

The Globalization of Clinical Drug Development

by

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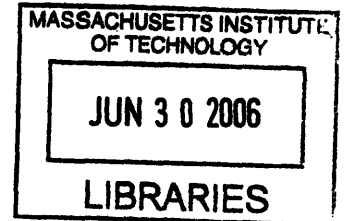
SUBMITTED TO THE HARVARD-MIT DIVISION OF HEALTH SCIENCES AND TECHNOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

SCIENCE MASTERS IN HEALTH SCIENCES AND TECHNOLOGY AT THE

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUNE 2006

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THE GLOBALIZATION OF CLINICAL DRUG DEVELOPMENT

by

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Submitted to the Harvard-MIT Division of Health Sciences & Technology on May 12, 2006 in partial fulfillment of the requirements for the Degree of Science Masters in Health Science and Technology

ABSTRACT

Industry-sponsored clinical research of investigational drugs (also called clinical development) has traditionally been carried out in relatively developed countries in the North American, Western European, and Pacific regions. However, lately it has been widely reported that clinical trials starting now are becoming increasingly diffused globally, with significant growth of activity in so-called emerging economies in Eastern Europe, Latin America, and Southeast Asia.

This change in location of clinical development activities has numerous implications for patients, health care providers, pharmaceutical companies, regulatory agencies and governments around the globe. Even though there is much debate about the topic, a public systematic quantitative assessment of the current status of the globalization of clinical drug development phenomenon is lacking. The objective of this thesis research is to provide such objective quantification while addressing some issues that are currently in active discussion.

This thesis documents that the participation of emerging countries is still relatively small (13%) and they most commonly participate in very large (involving more than five countries) phase IIb or III trials. Albeit perceived as small, this participation is growing at a rapid pace (23% average annual growth rate) and the number of clinical sites of global clinical trials located in all emerging countries (11,038) is comparable with the sum of Germany, France, U.K., and Italy (11,061). Eastern European and Latin American countries have the greatest participation in clinical trials among emerging countries, but Southeast Asia is the region that is experiencing fastest growth. Meanwhile, Western Europe has experienced negative average annual growth of -8%, and North America has seemingly been stable.

This thesis discusses findings and key drivers behind the globalization process. I also consider the argument that the sustainability of this model will depend on stringent protection of patients in these emerging countries and continued development of these nations, with eventual creation of an attractive market for pharmaceutical products. The extension of this process of globalization of clinical trials, if coupled with substantial improvements in health care delivery and research capacity in these emerging economies, has the potential of revolutionizing medical product development within the next two decades.

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I dedicate this Thesis to my beloved wife Silvia T. U. Cavalcanti and her wonderful family

Without their love, support and insights this work would not have materialized

ACKNOWLEDGMENTS

I would like to express my sincere gratitude and thanks to the many people of the Harvard-MIT Division of Health Sciences and Technology who have given me the great opportunity of conducting this line of study and research project. My special thanks goes to Ron Smith, Julie Greenberg, Jennifer Melcher, Joseph Nadol, Stefanie Shattuck-Hufnagel Domingo Altarejos, Fred Bowman, Nelson Kiang, Cathy Modica, and the Members of the Hugh Hampton Young Memorial Fund Committee.

I am also very thankful to the assistance and guidance given by advisors throughout the process. I was extremely fortunate to have truly outstanding thought leaders in the field of medical product development working with me in this project. It is very clear to me that this work would not have been possible without their help and insights. In particular, I want to acknowledge the great help Anthony Sinskey and Howard Golub have provided in the development of an objective and unbiased approach to the study of this controversial subject. They have guided me in the process of transforming immense amount of unintelligible data into information of relevance to society. I am also deeply indebted to my other co-advisor - Ernst Berndt. He devoted a considerable amount of time to this project and provided guidance, encouragement and resources that greatly expanded my ability to systematically analyze, process, and understand the information that was generated in this thesis. His time, effort and interest in my academic and professional development are much appreciated.

I am also glad that I got help from several other highly competent people that are seriously devoted to foster development of biomedical science and human health. Mansueto Almeida, a great friend and economist, was very instrumental in the very beginning of this project, when he gave some important ideas of ways to objectively address country-specific issues in global industries. Also during the initial planning phase of this project, inspiring conversations with Kenneth Getz and Eric Meyers were very important. More recently, I had the honor of getting valuable feedback from distinguished FDA officials (Randall Lutter, Ilisa Bernstein, Justina Molzon, Murray Lumpkin) that helped a great deal in the final framing of our analyses and conclusions. The insights and assistance of Frank Douglas, Mark Trusheim and other colleagues of the MIT Center for Biomedical Innovation are also much appreciated, as are the feedback from Susan Levinson and James Graham.

I am equally thankful to all members of my family and to my extraordinary friends. The warmth of your love, your wise words of support, and the moments of joy that you provided turned these challenging times into a wonderful journey. I love you all, more and more each day.

“Be the change you want to see in the world”

Mahatma Gandhi

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II - Background

Clinical Trials of New Drugs

The development of a new drug therapy for a poorly treated medical condition oftentimes brings hope and excitement to patients and their health care providers. But before a novel medicine can be widely used in patients, clinical trials are necessary. In these scientific studies the effects of the use of a new investigational drug is examined in a tightly controlled setting and in a limited number of carefully selected patients. These patients typically constitute a representative sample of the patient population to be ultimately treated [1-3].

Clinical trials are initially carried out to determine the primary toxicity of the novel intervention (also called phase I study), then to determine the optimal way to administer the new drug (phase II) and ultimately to establish the safety and efficacy of the optimized treatment (phase III). Subsequent (post-approval or phase IV) clinical studies are also carried out to study the effects and long-term safety of the drug in special populations [2, 4, 5]. The vital importance of all these types of clinical trials comes from the fact that even the best available biomedical science cannot fully anticipate the way that patients will respond to a new form of treatment. This insufficient ability of predicting the effects and/or toxicity of a new drug before the first use in humans is not expected to be fully overcome in the foreseeable future [6-9].

The investigational human use of newly developed drugs sponsored by biomedical enterprises is often called clinical development. This process is regulated in the United States by the Food and Drug Administration (U.S. FDA), and similar systems of regulation are in effect in most countries [1, 2]. These regulatory

agencies rely on statistical evaluation of the data generated in clinical development programs for each new drug to decide whether it should be made available for commercialization [3]. This type of clinical research that is designed to satisfy regulatory requirements before approval for commercialization is usually sponsored by pharmaceutical or biotechnology companies, which will ultimately sell the drug in the marketplace.

Globalization of Clinical Development of Investigational Drugs

Industry-sponsored clinical research has traditionally been carried out in relatively wealthy locations like the United States, Canada, Western Europe, Japan and Australia. It has been reported that the size and the number of clinical trials performed in these countries has been steadily increasing over the last decades [10, 11]. It has also been suggested that clinical trials are increasingly diffused globally, with significant growth of activity in so-called emerging economies¹ like: Russia, India, Poland, Brazil, China, South Africa, Argentina, Hungary, Mexico, and Czech Republic. This growth has been particularly pronounced in the last 15 years, and it is widely expected that it will be intensified in the upcoming decade [12-35].

It has been suggested that the main initial driver for the increased participation of these emerging countries in clinical drug development has been the need to accommodate the overall increase in the demand for clinical research [12, 14, 16-18, 20, 25-28, 31-33]. Over the last twenty years, the number of patients

¹ The term **emerging or developing** will be used from now on to designate countries listed as “emerging markets” by the publication The Economist[®] on March 25th 2006 (**China, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan, Thailand, Argentina, Brazil, Chile, Colombia, Mexico, Peru, Venezuela, Egypt, Israel, Saudi Arabia, South Africa, Czech Republic, Hungary, Poland, Russia, and Turkey**), plus a number of countries that were NOT in the list of high income countries tracked by The Economist[®] (**Romania, Ukraine, Bulgaria, Puerto Rico, Slovakia, Ireland, Croatia, New Zealand, Estonia, Greece, Portugal, and Lithuania**). Even though some of these countries have relatively high GDP, they can be seen as emerging from the clinical drug development perspective.

enrolled in clinical trials of new medical interventions has risen dramatically, with clinical studies enrolling several or even many thousands of subjects becoming relatively common [4, 10, 11, 14, 24, 26, 31, 36, 37]. Some of the factors implicated in this increase in number of subjects are the more complex nature of the diseases being targeted by newer therapies, increasingly common necessity of comparing the new drug with another one already in the market, and the increasing demands from regulatory agencies [10, 11, 16]. Regardless of the cause, the greater need for clinical data has gradually changed the nature and scope of these trials. From relatively small clinical research projects performed within academic centers of wealthy nations, clinical trials have morphed into sophisticated multi-national operations [4, 11, 13, 14, 16-18, 21, 22, 24-28, 30-33, 35, 36, 38-44].

