Clinical Research and Drug Development in Latin America: Weighing the Pros and Cons, Talking about the Future

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Two decades ago, clinical trials were carried out only in developed countries. Drug development and the need to speed up clinical trials lead the conduction of clinical trials to other countries. Among the regions of interest, Latin America (LA) has played its role successfully. LA has a large number of naive patients, qualified investigators, established regulatory systems and reasonable costs. Furthermore, LA might be also considered as a new option for any company looking for international patterns on drug research and development. The region has good professionals with scientific qualifications, well-established multinational pharmaceutical bases and an expansive pharmaceutical regional market. This work summarizes the recent advances that have occurred in drug research and development in the region and the expansion of the clinical trial market in the last couple of years.

Key words: clinical trial, drug, Latin America, research and development

One of the ideal objectives in clinical trials would be to have more target patient populations, which, in theory, might facilitate more rapid, more efficient, and less costly drug development. Globally, the market for conducting clinical trials presents a shortage of good researchers in some disease areas and the search for cost reduction. Two decades ago, clinical trials were carried out mainly in developed countries. The pressure to accelerate drug development, in particular the need to speed up clinical trials, drove the conduct of clinical trials to other countries.

Among the regions of interest, Latin America (LA) is fast becoming a much more attractive region in which to conduct clinical protocols. The interest in directing the conduct of clinical trials to LA has been primarily guided by the large number of naive patients, qualified investigators, established regulatory systems, and reasonable costs found in those countries. Nowadays, 7.5% of the studies carried out worldwide have been conducted in LA; the mean annual growth in this region has been greater than the growth experienced by developed countries, such as the United States—20% and 11%, respectively, in the last year.[1] Even early-phase clinical trials, including phase I trials, are currently under way in the region. Another relevant point is that the region is starting to offer a number of advantages as a location for drug research and development, including specialized products and services, pharmaceutical expertise, private and institutional facilities, multinational pharmaceutical bases, and innovative capabilities. For this reason, it is expected that the region may not only offer the possibility to conduct clinical trials and expand manufacturing facilities but may also be considered a new research and development avenue to support the untapped demand for global innovative drug development.

The aim of this work is to provide an overview of the main progress and the difficulties found in the conduct of clinical trials in LA, as well as provide a scenario of the efforts that have been made by government and private initiatives to establish a drug and development foundation for national and international companies.

Advantages of Conducting Clinical Trials in LA

The global market for drug development is highly competitive. The need to speed up the development of new drugs and vaccines has made major pharmaceu-

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tical companies export some stages of development to other countries, especially developing countries. One of those services, which has already efficiently migrated, is clinical trial conduct. Several developing countries have invariably offered a high-quality service with reduced costs, which, in turn, has led the continuous development of clinical trial fields around the world.

In the last decade, LA has experienced exponential growth in the number of clinical studies conducted in the region. Updated data from Thomson Center Watch, a Boston-based publishing and information services company; shows that 673 multicentric studies are currently being conducted in LA and 39 not yet recruiting studies will enter the recruiting phase soon.[2] In addition to those data, several national pharmaceutical companies have conducted all phases of domestic and bioequivalence protocols as a result of drug research and development expansion in the region.

For instance, Brazil, Argentina, and Mexico have enrolled the greatest numbers of patients. LA has approximately 500 million people, with approximately 70% of the population living in urban areas and thus relatively close to research centers, which are located in just a few cities in each country. It is generally agreed that the LA population still has some potential for growth. From 2000 to 2005, the region presented a growth rate of about 1.4% (Table 1). The United Nations estimates that the region's overall population will increase by about 5.5% over the next 20 years.[3]

LA also has other advantages concerning its population. First, because the region is vast and complex, the large number of patients can add a unique heterogeneous ethnic and epidemiologic profile to those studies. Second, LA can also contribute with a great diversity of diseases, ranging from those with great prevalence in undeveloped countries, such as infectious diseases, to chronic degenerative diseases, such as cancer and stroke. Third, as fewer patients are enrolled in trials in LA countries, it is easier and quicker to find patients to participate. Those patients have often used fewer medicines compared with those in Western Europe and the United States, making

Table 1 Population Characteristics of Latin America

Country	*Population (thousands), 2005*	*Population Growth Rate (%), 2000–2005*
Argentina	39,537	0.69
Brazil	168,405	1.4
Chile	16,295	1.1
Venezuela	26,749	1.8
Mexico	107,029	1.3

