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Facing the Trial of Internationalizing Clinical Trials to Developing Countries: With Some Evidence from Mexico

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Facing the Trial of Internationalizing Clinical Trials to Developing Countries: With Some Evidence from Mexico[*]

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Abstract

In pursue of innovation, developing countries play an increasingly relevant role for multinational pharmaceutical firms. Driven partly by cost considerations but also by some host country-specific scientific and technological factors, global drug companies increasingly relocate part of their drug development activities to those countries. In particular, expansion of clinical trials performed in some of the more advanced developing countries is notable over the last years. This paper critically addresses some of these issues with particular reference to Mexico. The latter case equally illustrates some challenges developing countries face to accommodate and govern local performance of clinical trials according to strict internationally accepted regulatory and ethical principles.

JEL Codes: 032; I18; F23; L65
Key words: Internationalization of R&D, Governance of clinical trials, Developing countries, Mexico

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1. Introduction

Recent years witness trends towards outsourcing and internationalization of clinical research by pharmaceutical firms; they increasingly run trials at numerous sites around the world. Several developing countries are emerging as relevant investigative sites. Although India and China appear as preferred destinations, good prospects to participate seem to lie ahead also for other advanced developing countries: Brazil, South Africa and as discussed here, Mexico. Besides large domestic markets, such countries have consolidated major regional manufacturing and export bases for multinational affiliates and some domestic firms. Moreover, they feature some country specific conditions shaping attractiveness of investigative sites.

In this context, there is currently a debate on the ethical implications of running clinical trials in developing countries: are people there mere "guinea pigs" serving "selfish" commercial interests of pharmaceutical firms? (Schüklenk, 2000; Daikos, 2004; Sharma, 20004; Singh, 2007; TheLancet, 2007) Is it possible for them to promote orderly developments in the local market for clinical trials in order to protect participating local populations? Probable answers seem contingent on the countries' capacity to shape suitable institutional and more precisely, regulatory structures around the operation of multinational firms (Dunning, 1994; Kuemmerle, 1999); in this particular case, pharmaceutical firms performing clinical trials.

This chapter analyses recent developments in the markets for clinical trials in Mexico and other developing countries to illustrate: (1) some factors driving the dynamics and attractiveness of such countries as investigative sites; and, (2) some challenges they face to adjust and modernize local regulatory environments governing such activities. Are there any policy lessons to learn? The chapter brings together literature: on (i) internationalization of R&D and, (ii) ethical implications and regulation of clinical trials. Section 2 characterizes clinical trials within the broader innovatory process in the pharmaceutical industry including some determinants of their internationalization and location to developing countries. Section 3 looks at some regulatory challenges in relation to clinical trials in Mexico. Section 5 concludes.

2. Clinical trials: innovation and markets

2.1 Pharmaceutical Innovation: clinical research in context

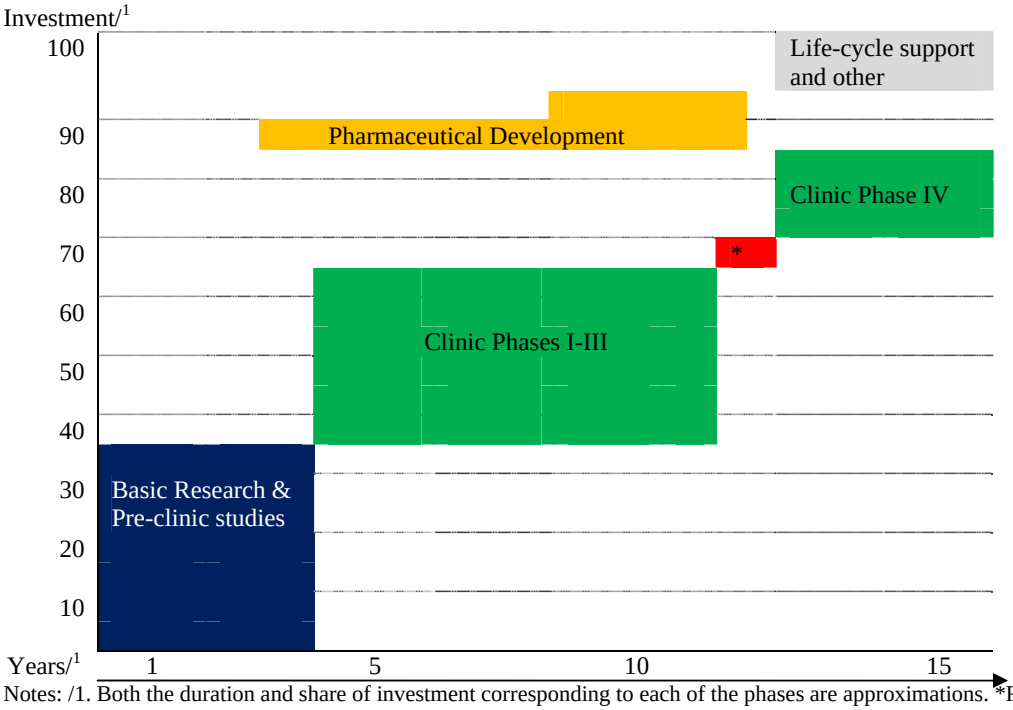
Pharmaceutical innovation comprises four major stages (Figure 1): (1) Discovery or basic research[1] leading to identification of new molecular targets, "New Chemical Entities (NCE's),[2]" and pre-clinical studies[3]. (2) Development or clinical research comprising activities before and post-marketing of new drugs; (3) Regulatory processes of evaluation and eventual approval/rejection of development/marketing of pharmaceutical products and; (4) Manufacturing, marketing and product life-cycle support. (Achilladelis and Antonakis, 2001; McKelvey and Orsenigo, 2002; Hara, 2003; Styhre and Sundgren, 2003) The length and sequencing of each stage depends on legal, ethical, scientific and economic factors (Jungmittag, Reger et al., 2000; Gaudillière, 2004). With regards to clinical trials, these are tests to certify efficacy, safety, overall socio-economic and technical viability of prospective new drugs or medical devices. New drug related clinical research is the more abundant, yet it includes: epidemic studies, life-style modifications, prognostic studies, health records, and test of non-pharmacology related therapies (Interviews). This paper focuses on tests of pharmaceutical products.

