

Strategies for Implementing Trials in Latin America



Dr Jorge Fiuza of Pharm-Olam examines the increasingly important role played by Latin America in clinical research for international drug development

Dr Jorge Fiuza is Director of Latin American Operations at Pharm-Olam International. He is a qualified Urologist and has over 15 years of experience managing clinical trials throughout the region, including regulatory expertise, clinical operations, project management across the countries in Latin American region. Before joining Pharm-Olam International, Jorge served with four multinational pharmaceutical companies, two SMOs, and two global CRO, all in Latin America. His experience includes the management of over 30 trials across 10 therapeutic areas.

While regulatory procedures and incidence rates vary across the world, all sponsors share the same standards for the conduct of clinical research – incorporating global patient needs, regulatory requirements, data quality, monitoring, safety reporting and audit standards. Sponsors will have the greatest success in Latin America if cultural and geographical differences are taken into consideration when development planning begins.

GEOGRAPHIC OVERVIEW

Latin America spans across two hemispheres and consists of over 20 nations. It has a population of over 560 million, yet only two official languages are spoken there. Spanish is the official language for all Latin American countries except for Brazil, whose official language is Portuguese. This allows sponsors significant translation cost and time saving advantages compared to running multinational studies with comparable populations such as Europe. While most investigators are able to speak English, all regulatory documents must be in the native language.

It is estimated that 77 per cent of the total Latin American population are concentrated in urban areas. The four largest metro areas in Latin America – Mexico City, São Paulo, Buenos Aires and Rio de Janeiro – have a combined population of over 58 million people (1). These population densities can offer sponsors great advantages for patient recruitment and trial logistics because fewer sites are necessary to achieve target patient populations.

Again, being geographically located in two hemispheres, Latin America experiences seasonal diseases occurring at different times of the year. Thus, it is crucial to plan for the enrolment period to include the winter in both hemispheres when conducting a seasonal study, such as community acquired pneumonia (CAP) to maintain year round enrolment. Another consequence of this climatic

difference is that enrolment rates remain almost stable during the entire year.

GROWTH OF DRUG SALES DRIVE CLINICAL TRIALS

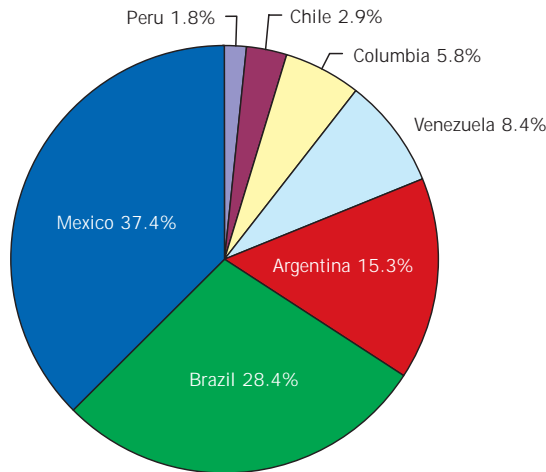
The Latin American pharmaceutical market has experienced continued growth. This serves as another incentive for companies to conduct trials there as drug approvals are often easier to obtain where local studies have been conducted. In 2005, the generic sector in Latin America was valued at \$1.7 billion, which represented a 26.9 per cent increase on the 2004 figure of \$1.3 billion (2).

The rapid growth of the pharmaceutical market in Latin America is likely to continue due to estimates in population growth. This in turn supports the growth of clinical trials in the region, which still has tremendous untapped potential and capacity for trials. Latin American clinical trial growth occurs not only because of its reputation for high recruitment of treatment-naive patients, but also due to increased recognition of the region's contribution to scientific research. In 2003, Latin American references in the Science Citation Index included 35

Table 1 – World population growth estimate (2004 UN report)

Area	2005	2015	10 year growth rate
Europe	728.4 million	721.1 million	-1%
Latin America	561.3 million	634.1 million	11.4%
North America	330.6 million	360.9 million	8.4%

Figure 1: Latin America pharmaceutical market



Source: IMS Global, 2005

out of 299 citations, and in MEDLINE 12 out of 359 citations. These represent a 14 per cent and 30 per cent increase respectively compared to the numbers in 1999. Of all Latin American citations, 80 per cent refer to Brazil, Argentina and Mexico (3).

REGULATORY AFFAIRS PLANNING

Timelines are of vital importance for the development of a new drug. Too often, Latin American nations are considered for involvement at the last moment when planning a trial. Regulatory approval processes typically average from 10 to 14 weeks longer than those governing trials in North America, but this is no longer than some European countries. The average timeline for approvals in Latin America is four to five months from the time the final protocol is translated into Spanish and/or Portuguese and available for submission.

Early planning should include a strategy for site selection that balances each country’s regulatory approval time, patient recruitment potential and site capabilities. The planning process must include a review of the most current regulatory procedures, drug importation and other issues, to ensure that expectations are appropriately set before the trials begin. Local knowledge of each country’s regulations and close communications with the respective regulatory agencies are essential.

Because these timeline differences are often not considered during development planning, including Latin America as part of a global study may not be feasible. This can leave sponsors with an incorrect impression regarding Latin American trial capabilities because they do not have an opportunity to take advantage of the rapid rates of patient

recruitment and higher patient retention that offset longer regulatory approval. According to a recent survey, only 41 per cent of clinical trials conducted at Latin American sites have more than a one month delay in enrollment, compared with 55 per cent at European sites and 70 per cent at US sites (4).

