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Outsourcing Drug Investigations to India: A Comment on U.S., Indian, and International Regulation of Clinical Trials in Cross-Border Pharmaceutical Research

*James Cekola**

I. INTRODUCTION

The traditional research and development model of large pharmaceutical companies is arguably unsustainable in current times. For example, estimated research and development costs increased as much as twelve percent over the last year while pharmaceutical sales grew only seven percent over the same period.¹ Current estimates put the price to develop a new drug and bring it to market between \$800 million and \$1.5 billion per drug.² These costs are increasing, driving large pharmaceutical companies to find more cost-effective research and development models. One cost-saving initiative is to globalize the system. In particular, companies have increasingly outsourced the required investigational drug trials from developed countries in which the drugs would be sold, such as the United States, to developing countries, such as India.³

Accordingly, the scope of human drug research and development is undergoing rapid globalization. Global economic factors and recent changes in Indian regulations have created a situation that could be described as a “perfect storm” for a clinical trial outsourcing boom in India.

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¹ CHARLES W. THURSTON, INSTITUTIONAL INVESTOR SPONSORED REPORT, INVESTING IN PHARMACEUTICALS: PHARMACEUTICAL COMPANIES STRUGGLE TO KEEP THE PIPELINE PRESSURIZED 1, (2006), available at <http://www.iimagazine.com/images/564/53187/Investing%20Pharmaceuticals.pdf>.

² *Id.*

³ Kounteya Sinha, *India to Follow US, UK Lead on Trials*, TIMES OF INDIA, Oct. 23, 2005, available at 2005 WLNR 17162488.

Just as India has become the premiere destination for outsourcing the work of technology call centers and software developers, the country is now positioned to become the global hotspot of this new outsourcing movement.

India has much to gain from such clinical trial outsourcing. Officials in India's Health Ministry stated that in 2003 the country earned \$70 million in revenue from clinical trials.⁴ According to estimates, this amount will grow to \$200 million in 2007 and reach \$1.5 billion by 2010.⁵ Despite the obvious economic benefit, critics decry the practice, positing that it makes India a "guinea pig to the world."⁶

The controversial practice of U.S. pharmaceutical companies outsourcing their clinical research to the Indian population raises several significant questions. For example, are U.S. pharmaceutical companies evading regulatory controls by outsourcing trials to India rather than conducting them in the United States? Will the safety and rights of Indian trial volunteers be protected as well as those of their U.S. counterparts? Is the Indian population unfairly abused in taking most of the risk of clinical research but little of the benefit? Lastly, does India deserve its disparaging nickname of "guinea pig to the world"?

Close oversight of trials and protection of test subjects are necessary in order to minimize the risks to which human test subjects are exposed, and to ensure that test subjects understand the risks of participating in drug research. Even in developed nations, the benefits of human drug research are only achievable with negative tradeoffs, particularly in the form of risks to the health of the people involved in the investigational trials. It was recently reported in the United Kingdom that an investigational drug trial of a drug meant to treat chronic inflammatory conditions and leukemia instead left two test subjects fighting for life.⁷ In total, six of the volunteers fell seriously ill after the trial.⁸ One student volunteer in the trial "want[ing] to make a bit of extra money" was reportedly "left looking like the Elephant Man."⁹ Although this tragic example may be extreme, it is evidence of the inevitable risk that human test subjects in drug research face, because drug experimentation is based on an incomplete knowledge of the drug's effects on the human body. The unfortunate reality of human experimentation proves the need for regulation of clinical trials to balance scientific progress with test subject protection.

⁴ *Id.*

⁵ *Id.*

⁶ Jennifer Kahn, *A Nation of Guinea Pigs*, WIRED, Mar. 2006, available at <http://www.wired.com/wired/archive/14.03/indiadrug.html>.

⁷ *Scandal of Drugs Trial Guinea Pigs*, WESTERN DAILY PRESS, Mar. 16, 2006, at 11, available at 2006 WLNR 4431717.

⁸ *Id.*

⁹ *Id.*

Further evidence of the need for close regulations is that repeated stories of abuse pervade the history of human experimentation. One need only recall the Nazi experiments on concentration camp prisoners during World War II (1939–1945) or the Tuskegee syphilis study (1932–1972). The lesser known—but equally disturbing—Human Radiation Experiments began in 1944 and continued until as recently as 1974.¹⁰ U.S. government scientists working on nuclear weapons research projects performed research to determine the effects of plutonium on humans by experimenting on more than 4,000 unknowing and non-consenting test subjects.¹¹ The test subjects were hospital patients thought to be either terminally ill or have a life expectancy of less than ten years due to age or chronic disease condition.¹² In some experiments, the scientists injected plutonium into patients, including a five-year-old child, without even informing them of the contents of the injection, much less giving them the opportunity to consent to or reject the procedure.¹³ Such tragic tales of abuse shroud the history of human experimentation and serve as a reminder and an impetus for strong regulations and protections of human test subjects in human experimentation and drug research.

Although terrible, the abuses and misfortunes of many test subjects have contributed to the development of law regarding medical research on humans. While there are international documents and agreements relating to human experimentation, the regulation of clinical research is dominated by legislation on the national level. This Comment will first discuss the reasons behind the growing trend of outsourcing investigational drug trials to India. After presenting the relevant background, the Comment will explain the regulation of clinical trials and protections for test subjects in the United States. Next, the Comment will explain the regulation of clinical trials and protections for test subjects in India and compare the regulatory system there with that in the United States. The Comment will then discuss pertinent international law and, finally, conclude with a summary and a discussion of the economic, regulatory, and ethical realities of U.S. pharmaceutical companies outsourcing clinical research to India.

¹⁰ See ADIL E. SHAMOO & DAVID B RESNIK, RESPONSIBLE CONDUCT OF RESEARCH 181–92 (2003) (explaining briefly each of the mentioned atrocities as well as others).

