CLINICAL STUDIES CONDUCTED OUTSIDE OF THE UNITED STATES AND THEIR ROLE IN THE FOOD AND DRUG ADMINISTRATION'S DRUG MARKETING APPROVAL PROCESS

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1. INTRODUCTION

The U.S. pharmaceutical industry represents a vast and lucrative sector of the economy. Resistant to the poor economic climate of the Great Recession, annual revenue from U.S. sales has remained above $300 billion.[1] Though annual growth has languished recently,[2] year-to-year growth will remain a fixture of this industry as the U.S. economy recovers and the industry looks to strengthen its global markets.[3]

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* J.D. 2012, University of Pennsylvania Law School and former Executive Editor of the *University of Pennsylvania Journal of International Law*. I would like to thank my family and friends for their support and encouragement, as well as Professor Theodore Ruger for offering his guidance and expertise. Additional thanks to Dr. Robert Swift and Dr. George Kenna of Brown University for introducing me to the field of clinical research, and to the *Journal of International Law* editorial staff for their diligence. All errors are my own.

[1] Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Grew 5.1 Percent in 2009, to $300.3 Billion (Apr. 1, 2010), http://web.archive.org/web/20100406004405/http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=d690a27e9d5b7210VgnVCM100000ed152ca2RCRD&vgnextchannel=41a67900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default [hereinafter 2009 Pharmaceutical Growth].

[2] *Compare* Ernst R. Berndt, *The U.S. Pharmaceutical Industry: Why Major Growth in Times of Cost Containment?*, 20 HEALTH AFF., 100, 100 (2001) (stating that the annual growth for U.S. pharmaceutical sales between 1994 and 1999 was 12.8%) *with* 2009 Pharmaceutical Growth, *supra* note 1 (stating that U.S. prescription sales grew by 1.8% in 2008 and remain at historically low levels, despite a 5.1% growth rate in 2009).

[3] While growth remains at low levels—2.3% in 2010—there is little to indicate that the market would actually contract at any point. *See* 2009 Pharmaceutical Growth, *supra* note 1 ("Stronger patient demand for prescription drugs throughout 2009 . . . underscores the resilience of pharmacotherapies in today's healthcare equation."); *see also* Press Release, IMS Health, IMS Health Reports U.S. Spending on Medicine Grew 2.3 Percent in 2010, to $307.4 Billion (Apr. 19, 2011),

In order to maintain high economic return, pharmaceutical companies must continually produce marketable new drugs, or acquire the U.S. Food and Drug Administration's ("FDA") approval to re-market current drugs for a different treatment purpose. One obstacle to a drug's profitability is U.S. patent law, which limits new drug patents to twenty years[4] with minimal opportunities to extend the patent life.[5] At the conclusion of the patent life, the drug becomes "generic," and it can be produced by any qualified manufacturer, often being sold at a much lower price. A second obstacle is the FDA's drug marketing approval process, which creates a significant lag between a company's initial investment in a drug and the eventual sale of that drug.[6] These initial investments are often substantial and threaten a company's viability the longer a drug takes to enter the market. In order to shorten the delay between investment and return, many pharmaceutical companies increasingly turn to clinical studies conducted outside of the United States to supplement, or in some cases to completely comprise, their New Drug Application ("NDA").[7] This trend toward using clinical studies conducted

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http://www.imshealth.com/portal/site/ims/menuitem.d248e29c86589c9c30e81c033208c22a/?vgnextoid=1648679328d6f210VgnVCM100000ed152ca2RCRD&vgnextfmt=default (acknowledging industry, but raising concerns over a weakening consumer base and lost revenue due to patent expiry); *but see PwC Report Forecasts a Golden Era Ahead for Pharmaceutical Companies, but Global Growth Markets Won't Guarantee Success*, PWC (Nov. 15, 2012), http://www.pwc.com/us/en/press-releases/2012/pwc-report-forecasts-a-golden-era.jhtml (projecting a future industry boom if companies can prove the long-term cost-savings benefits of their medications in those developed economies experiencing economic hardship, while at the same time investing in growth markets).

[4] 35 U.S.C.A. § 154(a) (West 2012).

[5] *See generally* WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RS 21129, PHARMACEUTICAL PATENT TERM EXTENSIONS: A BRIEF EXPLANATION (2002), *available at* http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RS21129.pdf.