[1] Unlike previous random trial-and-error processes, modern drug development builds on more accurate understandings of how the body works both normally and abnormally, at its most basic level. It is possible to determine how prospective drugs might prevent, cure, or treat a disease.

[2] NCE's are totally new drugs which in most cases represent significant therapeutic advances as 'chemical structures never previously available to treat particular disease(s)' (FDA)

[3] Pre-clinical studies in animals (*in vivo)* or other models (*in silico)* assess toxicity and other pharmacokinetic properties of prospective NCE's before tests in humans can begin. Similar tests however, are performed in humans during clinical research (Zivin, 2000).

Figure 1 –Phases of the innovation process in the Pharmaceutical industry



Notes: /1. Both the duration and share of investment corresponding to each of the phases are approximations. *Refers only to the process of Sanitary Registration. In practice, regulation is bound to intervene all over during the innovation process.

Source: Author based on information from AMIIF; Zivin, (2000); Reiss, (2000); and, Reichert, (2003)

Clinical trials split in Phases I-IV, each of which differs in complexity regarding technical knowledge, infrastructure, number and profiles of people involved, regulatory requirements, and so on. Phase I constitutes first-time administration of NCE's in humans (firstly on healthy volunteers); then, during Phase II the drug is administered to a small sample of volunteers featuring the target medical condition. These two Phases inform research questions, definition of analytical conditions and end-points[4] for the subsequent more lengthy and massive studies in Phase III (Zivin, 2000). Post-marketing studies (Phase IV) provide information about the long-term effects of the new drug, while exploring opportunities to develop improved/new applications that extend life-cycles of existing products. Clinical trials, particularly Phase III, account for the largest share of the 10-15 years required to bring a new drug to market and, a third or more of estimated investment, USD800-900 million (Boggs, Bayuk, et al., 1999; Maiti and

Raghavendra, 2007). Accordingly, speed, coordination, efficiency, accuracy and minimizing cost of trials are critical to reduce time-to-market, increase profits and enhance product quality; each day saved in development brings substantial gains in expected revenues for the firm.

2.2 Internationalization to developing countries

Seizing the global market for clinical trials is problematic as estimates of annual investment vary widely according to the source, between USD10-40 billion in 2006 only (LeadDiscovery, 2006; LamtechInstitute, 2007). Alternatively one can look at the distribution of trials among investigative sites throughout the world. To do so, we rely on data about trials carried out in the US and other 153 countries and registered by the US Federal Drug Administration (FDA) –NIH-NLM. Additional data refer to annual applications for Clinical Investigators -medical researchers responsible to carry out clinical trials' protocols- received by the FDA -BMIS.

At the end of February, 2008, about 51 987 protocols had been or were being carried out in the world since 1948. Considering that many of these are performed in multiple sites at once, the actual number may add up to 75 900[5] (Table 1). Global clinical trial activities record a tenfold increase since the year 2000, with a strong dynamism in those performed outside the US. Notably, whereas participant developing countries rose from 34 to 93 in less than a decade, their share practically doubled over the same period. Similar situation occurs with Transition economies. A breakdown by main developing country region shows Latin America has the largest share; yet, driven by India and China, East and Southeast Asia has the strongest dynamism. Table 1 equally documents the weight Brazil, South Africa and Mexico have as investigative sites in their respective regions. Calculations based on NIH-NLM reveal that in 2007 more than 1.1 million people would have participated in clinical trials in these five countries only (Figure 2).