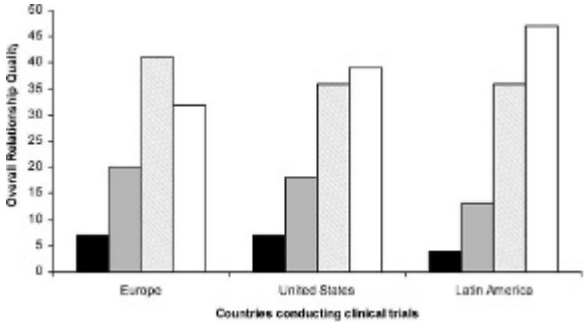

Figure 1 Composite sponsor rating of overall relationship quality, 2004 and 2005: poor/fair (*black bars*), neutral (*gray bars*), good (*hatched bars*), and excellent (*white bars*). European (2004, $N = 340$), US (2005, $N = 612$), and Latin America (2005, $N = 317$) investigative sites. Source: CenterWatch surveys. Thomson CenterWatch Survey, Boston, 2005. Available from: http://search.centerwatch.com. Acessed October 24th, 2006

them a special population of good naive candidates for new treatment protocols.[4] Lastly, as many of the country's health insurance (both private and public) companies experience financial difficulties, the possibility of participating in clinical trials is very attractive for those patients, which contributes to the faster speed and higher recruitment rate found in the studies performed in the region.

Another important issue regarding the conduct of clinical trials in LA is the good investigator-patient relationship. This good relationship is found at all assistance levels, from routine health care assistance to special patient attendance. The high standard of confidence in physicians was recently confirmed by CenterWatch data concerning the overall relationship quality in clinical trial protocols conducted worldwide (Figure 1). Those data showed that several countries in LA have higher relationship quality scores when compared with the United States and Europe.[5] Indeed, it is important to point out that the good relationship is extended to all members of staff working with clinical trials patients. The main domains are the confidence and the good standard of professional care provided, and the good relationship can be held directly responsible for the high adherence rates found in the protocols conducted in the region.

Furthermore, a new step toward improvement in the quality of clinical trial conduct in LA was recently established through the creation of the Latin American Ongoing Clinical Trial Register (LATINREC), the Colombian branch of the Ibero-American Cochrane Network. LATINREC has been developed to collect information on clinical trials undertaken in LA

countries.[6] The register was created in compliance with the Ottawa Statement criteria and the World Health Organization's International Clinical Trials Registry Platform (ICTRP), and it is expected that, in the near future, it will provide information about clinical trials conducted in the region to both the general public and the investigator.[7] It will also support trialists with methodologies, training, and other tools required for the management of clinical trial protocols.

The high scientific standard of the investigators and professionals involved in research studies is another good point in favor of clinical trial conduct in LA. The improvement in scientific skills in the region can be exemplified by the remarkable augmentation in the number of articles in journals classified and covered by the *Science Citation Index* and *Social Sciences Citation Index* noted in the past few years. This number has increased from 7,923 (1993) to 18,933 (2005),[8] approximately 110% in one decade. In comparison, in the same period, the increase in the United States and Europe was approximately 15% and 30%, respectively. Brazil is first in this ranking, followed by Mexico, Argentina, Chile, and Venezuela. Remarkably, a great proportion of those articles have been published as part of an international cooperation between LA and developed countries. Data released recently show that approximately 30% of the articles published in Brazil have international cooperation with the United States and European countries.

Moreover, compared with the United States, conducting trials in LA has lower costs and the advantage of having higher patient retention rates. The region presents a common language, Spanish, apart from Brazil, where Portuguese is spoken. Nevertheless, this does not represent a difficulty as most of the investigators and people involved in the trials are able to speak English and the sponsor's representatives and contract research organizations (CROs) headquartered in the region can also be used as a partner, facilitating communication at some stages of the study.

There are also adequate regulations established in most countries. In some LA countries, there are regional or national Independent Ethic Committees (IECs) (Brazil, Chile), and in others, institutional and extrainstitutional IECs coexist (Argentina, Peru, and Mexico). For the most part, regulatory approval is a sequential process. The first step involves Institutional Review Board/IEC approval, and the second step is regulatory agency approval. In general, LA regulatory timelines vary from 3 to 7.5 months, with Mexico and Colombia having the shortest timelines. Among the countries with major delays, Argentina and Brazil have the longest regulatory approval period.