[6] *See* FOOD AND DRUG LAW: CASES AND MATERIALS 577 (Peter Barton Hutt et al. eds., 3d ed. 2007) ("[O]n average it now takes 10 to 15 years to develop a new chemical entity (NCE), from initial chemical synthesis to FDA approval of a [New Drug Application]."); Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816, 816–17 ("In 2000, the cost to develop a new drug averaged $802 million, with time costs accounting for half of that amount.")

[7] *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApprov

outside the United States, also known as foreign clinical trials ("FCTs"), is attributed to: drastically reduced costs compared to domestic trials; easier subject recruitment;[8] and less regulatory red tape from foreign governments. Use of FCTs in the drug marketing approval process has been contentious at times, prompting questions regarding unethical conduct and data validity. Proponents of FCTs maintain that the studies are safe and reliable, and comply with international humanitarian standards. Critics believe that FCTs, especially those performed in less-developed countries, produce unreliable data and fail to protect against human rights violations. This Article intends to provide a historical context for the use of FCTs in the FDA's drug marketing approval process, explain the current law regarding the use of FCTs in the FDA's drug marketing approval process, analyze current criticisms of FCTs, and provide some recommendations about how to minimize these issues.

2. A BRIEF HISTORY OF THE FDA'S OVERSIGHT IN THE PHARMACEUTICAL INDUSTRY

The history of the FDA begins in the U.S. Patent Office in 1848 when Congress provided funds to the patent commissioner to "conduct chemical analyses of 'vegetable substances produced and used for the food of man and animals in the United States.'"[9] Since then, the organization that we now know as the FDA has undergone several changes in terms of its Congressional authorizations.[10] Some of the most influential changes were

ed/ApprovalApplications/NewDrugApplicationNDA/default.htm (last updated May 18, 2012) ("The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.").

[8] Adam H. Laughton, *Somewhere to Run, Somewhere to Hide?: International Regulation of Human Subject Experimentation*, 18 DUKE J. COMP. & INT'L L. 181, 190–92 (2007) ("Americans are increasingly hesitant to participate in [clinical] experiments. The lack of clinical volunteers has caused a back-up in the 'pipeline' of developing drugs.").

[9] Peter Barton Hutt, *Symposium on the History of Fifty Years of Food Regulation Under the Food, Drug and Cosmetic Act: A Historical Introduction*, 45 FOOD DRUG COSM. L.J. 17, 18 (1990).

[10] *See id.* at 17–18 nn. 16–25 (listing the relevant statutes locating the FDA predecessor within various parent agencies). The FDA in its current form was not

embodied in the Food, Drug, and Cosmetic Act ("FD&C Act") of 1938, which provided the FDA with its organic statute and the ability to assert itself as gatekeeper between the drug industry and the American public. The 1938 FD&C Act replaced the Federal Food and Drug Act of 1906[11] and greatly expanded the powers and role of the FDA as it attempted to rein in the unwieldy marketing of drugs in the United States.

The Elixer Sulfanilamide disaster of 1937 was a major catalyst of the 1938 FD&C Act.[12] In 1937, Elixer Sulfanilamide was approved for use in the United States in pill form, but was also being sold in its liquid form, which had not been clinically tested for toxicity.[13] Compared to its pill form, the untested liquid was much more potent, and the drug killed 107 misinformed people as a result.[14] At that time, it was legal for a company to market a drug in multiple forms without showing that each mode of delivery was safe and effective. The absence of mandated testing likely lead to countless injuries, as companies still grappled with the nuanced intricacies of chemical compounds.

The 1938 FD&C Act required only pre-marketing *notification* to the FDA for a new drug,[15] but eventually the FDA was given true gate-keeping authority in the form of pre-marketing *approval*.[16] This change in law occurred after a string of drug related tragedies, including the thalidomide disaster of the 1950s.[17] Congress responded to the problem in 1962 with the Kefauver-Harrison

formally established by statute until 1988. *Id.* at 18 n.22 (citing the Food and Drug Administration Act of 1988, 102 Stat. 3048, 3120 (1988)). *See* 21 U.S.C.A. § 393 (West 2011) (current version of the Act).

[11] *See generally* Federal Food and Drug Act of 1906, ch. 3915, 34 Stat. 768 (1906) (establishing federal regulations for all drugs intended for human use).

[12] James Thuo Gathii, *Rights, Patents, Markets and the Global AIDS Pandemic*, 14 FLA. J. INT'L L. 261, 341 (2002).