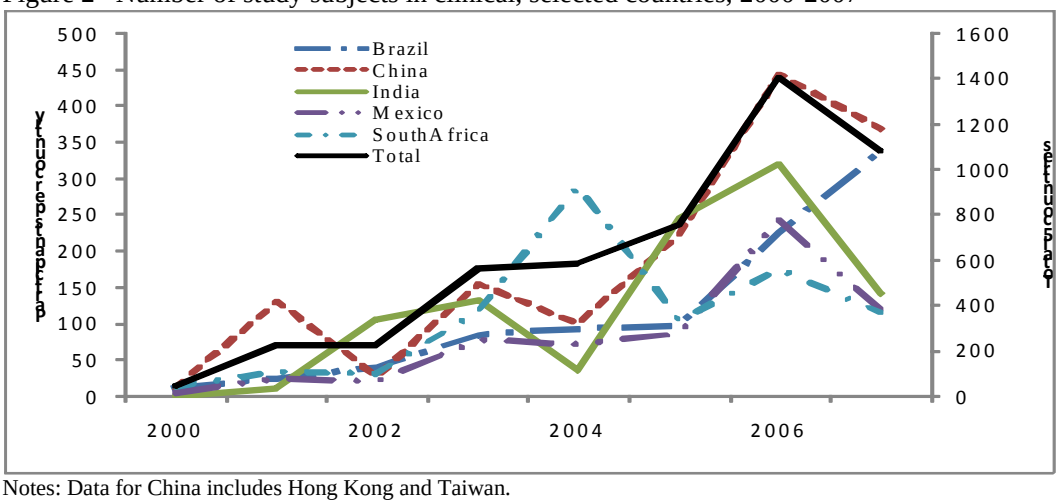
[4] End-points are 'unambiguous results that indicate exactly what the treatment can do', they signal changes in a patient's condition ranging from healing to reductions in the progression of disease or whether dead rates have fallen (Zivin, 2000:73).

Table 1. Distribution of clinical trials by main countries and regions, 1948-2008

	1948-2000	2001-2008	2008*	1948-2000	2001-2008	2008*
Region	per cent share of trials			Participating countries		
World[/1]	6590	69274	75900	72	137	137
Developing	6.4	12.7	12.1	34	93	93
Transition	1.0	3.6	3.4	9	15	15
Developed	92.6	83.7	84.5	29	29	29
	per cent by main region			By region		
Africa	1.2	1.9	1.9	7	37	37
-South Africa	0.9	1.0	0.9	---	---	---
Latin America	4.8	5.3	5.2	13	24	24
-Brazil	0.2	1.1	1.0	---	---	---
-Mexico	0.0	1.0	0.9	---	---	---
East, Southeast Asia and Pacific	0.3	4.9	4.5	9	19	19
-China[/2]	0.1	2.6	2.4	---	---	---
-India	0.0	0.9	0.8	---	---	---
Europe	0.9	2.5	2.3	10	11	11
Middle East	0.1	0.3	0.3	3	11	11
North Asia	0.0	0.3	0.3	1	6	6
Developed	2.0	1.5	1.6	29	29	29
-US	64.1	37.5	39.8	---	---	---
--Europe	18.7	30.3	29.3	18	18	18
--Japan	0.1	1.1	1.0	---	---	---

Notes: *February, 28. 1/ Absolute numbers. /2 Includes Taiwan and Hong Kong. Otherwise, the share would go down to 0.0, 0.9 and 0.9, for each respective period. Our regional classification differs from that used in the original source. We rearranged following World Bank, IMF and OECD classifications.
Source: Author with information from NIH-NLM

Figure 2 –Number of study subjects in clinical, selected countries, 2000-2007

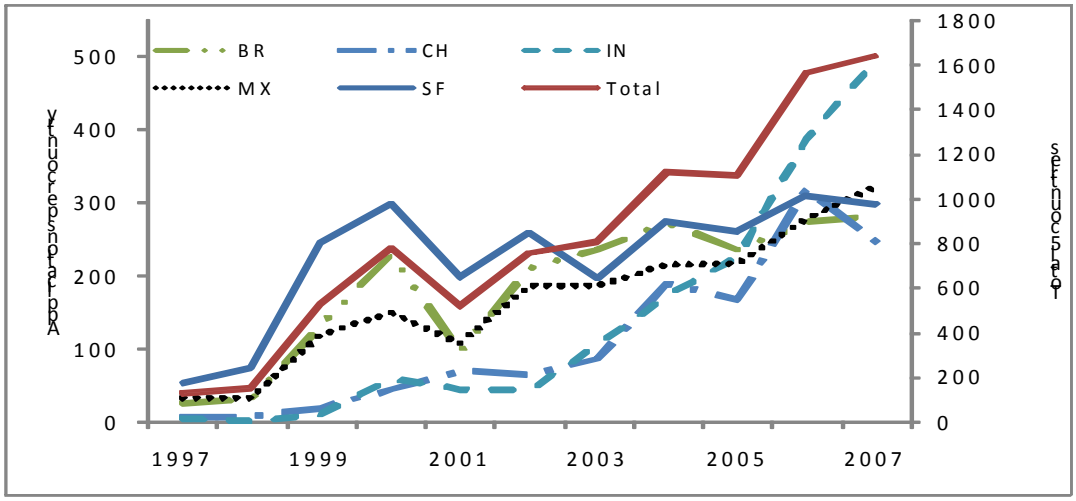


Notes: Data for China includes Hong Kong and Taiwan.
Source: Author with data from NIH-NLM

[5] "Double counting", particularly in breakdowns by region is evident in the source (NIH-NLM).