Disadvantages in Conducting Clinical Trials in LA

Indeed, real-life regulatory approval periods are a problem to be faced by LA government and sponsors. Extended and sometimes established timelines are not respected, which ends up delaying the recruitment phase. As most of the studies are multicentric and competitive, this undoubtedly causes great distress for people working in this field and can be considered a negative point against conducting clinical trials in the region.

Efforts have been made to resolve those problems. In most LA countries, CROs, sponsors, and pharmaceutical company representatives are gathering efforts to make the government aware of the prejudice that has been caused by the long regulatory delays. Several meetings have been held to persuade government agencies to reorganize themselves and to convince them that it is possible to improve clinical trial regulatory timelines without compromising ethics and quality. The process is ongoing and is judged as a critical and urgent matter.

Another unfavorable point is related to the trust that the subject places in the investigator. The difference in price between the standard visit versus the clinical research visit is a strong motivator to become a trialist and also can be a great concern for the ethical conduct of those trials. The recruiting pressure might push the investigator to recruit marginal and not adequately informed populations, and despite the good work performed by the ethics committee, little additional information is available for the majority of patients, who live in poverty, are poorly educated, and, consequently, have low comprehension skills.

Furthermore, as has been reported for human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) clinical trials in Africa, patients in developing countries may have different motivations for taking part in a clinical trial. They may consider that taking part in clinical trials is a unique opportunity to obtain access to innovative treatments that otherwise would not be offered by the public or private health care units.[9,10] Public hospitals represent the principal setting for internationally sponsored research in LA; these institutions provide health care to a sector of the population that does not have access to social security or private medical attention. Those patients' economic, social, and educational characteristics, as well as their medical condition, subordination, and desperation for any treatment that may offer them some hope, are paradigmatic characteristics of a vulnerable population.

The vulnerability of LA patients represents a great concern and confers special attention on the people involved in the required ethical issue analysis. Ethical considerations are sometimes misunderstood by the sponsors as a set of very lengthy procedures and sometimes as an exacerbation of the local ethics committee; however, these considerations are the unique mechanism that they have, at the moment, to protect vulnerable subjects.[11]

Moreover, even after two decades of conducting clinical trials in the region and despite the high-quality clinical practice and number of good investigators, LA still faces the challenge of a low clinical trial culture. Currently, there is little formal university training in the field, and most of the training must be provided by sponsors or private companies, mainly CROs. There is a lack of intermediary companies, which would focus on providing trainers, help in the management of the sites, give translation support, or even help in recruitment planning and patient retention programs.

Indeed, new university, private, and company education programs have been established in the region. Local and LA regional meetings have been conducted in some LA countries. Those meetings are mainly arranged to discuss the major problems found by those involved in the conduct of the clinical trials and to offer some training in good clinical practice. Therefore, as such an initiative still has some scope to grow and the interest in the region is still in focus, it is expected that in the near future, LA will have better trained and qualified staff.

Ultimately, although LA shares many cultural traits, the region has a heterogeneous culture. The cultures of the main countries involved in clinical trials, Brazil, Argentina, and Mexico, are very distinct.[12] Therefore, it is also advisable that sponsors willing to enter the region understand the regulatory and logistical process. To be successful, a sponsor must be familiar with that diversity. For this reason, when conducting a protocol in the region, it is mandatory that the sponsor look for a source of local knowledge, preferably a partner or a local branch that will provide insight to accommodate that uniqueness. To be aware of and respect those differences would certainly help to set up better work and communication skills by both parts, sponsors and trialists. Following those recommendations and with adequate support, it is quite reasonable that any company that considers LA a location in which to conduct clinical trials will have success.

New Scenario for Drug Development in LA

After decades of inflation and political instability, LA has finally experienced some economic stability. Several countries have introduced economic reforms and successfully reduced inflation over the past decade. Democracy has been established in most of the countries in the region, and the main concern of those governments is now related to the solid and continuous development of their country. As a consequence, the region's government representatives have adopted a common discourse, which is focused on the development of scientific and technological innovations and the construction of solid foundations to support and stimulate those initiatives.