It has been suggested that the need for larger and more complex trials has resulted in an increase in the expenditure in the clinical stage of drug development by almost 200% in the last 15 years [10, 11, 45], bringing the estimated cost to develop the first marketed tablet or capsule to values ranging from 400 million to 1.6 billion US\$ [10]. The association of larger trials with increased clinical development expenses comes primarily from the added administrative cost (more clinical sites to be managed and patients to be treated) and opportunity cost (longer time-to-market plus loss of patent-protected product lifetime).

There are also other increasingly important factors that should be included in this equation. The first is the fact that the cost per research participant has gone up. In the United States, this rise in cost is mostly due to increase in the expenses devoted to staffing the clinical sites, which takes up the greatest proportion of the calculated cost per subject [31, 46]. The second important factor is the substantial

increase during the past decade in the absolute number of drugs that are getting to the clinical development stage [11]. This phenomenon creates a situation where a substantial number of eligible patients are already enrolled in trials, especially in oncology studies performed within large academic medical centers in the U.S. The competition for research subjects makes recruitment efforts even more difficult and costly [1, 14, 31, 37, 46-48].

The increased cost of clinical development and the competition for subjects have led developers of medical products to search for non-traditional locations where they can: 1) perform clinical research having quality and patient protection standards that are acceptable to the regulatory bodies (especially the U.S. FDA); 2) pay less to appropriately staff a clinical site; and 3) recruit a large number of patients in a timely manner [4, 11, 13, 16, 18, 21, 25-27, 42, 43, 46, 49].

Even though, from an industry perspective, the initial attractiveness of global development proposition (allocation of some clinical trials operations outside traditional countries) has been centered on the points cited above, there have also been other important factors spurring this globalization phenomenon. These factors include the ease of communication, enhanced training of international scientists and health care administrators, the establishment of contract research organizations (CROs) focused on global clinical development operations, the fast pace of growth of market size, research capacity and regulatory demands in emerging economies, and the harmonization of guidelines for clinical research.

The substantial improvement in the means for international communication observed over the last fifteen years has enabled the globalization of clinical development. Groundbreaking innovations in telecommunications systems, the

development of the internet, relative ease of travel, and the establishment of English as the universal language in the medical scientific community have significantly facilitated communications within the medical scientific world [12, 31, 33].

Furthermore, numerous medical doctors, scientists and health care administrators with cultural and/or professional ties to the emerging economies obtained training in the United States or Europe and have decided to apply it in the international arena. Even the professionals that did not formally obtain training in academic centers in wealthy nations increasingly have had access to information needed to run international clinical trials through training in local professional schools, multinational institutions, or internet-based educational services. These international professionals oftentimes develop the initiative to take an active role in the creation of new medical interventions, because they have now a sustainable and rewarding way of doing it [11, 19, 25, 26, 30, 33, 41, 46, 49, 50].

These international scientists and health care professionals have either created local/regional research organizations or have been assimilated by multinational companies, especially CROs, which have been establishing increasingly complex ties among scientific institutions of different countries. During the last fifteen years, these CROs have been gradually capturing a substantial proportion of the global clinical trial operations from medical product developers, and the valuable contacts that they have with talented professionals within the emerging economies has been widely employed as a convincing selling point [25, 26].

Taking a broader perspective, the increasing participation of emerging economies in biomedical R&D is likely part of a relatively new trend in high-tech product development. Drawing a parallel with the software industry, the first kind of

activities in product development that were outsourced to developing countries like India were data-intensive, as opposed to knowledge-intensive, research operations [50, 51]. Such activities in India tended to be mostly related to testing and to code writing that was not core to the technology. This initial type of R&D partnerships has been considered cost-effective because of the ease of international communication and the presence of local well-trained computer engineers [52]. In the biomedical industry, the most data-intensive part of the medical product development process is the performance of late-stage clinical trials, and also in the large-scale preclinical medicinal chemistry and preclinical testing of experimental animals [18]. Given the precedent set by the software industry, it is not surprising that these data-intensive activities have been the first ones to be performed in the developing world [50].

Countries that are now seen as emerging economies will become important markets for medical products relatively soon, and this fact may well gradually change the rationale behind international R&D partnerships [48, 52, 53]. Using another example from the software industry, one of the most important R&D operations of Microsoft® is now located in Beijing, China. The mission of this R&D outpost is not only to create global products from scratch, but also to develop ideas targeted at the - to be huge - Chinese market [51]. In the biomedical field we have the example of the largest Indian pharmaceutical companies, which have made the strategic decision to become fully integrated biomedical innovators, competing in the global market and also creating products tailored to their local population [54]. Likewise, large pharmaceutical companies are increasingly establishing more knowledge-intensive product development operations in locations like China, India, Eastern Europe and Latin America [11, 14, 19, 25, 26, 49, 55-59]. These

multinational pharmaceutical companies are also looking forward, with one eye on the global market and the other one on local ones [14, 48, 53].

Governments of developing countries are also taking the opportunity to become involved in medical product development as a strategic matter. One example of such a strategic view is the initiative by the Brazilian government, in partnership with private entities, to build clinical research centers around the country, essentially to host international and local trials [60]. Likewise, Chinese officials are working hard to bring good clinical practice standards to their hospitals, so that they are more attractive to international developers [20, 24]. The Indian government has just implemented a drastic policy change as it relates to intellectual property protection, in which they are going to respect international patents [54, 61]. That is going to damage their generic pharmaceutical industry, but the fact is that some of the generic manufacturers were the main companies that lobbied for this move. The main reason why they did so was to ensure that the intellectual property associated with the drugs that they begin to create, as they became innovators, is protected. The second, and also important, reason for their move was that the same companies also have important clinical trial operations that serve international developers. Thus, they want to attract international trials by making sure that intellectual property related to drugs and devices are protected when they are tested in India [54].

All these recent news represent the increasingly forward-looking global view shared by governments and biomedical entrepreneurs of some developing countries. These officials are interested in developing stronger international trade relations and they are fully aware that there is more wealth to be generated in

information-based economic activities. In the biomedical field, these countries anticipate the creation of new types of employment opportunities for health care workers, who are obtaining highly valuable and specialized training. Physician and support personnel that are trained to perform according to international health care standards during clinical research activities can be expected to become more capable and judicious professionals outside the clinical research scenario, when treating regular patients [2, 3, 16, 22, 46, 59, 62-64]. The other potential benefit is that research and medical care infrastructure can initially be built mostly by using foreign direct investments from multinational corporations, possibly creating a capacity that can ultimately serve to foster development of an indigenous biomedical industry.

It should also be noted that government officials of progressively more sophisticated emerging economies are beginning to realize that the scientific evaluation of new investigational drugs in the local population is important. They are becoming increasingly aware that the relatively blind acceptance of clinical information obtained solely from foreign patients (traditionally from Caucasian populations of wealthy nations) that we have today may not be appropriate as local cultural and ethnic factors can substantially affect the patient's response to a new treatment.

The maturation of the guidelines for international clinical research can also be considered as a very important factor in the globalization of clinical drug development. Several codes of conduct have been created in response to apparent unethical practices in clinical research in wealth nations over the last century. The Nuremberg Code (with all its revisions), the Belmont Report, and the NIH's

guidelines for clinical research are important in this context as they represent the learning that has occurred from several most unfortunate experiences [2, 12, 22, 23, 29, 34, 37, 40, 41, 44, 59, 65-83]. Two more recent reports build upon these and consider especially the conduct of clinical trials in developing countries. The first one is from the U.S. National Bioethics Advisory Commission [28], which defined ways to protect vulnerable populations of developing countries from exploitation. The second report is divided up in a series, as are the results of the International Conference(s) on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for human use. This series of reports defines how clinical data should be obtained and presented, how informed consent should be obtained, and how institutional review boards should operate [5, 39, 67, 84-87].

These above-mentioned guidelines provide protocols on accepted ways to perform trials in developing countries, offering an equivalent level of patient protection that is afforded in developed countries. The existence of the guidelines, however, does not guarantee that subjects of emerging nations will be protected. The strength of the local legal system and quality of training of local investigators and support personnel will ultimately determine the level of compliance with international ethical standards. Based on the scale of the public reaction to recent clinical trials that were perceived not to be complying ICH's Good Clinical Practices standards [1, 12, 13, 27-29, 32, 36, 40-42, 47, 55, 56, 61, 69, 73, 76, 78-83, 88, 89], it is increasingly clear that the long-term sustainability of clinical trials operations of a given country will depend critically on its ability to protect human subjects.