[13] *Id.*

[14] *Id.*

[15] *See* FOOD AND DRUG LAW, *supra* note 6, at 577 (stating that under the original 1938 FD&C Act, drug manufactures had to file an NDA with the FDA, but could begin marketing the new drug if in sixty days the FDA did not postpone or deny their application).

[16] *See* Act of June 25, 1938, Pub. L. No. 75-717, 52 Stat. 1052 (providing authority to enjoin a new drug from being marketed in the United States without prior FDA approval).

[17] Gathii, *supra* note 12, at 334.

Amendments, which granted the FDA stronger regulatory powers in the pre-marketing approval stage of a new drug.[18] Today, before a new drug can be marketed in the United States, it must go through extensive clinical testing to show that it is both safe and effective under its prescribed and recommended use.[19] The purpose of the requirement is to ensure the public's safety, but it also delays the development of new drugs and increases their cost; rather poetically, the measure's remedial benefits continue to be weighed against its unintended side effects.

2.1. The Use of Clinical Studies in the FDA's Approval Process

To gain FDA approval to market a new drug[20] in the United States, a drug sponsor[21] ("Sponsor") must submit an NDA,[22] which, collectively with other application materials, is referred to as a "marketing application."[23] Among other things, an NDA must establish that a drug is both safe and effective for its prescribed use,[24] and it must meet this burden through the criteria established in section 505(d) of the FD&C Act.[25] To prove that a new drug is

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[18] *Id.* at 340.

[19] *See generally* 21 U.S.C.A. § 355 (West 2012) (outlining the FDA's new drug approval process).

[20] 21 U.S.C.A. § 321(p) (West 2012) ("The term 'new drug' means (1) [a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts . . . as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling . . . ; or (2) [a]ny drug [which] has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.").

[21] *See* 21 C.F.R. § 312.3(b) (2012) (*"Sponsor* means a person who takes responsibility for and initiates a clinical investigation.")

[22] First implemented in the 1938 FD&C Act. *See New Drug Application (NDA)*, *supra* note 7 (explaining how "the NDA application [sic] is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S."). *See also* 21 C.F.R. § 314.50 (2012) (describing the application process for receiving FDA approval to market a new drug).

[23] *See* 21 C.F.R. § 312.3(b) (2012).

[24] 21 U.S.C.A. § 355(b)(1) (West 2012) (requiring an applicant, when filing an NDA application, to submit "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use").

[25] FOOD AND DRUG LAW, *supra* note 6, at 624.

both safe and effective, the drug's Sponsor must provide substantial proof from adequate testing reasonably applicable to show such safety and effectiveness.[26] Sponsors demonstrate substantial proof of safety and effectiveness by conducting clinical trials.[27]

The Sponsor, who is often the drug manufacturer, is responsible for adequately testing a new drug. Clinical studies are typically performed in a controlled setting utilizing either a "blind" or "double-blind" design. The purpose of a controlled setting is to eliminate as much environmental interference as possible so that a drug's effects can be isolated. A blind study is one in which participants are not told what dosage of a drug they are receiving or, if multiple drugs are being tested, participants are not told which drug they are receiving. In contrast, a double-blind design prevents both the participant and the researchers from knowing how much of a drug—or if applicable, which drug—an individual participant is receiving. Additionally, in the United States, it is normal to utilize a placebo control group, meaning that some of the study participants are given an inert substance in lieu of the drug.[28] The purpose of the placebo control group is to set a baseline to measure the drug's effects against, and to provide further control over, environmental interference.

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[26] 21 U.S.C.A § 355(d)(1) (West 2012) (lacking "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" is grounds for refusing an NDA).

[27] *See* U.S. DEP'T OF HEALTH & HUMAN SERV., OFFICE OF THE INSPECTOR GEN., OEI-01-00-00190, THE GLOBALIZATION OF CLINICAL TRIALS: A GROWING CHALLENGE IN PROTECTING HUMAN SUBJECTS 1 (Sept. 2001) (outlining the FDA's oversight of new drug research) [hereinafter GLOBALIZATION OF CLINICAL TRIALS]; *see also* 21 C.F.R. § 312.3(b) (2012) ("Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.") (emphasis omitted).

[28] The use of placebo control groups is often considered unethical by countries other than the United States and is generally discouraged by the international community. *See e.g.* WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ¶ 32 (2008), *available at* http://www.wma.net/en/30publications/10policies/b3/17c.pdf.