Several multinational pharmaceutical companies are in search of partners to develop new drugs around the world. Among developing countries, China and India have been successfully inserted into those programs. Like China and India, LA can represent an attractive route leading to drug development. The region offers cost-saving benefits and good professionals with scientific qualifications and has an overcapacity in settled generic manufacturing. The majority of multinational pharmaceutical companies have been successfully established in the region for several decades and can be used as part of those processes. Furthermore, the region has a basic infrastructure, such as transportation systems, a modern communication network, and several years of continuous pharmaceutical market experience.

LA's pharmaceutical market represents an important fraction of the worldwide drug sales market compared with other developing nations—approximately 25% of global pharmaceutical sales in 2000.[13] Per capita expenditure on pharmaceuticals is considerably higher in some parts of LA than it is in other developing economies. Compared with China, countries such as Mexico and Venezuela spend more than double on pharmaceutical products—$23, $70, and $64, respectively.[3] Together those economic profiles have been directly responsible for the expansion and location of several multinational company facilities. In addition to the facilities that already exist, recently, Pfizer, GlaxoSmithKline, Roche, Merck, Hexal, and others have set up local plants in countries such as Mexico, Argentina, and Brazil, contributing to the organization of a quite strong manufacturing base.

In recent years, the region has also experienced exponential growth in the generic pharmaceutical market. In 2005, the generic sector in LA was valued at US$1.7 billion, which represents a 26.9% increase over the 2004 figure of US$1.3 billion. Even so, the generic sales in LA are still lower compared with those of developed countries, and there is great potential for growth in the near future. Indeed, considerable effort has been made by some governments, especially from

Argentina, Brazil, Mexico, and Chile, to promote the growth of generic pharmaceutical consumption and production. Most of the LA countries' governments have introduced regulations that force doctors to prescribe generic and similar drugs and the industry to perform bioequivalence protocols. Moreover, the traditional proliferation of nonbioequivalent branded generic pharmaceuticals has been slowly replaced by the steady introduction of bioequivalent generic pharmaceuticals and branded copies. The expansion of the generic market and the establishment of high standard bioequivalent protocols have a great impact on the local pharmaceutical economy. Indeed, the local companies that decided to invest in the generic market have experienced an exponential drug sales growth and, consequently, have become stronger and more competitive.

Surprisingly, the profits generated by the generic market have been partly attributed to an innovative route. Recently, several local companies looked for university and research institution partnerships and have initiated new drug research and development programs. As a consequence, innovative medicines and pharmaceutical molecules have been developed in the region. In June 2005, a Brazilian local company released Brazil's first innovative, patent-protected biomedical product, an anti-inflammatory cream composed of phytotherapeutic active ingredients. Following this initiative, other companies have invested in the research and development of local innovative molecules and drugs. So far, the company-university partnerships have yielded 11 international patents and a great number of innovative molecules are undergoing evaluation.[14]

However, it is important to point out that, despite the strong desire and initiatives launched by some LA countries, LA cannot be analyzed as a whole. As Mercosur, a South American trade pact, has not effectively set up a program for science, technology, and innovation, it is expected that the innovation continues to come from isolated countries, mainly from Brazil, Mexico, Venezuela, Chile, and Argentina. Indeed, in those countries, new government programs and laws have been created to stimulate those innovations.

For instance, the Brazilian government launched through FINEP, a Brazilian Project and Study Financial Agency, two new programs, which intend to invest US$200 million in the development of new drugs and technologies. The first program is focused in financing the development of biotechnology and nanotechnology products by local companies and institutions, and the second program intends to strengthen the scientific board of local companies, helping them hire qualified investigators with master's and doctoral degrees.[15]

With the support of the World Bank, the Chilean government also recently launched an ambitious project that aims to improve human resource qualifications, increasing the number of university doctoral and master's degree programs. The project aims to support the local scientific base and tighten up the university-company partnership. According to this program, five already developed initiatives will receive US$18.7 million in the next 5 years to develop projects in biomining, biomedicine, forest development, fruit culture, and wine making. Venezuela's government has also manifested the intention to invest in science and support technological development. As part of this effort, Venezuela's government recently announced the Science Mission Program, which intends to provide US$400 million to the Ministry of Science in the next 6 years.[16]

Simultaneously, considerable efforts have been done to adequate preclinical and clinical services to the Good Standard Procedures. Local companies have launched preclinical and clinical programs, in compliance with Good Clinical Practice-International Conference on Harmonization (GCP-ICH) high-standard guidelines, and are now performing high-standard all-phase protocols in the region. Private companies, services, and the government have adopted several measures to adjust to the qualifications required by multinational regulations. As part of this process, international advisers have been hired by some preclinical services to help improve quality and promote the needed adjustments. Moreover, new groups, composed mainly of university investigators and industry-qualified staff, have been organized, aiming to advise the government on the writing and needed adjustments of the regulatory process.