In summary, many factors are playing important roles in the globalization of medical product development, and it can be concluded that this is an inevitable and

most likely desirable trend. Even though the main initial driver for the globalization of medical product development was the need of product developers to obtain more access to research subjects and cut costs in data-intensive R&D operations, several other wide-ranging and important factors have been involved in the process. As I have discussed, the globalization of clinical trials appears to represent the initial phase of a far-reaching trend towards internationalization of product development, with a gradual assimilation of a global view into private enterprises and governments. It can safely be predicted that these international R&D operations will gradually become more knowledge-intensive and sophisticated within the next ten to fifteen years. It is also expected that within the upcoming twenty to thirty years some of the emerging developing countries that are currently hosting data-intensive R&D operations will be seen mostly as important markets for pharmaceutical products [14, 48, 51-53].

III - Characterization of Global Clinical Trials

The 2001 report of the United States Office of Inspector General (OIG) [41] entitled “The Globalization of Clinical Trials – A Growing Challenge in Protecting Human Subjects” was likely the first systematic quantification of the increased submission of data generated by investigators outside the FDA’s jurisdiction (U.S.) published in the Medline-indexed literature. The authors reported that between 1980 and 1999 the number of clinical investigators conducting drug research under FDA’s Investigational New Drug (IND) applications outside the U.S. increased 109-fold, from 41 to 4,458.

The globalization of clinical drug development heralded in the OIG report [41] has been referred to as one of the most important recent transformations in the biomedical industry [14, 26, 31, 46, 53, 54], but the globalization term in this context has varying meanings for different people. As mentioned earlier, some focus on the relatively low cost of running data-intensive and large-scale product development operations in emerging economies [12, 13, 16, 24-26, 31, 36, 41, 90]. Others point to the leveling of the playing field phenomenon [91], in which high-quality research centers, located in countries of any size or socio-economic status, can now participate in the global product development process because of today’s ease of communication and harmonization of Good Clinical Practice (GCP) guidelines [4, 14, 31, 32, 53]. There is also the view that the increasing bargaining power (larger market) and sophistication (better technical education) of regulatory agencies of certain emerging economies are gradually forcing drug developers to increase the number and quality of the clinical development operations in these countries [14, 16, 46, 52, 53, 90]. Regardless of one’s position on any of these interrelated issues, it

seems quite relevant and important to understand the evolution of the participation of emerging nations in drug development operations over the last few years.

Such evolution of the globalization process was addressed in the 2001 OIG report, which stated that the mid 1990's was the point in time when the geographic allocation of clinical trials began to change substantially (Figure 1). The growth in the number of these foreign clinical investigators participating in industry-sponsored international trials has been particularly dramatic in the last five years covered by the OIG study (1995-1999). A group of countries (Argentina, Brazil, Hungary, Mexico, Poland, Russia, and Thailand) were singled out as ones showing the greatest growth in their participation in clinical drug development through the 1990's.

Although interesting, the analysis presented in the report does not put the participation of each of these countries in a broader context. In other words, it is not clear how the number and growth of clinical investigators in each of these depicted countries compares to those of other more traditional countries, such as the U.S., Canada, U.K., France or Germany. Furthermore, the basic characteristics (therapeutic categories, phase, total number of countries participating, number of patients, and sponsor) of the trials with clinical sites located in these emerging countries have not been described and analyzed.

Country	91-93	94-96	97-99
Argentina	6	122	271
Brazil	16	52	157
Hungary	9	35	161
Mexico	29	48	157
Poland	4	100	100
Russia	0	5	170
Thailand	1	2	24

Source: OIG analysis of FDA data

Figure 1 (Source: 2001 Office of Inspector General Report)

Another important aspect not fully addressed in the OIG report is the magnitude of the participation (number of active clinical research sites) of very poor countries, especially in sub-Saharan Africa. This information is relevant as the performance of industry-sponsored trials in such countries is controversial. The main contention is that, in many cases, these countries do not have the health care infrastructure that would allow the performance of clinical trials following GCP guidelines (as defined by the International Conference on Harmonization (ICH) [5, 84]. Several reports have been published describing problems in clinical research performed in some of these countries [28, 29, 66, 78, 81], and it is not known whether there are still substantial clinical development activities in these locations.

A more precise quantification of the number of clinical research sites located in emerging countries is also lacking. These countries frequently have at the same time characteristics of both wealthy and poor nations, and inequalities in health care access and relatively underdeveloped patient protection systems are still serious problems. The socio-economic status of these emerging countries might create situations where key tenets of clinical research, like culturally-sensitive ethical review of research protocols and informed consent are compromised [3, 16, 18].

For that matter, one could look in the composition of countries participating in any given trial to determine whether trials performed most often in these emerging nations only have sites in countries of similar (lower) socio-economic status. This finding could be seen as an indicator that these trials have research protocols that would not be acceptable in places like the United States or Western Europe².

It might be the case that an alternative scenario is actually becoming dominant over the last few years: new trials have an equivalent participation of traditional and emerging countries, with a mix that can be correlated with their market potential and current clinical research capacity. Such finding could be seen as an indicator that new drugs are tested for efficacy and safety (in phase IIb/III trials) at the same time in all potential markets - traditional and emerging – so that concomitant global registration can be executed quickly and efficiently, using both international and local data [92].

Before the creation of the International Conference on Harmonization (ICH) guidelines in the early 1990's, major pharmaceutical companies conducted relatively independent clinical development programs in the U.S., large Western European countries and Japan. Data from each of these programs was then used for appraisal and eventual approval for commercialization by each of the respective regulatory agencies. Only after such approval in wealthy nations, relatively small post-marketing local registration studies (phase IV type) would be conducted in some of the largest developing countries in order to obtain approval for selling such drugs in these relatively small markets. Sometimes, these developing nations simply

² It might also be the case that emerging nations are hosting trials of therapies for diseases that are uncommon in wealthy countries, as is the case for certain infectious diseases like rotavirus enterocolitis and also for rare types of cancers like nasopharyngeal carcinoma (highest prevalence in Southeast Asia)

accepted the decision made by the FDA without requiring the companies to perform further local studies [92].

Within the possibly up-and-coming global registration paradigm mentioned above, two separate and parallel processes appear to be shaping strategic decisions regarding geographical allocation of clinical sites today. The first is that the ICH guidelines and the increased cooperation among the FDA, European Agency for the Evaluation of Medicinal Products (EMA), and other regulatory agencies across the globe has enabled the implementation of global clinical development programs that make use of numerous sites in each of the current major markets for pharmaceutical products (North America, Western Europe; and Japan) [4]. The second is that pharmaceutical developers most likely began to take notice of predictions that some of the emerging nations will have sizable markets when their new drugs go through their usual twelve year development cycle [10]. The expected result is the creation of large pre-approval confirmatory (phase IIb/III) trials involving a combination of wealthy and emerging nations, which would be designed to enable fast concomitant registration in a global scale once they are completed. But again, there are no empirical foundations to support or disprove this perception.

Likewise, the pace of evolution of the globalization of clinical drug development is not well-understood and without such information it becomes difficult to forecast near to mid term trends. In fact, in order to generate such predictions one ideally needs to identify the growth rate of participation in global clinical trials of all countries heavily involved in global clinical trials, and not just a few ones. The unsubstantiated conjecture that clinical trials in wealthy nations are being replaced by trials in emerging economies [14, 90] can also be addressed with such type of

empirical analysis.

The analysis of annual growth rates of countries involved in clinical drug development might also enable the assessment of the impact of country-specific public policies, implementation of local regulations governing clinical research and related intellectual property, building of health care infrastructure, training of medical and support personnel and major investments by the private sector. Of special interest is the growth rate of participation in global clinical studies of countries like India and China, which is not known, but nonetheless has been the subject of much public and scientific debate over the last 5-10 years [11, 16, 18, 21, 22, 24, 27, 31, 35, 36, 42, 53, 54, 57, 61, 90].

In summary, global clinical drug development is a rapidly evolving field and the evolution of this model of drug development will likely have great impact on the behavior of companies, regulatory agencies, hospitals, research enterprises, health care professionals, and ultimately patients. As pointed out in the 2001 OIG report, the globalization of clinical trials raises numerous critical issues, especially in terms of patient protection. At the same time, the value of global clinical drug development to patients and society as a whole is clear.