A clinical investigator orchestrates and leads the clinical studies.[29] An Institutional Review Board[30] ("IRB") and sometimes a Data Monitoring Committee[31] ("DMC") also oversee clinical studies. An IRB is expected to scrutinize study protocols before testing begins, monitor the progress of a study, maintain records, and assure clinical testing meets ethical standards including using a simple and clear patient/subject informed consent form.[32] A DMC reviews the data as a study progresses to ensure that the drug is not so dangerous that the clinical trial needs to be terminated, or conversely, that the drug is not so effective that it would be unethical to withhold the treatment from any participant receiving an inadequate dose.[33]

Before initiating clinical trials, manufacturers conduct non-clinical trials[34] using only animal subjects and computer modeling. During the pre-clinical stage, a manufacturer must establish some basic knowledge about the drug—in particular, what conditions the drug could potentially treat and toxicity levels.[35] If the drug appears promising after the pre-clinical stage, the Sponsor files an

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[29] U.S. DEP'T OF HEALTH & HUMAN SERV. ET AL., GUIDANCE FOR INDUSTRY AND CLINICAL INVESTIGATORS: THE USE OF CLINICAL HOLDS FOLLOWING CLINICAL INVESTIGATOR MISCONDUCT, 2 (Sept. 2004), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126997.pdf (describing the role of clinical investigators in clinical studies).

[30] *See generally* 21 C.F.R. § 56 (2012) (establishing the functions and operations of an IRB).

[31] *See generally* U.S. DEP'T OF HEALTH & HUMAN SERV. ET AL., OMB Control No. 0910–0581, GUIDANCE FOR CLINICAL TRIAL SPONSORS: ESTABLISHMENT AND OPERATIONS OF CLINICAL TRIAL DATA MONITORING COMMITTEES (Mar. 2006), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf (setting guidelines for when a DMC is needed, how a DMC should be structured, and scenarios that a DMC may need to manage).

[32] *See id.* at 6 (listing failure to obtain "adequate informed consent" and falsifying such forms as factors which indicate misconduct); *see also* 21 C.F.R. § 50.20 (2012) (outlining the minimum requirements of a subject/patient informed consent form).

[33] FOOD AND DRUG LAW, *supra* note 6, at 647.

[34] The term "non-clinical" or "pre-clinical" trial denotes that the trial will not involve human subjects, and is to be contrasted with the term "clinical trials" where human subjects will be used. REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 967 (David B. Troy ed., 21st ed. 2005).

[35] FOOD AND DRUG LAW, *supra* note 6, at 621.

Investigational New Drug application[36] ("IND") with the FDA in order to proceed with testing on human subjects. The basic content of an IND outlines what the drug is, what the Sponsor expects the drug's effects will be, and the protocol for the proposed clinical experiment.[37] The FDA has thirty days to put an IND on clinical hold,[38] otherwise the IND becomes effective and the Sponsor may begin the first phase of clinical testing.[39]

Phase 1[40] clinical studies involve administering the new drug to a small group of healthy human subjects; these studies are designed to determine the "metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."[41] If given approval by the FDA, the Sponsor may progress to Phase 2[42] clinical studies, which are designed to "obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug . . . [and] usually [involves] several hundred people."[43] If the objectives of Phase 2 are satisfied

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[36] 21 C.F.R. § 312.23 (2012) ("A sponsor who intends to conduct a clinical investigation . . . shall submit an 'Investigational New Drug Application'. . . ."). Note that an IND may be supported by clinical trials conducted under another IND, or a clinical trial that was conducted abroad and not under an IND.

[37] REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, *supra* note 34, at 966–67. An IND is also the means through which a new drug is exempted from many pre-marketing regulations so that it can be legally transported across state borders and tested. *See* 21 C.F.R. § 312.1(a) (2012).

[38] *See* 21 C.F.R. § 312.20(c) (2012). *See generally* 21 C.F.R. § 312.42 (2012) (stating that a clinical hold prevents investigators from administering the investigational drug to subjects, and stating the factors that will be considered by the FDA before imposing a clinical hold).

[39] 21 C.F.R. § 312.40(b)(1) (2012) (stating when an IND goes into effect). Also, be aware that the FDA can institute a clinical hold at Phases 1 through 3 of clinical testing if they determine the study is unsafe or ill designed to achieve its objective. *See* CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., THE CDER HANDBOOK 8-9 (Revised Mar. 16, 1998) [hereinafter CDER HANDBOOK]; 21 C.F.R. §§ 312.42(b)(1)(i), (b)(2)(ii) (2012).

