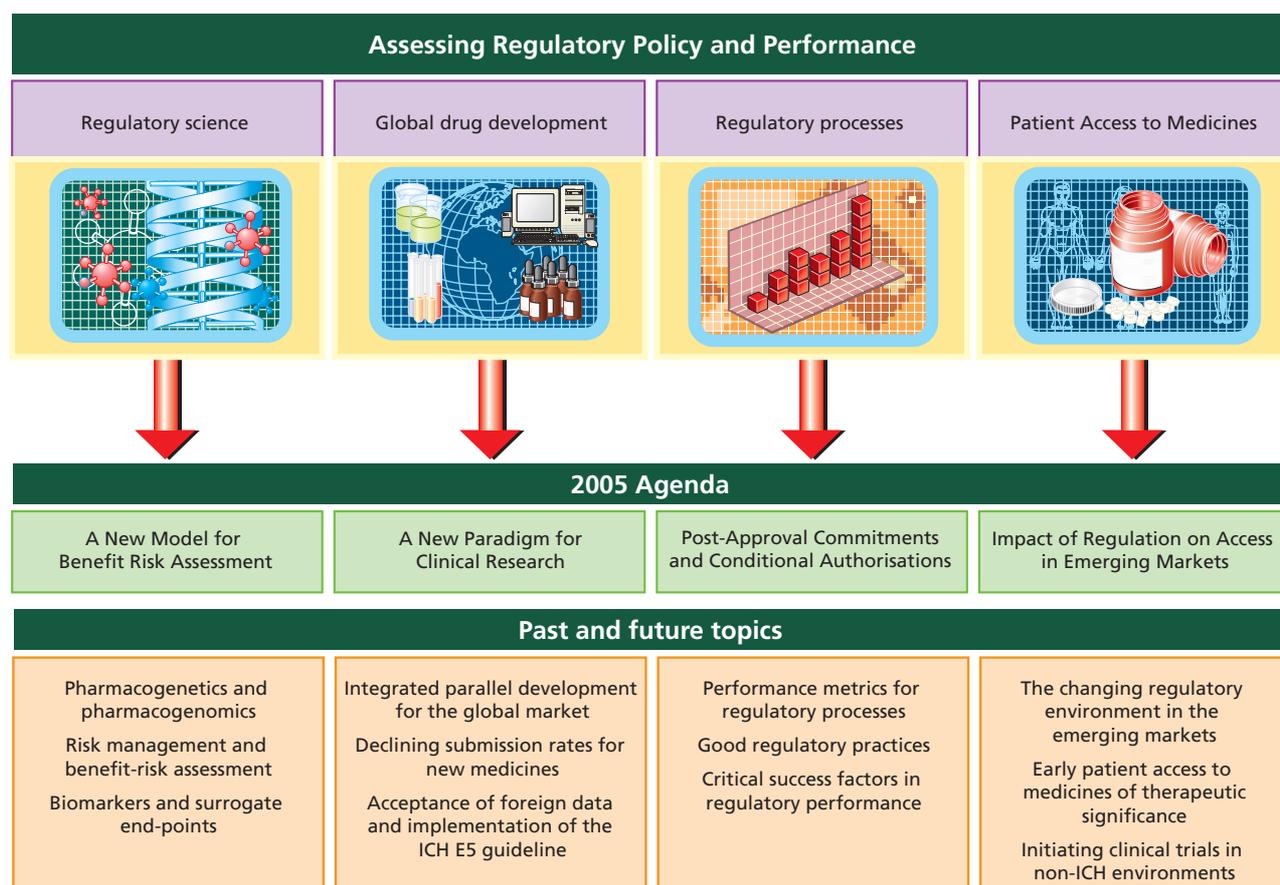
■ Is there an appropriate platform for discussions between industry and regulators, in the Latin American region, to ensure that there is awareness of issues and concerns that have been identified in this study?

■ 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 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? Where communications are poor, is this a question of policy or are efforts impeded by a lack of resources and/or poor IT infrastructure?

■ Is there a role for regulatory agencies in encouraging their governments to enforce and police, more rigorously, the laws relating to IP protection?

CMR International Institute for Regulatory Science



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