To date, most of the discussions on globalization of clinical trials to date have been based on, sometimes outdated, testimonials from professionals in the field. These do not necessarily present a broad and objective perspective on how the phenomenon presents itself today (2006). What is needed is an impartial and comprehensive quantitative mapping of today's industry-sponsored global clinical trials that can be used to address many of the pressing issues described above.

IV - Objectives and Hypotheses

One goal of this thesis research is to generate a quantitative assessment of the evolution of industry-sponsored global clinical trials of investigational drugs (hereafter, GCTs) that took place after the publication of the OIG report in 2001.

In order to provide such a quantitative assessment, the countries most heavily involved in global clinical development (the top 50) were divided according to two different classification schemes, the first one related to global clinical trial participation (ranking of total number of clinical sites and level of engagement in global economy) and the second one related to geopolitical region.

In the first classification scheme the groups were called: *tier 1 traditional*; *tier 1 emerging*; and *tier 2 emerging* (table 1). I have used the arbitrary cut-off point of 400 clinical sites to divide the countries into *tier 1* and *tier 2*. The *tier 1* group was further subdivided in *tier 1 traditional* and *tier 1 emerging*, with the *emerging* countries being the ones defined as “emerging markets” and the *traditional* ones referring to those tracked as established markets by the magazine The Economist[®] on April 25th of 2006³.

Most of *tier 2* countries were in the “emerging markets” list of The Economist[®] as well, while a few were neither the emerging nor in the traditional markets segment. For the sake of simplicity, all countries of *tier 2* will be referred to as *emerging* as well, based on the collective behavior of this somewhat heterogeneous group in relation to participation in clinical development operations⁴.

³ This classification is one that is published weekly on the back pages of the printed publication version, and not the e-readiness ranking published yearly by The Economist's Intelligence Unit[®].

⁴ No classification regarding complex entities like countries is perfect. I chose to rely on the somewhat incomplete classification used by The Economist[®] because it seems to be the one that best captures the positioning of countries related to their economic performance over a period of time, especially as it refers to market size growth potential and level of engagement in the global economy.

In the second classification scheme, the countries were subdivided in the following geopolitical regions (table 1).

GROUP	Countries
Tier 1 Traditional (17)	U.S., Canada, Germany, France, U.K., Italy, Spain, Australia, Japan, Belgium, Netherlands, Sweden, Denmark, Norway, Austria, Finland, and Switzerland
Tier 1 Emerging (10)	Poland, Russia, South Africa, Brazil, Czech Republic, Argentina, Mexico, Hungary, India, and China/Hong Kong
Tier 2 Emerging (23)	South Korea, Greece, Israel, Taiwan, Romania, Ukraine, Portugal, Bulgaria, Puerto Rico, Slovakia, Chile, Turkey, Ireland, Thailand, Philippines, Croatia, Malaysia, New Zealand, Singapore, Estonia, Peru, Lithuania, and Colombia

REGION	Countries
North America (3)	U.S., Canada, and Puerto Rico (U.S. Dependent Area)
Western Europe (15)	Germany, France, U.K., Italy, Spain, Belgium, Netherlands, Sweden, Denmark, Norway, Austria, Finland, Switzerland, Portugal, and Ireland
Eastern Europe (13)	Poland, Russia, Czech Republic, Hungary, Greece, Romania, Ukraine, Bulgaria, Slovakia, Turkey, Estonia, and Lithuania
Pacific (3)	Australia, Japan, and New Zealand
Latin America (6)	Brazil, Argentina, Mexico, Chile, Peru, and Colombia
Southeast Asia (8)	India, China/Hong Kong, South Korea, Taiwan, Thailand, Philippines, Malaysia, and Singapore
Africa (1)	South Africa
Middle East (1)	Israel

Table 1

Classification schemes of countries tracked in the study. The first classification is related to clinical trial participation (ranking of total number of clinical sites and level of engagement in global economy) and the second one is related to geopolitical region in which the country is situated.

In this context I will address the following hypotheses:

- 1) The top 50 countries that are most actively taking part in global clinical trials of investigational drugs either have high income per capita (more than US\$10,000⁵ in 2005) or are “emerging markets” tracked by The Economist®.
- 2) The participation share of *emerging* countries in global clinical drug development has continued to increase over the last four years, while the participation share of *traditional* countries has been decreasing.
- 3) *Emerging* countries have a greater level of participation in large multinational studies (with sites in more than five countries) than do *traditional* countries.
- 4) *Emerging* countries have a level of participation in the confirmatory phases (phases II/III) of clinical development at a rate that is comparable to that of *traditional* countries.

⁵ CIA World FactBook.

V - Methods

Source of Information

I obtained information on global clinical trials of investigational drugs from the Clinicaltrials.gov website up through March 1st 2006. This public web-based registry has become increasingly comprehensive in recent months as a result of initiatives enacted by the U.S. federal government and the editorial boards of major medical journals.

Clinicaltrials.gov contains information of clinical trials performed under a U.S. FDA investigational new drug (IND) application. Sponsors plan to ultimately use information obtained in these registered trials to obtain regulatory approval for marketing of a new drug or indication. The U.S. legislation requires registration only of trials for medical interventions designed to treat serious or life-threatening diseases. The guidelines for such submissions were developed as a mandate contained in the 1997 U.S. FDA modernization Act [93-96].

More recently (September 2004), members of the International Committee of Medical Journal Editors (ICMJE) published a joint editorial aimed at promoting registration of all clinical trials in the clinicaltrials.gov database, irrespective of the seriousness of the disease being studied, type of research protocol or source of funding [97]. This committee represents several of the most important publication outlets for clinical trials (e.g., New England Journal of Medicine, Lancet, Journal of the American Medical Association, among others), and the consortium announced that results from trials will only be considered for publication if they have been registered at clinicaltrials.gov before the enrollment of the first patient. This policy applies to trials that began recruiting on or after July 1, 2005. As many ongoing trials

were not registered at inception, the journals will consider for publication ongoing trials that were registered before September 13, 2005.

Database of Global Clinical Trials

General Description

A database containing information on 1,894 trials, and corresponding 59,487 clinical sites, was created as a Microsoft Excel[®] file. Detailed descriptions of trials that fitted the inclusion and exclusion criteria (listed below) were saved as Acrobat[®] PDF files on March 1st 2006. The data contained in these files were analyzed over the ensuing months without having to deal with the fact that the studied internet registry is modified to some extent almost daily. Information captured from each detailed trial description was manually entered into the Excel[®] spreadsheet.

The information retrieved from clinicaltrials.gov included: name of trial; clinicaltrials.gov identifier number, number of patients to be enrolled (when available); recruitment start date (when available - for currently recruiting trials); listings of clinical trial site locations; condition being treated; and sponsor.

Before beginning to collect such data points, I first generated a list of the top 50 performing countries in clinical development (including the U.S.). This list was created with the use of the "focused search" tool on clinicaltrials.gov. This interactive tool provided the total number of trials registered at clinicaltrials.gov that each country is participating, regardless of the magnitude of their contribution in terms of number of clinical sites. The numbers of all countries for which data was available were tabulated and the top 50 countries were then identified.

After the identification of the top 50 countries, I went beyond the level of analysis offered by the clinicaltrials.gov “focused search” interactive tool by counting the number of sites that each country had in each trial. This data compilation was driven by the assumption that there is a substantial difference between situations where a country has one site in a global trial compared to another where it participates with 100 sites. In both realistic scenarios the country would be listed in the same way on clinicaltrials.gov. After the data points about each trial were entered into the Excel[®] spreadsheet, it became quite straightforward to generate quantitative assessments related to specific countries, or groups of countries, taking part in global drug clinical development. It also became relatively simple to study groups of trials that shared common characteristics such as: trial phase, total number of countries participating in each trial, and recruitment start date.

Inclusion & Exclusion Criteria

I have collected information of “currently recruiting” and have excluded “not yet recruiting” or “terminated” trials. I have also gathered data from “completed” trials in the cases where the sponsor provided a date of start of recruitment.

As my ultimate goal is to characterize GCTs in this study, I have not collected information on purely domestic trials (with clinical sites only within the U.S.). According to the clinicaltrials.gov own analysis, about 30% of the trials fall into this category. Likewise, I have excluded trials funded and/or run by academic or public institutions from the analysis, because of the understanding that they are intrinsically different from the industry-sponsored trials. I determined that a given trial was

industry-sponsored when the sponsor name was listed in the field "Information Provided by" on the clinicaltrials.gov website.