¹¹ See *id.* at 189.

¹² See *id.*

¹³ See *id.*

II. INDIA AS THE GLOBAL HOTSPOT FOR CLINICAL TRIAL OUTSOURCING

A. Financial and Logistical Factors

The outsourcing of investigational drug trials is fueled by an increase in logistical and financial problems associated with conducting the trials in developed countries.¹⁴ It is increasingly difficult and expensive to perform investigational drug trials in the United States. Logistically, recruitment of research subjects is slow and costly because the population of potential test subjects is relatively small and unwilling to volunteer.¹⁵ While the number of volunteers needed for clinical trials is increasing, the number of Americans willing to enroll in trials lags. For example, only 1.7% of eligible cancer patients in the United States enroll in investigational drug trials.¹⁶

The reason for the shortfall has been attributed to the unwillingness of American patients, and also, more importantly, to the unwillingness of their doctors to recommend participation.¹⁷ While a primary misunderstanding for patients is the worry that they may be given a placebo instead of actual treatment,¹⁸ doctors are often reluctant to recommend or mention clinical trials for a variety of reasons.¹⁹ Some possible reasons are financially motivated; treating a patient through a clinical trial is usually more expensive for the doctor's office.²⁰ Clinical trials also require a heavy load of paperwork and doctors may have greater worries about malpractice litigation from patients in clinical trials.²¹

Furthermore, the costs in the United States associated with medical labor and infrastructure are among the highest in the world. For U.S. pharmaceutical companies, clinical trials currently account for around forty

¹⁴ See Patrick McGee, *Clinical Trials on the Move: Dropping Enrollment for Clinical Trials in the US and Western Europe Has Companies Looking to Countries Like India and China as a Solution*, DRUG DISCOVERY & DEV., June 1, 2006, at 16, available at 2006 WLNR 10305103.

¹⁵ See Samiran Nundy & Chandra M. Gulhati, *A New Colonialism? – Conducting Clinical Trials in India*, 352 N. ENGL. J. MED. 1633, 1634 (2005), available at <http://content.nejm.org/cgi/reprint/352/16/1633.pdf>.

¹⁶ See Glenn McGee, *Salt in the Wound: Will India Rise Up Against the Oppression of Foreign Clinical Trials?*, THE SCIENTIST, Apr. 1, 2006, at 26, available at <http://www.the-scientist.com/2006/4/1/26/1/>.

¹⁷ See E.J. Mundell, *Clinical Trials for Cancer Running Out of Volunteers*, HEALTHDAY NEWS, July 10, 2006, available at 2006 WLNR 11866220.

¹⁸ See *id.*

¹⁹ See *id.*

²⁰ *Id.*

²¹ *Id.*

percent of the total cost of developing a drug.²² U.S. pharmaceutical companies have a large incentive to find a more efficient and less costly solution to the financial and logistical problems associated with conducting trials in the United States.

An especially attractive solution for U.S. companies is the outsourcing of clinical trials to India, because it offers relief for their logistical and financial problems. Logistically, recruitment is faster and easier because for many in India, the chance to participate in an investigational drug trial is a healthcare windfall.²³ Financially, India provides a significant cost advantage for U.S. and Western European pharmaceutical companies because of its low-cost and English-speaking medical staff, large patient traffic, good health infrastructure, and credible, established clinical research organizations.²⁴ The *New England Journal of Medicine* reported that outsourcing clinical trials to India can save U.S. pharmaceutical companies up to sixty percent on the cost of the trials.²⁵ India is the second most populous country in the world, and another benefit to outsourcing drug trials to India is access to the large, diverse, and drug-naïve patient population. Drug naivety means that the patient has not previously taken any medication for their condition. This is a positive point for those conducting clinical trials because it lowers the chance of any unforeseen drug interactions and also avoids the burden of switching a patient from their current medication to the trial drug.

Companies that perform the clinical testing and then report the data to pharmaceutical companies—clinical research organizations (“CROs”)—advertise an “Indian Advantage,” touting the country’s huge patient base, diversity of diseases, drug-naïve population, and high trial enrollment rates.²⁶ For example, iGate Clinical Research International, an Indian CRO, advertises on its commercial webpage that India represents a “largely untapped resource for clinical trials.”²⁷ This CRO advertises and estimates India’s diseased patient populations at “40 million asthmatic,” “34 million diabetic,” “8–10 million people HIV positive,” “3 million cancer patients,” “>2 million cardiac related deaths,” “1.5 million patients with Alzheimer’s

²² Nundy & Gulhati, *supra* note 15, at 1634.

²³ See Kahn, *supra* note 6.

²⁴ Gireesh Chandra Prasad & James Mathew, *Doc India’s Got a Cure for Global Pharma*, *ECON. TIMES (India)*, Apr. 28, 2006, available at 2006 WLNR 7200824.

²⁵ Nundy & Gulhati, *supra* note 15, at 1634 (citing Gunjan Sinha, *Outsourcing Drug Work: Pharmaceuticals Ship R&D and Clinical Trials to India*, *SCI. AM. ONLINE*, Aug. 16, 2004, available at <http://www.sciam.com/article.cfm?articleID=00033282-DBF5-10F9-975883414B7F0000>).

²⁶ See, e.g., iGATE Clinical Research International, *Indian Advantage*, <http://www.igatecr.com/company/indiaadvantage/index.php> (last visited Nov. 25, 2007).

²⁷ *Id.*

disease,” and “1% of population suffer from schizophrenia.”²⁸

While it is getting harder to perform investigational trials in the United States, the availability of a large and desirable pool of potential volunteers as well as the reduced costs associated with labor and infrastructure in India make outsourcing the trials to India an attractive solution.

B. Regulatory Changes

Two recent changes in Indian law have also fueled the outsourcing of U.S. clinical work to India. One change was in Indian intellectual property law, which expanded the scope of patentable subject matter in India to include pharmaceutical products. A second change was in India’s regulations of clinical trials. The changes in Indian regulations complement the United States regulatory scheme²⁹ and work to drive the expansion of outsourcing.

