

LATIN AMERICA UPDATE: KEY ISSUES IN THE REGISTRATION OF PHARMACEUTICALS

Key messages

- 50% of respondent pharmaceutical companies conduct pivotal clinical trials in Latin America, thus involving the region in their global development plans
- Few companies are currently achieving their goal of simultaneous submission to major Latin American markets; the climate is not conducive to simultaneous submission and it is clear that harmonisation within the region has yet to be achieved
- Approval rates have remained relatively fast; despite this, the length of regulatory review times is commonly perceived by industry as a barrier to registration in Latin America
- A Certificate of Pharmaceutical Product (CPP) is required in most markets at submission and is usually legalised; the timing and legalisation of CPPs are two important barriers to registration for the pharmaceutical industry

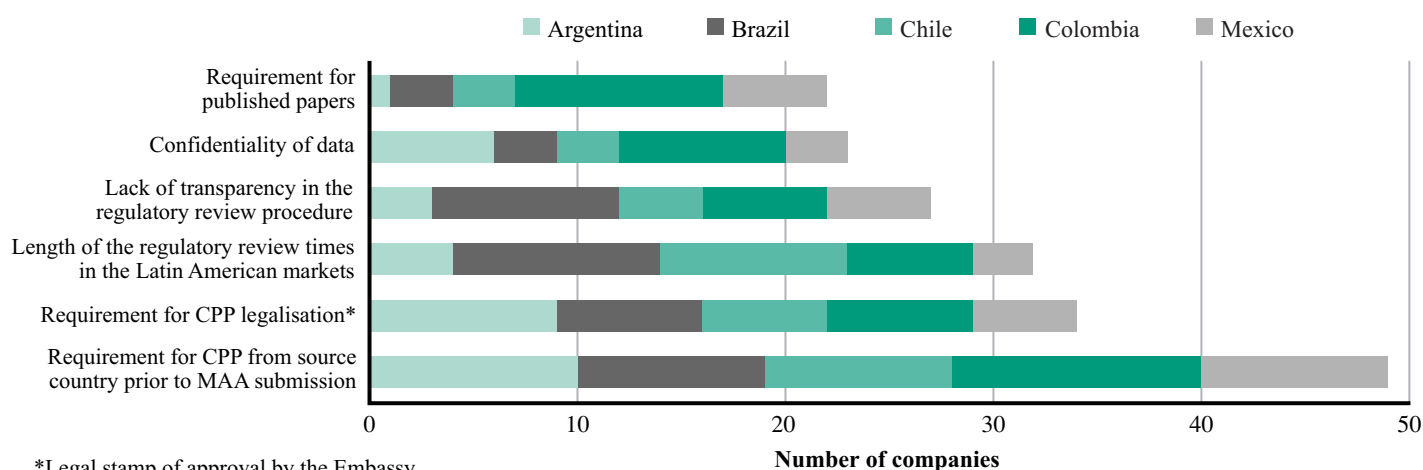
Perspective

Continued economic growth has ensured that Latin America remains attractive to the pharmaceutical industry. But for companies, there are hurdles that must be overcome before a new medicine achieves marketing approval. A CMR International survey in 1998 investigated the factors inhibiting successful and timely registration of new medicines in the region, and explored company strategies for development and registration.¹

The survey has been repeated in order to provide an update of the key issues currently affecting the registration of new active substances (NASs) in Latin America. The regulatory environment in this region has changed in recent years, and such change has the potential to affect the industry's ability to bring medicines to market in a timely manner.

Five of the major Latin American markets were investigated in the present survey - Argentina, Brazil, Chile, Colombia and Mexico. This R&D briefing contains aggregated results from 22 of the 46 international pharmaceutical companies invited to participate.

Figure 1 Major barriers to registration in Latin America



Participants were asked to identify which of a list of factors caused them major problems when registering new medicines in Latin American markets. This figure shows the six most commonly identified issues. The total number of companies responding to each question is greater than the number of respondents (n = 22) because each barrier could be identified for more than one country. Thus, the maximum response would be 110 companies. Overall, less than 50% of companies identified each barrier.

Barriers to registration

The main barrier to registration in Latin American markets is the requirement for a Certificate of Pharmaceutical Product (CPP) from the source country prior to submission of a Marketing Authorisation Application (MAA, Figure 1). This barrier was identified by between 41% and 55% of companies for each market. Other identified barriers are similar to those of the previous survey, however the necessity to legalise CPPs and the length of regulatory review times have been identified as additional issues of concern in the present study.

