Articles / Aufsätze

CSR boundaries in the pharmaceutical industry: Is outsourcing of clinical trials to developing countries really unethical?

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Abstract. *Does life have a different price according to the country where people are born? Should there be a customized definition of ethics in function of the country where clinical trials are being carried on? The actual international regulatory environment proves to be inadequate to guarantee a fair treatment of patients involved in drug trials around the world, a situation which is proven by the case of India. The incapacity of Indian national regulators to efficiently monitor trials and enforce the law, as well as the increasing use of outsourcing in clinical trials gives place to abuse of patients' rights in the name of science or for corporate profits. The article aspires to make a modest contribution to this field by analyzing to what extent pharmaceutical companies are interested in perpetuating the diffuse area around the responsibility and ethics of drug trials in developing countries. Moreover, it offers suggestions as to how they can improve their CSR practices.*

Keywords: bioethics, clinical trials, contract research organizations, drug trials, ethics, outsourcing, pharmaceutical industry

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Introduction

Probably more than any other industry, the pharmaceutical industry is confronting itself with the ethical dilemma of striking a balance between corporate profitability, on the one hand, and its "ethical mandate" (Nussbaum, 2008) to provide access to treatment for patients, on the other hand. Due to this fact, it has been the target for criticism of many NGOs (Non-governmental organizations), journalists and consumer advocacy groups for issues

such as pricing of medication, access to healthcare, protection of new discovered drugs by intellectual property rights and drug testing.

In order to reestablish their reputation and to ensure their access to markets, pharmaceutical companies have shown their motivation to become more socially responsible and begun to involve themselves in communities' problems by reducing the price of their medication to disadvantaged groups, relaxing their property rights and participating in training or awareness campaigns. However, ethical concerns around drug trials performed in developing countries such as India remain full of tensions. Responses given by pharmaceutical companies fail to show their commitment to apply a global standard of patient treatment involved in trials around the world.

Moreover, increased competition and the strengthening of regulations in Western industrialized countries have pushed pharmaceutical companies to change their business model and outsource clinical trials to developing countries, transforming the drug research market into a rapidly globalized one (Abodor, 2012).

Inspired by the case of India, this paper aims at pointing out some of the flaws that exist in the regulatory environment of medical research, both in the case of developed countries (US and European) and of India. Furthermore, it develops on the resulting consequences that these flaws have on the behavior of the actors involved (pharmaceutical companies, contract research organizations, ethics committees and individual researchers and doctors). The final goal of this analysis will be to provide some recommendations for the pharmaceutical companies as to how to improve their transparency in medical research and avoid future unethical allegations.

The regulatory environment

Global rules: the Helsinki Declaration

The supranational regime that sets universal principles in human research and consequently in clinical trials is represented by the Helsinki Declaration. This Declaration was inspired by the

Nuremberg Code and was first published in 1964 by the World Medical Association. In its current fifth revised edition, made in October 2000, it “puts patient safeguard before the advancement of science” (Abodor, 2012, p. 241) by introducing: a) the primacy of the informed consent of patients, b) ethics committees in charge with the supervision of the protocols of trials, c) the ban of ineffective placebos, d) the standards of conducting clinical trials and e) the definition of responsibilities between the parties involved in the management of clinical research. Moreover, since 2000, when it emphasizes the duty of doctors towards the patients involved in the trials and their right to profit from the results of the study, by having access to the treatment discovered, the Declaration takes the form of a “modern Hippocratic oath” (Abodor, 2012).

The importance of the Helsinki Declaration is crucial since it serves as a basis for the creation of national regulatory regimes. However, despite the clear ethical rules of conduct that it introduces, its main weaknesses are the voluntary character of the guidelines and the lack of mechanisms to monitor and sanction abuses (Abodor, 2012, p. 246).

Therefore, it falls in the responsibility of national institutions to shape their own policies in medical research and to allocate the resources needed, situation which creates the premises for large differences in the interpretation of the international regulation, as well as in the efficiency of national regimes.