Availability of qualified human resources is critical for the adequate performance of any system of innovation. Growing clinical trial activities would be hindered without the corresponding development of a pool of specialized personnel to carry them out. A positive response from developing countries would be the rise in the number of applications for clinical investigators to the FDA. For example, since 1997 those coming from Brazil, China, India, South Africa and Mexico have grown at an average 13.5 per cent per annum (Figure 3). In 2007, applicants from these five countries represented 6.9 per cent of the total. However, since many such applications would correspond to a single individual, the dearth of well trained and experienced personnel remains a major shortcoming in developing countries. Concerns of future shortages of qualified people would be on the rise as current difficulties to find well-trained and experienced personnel are compounded by rather slow responses from local education systems (Singh, 2007; interviews).

Figure 3 –Number of applications* to perform as clinical researcher, selected countries, 1997-2007



Notes: *Number of times an application is presented even if by the same person; accordingly, a researcher may appear in the dataset more than one time. Data for China includes Hong Kong and Taiwan.
Source: Author with data from BMIS

2.3 What drives internationalization of clinical research?

Globalization, rapid technological change, stronger competition and the development of pockets of scientific and technological excellence throughout the world compels

multinationals to continuously adjust and reorganize R&D activities both at home and abroad (Gassmann and von Zedwitz, 1999). Driven by both science and technology related and R&D cost related factors, firms may concentrate, spread or adopt a mix of these two strategies in pursue of R&D and innovation (Reddy, 1997, Patel and Vega, 1999, Gassmann and von Zedtwitz 1999, Cantwell and Kosmopolou, 2001; von Zedtwitz and Gassmann, 2002). Different authors name distinctly observed trends or patterns of internationalization and globalization depending on whether they consider R&D-specific or R&D-external factors (Reddy, 1997; von Zedwitz and Gassmann, 2002); motives, location characteristics, inter-temporal characteristics and modes of entry of FDI (Kuemmerle, 1999); degree of cooperation between individual R&D units (Gassmann and von Zedwitz, 1999). It is not our intention to review them here; it suffices to say they entail distinct interactions, conditions to participate and more importantly, different influences on the structure and performance of regional, sectoral and national systems of innovation (Dunning, 1994; Reddy, 1997; Le Bas and Sierra, 2002; Archibugi and Pietrobelli, 2002; Chen, 2006a,b; Milstien et al., 2007).

In identifying particular types of internationalization, country, industry and firms' characteristics matter, it is problematic to set clear-cut distinctions at least between countries and industries (Dunning, 1994; Kuemmerle, 1999; von Zedwitz and Gassmann, 2002). Clearly however, multinational firms split research and at a larger extent, development, across geographical locations (von Zedwitz and Gassmann, 2002)[6]. In such a way firms may tap on scientific and technical capabilities and other country-specific characteristics in "relevant markets" while protecting, enhancing or complementing the core knowledge developed at home (Kuemmerle, 1999, Patel and Vega, 1999; Le Bas and Sierra 2002). Host countries in turn, may serve different roles for multinationals overtime; they can either be a place to exploit knowledge and innovation produced at home or, part of complex regional and/or global innovation generating networks (Reddy, 1997; Dias and Bresciani, 2006).

The pharmaceutical industry in particular, is one of the more globalized and compared to other industries, would show a more ample tendency to internationalize and

outsource R&D (Kuemmerle, 1999; von Zedwitz and Gassmann, 2002). The strategy would be supported by possibilities to include data from trials performed outside the US in any new drug/investigational drug application to the FDA (FDA, 2001).

Since the rate at which clinical trials are conducted depends predominantly on the number, quality and cost of investigators and study subjects (Zivin, 200), it is critical for firms to enrol early and retain both these groups during drug testing and development, developing countries offer attractive options for this[7] (Maiti and Raghavendra, 2007; interviews). Indeed, heterogeneous and growing populations, high prevalence of targeted diseases and lower research costs -even for fairly similar manpower's quality and research conditions relative to developed countries[8]- partly explain expansion of clinical trials to developing countries; more and more, data from these countries support registration of new products in relevant markets such as the US. Relocation supports early positioning of potential new products in prospective markets too (PhRMA, 2006b; interviews).

Firms would benefit from proximity and access to organizations that either shape demand for their products, notably drug regulatory authorities, or that create positive externalities for their manufacturing and research activities in host countries (Kuemmerle, 1999). Hence, they would prefer sites with relatively strong regulatory environments, swift evaluation and approval of research protocols, reduced times for drug registration and marketing authorizations (DiMasi, 2001; Piachaud, 2002). Host countries should also comply with tough international standards on Good Clinical Practices (GCP) and Good Laboratory Practices (GCP) respectively,[9] so as to ensure quality and integrity of data and more importantly, to safeguard wellbeing of study

[6] According to the authors, the split of Research and Development reflects the distinct nature of such processes in terms of knowledge requirements, infrastructures, personnel, social perception, and so on.