I also did not collect information on studies in which the clinical phase (I/II/III or IV) was not provided by the sponsor. From the provided description of trials that fell in this category, it could be determined that in these trials the sponsors were not testing or observing the effect of an industry-owned medical intervention. Most of the industry-sponsored clinical studies of this kind had the objective of determining the prevalence of a condition in a selected population that is not using the drug, making them intrinsically different from the most common type of trial in which a company is seeking information that will be ultimately used to make statements that are specifically related to the effects of their drugs in humans.

Trials that did not have information on location of clinical sites or condition treated were excluded as well. Trials that fell in either category were uncommon and were considered of no use for the purposes of this study. I have also excluded trials of medical devices that did not rely on a drug for its therapeutic effect as my focus in this study is on pharmaceutical development.

A total of 50.2% of the trials that were identified as industry-sponsored by the clinicaltrial.gov website on March 1st 2006 were excluded according to the above-described criteria. This left me with the sample of 1,894 trials and corresponding 59,487 clinical sites.

Analytical Methods

Rankings

The ranking of country participation in GCTs was based on the total number

of clinical sites of all top 50 countries⁶. Sites located outside the top 50 countries were counted collectively and numbers were placed in a bin labeled “others”. I have also quantified the proportion of clinical sites that each country contributed to GCTs by dividing the country’s total number of sites by the total number of clinical sites tracked in the current study, which was 59,487.

Growth Rates

The first step in the determination of growth rate was the separation of trials according to date of start of recruitment (2002, 2003, 2004, and 2005). Separate rankings were generated that corresponded to trials that were initiated in each given year⁷. The second step was to determine the share of clinical trial participation of all countries in each year. These shares were determined by dividing the number of clinical sites of individual countries in each year by the sum of the clinical sites of all countries in the same year⁸.

The average annual growth rate of share participation for each country was determined with the arc (arithmetic mean) formula⁹: $\text{arc} = (St - St-1) / ((0.5*(St + St-1)))$.

⁶ Each clinical site in this context refers to a recruiting location for an individual clinical trial. Specific identity of the medical center in which the site is located is usually not provided by the registry. Even though it is possible that any given hospital or clinic might be recruiting patients for more than one trial, sites were counted individually for each trial, and added up as separate entities.

⁷ I did not include information for trials starting during the years below 2002 and for the two first months of 2006 because of an insufficient number of data points.

⁸ It was assumed that most of the systematic increase in number of trials from 2002 to 2005 was due to a higher reporting of more recent trials. For the purpose of the growth rate calculation, it was then assumed that the overall number of sites in global trials was kept constant over the last four years, and the only thing that changed was the reporting. This analytical strategy was used because an overall annual growth rate over the last few years is not known precisely and any given figure can be easily included in the mathematical model during the discussion of the results.

⁹ This formula was chosen because it captures the year-to-year changes and also handles small numbers of clinical sites that some countries present in a reasonable manner. St means numbers of trials in a given year. St-1 means number of trials in the previous year.

The weighted¹⁰ average annual growth rates for the groups of countries classified according to global clinical development participation and geographic location were also determined.

Participation in Very Large Clinical Trials

One way to measure the size and complexity of a given clinical trial is to determine the number of countries that participate in the trial. In this study, clinical trials were separated according to the number of countries participating in them. I then determined the number of clinical sites that each country had in trials involving more than five countries, which is my working definition of large multinational trials. The proportion of sites that each country had in these large trials (as opposed to in trials with four or less countries) was then established for each country. The weighted average proportion of participation in these large trials was also determined for the groups of countries classified according to global clinical development participation and geographic location.

Participation in Confirmatory (Phase II and III) Clinical Trials

The clinical sites of all top 50 countries were also separated according to the phase of the trial in which they were participating. The proportion of clinical sites that each country had in confirmatory trials (phase II/III), as opposed to post-marketing (phase IV), trials was determined for each country. The weighted average proportion of participation in these phase II/III trials was also determined for the countries

¹⁰ The weighing procedure to calculate the rate of a given group or region was performed by the division of a/b , where a is addition of the results of the multiplication of total number of clinical sites of each country of a group or region with their perspective individual rates; and b is the sum of number of clinical sites of all countries within a given group or region.

classified according to global clinical development participation and geographic location.

VI - Results

Ranking	Country	# of Sites	% of Total	Ave. Ann. G.R.	% in Large Trials	% in Phase III/IV
1	U.S.	23144	38.9%	1.5%	26.8%	89.7%
2	Canada	3902	6.6%	-9.5%	52.3%	86.0%
3	Germany	3705	6.2%	-21.9%	71.4%	89.4%
4	France	3451	5.8%	1.7%	62.9%	81.5%
5	UK	2011	3.4%	-17.6%	82.8%	81.2%
6	Italy	1894	3.2%	-26.1%	70.3%	79.5%
7	Spain	1851	3.1%	2.7%	84.4%	79.5%
8	Australia	1346	2.3%	-0.2%	75.3%	87.3%
9	Japan	1302	2.2%	2.6%	0.1%	92.3%
10	Belgium	1099	1.8%	-4.2%	86.4%	89.6%
11	Netherlands	1075	1.8%	14.5%	73.8%	69.3%
12	Sweden	1048	1.8%	-6.1%	76.3%	77.9%
13	Poland	1003	1.7%	13.6%	87.2%	92.0%
14	Russia	844	1.4%	27.6%	77.4%	84.8%
15	South Africa	729	1.2%	-2.3%	89.8%	86.8%
16	Brazil	722	1.2%	0.9%	92.5%	88.5%
17	Denmark	687	1.2%	11.9%	57.6%	63.5%
18	Czech Republic	634	1.1%	27.7%	90.4%	89.6%
19	Argentina	624	1.0%	27.2%	96.3%	91.2%
20	Norway	601	1.0%	-13.0%	83.5%	83.0%
21	Mexico	585	1.0%	28.7%	88.7%	87.0%
22	Hungary	564	0.9%	36.3%	90.1%	91.0%
23	Austria	465	0.8%	-12.8%	64.9%	87.0%
24	Finland	463	0.8%	11.6%	76.9%	85.9%
25	India	420	0.7%	40.1%	85.2%	86.7%
26	Switzerland	405	0.7%	-17.5%	63.7%	81.9%
	Others	403	0.7%	30.7%	73.0%	80.8%
27	China (w/ H. K.) *	399	0.7%	61.9%	49.6%	79.3%
28	South Korea	322	0.5%	18.7%	66.8%	82.3%
29	Greece	316	0.5%	25.5%	85.1%	72.5%
30	Israel	317	0.5%	12.4%	85.2%	92.4%
31	Taiwan	290	0.5%	12.8%	79.3%	83.6%
32	Romania	281	0.5%	32.0%	86.5%	90.7%
33	Ukraine	270	0.5%	29.7%	75.2%	95.6%
34	Portugal	251	0.4%	20.3%	91.6%	78.5%
35	Bulgaria	247	0.4%	62.0%	76.9%	97.2%
36	Puerto Rico	237	0.4%	8.2%	55.3%	77.6%
37	Slovakia	164	0.3%	24.7%	99.4%	90.8%
38	Chile	141	0.2%	51.2%	95.0%	86.6%
39	Turkey	140	0.2%	16.9%	86.4%	63.6%
40	Ireland	137	0.2%	-3.4%	93.4%	83.9%
41	Thailand	127	0.2%	37.4%	80.3%	74.8%
42	Philippines	126	0.2%	80.8%	92.9%	92.9%
43	Croatia	113	0.2%	37.6%	81.4%	85.0%
44	Malaysia	113	0.2%	42.1%	91.2%	87.6%
45	New Zealand	110	0.2%	27.9%	86.4%	89.5%
46	Singapore	90	0.2%	23.2%	90.0%	85.2%
47	Estonia	87	0.1%	12.8%	97.7%	87.4%
48	Peru	86	0.1%	89.8%	84.9%	89.5%
49	Lithuania	76	0.1%	-12.5%	90.8%	75.0%
50	Colombia	70	0.1%	61.9%	91.4%	80.0%

Ranking	GROUP	% of Total	Ave. Ann. G.R.	Ave. % in Large Trials	Ave. % in Phase III/IV
1	Tier 1 Traditional (17)	81.4%	-3.2%	47.4%	86.4%
2	Tier 1 Emerging (10)	11.0%	22.9%	86.0%	88.1%
3	Tier 2 Emerging (23)	6.9%	25.6%	83.8%	83.7%
4	Others	0.7%	31.3%	73.0%	80.8%