The change in Indian intellectual property law occurred in 2005 when India amended its Patents Act to bring it into compliance with the World Trade Organization’s (“WTO”) Trade Related Intellectual Property Rights agreement (“TRIPS”).³⁰ Article 27.1 of TRIPS requires member countries to make patentable “any inventions, whether products or processes, in all fields of technology”³¹ Furthermore, Article 39.3 requires protection of data acquired in clinical trials against any “unfair commercial use.”³² Prior to the amendments, India did not allow patents on pharmaceutical products, thus discouraging foreign companies from entering India out of fear that their products would be reverse-engineered and generically mass manufactured. The new intellectual property protections will undoubtedly encourage outsourcing clinical trials to India.³³

Second, the Indian government also made important changes in its regulations regarding clinical trials. The Indian regulations affecting new

²⁸ *Id.*

²⁹ U.S. regulations, discussed *infra* Part III, permit data from foreign clinical studies to be used in an application for the marketing approval of a new drug. See 21 C.F.R. § 314.106 (2005) (explaining the acceptance of an application when it is solely supported by foreign clinical data); 21 C.F.R. § 312.120 (2005) (explaining the acceptance of foreign clinical data generally).

³⁰ See The Patents (Amendment) Act, No. 15 of 2005; India Code (2005), available at <http://lawmin.nic.in/patentsact2005.pdf>.

³¹ Agreement on Trade-Related Aspects of Intellectual Property Rights art. 27.1, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Legal Instruments—Results of the Uruguay Round, 33 I.L.M. 1197 (1994) [hereinafter TRIPS], available at http://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

³² *Id.* art. 39.3.

³³ See Laura Thomson, *Changing Times for Patenting in India*, KNOWLEDGELINK NEWSLETTER, Feb. 2005, at 2, available at <http://scientific.thomson.com/ts/media/newsletterpdfs/2005-02/patenting-india.pdf>.

drugs and clinical trial are found in Schedule Y of the Indian Drugs and Cosmetics Rules.³⁴ In January 2005, the Indian government changed Schedule Y and removed a “phase lag,” allowing foreign pharmaceutical companies to perform trials of new drugs in India at the same time as trials of the same phase in other countries.³⁵ The “phase lag” rule had required that a trial of a drug not discovered in India must have already occurred in another country. For example, such a drug could not be tested in a Phase II trial in India unless it had already been tested in a Phase II trial elsewhere. The rule’s purpose had been “to protect Indians from being used as guinea pigs in the testing of unproved drugs of foreign origin.”³⁶

The regulatory scheme in the United States complements the changes made in India, because it allows for the drugs to be approved for sale based on data from foreign clinical trials.³⁷ Under Section 314.106(b)(1) of Title 21 of the Code of Federal Regulations, an application to market a new drug under an investigational new drug application (“IND”) may be approved by the FDA even if such application is based only on data from foreign clinical trials, as long as the following three requirements are met:

- (1) the data are applicable to the U.S. population and medical practice;
- (2) the clinical investigators are of recognized competence; and
- (3) the data “may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means.”³⁸

The FDA will also accept research for foreign clinical studies not conducted under an IND.³⁹ Such studies are accepted if they are “well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community.”⁴⁰ By mentioning “ethical principles acceptable to the world community,” the regulation is referring to Helsinki V of the Declaration of Helsinki, discussed below in Part V.A. The broad wording and the inclusion of an out-of-date international document in the regulations regarding acceptance of foreign clinical trials allow many U.S. pharmaceutical companies to outsource their clinical trials abroad.

In summary, the changes in Indian intellectual property law and the

³⁴ The Drugs and Cosmetics Rules, 1945 (as Amended up to the June 30th, 2005) [hereinafter *Drug and Cosmetics*], available at <http://cdsco.nic.in/html/Drugs&CosmeticAct.pdf>.

³⁵ Nundy & Gulhati, *supra* note 15, at 1633.

³⁶ *Id.* at 1634.

³⁷ See 21 C.F.R. § 314.106(b)(1) (2003).

³⁸ *Id.*

³⁹ See *id.* § 312.120.

⁴⁰ *Id.* § 312.120(a).

removal of the “phase lag” in clinical trial regulations complement the regulatory scheme in the United States, and have fueled the outsourcing boom by expanding the number of trials that may be performed and allowing the most cutting-edge clinical drug research to be conducted in India.

III. REGULATION OF CLINICAL TRIALS AND THE PROTECTION OF TEST SUBJECTS UNDER UNITED STATES LAW

A. Regulation of Clinical Trials

The United States Food and Drug Administration (“FDA”) regulates clinical trials in the United States.⁴¹ Before starting a clinical trial, a sponsor submits an IND to the FDA.⁴² Generally, an IND must include information in three broad areas:

- (1) Animal pharmacology and toxicology studies to permit an assessment of whether the product is reasonably safe for initial testing in humans;
- (2) Manufacturing information to ensure that the company can consistently and adequately supply batches of the drug; and
- (3) Clinical protocols and investigator information to assess whether the investigators are qualified to conduct the trials and assess the potential risks to which the human test subjects will be exposed.⁴³

The IND must also specify an Institutional Review Board (“IRB”) to supervise the clinical research done under the IND.⁴⁴ The IRB is the responsible party to ensure that the clinical trials are properly set out to protect the welfare and rights of the human test subjects.⁴⁵ An IRB may be “any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.”⁴⁶

After an IND submission, the FDA will evaluate the application and

⁴¹ Statutory authority is found mainly in the Federal Food, Drug and Cosmetic Act. See 21 U.S.C. § 301 (2005).

⁴² See 21 C.F.R. § 312 (2005).