US and EU standpoints on regulation of clinical trials

The US and the EU are the two largest pharmaceutical markets, thus pushing the drug companies to pay extreme attention to comply with the regulations they pass. It is believed that the tightening of regulations in US and EU has triggered “a trend of offshoring” to developing countries the high risk clinical trials that would not be allowed by the American or European ethics committees (Politzer & Krishnan, 2012).

If in 1962, when the US Food and Drug Administration (FDA) promulgated the first regulation on drug testing, the results from foreign trials were not easily accepted, the situation has completely changed at present. Nowadays, nearly 80 percent of drug applications for marketing approval use data obtained from foreign clinical trials and in some cases drug applications are approved entirely on foreign data (Schuman, 2012, p. 2). American policies tend to concentrate more on assuring the transparency of clinical trials, than on their ethical-related aspects.

Examples are the National Institutes of Health (NIH) Data Sharing Policy, or the Annals of Internal Medicine policy, which publish data on study protocols, statistical codes and datasets. Moreover, the NIH manages the ClinicalTrials.gov site since 2000, which is the largest single registry of clinical trials (Zarin & Tse, 2008, p. 1). To increase the number of trial registrations of all types of interventions around the world, the International Committee of Medical Journal Editors (ICMJE) has introduced in 2005 a policy that requires “prospective trial registration as a pre-condition for publication” (Zarin & Tse, 2008, p. 2). The latest improvement is the 2007 FDA Amendments Act (FDAAA). Section 801 of the FDAAA provides the first federally-funded trial results database and enlarges the scope of sponsors type and information that needs to be disclosed. However, the FDAAA 801 still leaves areas of opacity because it does not cover any issue related to the ethical conduct or design of clinical trials. Moreover, the FDA does not use injunctions or criminal proceedings to enforce its informed consent requirement abroad (Schuman, 2012).

Consequently, its sole way to react to the deployment of unethical trials in the developing countries is to reject data coming from foreign research. However, since this measure occurs only ex post it does not offer any protection to the victims of clinical

trials. According to Arthur Caplan, a bioethicist at the New York University Langone Medical Center, the main problem in preventing unethical trials abroad is the absence of an international database of initiated trials. Consequently, the FDA is aware of a trial only when the drug companies submit the application to market the new drug: “We don’t have good information about what is really going on there, until there is a scandal, a problem or a death—but the overall picture is tough to know, because no one is responsible for monitoring it” (Politzer & Krishnan, 2012).

The European pharmaceutical market is known to be one of the most regulated. Directive 2001/20/EC of 4 April 2001, inspired by the Declaration of Helsinki, sets standards for the conduct of clinical trials in the EU itself and explicitly requires that any application for market authorization in the EU needs to prove that the implied clinical trials, no matter in what country they were conducted, respect the same ethical standards applied to trials in the EU.

However, according to a research by the Centre for Research on Multinational Corporations (SOMO), the provisions of the directive are not fully respected and the “European authorities devote little to no attention to the ethical aspects of the clinical trials submitted, and they accept unethical trials as well as trials of poor quality” (Schipper & Weyzig, 2008). For example, SOMO researchers identified a discrepancy between the requirements of the European Medicines Agency (EMA) which demands placebo-controlled studies to grant market authorization and the ethical criteria of the Research Ethics Committees who do not approve this type of trial in most Western countries (Schipper & Weyzig, 2008, p. 70).

Therefore, pharmaceutical companies are pushed to go to low or middle income countries where regulation is more lax. Both regulation systems, the American and the European one, have flaws in what concerns the ethical character of foreign research data, and it appears that one of the main causes is the lack of coordination between the legal measures and instruments applied by national medical regulators in developed and developing countries.

Drug manufacturers between commitment to ethical trials and aggressive outsourcing

The decision of pharmaceutical companies to outsource the stage of clinical trials to developing countries has been essentially cost driven. The tightening of the regulation in the Western countries, the increasing R&D costs and time in recruiting patients to perform drug trials in developed countries (85 percent of days lost in clinical trials are due to a failure to get enough patients (McKinsey, 2009)) are factors that put pressure on their competitiveness. A special aspect not to be neglected is the time- and cost-intensive characteristic of the R&D process to discover and introduce a new drug on the market: approximately 10-15 years, with an average cost per successful drug of \$800 million to \$1 billion. This amount includes also the cost of thousands of failures (IFPMA Clinical Trials Portal, 2013). Clinical trials expenses represent an important part in the cost break down, namely 60 percent of the drug development cost (Abodor, 2012).