Ranking	REGION	% of Total	Ave. Ann. G.R.	Ave. % in Large Trials	Ave. % in Phase III/IV
1	North America (3)	45.9%	0.0%	30.7%	89.1%
2	Western Europe (15)	32.2%	-7.9%	73.8%	81.7%
3	Eastern Europe (13)	8.0%	26.3%	85.3%	87.8%
4	Pacific (3)	4.6%	2.2%	40.2%	89.8%
5	Latin America (6)	3.7%	24.1%	92.4%	88.5%
6	Southeast Asia (8)	3.2%	29.8%	81.1%	83.6%
7	Africa (1)	1.2%	-1.9%	85.9%	86.8%
8	Middle East (1)	0.5%	8.2%	86.3%	92.4%

Table 2

Quantitative assessment of global clinical development operations of individual countries, groups of countries and geographic regions. Rankings of clinical trials participation is represented by the number of clinical sites, with the *tier 1 traditional* countries labeled in brown (regular font), *tier 1 emerging* in green (bold italics), *tier 2 emerging* in yellow (bold), and "Others" is white (bold). Average annual growth rate (2002 through 2005) of all countries and regions was established. Proportion of instances where countries or regions participated in large (>than 5 countries) trials, or in confirmatory trials (phases III/IV), as opposed to IV) are also depicted. Numbers of countries in each group or region are shown inside parenthesis. *China was classified as *tier 1 emerging* because its number of sites (399) was very close to the arbitrary cut-off of 400 sites that divided *tiers 1* and *2*.

Rankings

The ranking of country participation (based on number of clinical sites) suggests that the overwhelming majority of GCT clinical sites today is still located in the *tier 1 traditional* countries (81.4% of total – in light brown). Of the remainder 18.6%, the *tier 1 emerging* countries (in light green) accounted for 11% and the *tier 2 emerging* (yellow) accounted for 6.9%. If one includes in the computation of the overall number clinical development activities globally the rough estimate of 25,949 sites¹¹ that would correspond to “U.S. only” domestic trials excluded from the database, it can be inferred that the participation of *emerging* countries amounts to about 13%.

The number of clinical sites in the U.S. is at least six times greater than in any other country, and this difference is probably even greater considering that the clinical trials with sites only in the U.S. are not represented in this database of GCTs. Canada is the prime destination for clinical sites outside the U.S., and it is closely followed by Germany and France.

The emerging countries in Eastern Europe have more than double the amount of sites in Latin America, but Eastern Europe involves a greater number of countries (13 vs. 6). Southeast Asia has only two representatives at the bottom of the *tier 1* group, and has fewer sites than Eastern Europe and Latin America, even though it has a much larger population.

Some of the top performing tier 1 emerging countries - especially Poland, Russia, South Africa, and Brazil – have a level of participation that is quite comparable to that of some traditional countries. There is only one representative of

¹¹ If 59,487 amount to 70% of the trials, 25,494 would correspond to the other 30%.

the Middle East (Israel) and of the African continent (South Africa) in the top 50 performing countries. The sites represented in the “others” bin amount to a small proportion of GCTs (0.7%), especially considering that they refer to at least 20 countries. Most of the countries included in this bin were in Europe, Latin America and Asia. Latvia, Serbia & Montenegro, Luxemburg, Slovenia, Panama, Costa Rica, Venezuela, Ecuador, Indonesia, Vietnam, Pakistan, Algeria, Morocco and Saudi Arabia were the countries that had the most prominent participation in this group.

It can be concluded that hypothesis 1) is valid. The top 50 countries that are most actively taking part in global clinical trials of investigational drugs either have income per capita higher than US\$ 10,000 (based on CIA World FactBook 2005) or are emerging markets.

Growth Rates

As seen in the middle panel of table 2, the *tier 1 traditional* countries had a negative average annual growth rate of -3.2%, while the *tier 1 emerging* countries had a positive rate of 22.9% and the *tier 2 emerging* ones had a positive rate of 25.6%. The greatest proportion of the *traditional* countries (8 out of 17) posted an average growth close to 0% (-10% to +10%) in relation to the overall annual rate of increase in overall clinical trial activities, which is an unknown figure. Some of the traditional countries had a rather pronounced (more than 10%) negative growth rate, and these included Germany, U.K., Italy, Norway, Austria and Switzerland, while others (Netherlands, Finland, and Denmark) had positive growth in excess of 10%.

The great majority (91% - 30 out of 33) of the *emerging* countries (30 of 33) experienced a positive growth rate, with an average for the whole group running

above 20%. Growth has been most pronounced in Southeast Asia (29.8% per year), but is also strong in the two other main emerging regions (Eastern Europe and Latin America, 26.3% and 24.1% respectively). The growth in *tier 1 emerging* countries can be considered more relevant since it is coming from an already relatively large base. The other interesting finding is the relative stabilization of growth in two of the top performing *tier 1 emerging* countries - South Africa (-2.3%) and Brazil (0.9%).

It can be concluded that hypothesis 2) can not be refuted. The participation share of *emerging* countries in global clinical drug development has continued to increase over the last four years, while the participation share of *traditional* countries has been decreasing.

Participation in Very Large Clinical Trials

Over 80% of the clinical sites located in *emerging* countries were related to very large trials in which the same clinical protocol was followed in more than five countries at once. The rate of participation *emerging* countries was greater than that of *traditional* countries (47.4%).

Most of these trials which had participation of *emerging* countries also had participation of *traditional* countries. The most common scenario was a trial with several dozen sites in *traditional* countries (especially in the U.S.) and a few (2-5) sites in several of the *emerging* countries. The most notable exception to this kind of distribution of site locations is China. It was observed that a substantial portion of reported trials that started recently in China only had Chinese sites. This kind of situation was also observed to a lesser extent with Eastern European countries, especially Russia and Poland. The Latin American countries are at the other side of

this spectrum. A trial with sites only in Latin American countries was rarely encountered.

As for the *traditional* countries, one of the most interesting findings is the nature of Japanese trials. Japan rarely (0.1% of cases) participated in the very large multinational trials, and its trials most often involved only Japanese sites. It was also interesting to observe the large number of trials that involved solely the U.S. and Canada, which sometimes had a few sites in Puerto Rico as well.

The presented data supports the notion stated in hypothesis 3), which infers that *emerging* countries have a greater level of participation in large multinational studies (with sites in more than 5 countries) than do *traditional* countries.

Participation in Confirmatory (Phases II and III) Clinical Trials

The *emerging* countries have been participating in confirmatory phases (II/III) of clinical development at a rate comparable to that of most *traditional* countries. The great majority of clinical sites in *tier 1* (88.1%) and *tier 2* (83.7%) *emerging* countries are enrolling patients for phase II or III clinical trials (as apposed to phase IV trials). These average proportions are similar to the ones found in traditional countries (86.4%).

Given the described evidence, hypothesis 4) seems to be a valid statement, as it indicates that *emerging* countries have a level of participation in the confirmatory phases (phases II/III) of clinical development at a rate that is comparable to that of *traditional* countries.

VII - Discussion

Participation of *Emerging* Countries in Clinical Drug Development

The participation of *emerging* nations in clinical development is relatively low (13%) when compared with that of *traditional* countries, but still relevant for the following reasons: 1) it amounts to a large number of clinical sites (11,038) in absolute terms; 2) it involves many countries representing numerous different realities and regulatory systems; 3) it is growing rapidly; and 4) it is clearly an underestimate.

One way to put the number of clinical sites in *emerging* nations (11,038) in perspective is to compare it with the sum of sites in the top four European countries (Germany, France, U.K., and Italy), which amounts 11,061. Another way to look into this figure is to consider the number of patients that are probably enrolled in trials in all these *emerging* countries. If one uses the conservative estimate of having only one patient recruited per site, it amounts to over 10,000 patients serving as subjects in GCTs. This number is likely to be larger, and these research subjects are distributed across a large number of countries with very diverse characteristics as it refers to socio-economic status, cultural values and health care delivery systems. The flip side of this diversity argument is that this clinical research seems to be taking place within a common ground that is represented in each one of these countries, and these “islands of excellence” are serving as stepping stones for a remarkable form of international collaboration.

Although important, this common ground present in each of the represented *emerging* countries seems to be quite limited when compared to the one of *traditional* countries at this point in time. The analysis of individual trials included in

this study shows that even though *emerging* countries are participating in many trials, they usually contribute with a few sites in each of the trials. More specifically, they usually have 2-4 sites and only rarely have more than 15 sites enrolling sites for any given trial.