[7] In addition to outsourcing at home and abroad, intensive use of ICT's –Internet, for example - to advertise, pre-screen and recruit study subjects complement strategies to attract them (van Brunt, 1999; Piachaud, 2002; Marks and Power, 2002; Lamb and Setley, 2005;TCSDD, 2007).

[8] Maiti and Raghavendra, (2007) for example report savings of 30-50 per cent in India for comparable clinical trials carried out in Europe or the US.

[9] Adoption of GCP's in the post-II World War period responded to the need to protect integrity of subjects participating in clinical trials; key practices include informed consent and observance of ethical aspects of tests in humans. GLP's in turn, refer to systems of management controls conditioning work in laboratories and research organizations ensuring quality, consistency, validity and reliability of test data. (FDA)

subjects. Good infrastructure and favourable research environments are critical as well. In what follows we illustrate some of these points with reference to Mexico.

3. Clinical research in Mexico

Mexico is the world's 9th largest pharmaceutical market and the 2nd in Latin America. Strong dynamism reflects in retail sales in the private drug market growing at 6.0-8.0 per cent per annum (IMS). It is a relevant manufacturing and export base to tender Latin America and at a lesser extent, the US, Europe and Asia (Interviews). With regards to clinical trials, there is a growing local activity as pharmaceutical related trials rose from 285 protocols in 2000 to 1,360 protocols in 2007 (COFEPRIS, 2007). Data from Mexico-based trials would support registration of new products in the US and other relevant markets. Take for example, an affiliate of European origin in which local personnel developed a multivitamin product for people with diabetes in Mexico. However, as locally-performed trials suggested the product would have positive effects on some post-operation side-effects for cardiovascular diseases, at the time of the interview, the company's headquarter was evaluating performance of clinical trials at a more global scale to test for an eventual new application. How can we explain this? In line with the discussion in Section 2.3, a number of country specific factors may be at stake.

Mexico is the 11th most populated country in the world (World Bank); estimates for 2007 set total population at 108.6 million, with about 43 million (~39 per cent) aged 19 years or less (SINAIS). This is a potential market for paediatric products, offering opportunities to exploit well reputed and specialized research infrastructure in the area (Castellanos and Chiprut, 2002; LamtechInstitute, 2007; Interviews). Agglomeration of about 37.6 per cent of the population in Mexico City, her two largest neighbouring states, Estado de Mexico and Puebla, and in the industrial states of Jalisco and Nuevo León, coincides with concentration of some of the country's largest public health premises, many of the most modern health related education and research facilities, and location of most local and foreign pharmaceutical firms in the country (CANIFARMA; Dussel, 1999; CCINSHAE).

Local demographics and epidemics lead to a mix of diseases characteristic of developing countries but also of more developed ones –Table 2 and SS, (2005). Urbanization, augmented life-expectancy at birth and improved sanitary conditions imply that although poverty related diseases such as Gastrointestinal and Respiratory infections or Malnutrition, are now in check or slightly decreasing, they persist among main causes of dead, particularly among children and in highly impoverished regions (SS, 2005). In contrast, chronic illnesses and other associated with metabolism and age have gained prevalence. Nowadays, "life-style" diseases such as Diabetes and Ischemia account for nearly a quarter of dead rates per 100 000 people; Mexico is expected to host one of the largest diabetic populations by 2025 (Kuri, Vargas et al., 2001). Shrinking natality rates, from 34.7/1000 in 1980 to 18.6/1000 in 2007, accompany a smooth demographic transition with the share of elderly people (65+ years old) increasing from 4.3 per cent to 5.5 per cent over the same period (Calderón, 2007). This raises expectations of growing, multiple and longer lasting future drug intakes (Kuri, Vargas et al., 2001; SS, 2005).

Table 2 – Mexico: Main causes of dead, 2000-2005[1/]

Item	2000	2005
Diabetes mellitus	10.7	13.6
Ischemic and related heart diseases	10.1	10.8
Cirrhosis and other chronic affections of the liver	5.8	5.6
Brain vascular diseases	5.8	5.5
Malign Tumours	5.5	5.3
Lung obstructive chronic disease	3.7	4.1
Diseases related to prenatal period	4.5	3.3
Acute low respiratory infections	3.3	3.0
Hypertension	2.2	2.6
Nefresie & related	2.3	2.3
Malnutrition	2.0	1.7
HIV/AIDS	1.0	0.9
Gastrointestinal infections	1.2	0.9

Notes: 1/ Percentage of total dead ratios per 100,000 inhabitants
Source: (SINAIS)

At least compared to other Latin American countries, Mexico has a fairly strong public healthcare system that next to large population coverage, hosts some of the country's more advanced health research capabilities (SS, 2005). Instituto Mexicano del Seguro

Social (IMSS) and Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado (ISSSTE) are the largest public medicare organizations with about 61 million affiliates (INEGI). Other relevant public organizations include the National Health Institutes (NHI's) featuring ample capacity to perform clinical and some basic research, together with highly specialized health-assistance and training across 12 different therapeutic areas (CCINSHAE). Complement the sector a number of public hospitals and universities throughout the country. Linking to these public organizations saves firms the need to create specialized centres as required by Mexican authorities to perform clinical trials; more importantly, they grant access to huge and captive populations under fairly standardized research conditions (Interviews).