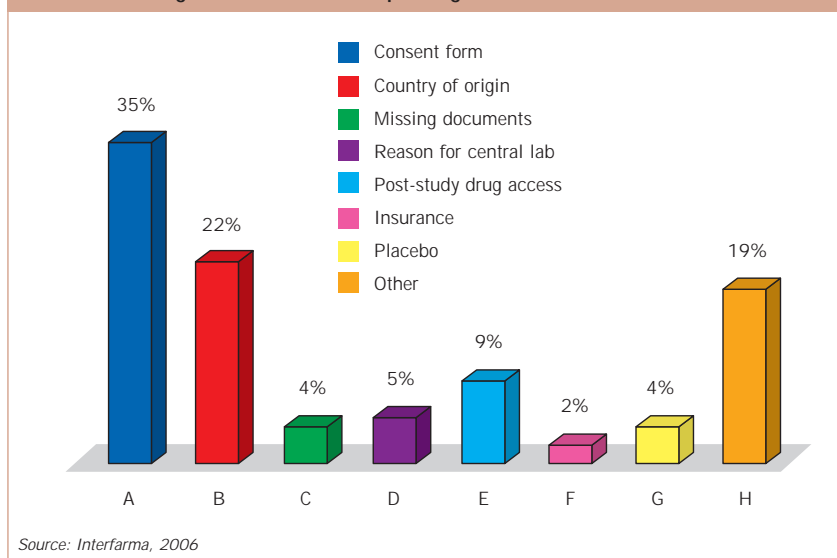
Most countries have strict import regulations for drug supplies and the export of biological materials such as subject samples. A partner with expertise in local customs regulations to aid in the review of import documents ahead of study supply shipments, as well as the capability to facilitate the local distribution can save considerable time and help avoid customs delays. Sponsors should keep in mind that while trials in Latin America have lower treatment and patient recruitment costs, these nations typically have significantly higher importing/exporting fees.

INFORMED CONSENT FORM AND ETHICS APPROVAL

One very important cultural difference between studies in the US and Latin America are issues regarding the informed consent form (ICF). The most common reason for regulatory delays in clinical trials is due to problems with the ICF, which can be avoided with proper preparation. Many sponsors overestimate the education level of the population, and regulatory authorities will often reject translations of approved ICF forms originating from better educated populations, such as the US. The level of information that most sponsors require from their ICF needs to be readdressed, especially for trials that involve complex procedures such as an MRI, which can confuse the patient’s decision.

For example, in Mexico while they follow informed consent procedures that are recommended by international pharmaceutical companies and that have FDA approval, most Mexican health institutions usually request that subjects sign a second consent form, written in simple language and requiring

Figure 2: Most common pending issues from Brazil MoH



Source: Interfarma, 2006

Examples of Latin American Therapeutic Needs

Understanding the incidence and prevalence of the therapeutic needs in Latin America allows for more accurate estimates of the number of sites and countries that will be involved in a specific clinical trial.

Diabetes: The prevalence of diabetes in Mexico (8.1) exceeds even that of the US (7.6) (King, Aubert and Herman, 1998).

Cervical Cancer: The estimated age-adjusted incidence rate for cervical cancer in North America was 7.7 compared to 30.6 in Central America and 28.6 in South America (per 100,000 women) (Ferlay et al, GLOBOCAN, 2002).

Osteoporosis: In Mexico women aged 50 years or older have a 19.5 per cent prevalence of osteoporosis, those over 80 have a 40 per cent rate (LAVOS study, 2006).

the signatures of two additional witnesses. In paediatric trials, the parents or guardians must sign the form and, when age permits, adolescents sign an acceptance form.

Ethics committees also have concerns about the capacity of potential subjects to understand complex concepts such as randomisation; and there are cultural issues of a doctor who does not know, resulting in unknown risks and blinded study groups, for example (5). In addition to the standard risk : benefit assessment, Latin American ethics committees focus on beneficence for the patients and carefully evaluate the healthcare context and social situation of the potential subjects (6). The use of placebo, payment for participation, consent process and the expectation of post-study treatment may be required to achieve ethics approval.

CULTURAL ISSUES

In Latin America, each country has a unique culture despite their close geographic proximity, and awareness of those differences will allow sponsors greater success. For example, while most principal investigators can speak English, the ability of a sponsor's representatives to communicate in Spanish (or Portuguese) is helpful in establishing positive communication and respect within native populations.

Religious issues can also affect enrolment in Latin America, where nations are predominantly Catholic. For example, trials that require a complete sexual history from women may be rejected by the site if it is in conflict with their ethics, whether religious or secular. The sponsor may consider selecting a different country or modifying the protocol.

DOCTOR-PATIENT RELATIONSHIP

One study estimates that in the US, 66 per cent of subjects enrol independently of their doctors. In Latin America 80 per cent of subjects are offered enrolment by their doctors. This difference is important when preparing recruitment plans and materials (7).

Patients in public institutions are generally deemed incapable of making a rational medical decision, therefore doctors are often extremely protective. The social susceptibility of their patients predisposes them to provide healthcare in a controlling and paternalistic way (8). They presume the right to decide what is best for patients and feel committed to making every possible effort to obtain resources for their treatment, but they must conform to a less than optimal standard.

Public institutions often participate in clinical research to provide access to treatment which is otherwise unavailable to disadvantaged patients. Doctors expect treatment for their patients as a compensation for their participation, and will encourage them to participate provided that the study provides some benefit. Therefore, investigators often reject placebo controlled studies because available treatment is regarded as a better choice (8). ♦

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