CPP requirement

The practice of requiring a CPP is often a necessary prerequisite to the approval of medicines in certain markets as it guarantees that the product has undergone a thorough review in one of the more experienced agencies. In fact, almost all companies will have already submitted MAAs to the EU, and approximately two-thirds to the US, prior to submitting to Latin American markets.

CPPs are generally supplied by companies at the time of MAA submission (Figure 2), although in some cases CPP provision was delayed until just prior to product marketing approval. Some companies indicated that CPPs were not required in some countries, but these cases were rare. Such a situation could arise if the product was manufactured locally.

Companies, agencies and patients must therefore usually await approval of the medicine in the source country before the approval process can begin in Latin America. Encouragingly, the regulations in Brazil have recently changed allowing companies to delay the provision of CPPs until prior to approval. This measure should speed up patient

access to new medicines in Brazil, and may encourage companies to submit to Brazil alongside ICH regions.

CPP legalisation

An additional step in the production of a CPP is its legalisation, a process deemed unnecessary by the World Health Organization.² CPP legalisation causes additional delays to marketing approval, and hence to patient access to new medicines.

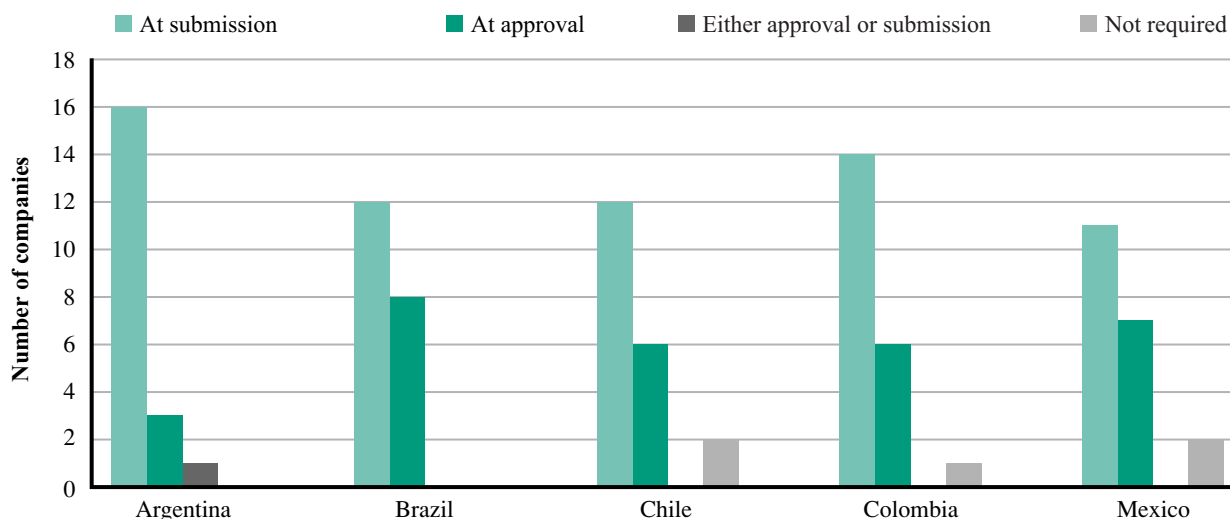
At least 80% of companies generally had their CPPs legalised prior to presenting them to Latin American agencies, an action which emerged as the second major barrier to registration in Latin America (Figure 1). Recent regulatory changes in Mexico should enable CPPs to be provided without legalisation. However, this has not affected the results of the present survey since 18 of 22 companies (82%) have generally ensured that their CPPs are legalised for submissions to Mexico.

Regulatory approval times

The third most common barrier is the length of regulatory approval times in Latin American markets (Figure 1). The regulatory review is perceived to be particularly slow in Brazil and Chile, this being the principal barrier to registration in both countries.

Approval times for individual compounds were not collected in the present survey, however the approval rates in all markets have remained reasonably high. More than 70% of NASs submitted to Latin American markets since 1998 have been approved, with Chile having the lowest and Argentina the highest rates of approval (74% and 88%, respectively). These rates are comparable to those of the previous survey.