3.1 The institutional environment underpinning clinical trials

This paper enquires about the extent developing countries may be able to promote orderly developments in their local markets for clinical trials. Available literature suggests such goal is contingent on their ability to adopt proactive policy stances towards operation of multinational firms (Dunning, 1994; Archibugi and Pietrobelli, 2003, Meyers, 2006; Chen, 2007). Following Dunning (1994), influences from public policy may either be *direct* -through funding and regulating R&D activities; or *indirect* by influencing the overall environment in which firms undertake innovation[10]. Regarding the latter influences, the current debate on the ethical implications associated with clinical trials hints at, among others, two interrelated areas relevant for policy intervention: (1) characteristics of the regulatory environment and, (2) the structure and functioning of mechanisms responsible to evaluate and monitor clinical trials (Drews, 2000; Zivin, 2000; Castellanos and Chiprut, 2002; Fleck, 2004; Kermani, 2006; Lombera, 2006; Meyers, 2006; PhRMA, 2006a; Valdez-Martinez, Turnbull et al., 2006; Maiti and Raghavendra, 2007). These areas highlight some minimum conditions increasing the likelihood that local performance of clinical trials meets international standards about protection of study subjects, while promoting adequate interactions between local agents and multinational firms.

[10] Until recently India banned the performance of clinical trials within its territory before similar trials had being carried out elsewhere already (Kermani, 2006).

3.1.1 Regulatory Issues

Relative strength and compliance with regulatory frameworks and internationally accepted standards condition attractiveness of investigative sites. In Mexico, the regulatory authority is the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS). Created in 2001 COFEPRIS institutionalized efforts to integrate, simplify and homogenize, within a single government organization, regulation on sanitary and related risks; items under scrutiny include pharmaceutical products but also basic sanitation, environmental risks, publicity on health, food and related products and so on (Enríquez, 2006). Regarding clinical trials, COFEPRIS has strengthened and increased transparency of the regulation, yet governance of trials features shortcomings prone to holdback their adequate development in the future (Enríquez, 2006; LamtechInstitute, 2007).

Pending in the agenda is modernization of the regulatory framework, notably in relation to research. The current framework rests on The General Health Act (Ley General de Salud), and the associated Bill on Health Research (Reglamento de la Ley General de Salud en material de Investigación) dating back to 1984 and 1987, respectively (SS, 1984 and 1987). These documents specify the steps and conditions necessary to perform clinical trials in Mexico. Both of them however, were conceived when such activities were relatively limited in the country; consequently, current guidelines are rather general, weaker compared to current industry standard practices -e.g. International Conference on Harmonization (ICH); and somehow inadequate to tackle challenges resulting from an expanding market (LamtechInstitute, 2007; interviews). Generality means the need to harmonize research, clinical and laboratory procedures throughout the country too. Initiatives for a Mexican Norm on Clinical Research thereby procedures meet highest standards agreed upon by all relevant parties need to progress at a greater rate (Interviews).

COFEPRIS is responsible to approve and monitor clinical trials according to tight legal, safety, technical, ethical and other requirements set in current legislations. The agency however, is able only to partially fulfil the task; gaps persist in monitoring work in progress (Interviews). This is an issue of equal concern in India where notwithstanding

improved regulation of the industry, weak enforcement remains an item (Singh, 2007). Regulatory agencies in both countries suffer from a dearth of well trained and experienced personnel, financial resources and infrastructure to carry out monitoring. In Mexico, poor remunerations and salaries compound the picture (Interview). Mexican officers would lack full awareness and hands-on experience conducting clinical trials; learning processes would run parallel to actual performance of supervisory duties (Interviews). Accordingly, COFEPRIS often has to lean on "experts" from hospitals, research centres, universities and the industry itself to conform supervisory and monitoring teams (Interviews). Authorities would avoid conflicts of interest or inappropriate behaviours by requesting "blind" evaluations, leaving actual decision-making on ethics committees (Interviews). The extent this practice rules out conflicts of interest and other problems calls for further study as, in line with the discussion in Section 3.1.2, major shortcomings remain in the operation of such committees. In any case, disappointment with an agency expected to stand as tall as the FDA but that instead, remains poorly empowered and financially endowed is clear (Interviews).