Compared to the US, India offers 30 percent time advantage in recruiting patients for trial, and cuts the cost per patient to half from approximately \$4,000 - \$10,000 in the US. Thus, in average it leads to savings of more than 50 percent for the three clinical trial phases (Veembur, 2004, p. 51).

Nevertheless, the price components of medicines have been changing and in the case of the German pharmaceutical giant

Bayer for instance, it has been observed a different evolution of R&D costs compared to. According to their 2011 annual report, sales and advertising costs have outset the R&D costs by three times: in 2011, €8.96 billion were spent on advertising and €2.9 billion on research (Bayer Annual Report, 2011).

Emerging economies represent an economically rational choice for pharmaceutical companies to outsource phase II and III of the clinical trials (see Figure 1 below) and the reasons are manifold. On the one hand, there is the large number of population, the variety of diseases and the fact that patients are somewhat “naïve” to modern treatment. On the other hand, regulation is more lax. This is the breach that raises the question of unethical treatment in clinical trials made in developing countries and because of which Big Pharma has come under criticism. Moreover, attractiveness of outsourcing clinical trials to contract research organizations (CROs) which allow drug companies to save time and money has its disadvantage of blurring the responsibility of contractual parties in case of misconduct or deaths occurring because of the trial.

Figure 1 – The process of drug discovery (IFPMA Clinical Trials Portal, 2013)

Pushed by national regulators in US or EU to publish their trials on publicly available sites and trial directories, the pharmaceutical companies are becoming more transparent. It has been shown, however, that without a legally constraint, they are not voluntarily disclosing information (Zarin & Tse, 2008).

This type of opacity can become very harmful for the pharmaceutical industry and damage badly the confidence of their stakeholders and patients. Citing the case of Bayer, in allegations of causing clinical trial-related death to more than a hundred of patients in India, shareholders have been demanding more transparency from Bayer's Board of managers. Finally, the savings that the companies realize by recurring to cheaper drug trials in developing countries can be several times overset by the losses in image and reputation due to unethical treatment of patients, recalls of medicines from the market and cost of lawsuits.

If pharmaceutical companies do not take action in due time, consequences can be very dangerous for the industry in the long term. Already, in some cases, regulatory institutions in developed countries have refused to validate the results of trials conducted in outsourcing countries due to the uncertainty that the trials have respected the occidental standards. Moreover, because of differences in lifestyle and of the different exposure to drugs between Westerners and populations from developing countries, people can have different reactions to medicine and therefore, the regulators might soon demand that the drug tests should be conducted on the people for which the drug is developed or that they perform a more balanced enrollment of patients around the world.

As well as economically sound, the choice to contract a CRO gives the pharmaceutical companies the possibility to “out-source” responsibility, or at least to harden the process of identifying the culprits. However, this is not always in the benefit of the company. In some cases, the pharmaceutical companies have

decided to cancel the outsourcing contract and continue doing trials in-house because of the high cost of monitoring the activity of the CRO (Politzer & Krishnan, 2012).

India's attractiveness

India's pharmaceutical market is believed to become the tenth largest market by 2015 attaining US\$20 billion by 2015 (McKinsey, 2009) (see figure 2), with its growth driven by a positive sustained economic evolution, an increase in healthcare spending, a reform of the healthcare system and an improvement in patent-related regulation.

Figure 2 – Top pharmaceutical markets (IMS World Review)

Starting from 2005 when the Indian government changed its patent law to recognize product patents and streamlined the process of clinical trials, India has become a very attractive market for pharmaceutical companies, transforming itself into a “Mecca of drug trials” (CRIN, 2012). This move was deliberately made by the Indian government to attract multinational corporations and foreign investments, arguing that their presence would on one hand benefit the economy, and on the other hand help better treat the Indian patients.