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

Despite these barriers to registration, results suggest that companies are putting more effort into achieving approval of their NASs in Latin America. In recent years, an average of 34% of NASs have been submitted to Latin American markets within 12 months of the first submission to an ICH market. The number of these submissions, although small, is greater than that in the previous survey and may signal an intent by the pharmaceutical industry to synchronise regulatory submissions.

Consistent with the move towards higher rates of simultaneous global submissions, most respondents indicated that their ideal submission strategy is simultaneous submission to all major Latin American markets (Figure 3). Disappointingly, fewer companies are actually achieving this ideal than in the previous survey. Instead, the number of companies submitting on a case-by-case basis or on a country-by-country basis has increased. These results indicate that despite the widespread industry support for simultaneous submissions and harmonisation within the region, the harmonisation process still has hurdles to overcome. Some Latin American harmonisation initiatives are shown in Table 1.

Table 1 *Harmonisation initiatives in Latin America*

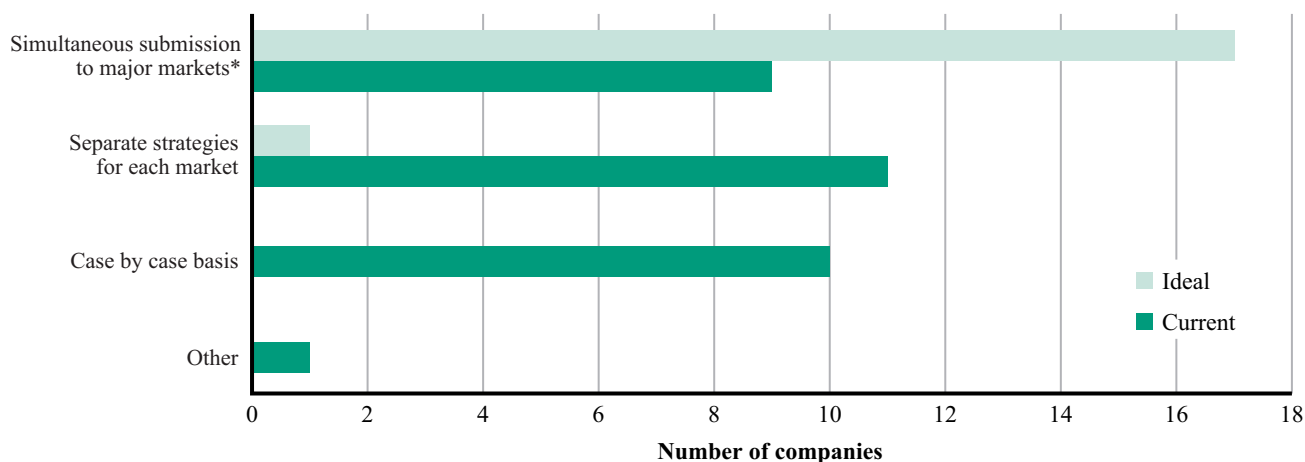
Andean Pact	Trading bloc involving Bolivia, Colombia, Ecuador, Peru and Venezuela
Mercosur	Trading bloc involving Argentina, Brazil, Paraguay, Uruguay and associate members Bolivia and Chile
North American Free Trade Agreement (NAFTA)	Trading bloc involving Canada, Mexico and the USA
Pan American Health Organization (PAHO)	PAHO is the Americas arm of the World Health Organization

Clinical development

Clinical development is commonly conducted in Latin American markets and, for 50% of respondents, trials in Latin America provided pivotal evidence in support of global clinical development plans. This reflects the quality of clinical research conducted in the region. Pivotal trials were particularly common in what are considered to be the major markets of Latin America - Argentina, Brazil and Mexico.

Other reasons for conducting trials in these markets are to provide local experience of the compound and because of local expertise in the clinical area (Figure 4). Clinical trials are not a prerequisite for registration in any of the five markets studied. At the time of the previous survey, however, completion of a local trial was a regulatory requirement in Mexico.