⁴³ Areta L. Kupchik & Josephine M. Torrente, *R&D 101: Legal Issues During Research and Development*, 878 PLI/PAT 9, 18 (2006).

⁴⁴ See 21 C.F.R. § 56 (2005).

⁴⁵ See *id.*

⁴⁶ 21 C.F.R. § 56.102(g) (2005). FDA regulations further require that an IRB consists of at least five experts and lay people who have different backgrounds, experience, and expertise “to ensure a complete and adequate review of research activities.” Kupchik & Torrente, *supra* note 43, at 19.

determine within thirty days whether there are any issues that should prevent the study from going forward.⁴⁷ Under the law there is no requirement that the FDA inform the sponsor of the IND of an approval.⁴⁸ Therefore, if the sponsor has heard nothing from the FDA regarding the IND submission on day 31 after the submission, the study may proceed as described in the IND.⁴⁹ However, if the FDA has any concerns with the IND then it may issue a “clinical hold.”⁵⁰

A clinical hold is an administrative order from the FDA to delay or suspend the study.⁵¹ When a clinical hold is imposed on a proposed study, the hold prohibits the sponsor from giving the investigational drug to test subjects and also prohibits the recruitment of any new test subject.⁵² The sponsor must address the issues related to a clinical hold by submitting a response to the FDA.⁵³ The clinical hold will be removed if the sponsor adequately resolves the issues and, again, the FDA will review the sponsor’s response within thirty days and notify the sponsor of its decision.⁵⁴

Under an IND, there are three phases (I, II, and III) for clinical research on drugs for humans.⁵⁵ In general the phases are thought of as sequential but there may be some overlap between consecutive phases.⁵⁶

Phase I is the introduction of the investigational drug into human test subjects and is used to evaluate drug metabolism, structure-activity relationships, the pharmacological mechanism of action, and the side effects associated with increasing doses.⁵⁷ Typically, Phase I trials involve a small number (approximately twenty to eighty) of healthy volunteers or patients.⁵⁸ The data obtained from the Phase I trials assists in the design of Phase II studies.

Phase II studies are used to obtain data on the effectiveness of the drug on treatment of patients with the disease or condition the drug is meant to combat.⁵⁹ Phase II studies typically involve a larger number of participants

⁴⁷ See 21 C.F.R. § 312.20 (2005).

⁴⁸ Kupchyk & Torrente, *supra* note 43, at 19.

⁴⁹ *Id.*

⁵⁰ See Clinical Holds and Requests for Modification, 21 C.F.R. § 312.42 (2005).

⁵¹ *Id.*

⁵² *Id.*

⁵³ *Id.*

⁵⁴ Kupchyk & Torrente, *supra* note 43, at 20.

⁵⁵ See Frequently Asked Questions on Drug Development and Investigational New Drug Applications, <http://www.fda.gov/cder/about/smallbiz/faq.htm> (last visited Nov. 26, 2007) [hereinafter *FAQ on Drug Development*].

⁵⁶ *Id.*

⁵⁷ Kupchyk & Torrente, *supra* note 43, at 21.

⁵⁸ *Id.*

⁵⁹ *FAQ on Drug Development, supra* note 55.

(several hundred patients) and also help to determine short-term side effects and risks of taking the investigational drug.⁶⁰ The information obtained from the Phase II trials may lead to the final and largest phase, Phase III.

Phase III clinical trials are intended to obtain data on the effectiveness and safety on the widespread use of the drug so that an overall benefit-risk relationship of the drug may be assessed.⁶¹ Phase III studies must provide an adequate basis to extrapolate results from the tested population of patients for application to the general population. The results of Phase III trials determine whether there is enough evidence of efficacy in treating the disease or condition needed for approval of the investigational drug by the FDA.⁶² The data obtained in Phase III studies are also used by the FDA in determining proper physician labeling.⁶³ Typically, Phase III studies include several thousand people.⁶⁴

However, the FDA will also accept research from foreign clinical studies not conducted under an IND.⁶⁵ Such studies are accepted if they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community."⁶⁶ Thus, regulations in the United States will allow approval of an investigational drug even if all the clinical data were acquired using patients in India.

B. Protecting Test Subjects

Federal regulations protecting human test subjects in investigational drugs trials are found in the Federal Food, Drug and Cosmetic Act.⁶⁷ The FDA regulations for human clinical trials are mostly codified in Title 21 in the Code of Federal Regulations, Parts 50, 54 and 56.⁶⁸ The FDA regulations apply to all clinical trials for new drugs under Sections 505(i) and 505(g) of the Food, Drug and Cosmetic Act.⁶⁹ Named "Protection of

⁶⁰ *Id.*

⁶¹ Kupchyk & Torrente, *supra* note 43, at 21.

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *FAQ on Drug Development*, *supra* note 55.

⁶⁵ See 21 C.F.R. § 312.120 (2005).

⁶⁶ *Id.* § 312.120(a).

⁶⁷ See Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 (2005).

⁶⁸ See 21 C.F.R. § 50 (2005); 21 C.F.R. § 54 (2005); 21 C.F.R. § 56 (2005). Other FDA regulations do relate to clinical trials and human research subjects, such as 21 C.F.R. § 312 (regulating IND applications); 21 C.F.R. § 314 (regarding FDA approval to market a new drug). These regulations are related to the conditions set forth in 21 C.F.R. §§ 50, 54, and 56 to FDA authorization of applications for investigational and new drug activities.

⁶⁹ Section 505(i) in the Federal Food, Drug and Cosmetic Act is Title 21 of the United States Code Section 355(i). 21 U.S.C. § 355(i) (2005). Section 505(g) of the Act is Title 21 of the United States Code Section 355(g). 21 U.S.C. § 355(g) (2005).