Steps towards improving the regulatory framework in Mexico include recent creation of a permanent Pharmacovigilance programme and enactment of a Mexican Norm on the matter (Becerril, 2006). Pharmacovigilance in Mexico is therefore divided in: (1) Early Pharmacovigilance: mandatory by Law, it requires watching for any sanitary risk arizing during the first two years of commercialization of a new drug; and, (2) Intensive Pharmacovigilance that considers specific tests of particular features of a drug after commercialization, thereby requiring more active stances by firms. Requests for specific studies are expected to warn early on any sanitary risks associated with trials and consumption of pharmaceutical products. In addition, and mirroring similar experiences in India[11], the Norm induces firms and research organizations to agree on who takes responsibility to notify COFEPRIS of any major sanitary risk occurring during clinical trials either at home or abroad (LamtechInstitute, 2007).

A final none the least important aspect relates to dissemination of detailed and accurate information about clinical trials, this is critical to prevent potential volunteer study

subjects about the pros and cons of taking part in a given study; such is the essence of informed consent (PhRma, 2006a). In Mexico, lack of data or at least readily available access to them is regrettable especially considering that, as Section 2.2 documents, strong regulatory agencies may induce firms to provide some minimum information about their activities[12]. Better understanding of market dynamics would begin by solving this basic but critical statistical gap. COFEPRIS is developing an ad hoc database containing all research protocols in the country (Interviews); the concrete impact of the initiative is yet to be seen.

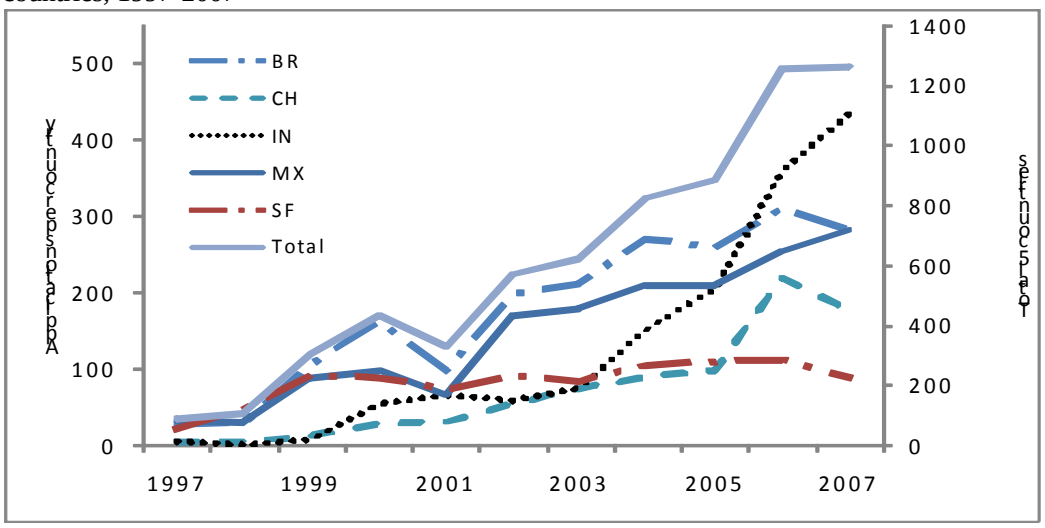
3.1.2 Ethics Committees

According to internationally accepted standards, performance of clinical trials is contingent on approval and close monitoring by ad hoc, independent bodies known as ethics committees or Institutional Review Boards[13]. This would explain the significant increase in the number of such committees throughout the world, and in particular, in the countries included in this study (Figure 4). In Mexico, conformation and operation of IRB's, particularly within large organizations, follows paradigms set by the FDA[14] (Castellanos and Chiprut, 2002). In practice however, evidence is rather mixed about compliance with accepted principles of operation. In line with a study by Valdez-Martinez, Turnbull et al., (2006) about the functioning IRB's at IMSS -the most important locus for clinical trials in Mexico-, we found problems derived from the dearth of people with sufficient knowledge and experience to integrate the committees (Interviews). Responsibility to ethically evaluate protocols would often fall onto "key" persons -the Dean of the teaching program or the Service Head at the host organization, for example (Interviews). To the extent that such characters may frequently act as Principal Researchers -those responsible to lead the research teams conducting a trial in

[11] According to (Maiti and Raghavendra, 2007), amendments made in 2005 to the Schedule Y of Drugs and Cosmetic Act 1945 in India, made reporting duties 'clearer and unambiguous' for firms.
[12] I requested COFEPRIS official data about the market for clinical trials in Mexico, the response was that such detailed information is nonexistent COFEPRIS (2007).
[13] Following US paradigms, 'institutional review board/independent ethics committees (IRB/IEC)' are a group of people formally designated to approve, monitor, and review biomedical and behavioural research involving humans with the aim to protect the rights and welfare of study subjects (FDA).
[14] Ideally, a minimum of 5 persons should integrate the Committee, with at least one independent from the host organization and one a member of the civil society in a non-scientific area (usually from a religious community or minority group)

those host organization- the risks of potential conflicts of interests, insufficient transparency and objectivity in decision making seems high. This is relevant as COFEPRIS' lack of resources and expertise undermines her capacity to ensure that protocols are evaluated and carried out according to proper ethical and other relevant standards. Enforcement of existing legislation is a real challenge (Interviews).