This situation is not true for any of the *traditional* countries, which have been shown to have the research capacity that enables them to participate with more than 50 sites on a number of occasions. The Scandinavian countries are good examples of countries that, albeit small in terms of population, have large research capacity. As for the larger traditional countries, like Germany, France, Canada, U.K., or the U.S., it is hard to compare as they oftentimes have more than 100 sites enrolling for the same trial.

These *emerging* countries might have a limited research capacity, but given the impressive growth rate in GCT participation that these countries are exhibiting, it is quite probable that their research institutions are becoming busy and diversified in terms of the therapeutic categories they are studying. Special attention should be paid to the *tier 1 emerging* countries that were highlighted in the 2001 OIG report [41] covering the late 1990's (Poland, Brazil, Russia, Argentina, Czech Republic, Mexico, and Hungary) as they had started their growth spurt in the last decade. It is likely that the current growth is based on positive feedback obtained over the last 10 years of experience.

As for China and India, which are the fastest growing countries of the *tier 1* group, such track record in participation on GCTs is very limited. India was not even mentioned in the 2001 IOG report, and China had only one site (located in Hong Kong) in trials starting in 2002, but growing into 177 sites across the country for trials

starting in 2005. These countries are not only growing fast, but are also quickly expanding their capacity. For trials starting recruiting in 2005, it is easier to find participation with more than ten sites in India and China than in the other *tier 1 emerging* countries.

This growth rate is especially relevant because it fits relatively well with reported projections of the pharmaceutical industry regarding allocation of sites of GCTs into the near future [91, 98, 99]. It has been reported in informal communications among industry representatives that the goal for trials starting today is to place about 50% of the clinical sites in the U.S. and Canada, 25% in other *traditional* countries and the other 25% in *emerging* nations [98]. Other industry representatives involved in the decision making of clinical site allocation around the globe informally project a participation of *emerging* economies in the order of 30 to 45% by 2010 [91, 98]. In this thesis, the presented number that refers to participation of *emerging* countries in global clinical development activities is 13%, but it probably does not capture the whole picture.

One of the main limitations of the current analysis is that it does not capture the number of patients enrolled in each of the sites located in *emerging* countries. Such information is not in the public domain, and for the currently recruiting trials, it is oftentimes unknown by the sponsors at the time of reporting. Regardless of the cause, this limitation is important, especially given the common understanding in the industry that about 30% of clinical sites set up in the U.S. never recruit any patients, while the ones which are effectively set up in *emerging* countries are notoriously fast and effective recruiters [14, 16, 21, 31, 41, 99].

Industry officials also informally indicate that the retention rate of patients in *emerging* nations is greater than that of the U.S. [91, 98], therefore, patients that are recruited in *emerging* countries more often result in usable data points at the end of the study. Moreover, patients of *emerging* countries are less commonly taking other medications that complicate, and sometimes impede, an independent assessment of the effect of a given investigational drug on research subjects and their disease [14, 53, 90]¹².

Another limitation of the study presented in this thesis has to do with the fact that not all industry-sponsored trials are reported in clinicaltrials.gov. It is virtually impossible to gauge how much is left out of clinicaltrials.gov, but industry insiders estimate this number to be around 30% as of May 2006. This number is rapidly decreasing and it is quite surprising to see how much detail about clinical development activities has become available through clinicaltrials.gov just in the last six months. As for the trials that are reported, sometimes the information is incomplete. This is relevant for this study as the field that is most frequently incomplete is the list of clinical sites outside the U.S.

The study limitations presented here actually point to an even greater role of *emerging* economies that could be documented. However, if one limits the discussion only to the data points that have been accounted for in this study, there is evidence for relative stabilization of growth (if not negative average annual growth) in *traditional* economies and substantial growth in the *emerging* ones.

In order to interpret appropriately the growth rates presented in the results section, one has to remember that a 0% annual growth rate of the overall global

¹² However, to the extent they represent drug-naïve populations, their similarity to patient populations in the developed countries can be called into question, as can the generalization of the clinical findings.

clinical trials activities over the last four years was an underlying assumption used in the generation of the results. As mentioned, this 0% overall growth rate was chosen basically because the underlying rate is unknown and the time period (2002-2005) is relatively short. I have performed sensitivity analysis on the model by artificially including an annual growth rate of 5 or 10%. Not surprisingly, the inclusion of a positive 5 or 10% overall average annual growth rate for the most part moves up the values of all the countries by 5 or 10% correspondingly. A negative growth rate also has the same effect on the opposite direction. Therefore, it can be concluded that the most appropriate way to qualitatively represent the slightly negative growth rate (-3.2%) of *traditional* countries presented in this study is to say that is slightly below the overall growth rate, whatever that might be. Likewise, it can be inferred that the share participation of *tier 1 emerging* countries grew at a rate that is 22.9% above the overall growth rate, or 26.1% above the rate of *traditional* countries.

This pronounced growth rate of these *emerging* countries was not related to increased participation in any kind of trial. The *emerging* countries are most often (>80% of the cases – as opposed to 47.4% in the *traditional* countries) participating in very large trials, which are the ones that recruits patients in at least five countries at the same time¹³. The fact that these trials frequently have numerous sites in the *traditional* countries as well might make their approval by ethical review boards in *emerging* nations more straightforward, as it goes against the perception that the trial location was chosen to run a clinical experiment that would not be acceptable in *traditional* countries.

¹³ These large multinational trials are characteristically simple trials (in terms of number of clinical endpoints or complexity of medical care provided) that have the goal of enrolling a very large number of patients as quickly as possible.

As for trial phase, I did not quantify how many of the phase II and III trials had the participation of emerging economies, but this number is certainly substantial. This participation can be inferred by the number of instances (> than 80% of the cases) in which these *emerging* countries were engaged in these types of trials¹⁴ and by the overall participation of *emerging* countries in GCTs. This rate of participation of *emerging* countries in pre-approval confirmatory (phases II and III) trials, as opposed to post-approval (phase IV) trials is very close to that of *traditional* countries¹⁵. The substantial participation of *emerging* countries in these phase II and III trials strongly suggests that they are becoming significantly engaged in pre-approval global development operations.

Clinical Drug Development in Different Regions of the Globe

Clinical development participation can also be characterized by geopolitical regions, which share some common characteristics. Not surprisingly, the quantification of participation by region demonstrated the clear dominance of North America, Western Europe, and the Pacific. The other regions have a smaller participation, but a very high growth rate.

As for North America, it comprises almost half of all sites contributing to GCTs. If one includes the estimated number of sites (25,949) that were excluded

¹⁴ Participation of *emerging* countries in phase I studies was very small, but as the regulation governing trial registration on clinicaltrials.gov is not very strong in relation to this type of trial, I assumed that very little was actually registered and chose not to quantify the features of these trials. Furthermore, it is not surprising that drug innovators chose to keep these phase I trials close to the sponsor's headquarters within the *traditional* countries. The main issues with bringing phase I trials to *emerging* nations is the fear of losing key intellectual property, the relatively small sizes and costs of these trials, and the heightened sensitivity around drug testing with financial compensation in normal subjects living in impoverished locations.

¹⁵ A good number of the post-approval studies that are specific to each country were clearly not captured in this database, either because of my exclusion criteria or because some of them do not need to be in the U.S.-centric clinicaltrials.gov database.

because they were only in domestic (U.S. only) trials, the estimated participation share of this region goes to 62%. The growth rate of this region was coincidentally the same as the assumed overall growth rate (0.0%), but I can not ascertain that this is true because I do not know how the proportion between domestic and GCTs with U.S. participation changed over the last years, as these trials were excluded from the database. Even though the U.S. story is not clear, the negative (-9.5%) average annual growth observed in Canada is of interest. This country is still the preferred destination for clinical sites outside the U.S., but now seems to be losing some ground.

Likewise, Western Europe has a very large number of clinical trials, especially considering that it also hosts numerous academic and/or public funded studies that were not included in this database. Notwithstanding, the negative (-7.9%) average annual growth rate of this region is substantial. Many countries presented significant (<-10%) negative growth (Germany, U.K., Italy, Norway, Austria, and Switzerland), while some actually were in the positive or neutral space (France, Spain, Belgium, Netherlands, Sweden, Denmark, Finland, Ireland and Portugal). It seems clear that the allocation of clinical trial activities is changing substantially within Europe.

The story for the arbitrarily defined (includes Greece and Turkey) Eastern Europe is also quite extraordinary. This region has been experiencing substantial growth (26.3%), and is the one that presents the largest participation share in GCTs (8.0%) when compared to that of other mostly emerging regions like Latin America (3.7%) and Southeast Asia (3.2%). The combination of this growth rate with the fact that these countries are already coming from a relatively large base makes them increasingly important.