Human Subjects,” Part 50 of the regulations requires informed consent and additional safeguards regarding research on children.⁷⁰ Part 56 of the regulations, “Institutional Review Boards,” puts forth the general standards for the composition, operation, and responsibility of IRBs, mentioned in Part III.A, above, which oversee clinical trials.⁷¹ By periodic reviews both before and during the clinical testing, IRBs serve to assure that adequate actions are taken to protect the rights and welfare of humans participating as subjects in clinical research.⁷²

Part 50 of the regulations sets forth the requirements for informed consent.⁷³ Part 50.25 enumerates eight elements that must be explained to a volunteer before receiving an informed consent: (1) the purposes, duration and procedure of the research; (2) reasonably foreseeable risks; (3) benefits subject may reasonably expect; (4) alternative treatments that may be advantageous to subject; (5) extent of confidentiality; (6) whether compensation or medical treatments are available if injury occurs (for research involving “more than minimal risk”); (7) whom to contact with questions; and (8) voluntary nature of participation.⁷⁴ Part 50.27 also requires that the informed consent be documented in a written agreement.⁷⁵

Part 56, regulating IRBs, contains even more regulations that provide a greater level of protection to human test subjects. In order to approve clinical research, an IRB is required under Part 56.111 to determine that seven elements related to the clinical trial are satisfied.⁷⁶ They are:

- (1) The risks to subjects are minimized by using sound research procedures and, if appropriate, by using procedures already being performed on the subject;
- (2) The risks to subject are reasonable in comparison to the anticipated benefits and knowledge that may be expected from the research;⁷⁷
- (3) The selection of subjects is “equitable”;⁷⁸
- (4) Informed consent is required for each subject;⁷⁹

⁷⁰ 21 C.F.R. § 50 (2005).

⁷¹ *Id.* § 56.

⁷² *FAQ on Drug Development*, *supra* note 55.

⁷³ See 21 C.F.R. § 50.

⁷⁴ *Id.* § 50.25.

⁷⁵ *Id.* § 50.27.

⁷⁶ *Id.* § 56.111.

⁷⁷ The regulation also mentions that IRBs should “not consider possible long-range effects of applying knowledge gained in the research.” *Id.* § 56.111(a)(2).

⁷⁸ “In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.” *Id.* § 56.111(a)(3).

- (5) Informed consent must be documented;⁸⁰
- (6) The research plan has a provision to monitor the safety of subjects, where appropriate; and
- (7) The research plan has adequate provisions to protect the privacy of the subject.⁸¹

Also importantly, in the case when some or all of the test subjects are from vulnerable populations, such as being educationally or economically disadvantaged, the regulation explicitly requires that “additional safeguards” are present in the study “to protect the rights and welfare of these subjects.”⁸²

Overall, U.S. law offers many protections for the test subjects, including the informed consent requirement and special consideration for vulnerable populations. This Comment now turns to an explanation of the counterpart regulations and protections under Indian law and a comparison between India and the United States in this area.

IV. REGULATION OF CLINICAL TRIALS AND THE PROTECTION OF TEST SUBJECTS UNDER INDIAN LAW

A. Regulation of Clinical Trials

The Indian regulations for clinical trials are found in Schedule Y of the Indian Drugs and Cosmetics Rules.⁸³ The regulations in India are similar in many ways to those in the United States.

Before starting a clinical trial, a foreign sponsor must get permission from the Indian government and an institutional ethics committee.⁸⁴ An ethics committee must be responsible for each site where the trial will occur.⁸⁵ The ethics committee must consist of seven or more members.⁸⁶ Members should be “a mix of medical/non-medical, scientific and non-scientific persons, including lay public, to reflect the different viewpoints.”⁸⁷

Permission is obtained by submitting proper forms and information to the government and institutional ethics committee.⁸⁸ Generally, the

⁷⁹ The requirement is according to the regulations in Part 50.

⁸⁰ The documentation must be in accord with the regulations in Part 50.27.

⁸¹ 21 C.F.R. § 56.111.

⁸² *Id.*

⁸³ Drug and Cosmetics, *supra* note 34, Schedule Y.

⁸⁴ *Id.* art. 2(1)(i).

⁸⁵ *Id.* apx. VIII, item 1.

⁸⁶ *Id.*

⁸⁷ *Id.*

⁸⁸ *Id.* art. 1.

information is in three areas: (1) animal pharmacology and toxicology studies, (2) manufacturing information, and (3) clinical data from Phase I trials (even after the change in “phase lag” rule, Indian law still does not allow Phase I trials of drugs not discovered in India). Furthermore, the Indian government requires information on the regulatory status of the new drug in other countries.⁸⁹ However, unlike the U.S. regulations, the Indian statutes do not require submitting detailed clinical protocols to the government; this is left to the evaluation by an institutional ethics committee.⁹⁰

The institutional ethics committee under the Indian regulations is similar in structure and function to the IRBs under the U.S. regulations. Like an IRB, the ethics committee becomes the responsible party in regards to making sure that the clinical protocols are properly set out and the welfare and rights of the human test subjects are protected.⁹¹

The Indian regulations recognize four phases (I, II, III, and IV) of clinical research on humans.⁹² For all practical purposes the first three phases are the same as in the U.S. regulations. The Indian regulations have added Phase IV trials named “Post Marketing Trials,” which are optimizing trials performed after the approval and include additional drug-drug interaction, dose-response, or safety studies to “support use under the approved indication(s).”⁹³

Overall, it can be said that the regulation of clinical trials in India and the United States are similar. Both require a governmental approval before a clinical trial may occur. The most important similarity is the existence of the third party reviewers: the IRBs in the United States and the institutional ethics committees in India. However, the Indian scheme tends to delegate more oversight of the trials from the government to the institutional ethics committee. Specifically, the institutional ethics committees in India are the only parties that review the detailed protocols and assess the risk of an investigational trial on test patients. In the United States, both the FDA and the IRBs assess the protocols and risks. Despite some minor differences in the details, the overall regulatory systems in India are similar to the United States when U.S. pharmaceutical companies outsource clinical trials to India.