[40] 21 C.F.R. § 312.21(a) (2012).

[41] CDER HANDBOOK, *supra* note 39, at 8.

[42] 21 C.F.R. § 312.21(b) (2012).

[43] CDER HANDBOOK, *supra* note 39, at 8.

then the Sponsor may, with FDA approval, begin Phase 3[44] clinical studies, which are designed

> to gather [] additional information about effectiveness and safety [which] is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.[45]

3. FCTs

3.1. Historical Context Surrounding the Use of FCTs in a Marketing Application

For most of its history, the U.S. government has taken a hands-off approach to drug testing. Ethical rules governing clinical studies were not formally established until after the Second World War,[46] and prior to the 1950s, there was no duty to root out unethical conduct in clinical trials.[47] Likewise, the notion that an independent agent should audit study materials to verify that scientifically proven methods were actually implemented in an ethical manner, or that data was accurately reported, is also a recent phenomenon. Yet, these practices eventually became endemic in the pharmaceutical industry.

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[44] 21 C.F.R. § 312.21(c) (2012).

[45] CDER HANDBOOK, *supra* note 39, at 8–9. The FDA may also require Phase 4 clinical studies, but these are performed as follow-up on a specific issue after the manufacturer is already permitted to sell the drug to the public. REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, *supra* note 34, at 968.

[46] For an in-depth treatment of early ethical codes for human research, see BRUCE MACFARLANE, RESEARCHING WITH INTEGRITY: THE ETHICS OF ACADEMIC ENQUIRY 9–20 (2009) (discussing the legacy left by Nazis research at Nuremberg); PAUL M. MCNEILL, THE ETHICS AND POLITICS OF HUMAN EXPERIMENTATION 37–50 (1993) (discussing the development of ethics regarding human experimentation); *see generally* Fazal Kahn, *The Human Factor: Globalizing Ethical Standards in Drug Trials Through Market Exclusion*, 57 DEPAUL L. REV. 877 (2008) (advocating for exclusion of drug products from the market that are not tested ethically).

[47] MCNEILL, *supra* note 46, at 20–21 (discussing how the Second World War instigated more clinical trial funding without creating a parallel increase in ethical review).

The business necessity of clinical trials began when the FDA received limited pre-marketing regulatory power under its organic statute in 1938 and created what today is known as the NDA approval process.[48] This regulatory shift—requiring businesses to support their NDA with scientific studies—caused a marked increase in the number of clinical trials being conducted and a movement from academically orchestrated trials to privately run trials.[49] Over time, drug regulations became more stringent, requiring greater statistical proof of safety, and eventually proof of efficacy. As the regulatory demands rose, so too did the amount of testing necessary to provide the requisite levels of statistical certainty.[50] In light of the burden placed on applicants, the FDA should not have been surprised when Sponsors began to include FCTs to supplement INDs and NDAs. Other factors may also have encouraged Sponsors to conduct their studies outside the United States, such as: funding from a foreign government or organization to conduct a study in their region; a foreign country's regulatory requirement that research on a drug be conducted on their population before being locally marketed;[51] seasonal or

[48] *New Drug Application (NDA)*, *supra* note 7 (providing general information to the drug industry about the history of and current regulations governing NDAs); *see also* 21 C.F.R. § 314 (2012) (governing code for marketing applications submitted to the FDA).

[49] *See* Jennifer Washburn, *Undue Influence*, AM. PROSPECT, Aug. 13, 2001, at 17–16.

[50] Between 1986 and 2005, the annual number of IND submissions to the FDA rose from slightly less than 350 submissions in 1986 to more than 550 submissions in 2005, with much of the increase occurring between 2003 and 2005. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-07-49, REPORT TO CONGRESSIONAL REQUESTERS: NEW DRUG DEVELOPMENT, 13 (Fig.3) (Nov. 2006). From 1993 to 2004, annual research and development expenses for drug marketing approval increased 147%. *Id*. at 14. However, from 1993 to 2004, the number of NDA submissions increased only thirty-eight percent and was generally declining from 2000 to 2004. *Id*. at 15. This suggests that increases in research and development of drugs have been steadily outpacing the number of new marketing applications. *Id*. at i.