Figure 3 *Submission strategies in Latin America*



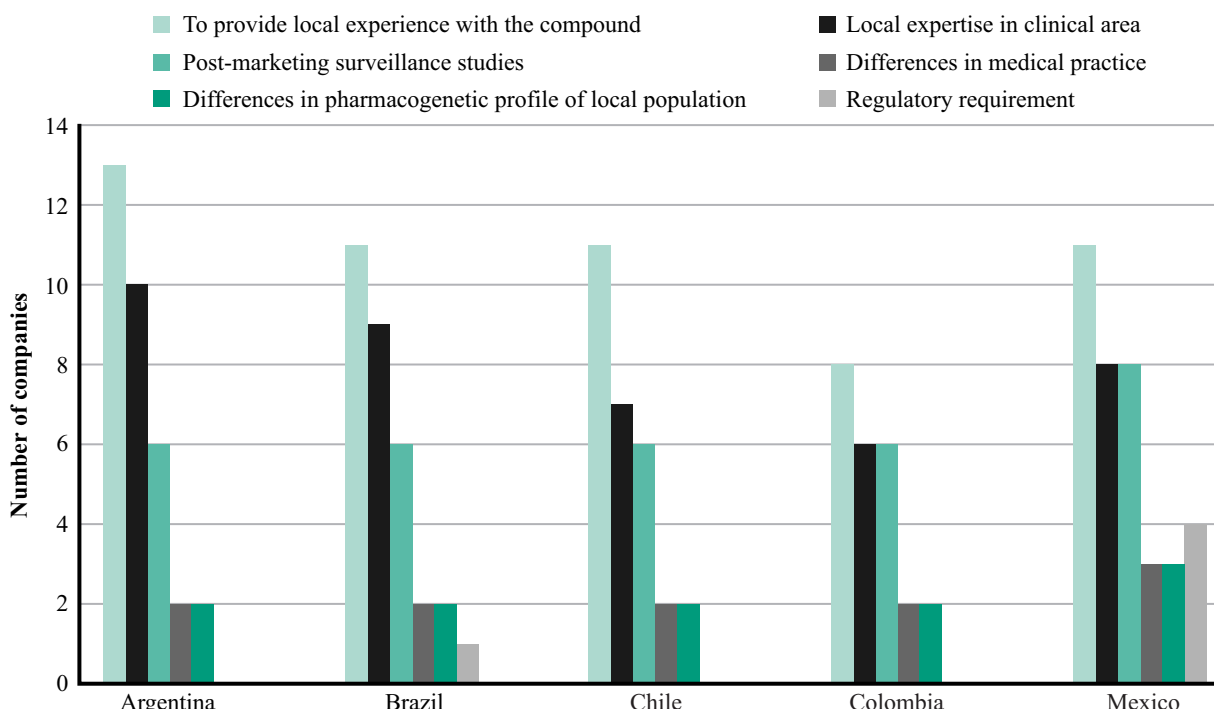
*Major markets in Latin America: Argentina, Brazil, Mexico.

Companies were asked to identify their ideal submission strategy for the markets of Latin America, and also their current submission strategy. Currently, the most popular strategy is a separate strategy for each market. Some companies identified more than one current strategy.

In the future, it is anticipated that the requirement for a CPP from the source country prior to MAA submission will become less of a barrier. In Argentina, for instance, CPPs do not need to be supplied by the source country but can be issued by a range of countries in which the medicine has been approved. Also, legislation in Brazil has recently changed to allow companies to delay providing their CPP until prior to approval. Such moves should further encourage companies to submit dossiers simultaneously to Latin America and the ICH regions. Ultimately, it is hoped that this will benefit healthcare in Latin America by improving patient access to new, important medicines.

- Regulatory agencies can improve patient access to new medicines by lessening restrictions on the timing of CPP provision and the need to legalise CPPs
- Harmonisation efforts should be strengthened within Latin America, and between Latin America and the rest of the world

Figure 4 Reasons for conducting trials in local markets



Companies most commonly conduct trials in Latin American markets to provide local experience of the compound, because of local expertise in the clinical area and to conduct post marketing surveillance studies. Companies were able to select more than one reason for conducting trials in each market.



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References

1. Thomas, KE, McAuslane, JAN (1999) The Registration of Pharmaceuticals in Emerging Markets. Submission strategies and issues of concern. CMR99-108R.
2. World Health Organization. Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce. Available at: <http://www.who.int/medicines/teams/qsm/certifguide.htm> (accessed April 2001).

Copies of R&D Briefings, including the previous R&D Briefing concerning registration in Latin America, can be found at <http://www.cmr.org>

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