B. Protecting Test Subjects

Indian regulations to protect human test subjects are also found in

⁸⁹ Drug and Cosmetics, *supra* note 34, Schedule Y, art. 1(1)(v).

⁹⁰ *See id.* art. 2(5).

⁹¹ *Id.*

⁹² *Id.* art. 2(6)–(9).

⁹³ *Id.* art. 2(9).

Schedule Y of the Indian Drugs and Cosmetics Rules.⁹⁴ The Drug and Cosmetics Rules require informed consent by the test subjects and call for extra protection when certain classes of patients are subject to trial.⁹⁵ The laws also place requirements on the composition, operation, and responsibility of the institutional ethics committees that are responsible for ensuring the protection of test subjects.⁹⁶

Appendix V of Schedule Y in the Rules sets forth the essential elements of informed consent.⁹⁷ The law enumerates fourteen elements that are essential to the test subject's informed consent (compared to eight elements in the U.S. system): (1) statement of the purpose of the research; (2) anticipated duration of volunteer's participation; (3) the procedures and/or protocol to be followed; (4) reasonably foreseeable risks or discomforts; (5) benefits the volunteer may reasonably expect;⁹⁸ (6) disclosure of specific appropriate alternative procedures or therapies available; (7) extent of confidentiality; (8) trial treatment schedule and the probability for random assignment to each treatment (for randomized trials); (9) compensation and/or treatment(s) available in case of investigation-related injury; (10) whom to contact with any questions related to the investigation; (11) anticipated payment, if any, to the volunteer for participating; (12) description of volunteer's responsibilities; (13) statement that "participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits"; and (14) any other relevant information.⁹⁹ As in the United States, the regulations require that the informed consent be in a written agreement that was freely entered into.¹⁰⁰ Although enumerated differently, there are no major differences between the required elements of informed consent in India and those under U.S. law.

Appendix VIII provides certain requirements for the composition, operation, and responsibility of the institutional ethics committees.¹⁰¹ The institutional ethics committees assure, by ongoing periodic review both before and during the clinical testing, that the rights, safety, and well-being of test subjects are protected.¹⁰² Under Indian law, the ethics committee guarantees that the research is conducted in accordance with the Declaration

⁹⁴ Drug and Cosmetics, *supra* note 34, Schedule Y.

⁹⁵ *Id.* art. 2(4) & (5) (describing generally the requirement of informed consent and the responsibilities of the ethics committee).

⁹⁶ *See id.* apx. VIII (discussing requirements related to the institutional ethics committees).

⁹⁷ *Id.* apx. V, item 1.

⁹⁸ *Id.* ("If no benefit is expected subject should be made aware of this.").

⁹⁹ *Id.*

¹⁰⁰ Drug and Cosmetics, *supra* note 34, Schedule Y, art. 2(4)(i).

¹⁰¹ *See id.* apx. VIII.

¹⁰² *Id.* art. 2(5).

of Helsinki.¹⁰³ Unlike the U.S. regulations,¹⁰⁴ Indian law refers to the most current Declaration and an outdated version of the Declaration of Helsinki is not codified into law.

V. THE PROTECTION OF TEST SUBJECTS UNDER INTERNATIONAL LAW

The most general of international standards related to human experimentation is stated in Article 7 of the International Covenant on Civil Political Rights (“ICCPR”): “[N]o one shall be subjected without his free consent to medical or scientific experimentation.”¹⁰⁵ In addition to this general declaration from the United Nations, there are additional international documents that more closely address human experimentation. The Declaration of Helsinki and the Nuremberg Code are the most relevant to this Comment and are discussed next.

A. The Declaration of Helsinki

The Declaration of Helsinki, mentioned in both Indian¹⁰⁶ and U.S.¹⁰⁷ regulations, is the most relevant international document to this comment. The World Medical Association (“WMA”) endorsed its first document on human experimentation in 1964, known as the Declaration of Helsinki.¹⁰⁸ The Declaration of Helsinki is a statement of ethical principles that offers guidance to participants in medical research involving human subjects.¹⁰⁹ The Declaration has been amended five times—in 1975, 1983, 1989, 1996, and 2000.¹¹⁰ Notes of clarification were added in 2002 and in 2004.¹¹¹

1. Helsinki VI

The newest version of the Declaration is the version amended in 2000, Helsinki VI.¹¹² This is the version applicable to Indian trials, while U.S.

¹⁰³ *Id.* apx. II, item 6. The Declaration of Helsinki is an international agreement and is discussed *infra* Part V.

¹⁰⁴ See 21 C.F.R. § 312.120(c)(4) (2005).

¹⁰⁵ International Covenant on Civil and Political Rights, G.A. Res. 2200A (XXI), art. 7, U.N. Doc. A/6316 (Dec. 19, 1966).

¹⁰⁶ Drug and Cosmetics, *supra* note 34, Schedule Y, apx. II, item 6.

¹⁰⁷ 21 C.F.R. § 312.120(c)(4).

¹⁰⁸ WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964) [hereinafter HELSINKI], available at <http://www.wma.net/e/policy/pdf/17c.pdf>.

¹⁰⁹ Medical research involving human subjects, as defined in the Declaration, includes research on identifiable human material. *Id.* at 1.

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

law relies on the earlier version, Helsinki V. Helsinki VI begins with a nine-provision introduction that recognizes the conflict between the physician's duty to serve the best interests of his/her patient and the need to expose test subjects to risks in the pursuit of medical advancement.¹¹³ The well-being of an individual test subject is most important; it is stated in the declaration that "[m]edical progress is based on research which ultimately must rest in part on experimentation involving human subjects" and "[i]n medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."¹¹⁴ Furthermore, in Provision 8 of the Introduction, the Declaration acknowledges that some research populations, particularly the economically and medically disadvantaged, are especially vulnerable to unethical treatment and require special protection:

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.¹¹⁵

Section B of the Declaration sets out basic principles for all medical research.¹¹⁶ Provision 19 in Section B is relevant to outsourcing of clinical trials from developed countries into developing countries and states: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."¹¹⁷

The final section, Section C, states additional provisions necessary when research is combined with medical care.¹¹⁸ Of particular interest is Provision 30, stating "[a]t the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."¹¹⁹ Provision 30 has been subject to criticism for being impractical and it is also thought to place too heavy a burden on research institutions as well as to create

¹¹³ See *id.* at 1–2.