Nevertheless, despite the great effort made by some LA governments and private companies to meet those high standards and the changes noted in the region, some problems still must be resolved before LA will definitely be considered a region for outsourcing research and development. The region still experiences few initiatives, and the lack of a generalized innovation culture has been gradually replaced by the new movement and innovation efforts.

In fact, as part of international cooperation, in recent years, some relevant developments and research agreements have been made in the region. Recently, a Brazilian firm signed a licensing deal with a Canadian partner to take advantage of a biopharmaceutical proprietary manufacturing technology. This is the

Table 2 Patent Legislation in Latin America

Country	*Legislation and Agreements*
Argentina	Law 24.572 (1996)–Patent Laws for Invention and Utility Model Law 24.766 (1996)–Confidentiality Law Law 18 (2001)–Patent Law Signed agreement with United States in 2003 to improve the judicial measure related to patents
Brazil	Law 9.279 (1996)–Industry Property Law Law 10.196 (2001)–Amendment to Law 2.279 (1996) Law 10.603 (2000)–Confidentiality Law Compulsory license to HIV/AIDS products in 2003 (2007)
Andean community (Bolivia, Colombia, Peru, Ecuador, and Venezuela)	Decision 486 (2000)–Common Regime of Industrial Property
Mexico	Industry Property Law (1999)
Chile	Signed free trade agreement with both the European Union and the United States in 2003
Uruguay	Law 17.164 (1999)–Patent Law for Inventions, Utility Models and Industrial Design

Adapted from Chaves GC and Oliveira MA.[17]
HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome.

greatest technology transfer agreement that has been set in LA for awhile. As a result of this agreement, the amount of US$19 million has been set aside to improve current Brazilian manufacturing facility with equipment and to adapt the validation process. It is expected that this will allow the company to locally manufacture complex biopharmaceuticals, destined at first for the South American market by early 2009.

One relevant issue concerning the evaluation of new sites for potential investment in research in developing countries is the presence of effective intellectual property legislation. The Trade Related Aspect of the Intellectual Property Rights (TRIPS) Agreement was signed in 1994. Since that time, several countries in LA have introduced patent regional legislation (Table 2). Most LA patent regulations are not exclusively in line with the TRIPS agreement; they are a kind of ''healthy-sensitive'' patent legislation that, in some instances, incorporates some of the TRIPS flexibilities and in others enables governments, in cases of national emergency, to allow production and importation of generic copies of indispensable medicines. The degree of ''healthy sensitivity'' varies from highly sensitive (countries such as Brazil and Paraguay include, for example, health ministry participation in some pharmaceutical industry patent claim analysis) to less sensitive (Barbados, Belize, Mexico, Trinidad and Tobago, and Panama only have compulsory license and experimental use as one of the TRIPS flexibility).[17]

The degree of patent vigilance also varies in LA. Some LA countries still fail to accomplish some patent obligations, but some of them, such as Brazil and Mexico, have quite structured patent rights protection. Indeed, many pharmaceuticals sold in LA are actually produced outside the region, in countries with even less patent protection and less flexible bioequivalent standards. The heavy price and royalties paid for patented products is mainly responsible for their low consumption and expansion of generic drugs in the region. Therefore, some would agree that only widespread international cooperation and a sustainable drug development program would favor the introduction of more rigorous patent legislation and vigilance.

In short, the shortage of GCP training programs, the extended time required for some regulatory instances, the weak university-company partnership, and the scarcity of qualified professionals in the drug development area are the main impairments that have to be solved to meet the efficiency, equity, and high-quality standards required by the drug development field. Meanwhile, it is advisable that anyone who decides to invest in any phase of the research and development process in the region look for specialized services and consider the fact that they will have to help improve the quality standard through systematic training. Companies that have already established a base in the region will preferentially drive this movement. The process will be gradual and should be monitored for domestic partners, who already have a reasonable understanding of the local market.

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