Figure 4 –Number of applications*to the FDA by Institutional Review Boards, selected countries, 1997-2007



Notes: * Data for China includes Hong Kong and Taiwan.
Source: Author with data from BMIS

Deficient conformation of IRB's would slow evaluation of new protocol applications too. Waiting times depend on the institution, type and number of protocols. Bureaucratic procedures, lack of coordination, duplication of responsibilities and even contradictory decision-making, particularly within large organizations, complicate operation of IRB's (Interviews). Although approval times would in general, mirror that of developed countries (Castellanos and Chiprut, 2002); sometimes they may take up to 3 months to emit their judgment (Interviews). Speeding up evaluation processes is critical as overall waiting times for regulatory approval in Mexico -including ethical evaluations, import licenses for investigational drugs, customs paperwork and logistics, and so on (Lamb and Setley, 2005)- may add-up up to 9 months (Interviews). Similar processes may take about 3 months in most Western European countries (BMI, 2006). Times for regulatory approval in Mexico would be more competitive however,

compared to China where this may take up to one year (Lamb and Setley, 2005). Industry's proposals for the creation of *ad hoc* independent evaluation committees to compensate for the absence of IRB's in some Mexican organizations, financed by the industry and actively involving regulatory authorities are currently under debate; the process seems to progress rather slowly, though. (Interviews)

4. Concluding remarks

This chapter explored recent developments in the market for clinical trials in Mexico and other developing countries. Hence, we illustrated a series of country specific characteristics underpinning attractiveness of those countries to host clinical trials; demographic, commercial, regulatory and, R&D related factors became much intertwined. From this perspective, a bunch of advanced developing countries would have interesting potential to continue increasing their presence as investigative sites. After all, multinationals would somehow complement their already established regional split of operations.

A more relevant conclusion however, is that a number of ethical considerations call for a more proactive stance from developing countries vis-à-vis the activities of multinational firms. More specifically, they need to address important bottlenecks characterizing the overall institutional and regulatory environments underpinning local conduction of clinical research. Weak enforcement of inadequate and out of date regulations, alternatively slow or incomplete processes of reform and modernization of such frameworks supports concerns about the extent potential benefits may outperform the inherent risks faced by local populations participating in clinical trials. Creation of ad hoc regulatory agencies is insufficient if they are not properly endowed and empowered.

Taping on local healthcare providers and health related education and research organizations with experience conducting clinical trials sponsored by multinational firms would assist to improve the structure and coordinating powers of regulatory agencies. For example, they could provide more adequate flows of qualified and

experienced manpower to meet demands from rising clinical trial activities. Strong regulatory agencies in turn, seem instrumental to shape and operate research systems meeting internationally accepted ethical and related standards. At a more basic level, stronger commitment of regulatory agencies to gather and make publicly available information about trials taking place in their circumscription would help to improve our understanding of the socioeconomic factors driving internationalization of clinical trials and their corresponding implications on developing countries.

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CCINSHAE Comisión Coordinadora de Institutos Nacionales de Salud y Hospitales de Alta Especialidad: http://www.salud.gob.mx/unidades/cgins/acerca.html

COFEPRIS Comisión Federal para la Protección contra Riesgos Sanitarios http://www.cofepris.gob.mx/quees/cofepris.htm

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Annex: Methodology and data sources

This paper builds on both primary and secondary data sources. Primary data were gathered through semi-structured interviews carried out during fieldwork in Mexico between February-August 2007. Informants included people from multinational affiliates and Mexican pharmaceutical firms–General Directors, Medical Directors, Human Resource Managers, R&D Heads, Development analysts- and, representatives from the main local Trade Organizations CANIFARMA and AMIIF –these include mostly multinational affiliates accounting for 85 per cent or more worth of the local private market (Hernandez, 2007 and interviews). We also interviewed people from the Mexican regulatory agency, COFEPRIS, and the coordinating body of the public health and research centres hosting most clinical research protocols in Mexico (CCINSHAE). Interviews took an hour long on average and in most cases were audio-taped and fully transcribed afterwards. For reasons of an explicit commitment to confidentiality, identity of informants and participating firms remains anonymous.

Secondary sources of information included presentations and other documentation from industry experts, scholars and public officers. Statistical data came from:

(1) ClinicalTrials.gov, online database with information about the number, distribution and some general characteristics of clinical trials carried out in the US and other 153 countries. Data in this paper was last accessed on February 28th, 2008. Then, there were 52,006 records, of which 51,987 complete. We aggregated the data in order to distinguish between developed and developing regions, following classifications by the World Bank, the IMF and the OECD.

(2) The Bioresearch Monitoring Information System (BMIS) provides information submitted to FDA about clinical investigators, contract research organizations and institutional review boards involved in conduction of Investigational New Drug (IND) studies with human investigational drugs. The data contains a separate entry for each time an investigator, CRO or IRB is identified in a new submission, hence, multiple entries are possible for single individuals or organizations. Our data correspond to the latest available version: 11 January, 2008.

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