In terms of performance, the situation of Latin America is intermediary between Eastern Europe and Southeast Asia. The Latin American countries already have a substantial base, especially considering that their number of players (6 countries) is less than half of the one of Eastern Europe (13 countries) and less than Southeast Asia (8 countries). The growth of Latin America is still substantial (24.1%), with the notable exception of their top performer (Brazil), which is basically keeping up with the overall annual growth rate (0.9%).

Southeast Asia is the region that is experiencing the highest growth rate (29.8%). It comprises many countries with huge populations and reportedly the potential to take on the world of clinical development [53, 90]. Even though this phenomenon has not happened yet, one might be able to see it on the horizon. China and India have grown from basically nothing to occupy respectable positions in just four years, with average annual growth rates of 40.1% for India and 61.9% for China. In any case, the quantification of annual growth rate is problematic when one starts from a very small base. I dealt with this problem in this study with the application of a mathematical formula that is designed to handle this situation (arc elasticity – arithmetic mean).

Most of the Pacific countries, on the contrary, are large players (Japan and Australia). Even though these countries seemed to be less engaged in GCTs than countries in Western Europe or in *emerging* markets, such relationship did not change substantially in the last few years. The exception to this profile for wealthy Pacific countries is New Zealand, which has a small participation in GCTs (0.2%), is growing rapidly (27.9%), and is most commonly involved in large multinational trials (86.4% of its sites).

The only country in the African continent that made it to the top 50 list was South Africa. This country is presenting moderate negative growth (-2.3%), which was not frequently seen for *emerging* countries. Notwithstanding, South Africa is a top performing *tier 1 emerging* country, which is most heavily involved in large multinational trials (89.8% of the cases).

In the Middle East, Israel is the only representative. This country has experienced significant positive growth (12.4%) and has a participation (317 trials) that puts it close to the *tier 1* countries.

Since I did not capture the identities of the countries for which sites were represented in aggregate (“others” bin), I can only limit myself to say that the individual participation of countries outside the top 50 list was very small (less than 0.1% each). The choice of studying only the top 50 countries in detail was shown to be appropriate as it has captured the performance of the major players while identifying trends in almost all the small *emerging* economies that had significant participation.

Globalization of Clinical Drug Development and its Implications

The role of *emerging* economies in global clinical development is already substantial. Considering that there is evidence that this participation is going to grow even more in the near future, the major stakeholders (governments, companies, regulatory agencies, and health care delivery systems) need to adjust to this new reality accordingly.

At the end of the day, growth rates in emerging countries will only be sustained if these countries continue to invest in education (population and health

care professionals), health care infrastructure, intellectual property protection, effective and expeditious systems for ethical review of human research, transportation and communication systems, and ultimately develop a substantial market for pharmaceutical products. If all those things do not occur concomitantly, the long-term viability of this drug development model will probably be quite limited and it will continue to be under the considerable risk of a major set-back based on possible incidents involving lax subject protection of vulnerable populations.

On the other hand, if these countries move in the right direction in terms of patient protection and continue to strengthen their research capacity, it is easy to see how they can continue to grow at a rapid pace to become prominent players in global clinical development in the next twenty years. The current paradigm of having a relatively small number of centers of academic excellence located in these *emerging* nations participating in GCTs might gradually change. These countries may continue to add land to their “islands of excellence”, turning the common ground that they have with the developed world into the rule, rather than exception. This transition would likely expand the global clinical research capacity to an unprecedented scale.

One of the ways that this mentioned transition might change medical product development has to do with neglected diseases that are characteristic of the developing world. A substantial improvement in health care delivery systems, and corresponding research capacity, in *emerging* nations would enable them to effectively deal with their own diseases. One important impediment today to the R&D of drugs targeted at neglected diseases of the developing world is the insufficient number of local trained health care professionals with research experience, and the

inappropriate health care infrastructure to run the clinical trials of the drugs that are getting into the pipeline more recently [3, 16, 63].

This pipeline has been created with the support of public-private partnerships such as the Gates Foundation, which now has increasing collaboration with large pharmaceutical companies. This interest of drug developers in neglected diseases is tightly coupled with the mentioned gradual involvement of pharmaceutical companies in *emerging* markets through the adoption of a global clinical development paradigm for diseases common to the developed and developing world.

While the initial driver for global trials on the types of diseases that are common to all countries was the need for more cost-effective access to research subjects, companies have been also increasingly seeking concomitant global registration so that no product lifetime for truly global products is wasted in these fast growing *emerging* markets. This global/local registration effort is driven by market forces, but ends up changing the way that drug developers interact with regulatory agencies, which are not necessarily set up to deal with global clinical drug development activities.

Even though harmonization of clinical guidelines (ICH) was a very important positive change, regulatory agencies – especially the U.S. FDA – now have to deal with information coming from a much greater number of clinical sites and countries that they are not familiar with [99]. Inspections from the FDA or EMEA on these international sites can only do part of the job, and it is clear that in the long run strong collaboration among regulatory agencies of all these involved countries will be needed. The Chinese FDA (sFDA) has taken a step in this direction, and has

begun to do its own inspections, gradually building a list of clinical sites that are considered suitable to recruit patients for GCTs. This Chinese agency seems to be very interested in becoming harmonized with the work performed at the U.S. FDA, attested by the choice of its official name (sFDA).

It is clear that in this globalized scenario countries, companies, regulatory agencies, clinical research institutions, health care providers and patients are moving closer together. The interesting piece is that they are moving closer in a world that is rapidly expanding with possibly beneficial outcomes to all these stakeholders.

In this new world patients of *emerging* nations are vulnerable, as there is still so much income inequality, inadequate access to health care, and ineffective education. On the other hand, if patient abuse does not occur at this initial stage and these *emerging* countries continue to move towards full blown development, the same patients will greatly benefit. They will have better drugs tailored to their biological and cultural condition and local health care systems that can deliver state-of-the-art medical care, just like their counterparts in the developed world.

VIII – Conclusions and Future Research

The key findings of this study are:

- 1) The top 50 countries that are most actively taking part in global clinical trials of investigational drugs either have high income per capita (more than US\$10,000¹⁶ in 2005) or are “emerging markets” tracked by The Economist®.
- 2) The participation share of *emerging* countries in global clinical drug development has continued to increase over the last four years, while the participation share of *traditional* countries has been decreasing.
- 3) *Emerging* countries have a greater level of participation in large multinational studies (with sites in more than five countries) than do *traditional* countries.
- 4) *Emerging* countries have a level of participation in the confirmatory phases (phases II/III) of clinical development at a rate that is comparable to that of *traditional* countries.

It is clear that the globalization of clinical drug development is a highly complex process that has the potential of changing standards of health care delivery around the globe. This thesis provides a quantitative assessment of this phenomenon and describes some of its key characteristics, including the recent evolution of the participation of important players in this process, which are the *emerging* countries. I have also described the types of trials that have been conducted in these countries, and discussed some of the major trends in the field of global clinical drug development.

This presented work would not be possible without the recent disclosure of

¹⁶ CIA World FactBook 2005.

information on clinical development activities at the clinicaltrials.gov website. It is clear that the kind of approach used to analyze drug development information in this study can objectively address many issues of importance to policy makers of all involved countries, managers in the pharmaceutical industry, health care providers, and their patients.

This study will be expanded in several ways to address some key questions that remained mostly unanswered in the presented thesis. One key question that is not yet adequately addressed is the growth rate of the U.S., which is by far the major player in clinical development today. The inclusion of U.S. clinical trials in my database in the near future will enable me to answer this question. One can actually take a step further to look at the evolution of clinical site allocation within the U.S. over the last years in order to address the raised question that trials are moving from northern states towards the south [99].

The inclusion of U.S. clinical trials will also enable me to address several other questions, including the overall proportion of phase II and III trials going to *emerging* countries and how that is changing with time. I can also determine how the allocation of trials of different therapeutic categories has been changing over the last years. Furthermore, I might be able to correlate year-to-year growth rate of key countries in clinical development with their public policies and major initiatives by the private sector.

My ultimate goal is to create a live document that is updated as the clinicaltrials.gov registry is updated daily. The other goal is to establish relationships with drug developers to see if data that is not published in the clinicaltrials.gov can be included in the database of clinical development to be analyzed in aggregate. It is

clear that a continued systematic and objective analysis of global clinical development activities moving forward is going to be an important contribution to all stakeholders involved in the drug development process.

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