This view is supported by the Indian Society for Clinical Research (members of which are industry giants such as Bayer and Pfizer) who argues that it is in the best interest of India to provide an accommodating environment for pharmaceutical companies. This would favor the innovation process and prevent companies from fleeing to other concurrent countries such as China, Vietnam or Philippines (Doherty, 2013).

The Indian Society for Clinical Research suggests that India has a big potential for the drug trial and outsourcing industry due to its good infrastructure (more than 14,000 hospitals), the well trained doctors speaking English (more than half million practicing doctors and over 200 accredited medical colleges) and the availability of “drug-naïve” patients with diverse genetic characteristics and a good representation of Western diseases (Sinha, 2012).

However, the Indian regulatory framework is not adequate to the number and scale at which drug trials are conducted in the country. Despite the existence of appropriate laws, there is a considerable space for abuses due to the understaffed and unskilled ethical committees that have in charge the supervision of trials and protocols. The Central Drugs Standard Control Organization (CDSCO), which is the Indian governmental regulator, is in between keeping a flexible market for drug research, which

constitutes its main advantage, and applying a strict rule of law, which might be negatively perceived by the industry.

The controversy around the number of clinical trial-related deaths and the notifications of abuses made by the National Human Rights Commission (NHRC) has pushed the Drug Controller General of India (DCGI) to propose a further strengthening of the regulations. The deaths revealed by the CDSCO since 2005 are estimated at 2644, of which 80 cases have been confirmed as having been caused by the drug that was tested and of which only 38 families have been compensated (Doherty, 2013).

The provisions made under Schedule Y of the Drugs and Cosmetics Rules concern providing financial compensation to trial subjects in case of trial related injury or death and stipulate the responsibilities of ethics committees, pharmaceutical companies and CROs (CBG, 2011). CROs are consequently made partly accountable for trial-related injuries and the sponsor company will have to market in the country the drug tested on Indian patients (Mathew, 2010).

Despite the good intent to protect Indian patients, the practical method drafted by the CDSCO to calculate the amount of compensations, is very controversial as it relies on the income of the injured or dead person along with age and severity of disease, transforming the poorest into a cheap target for investigators and leaving considerable place for subjectivism in the appreciation of the health condition of the patients (assessment made by the investigators themselves) (Nagarajan, 2012).

The “format for obtaining informed consent of trial subjects is also proposed to be amended to include the details of address, occupation, annual income of the subject so as to have information regarding socio-economic status of trial subjects” (Alexander, 2011). Another complementary proposal has also been made by the Drug Technical Advisory Board (DTAB) which stipulates that the investigators provide an audio/video recording of the informed consent of participants (Sinha, 2012). Because there is a large record of trials run without notice, the registration of clinical trials in the Clinical Trial Registry of the Indian Council of Medical Research has been mandatory.

In conclusion, there is a clear commitment of the Indian government to further regulate medical research in the country, but the efficiency of the rules will be highly dependent on the human and financial resources that the government will deploy in order to enforce them and control the system.

Current criticism of the practices in India

Pharma companies and CROs who carry out drug trials in India are currently under serious allegations of unethical behavior. Criticism mainly deals with the ambiguity in proving the informed consent of patients enrolled, the lack of transparency and the discriminatory treatment in terms of compensation for the patients who were injured or died as a result of the drug tested.

The principle of informed consent is the fundamental cornerstone of human medical research, set by the Declaration of Helsinki and approved by all national regulators. However, there are serious concerns that this rule is not respected in the case of developing countries where most of the people enrolled in trials are poor, illiterate and in the case of India, belong to the deprived *dalits*, or the “untouchables” who are at the bottom of the Hindu caste system.

Indian health organizations estimate around 350,000 to two million Indians involved in clinical trials and in some of the cases there is proof that the patients were not asked to sign a consent form and were not informed about being enrolled in drug trials. Sometimes the only information they were given was that they were offered “expensive new medicines free, paid for by a special governmental program for families living below poverty line” (Doherty, 2013). Moreover, when the death of patients

occurred after they were discharged from hospital, as the families were not informed of previous involvement in drug trials, no “post mortem” investigations were made to establish the cause of the death. Since no evidence remained, the families were in the impossibility of asking for compensations. According to the figures reported to the DCGI, the number of drug trials and of clinical trial-related deaths has increased the latter evolving from 137 in 2007 to 668 in 2010 (Shankar, 2011).