¹¹⁴ HELSINKI, *supra* note 108, at 1.

¹¹⁵ *Id.* at 2.

¹¹⁶ See *id.* at 2–4.

¹¹⁷ *Id.* at 3.

¹¹⁸ See *id.* at 4–5.

¹¹⁹ *Id.* at 4.

undue incentives to participate in a clinical trial.¹²⁰ However, the WMA General Assembly has not chosen to amend the provision. Rather, in 2004, the Assembly added a note of clarification to the Declaration in regards to Provision 30, stating:

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.¹²¹

Overall, the current version of the Declaration of Helsinki offers a fairly detailed and comprehensive set of rules and standards to protect test subjects. The document offers stronger protections than either of the codified laws in the United States and India and is particularly applicable to the situation relevant in this comment: outsourcing clinical trials to developing countries.

2. Helsinki VI Applied to Indian Trials

As stated in Helsinki VI Provision 8, special consideration needs to be made in performing clinical trials on economically and medically disadvantaged populations.¹²²

Special considerations may be necessary to ensure that informed consent is “freely given” in India. For example, economically disadvantaged Indians may receive more money per month to participate in a trial than they could earn working their jobs.¹²³ For Indians without access to health care, the chance to participate in a clinical trial may amount to a healthcare windfall. For example, in one Indian trial outsourced by the German drug maker Boeringer Ingelheim, every test subject received free routine medical checkups during the course of the study.¹²⁴ The doctor’s offices and hospitals also stand to gain a relatively large amount of money. In the same Boeringer Ingelheim trial, each participating hospital or office would receive 30,000 rupees (\$675) from the drug company for each

¹²⁰ See WORLD MEDICAL ASSOCIATION, WORKGROUP REPORT ON THE REVISION OF PARAGRAPH 30 OF THE DECLARATION OF HELSINKI (2004), available at http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf.

¹²¹ HELSINKI, *supra* note 108, at 5.

¹²² *Id.* at 2.

¹²³ Nundy & Gulhati, *supra* note 15, at 1634.

¹²⁴ *India: Test Bed for Drugmakers*, PHARMA MARKETLETTER, Mar. 6, 2006, available at 2006 WLNR 3820168.

patient signed up for the trial.¹²⁵ The enticement of medically disadvantaged volunteers with health care checkups and drugs that are worth more than their annual salary, as well as relatively large amounts of money given directly to hospitals, may trigger the need for additional safeguards to ensure that informed consent takes place under the Declaration of Helsinki.¹²⁶

Provisions 19 and 30 of the Declaration also present interesting points of conflict in the realm of outsourced clinical trials. Provision 19 would require that the population tested—most likely impoverished Indians—benefit from the results of the research.¹²⁷ Similarly, Provision 30 would require that successful drugs tested on Indian clinical subjects be made accessible to them after the trials.¹²⁸ However, reality calls into question exactly what level of affordability is required for “access” to the new drugs. That is, the price on most drugs tested on Indians will end up being so high that most of the Indian population will not be able to afford them. For example, Eli Lilly plans to price just one 10-mg tablet of tadalafil, known by its trademark name Cialis, “at \$9 (400 rupees) which is equivalent to four days’ wages for a well-paid manual worker [in India].”¹²⁹

3. *Helsinki V: United States Law*

For FDA approval of a clinical study not conducted under an IND, it is important to consider not the newest version of the Declaration of Helsinki (“Helsinki VI”) but rather Helsinki V, the version preceding the amendments in 2000. Helsinki V is important because it is codified in Part 312 of Title 21 of the Code of Federal Regulations.¹³⁰ For the FDA to accept foreign clinical studies not conducted under an IND, “[f]oreign clinical research is required to have been conducted in accordance with the ethical principles stated in the ‘Declaration of Helsinki’ . . . or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.”¹³¹ The regulation refers to the “Declaration of Helsinki” as reproduced in Title 21 of the Code of Federal Regulations Section 312.120(c)(4).¹³² The version of the Declaration in the Code of Federal Regulations is Helsinki V, rather than

¹²⁵ *Id.*

¹²⁶ See HELSINKI, *supra* note 108, at 5.

¹²⁷ See *id.* at 2.

¹²⁸ See *id.* at 4.

¹²⁹ Nundy & Gulhati, *supra* note 15, at 1635 (citing James Mathew, *Eli Lilly gets EMR for Week-end Pill Cialis*, ECONOMIC TIMES (India), Sept. 16, 2004, at 11).

¹³⁰ Foreign Clinical Studies Not Conducted Under an IND, 21 C.F.R. § 312.120 (2005).

¹³¹ *Id.* § 312.120(c)(1).

¹³² *Id.* § 312.120(c)(4).

the more recent Helsinki VI.¹³³ The FDA is aware of the amendments to the Declaration of Helsinki but it has taken no action to incorporate the newest version of the Declaration into its regulations.¹³⁴ Specifically, the FDA provides guidance that “the action of the World Medical Association [in making the amendments in 2000] did not change FDA regulations.”¹³⁵

There are significant differences between Helsinki V codified in the FDA regulations and the most recent version released by the WMA. Highly relevant to the subject matter of this Comment, Provision 8 in Helsinki V does not mention a need for special consideration of ethical issues when testing on economically or medically disadvantaged populations.¹³⁶ Furthermore, in Helsinki V there is no requirement the population involved in the experiments benefit from the results of the research.¹³⁷ Also unlike the newest version, Helsinki V does not require that successful drugs be made accessible after the trials to the participants.¹³⁸ These differences are particularly relevant to research outsourced by U.S. pharmaceutical companies to India, because, in India, the institutional ethics committees must hold the clinical trials to the standards of the newest version of the Declaration. However, in the United States a trial not conducted under an IND only has to conform to Helsinki V for acceptance by the FDA.