Nevertheless, no compensations were made till the end of 2009 and later, a total of 10 companies, including Bayer, Sanofi Aventis, Pfizer, Novartis and Eli Lilly, submitted a list of 22 patients to whose families’ compensation was paid (five out of 138 deaths in the case of Bayer and three out of 152 patients in the case of Sanofi Aventis) (Shankar, 2011).

There is a fierce debate over the death causes of patients involved in medical research because most of the people involved are in terminal stages or are suffering from some types of diseases for which there is no discovered treatment yet. This is an argument that most of the pharmaceutical companies use to explain the small number of compensations.

According to a Novartis spokesperson, “the clinical trial investigator (who conducted the trial for Novartis) had asserted the deaths were not because of the study medication but due to progression of underlying disease (which won’t necessitate compensation)” (Mathew, 2011).

However, even in the cases where compensations were made, sums paid were not comparable to similar cases in the US or Europe. Consequently, the pharmaceutical companies were accused of applying double standards in compensation. There are also opinions that due to the lax enforcement of law in India, the entire system is biased, thus favoring financial benefits over ethical concerns. According to C. M. Gulhati, editor of the *Monthly Index of Medical Specialties*:

Many trials are taking place in private clinics of individual doctors whose sole motto is to make money. Can they be trusted to protect the interests of the subjects? Ethics Committees of private hospitals, where most trials are taking place, are appointed by owners and have hardly any powers to take decisions that can hurt their employers’ income. Independent ethics committees are privately run and totally dependent on drug companies for their very survival. (Nagarajan, 2012)

Even though pharmaceutical companies sustain that they respect the international standards, their lack of transparency makes them very vulnerable to criticism. Moreover, by outsourcing the clinical trials to CROs, they lack control over the methods used by the investigators. Even if on a contractual basis, the legal responsibility is transferred to CROs, there is no provision for the transfer of moral responsibility and therefore, there is a difficulty in assigning accountability when ethical malfeasance occurs (Abodor, 2012). When it occurs, the reputation of pharmaceutical companies is more affected than that of CROs, which are, unlike Big Pharma’s firm and brand names, mostly unknown to the public. It is a considerable risk. Yet the principle problem is India’s inadequate regulatory environment which permits the appearance of a “collusive nexus” between drug manufacturers, functionaries of the CDSCO and ethics committees, and medical practitioners (Doherty, 2013).

Conclusions

Despite recent improvements, the national regulatory frameworks both in developed as in low and middle income countries lack the enforcement power to prevent further unethical clinical trials to be conducted, situation which emphasizes the increasing need of national medical regulators to cooperate and harmonize

their measures so as not to create an image of “cheap lives” of the people in developing countries.

The case of India shows that there is a delicate balance between protection of commercial interests and promotion of public health. It is only through an ethical conduct of pharmaceutical companies, CROs and practitioners that both they and the Indian patients will benefit on the long term.

Even if the lax enforcement of law in India considerably decreases the costs for pharmaceutical companies, the inexistence of a clear cut regulatory framework can have boomerang effects such as the rejection by US or EU authorities of research evidence coming from Indian clinical trials due to allegations of unethical treatment or misappropriate and corrupt clinical protocols.

Moreover, the outsourcing of clinical trials to CROs can be double-edged for pharmaceutical companies because it exposes them to serious image loss in case of misconducts of the outsourcing company.

One method for the pharmaceutical industry to maintain its credibility is by becoming more transparent and providing adapted information to medical specialists and to the general public concerning the number, location, protocol and results of conducted trials.

Maintaining the obscurity of the current research system would only increase the suspicion of medical regulators that illegal or unethical practices are being used and would prevent potential patients from trusting the pharmaceutical companies and enrolling into clinical trials. Furthermore, Big Pharma could and should use its negotiation power to impose ethical guidelines to its sub-contractors and local investigators to make all the research chain more responsible.

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