B. The Nuremberg Code

During World War II, Nazi physicians and scientists committed atrocious crimes by performing medical and drug research on unwilling test subjects, who were primarily held at concentration camps.¹³⁹ Following the war, twenty-three physicians and scientists who had performed this research

¹³³ See HELSINKI, *supra* note 108, at 5 (Helsinki VI, amended in 2000); *Cf.* 21 C.F.R. § 312.120(c)(4) (Helsinki V, last amended in 1989).

¹³⁴ See FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: ACCEPTANCE OF FOREIGN CLINICAL STUDIES 2 (2001), *available at* <http://www.fda.gov/ohrms/dockets/98fr/010079g2.pdf> (“In October 2000, the World Medical Association revised the Declaration. FDA has not taken action to incorporate those revisions into its regulations. FDA is making available this guidance document to clarify that the action of the World Medical Association did not change FDA regulations”).

¹³⁵ *Id.*

¹³⁶ See 21 C.F.R. § 312.120(c)(4) (2005). Absent in Helsinki V, the requirement of special consideration for economically or medically disadvantaged populations is found in Provision 19 of Helsinki VI. See HELSINKI, *supra* note 108, at 4 (Helsinki VI, amended in 2000).

¹³⁷ *See id.*

¹³⁸ *See id.* This requirement could be found in Provision 30 of Helsinki VI. See HELSINKI, *supra* note 108, at 5 (Helsinki VI, amended in 2000).

¹³⁹ See generally Rebecca A. Finkenbinder, Comment, *New Recommendations on International Human Research: Can Minimum Standards Prevent the Exploitation of Vulnerable Human Subjects in Developing Countries?*, 21 PENN ST. INT’L L. REV. 363, 371–72 (2003).

were charged with war crimes' and crimes against humanity before a military tribunal of American judges in what has been called the "Doctors' Trial" in Nuremberg, Germany (1946–1947).¹⁴⁰ The trials ended with the conviction of fifteen of the defendants and, as a part of the final judgments, the judges included a set of conditions to govern the practice of medical experimentation on humans now known as the "Nuremberg Code."¹⁴¹

The Nuremberg Code enumerates ten provisions meant to govern medical experimentation performed on human subjects. The first of the ten provisions begins with a strong assertion: "[t]he voluntary consent of the human subject is absolutely essential."¹⁴² This means that the volunteer must "have the legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion"¹⁴³ The other provisions in the Nuremberg Code deal mainly with assurances that the experiments are based on the scientific method and ethically responsible in design.¹⁴⁴

Unlike the FDA regulations and the Declaration of Helsinki, the Nuremberg Code does not require that research be monitored and approved by an independent party. Also unlike the FDA regulations and the Declaration of Helsinki, the provisions in the Nuremberg Code are directed at scientists rather than institutions. In regard to the voluntary consent, the Nuremberg Code places the duty solely on the scientists, stating "[t]he duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."¹⁴⁵ The Nuremberg Code is not specifically adopted by either the FDA or the Indian government and, therefore, it is generally not a legally binding force. However, it was the first international legal document relating to human experimentation and has clearly been influential in the drafting of future regulations in both countries.

¹⁴⁰ *Id.* at 371.

¹⁴¹ The Nuremberg Code, in 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, at 181–82 (U.S. Gov't Printing Office 1949) [hereinafter Nuremberg Code], available at <http://history.nih.gov/laws/pdf/nuremberg.pdf>.

¹⁴² *Id.*

¹⁴³ *Id.*

¹⁴⁴ For example, Provision 2 states that all experiments should "yield fruitful results for the good of society" and not be "random and unnecessary in nature." *Id.* Also, Provision 4 states that experiments should "avoid all unnecessary physical and mental suffering and injury." *Id.*

¹⁴⁵ *Id.*

VI. CONCLUSION

India has positioned itself to maximize the value of its unique resources: the large and diverse patient population, the developed medical infrastructure and the well-trained, inexpensive, and English-speaking medical professionals. In modifying its intellectual property laws and its regulation of clinical trials, the Indian government has taken steps to protect foreign investment in clinical trials as well as the rights and safety of Indian trial volunteers. The country seeks to capture a share of the value it adds to the U.S. pharmaceutical companies' research and development models. Also, for many diseased Indians, the chance to participate in an investigational trial is a healthcare windfall, because these patients may otherwise have received no health care services. India is poised to make significant gains as a result of the upcoming boom in outsourcing clinical trials, and U.S. companies (and ultimately the consumers) also stand to gain as such outsourcing provides a more cost-effective solution to their drug development activities.

Outsourcing clinical research to India is not a story of profit-driven U.S. companies pushing unproven pharmaceuticals into India's highly vulnerable test subjects. U.S. companies do not escape their obligations to protect the trial test subjects in India that would be required if such trial was conducted domestically. In fact, the regulations in India are arguably more pro-patient than in the United States as witnessed by the acceptance of the newest version of the Declaration of Helsinki under Indian law while the U.S. government only recognizes the outdated 1989 version of the Declaration. Still, there is a legitimate concern over the Indian government's enforcement of its own regulations and the oversight of the ethics committees.¹⁴⁶ As India has acted to maximize the value of its unique resources, it must also leverage them to force U.S. companies to comply with the most current international ethical standards and all Indian regulations.

¹⁴⁶ See Nundy & Gulhati, *supra* note 15, at 1635.