[51] *See, e.g.*, FL Arnold et al., *Exploring Differences in Drug Doses Between Japan and Western Countries*, 87 (No. 6) CLINICAL PHARMACOLOGY & THERAPEUTICS 714, 714 (June 2010) (explaining that Japan is unique in requiring the inclusion of substantial domestic clinical trial data in new drug application data packages).

geographic specific diseases;[52] and potentially lower costs when conducting research in less-developed countries.[53]

Over the past forty years, there has been a continuous increase in the number of clinical trials moved to locations outside of the United States, which have been used to supplement marketing applications submitted to the FDA.[54] Within this trend emerged a subculture of manufacturers that conducted their studies abroad without seeking FDA approval or supervision via an IND, only to later submit the study to the FDA in a marketing application. Though the FDA has never prohibited unregistered foreign studies from being submitted as part of a marketing application, the FDA has historically been wary of FCTs in general;[55] prior to the 1962 Kefauver-Harrison Amendments, it was uncommon for a Sponsor to submit FCT data.[56] Over time, however, the FDA gradually came to accept FCTs as equal to their domestic counterparts,[57] and during the 1970s began drafting provisions that would officially permit the submission of an FCT that was not conducted under an

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[52] Michael Thoma, *Clinical Trials Go Global: Overseas Locations Offer Huge Benefits – But Also Pose Complex Challenges*, MDDI (Mar. 1, 2008), http://www.mddionline.com/article/clinical-trials-go-global.

[53] *See* Carolyne Hathaway et al., *Looking Abroad: Clinical Drug Trials*, 63 FOOD & DRUG L.J. 673, 674 (2008) (listing "lower overall trial costs" as one of several key factors for the recent proliferation of drug trials in Central and Eastern Europe).

[54] *See* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, *supra* note 34, at 650 (contrasting the minimal appearance of FCTs in the FDA's drug marketing approval process prior to 1980 with the mass migration of clinical studies to places outside of the United States during the 1980s). *Compare* Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally*, 30 Cornell Int'l L. J. 245, 246 (1997) (reporting that eighteen percent of studies funded by U.S. companies were being conducted outside the United States) *with* DEP'T. OF HEALTH & HUMAN SERV., CHALLENGES TO THE FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS, 10, OEI-01-08-00510 (June 2010) (reporting that in 2008 an estimated forty to sixty-five percent of all clinical trials involving FDA-regulated products were being conducted abroad and that seventy-eight percent of all subjects who participated in clinical trials were enrolled at foreign sites) [hereinafter CHALLENGES TO THE FDA].

[55] *See* John J. Gorski, *An FDA-EEC Perspective on the International Acceptance of Foreign Clinical Data*, 21 CAL. W. INT'L L. J. 329, 333 (1991) (stating that even after the 1962 Kefauver- Harrison Amendments to the 1938 FD&C Act, the FDA limited the use of foreign data to literature review).

[56] FOOD AND DRUG LAW, *supra* note 6, at 650.

[57] *Id.*

IND to support a Sponsor's marketing application.[58] In 1975 these provisions were codified in 21 C.F.R. 312.120, which, at the time, stated that an FCT not conducted under an IND was an acceptable submission so as long as it was conducted under the ethical standards of the 1964 Declaration of Helsinki or the ethical standards of the host country, whichever was stricter.[59] This outright approval opened a floodgate through which the growing number of FCTs not conducted under an IND could flow into the drug marketing approval process.[60]

The FDA has periodically amended 21 C.F.R. 312.120 to incorporate changes in the Declaration of Helsinki. This occurred in 1981 when the FDA incorporated the 1975 version and again in 1991 when the FDA set the 1989 Declaration as the statutory floor.[61] These revisions, however, applied only to FCTs not conducted under an IND. When a manufacturer conducts a study outside of the United States but under an IND, the study, like domestic studies, must comport with all relevant U.S. laws and FDA regulations.[62] Regardless, this difference may be more substantial in form than in substance as U.S. laws and regulations have typically adhered to most provisions of the Declaration of Helsinki.[63]

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[58] *See* 38 Fed. Reg. 24220 (Sept. 6, 1973) (pinpointing concerns over the lack of access to data from FCTs as motivation for promulgating the regulation); 40 Fed. Reg. 16053 (Apr. 9, 1975) (incorporating comments made in response to the September 1973 proposed regulation).

[59] *See* FOOD AND DRUG LAW, *supra* note 6, at 650. *See also* Gorski, *supra* note 55, at 333 ("It was not until 1975 that the FDA accepted foreign clinical studies as primary evidence of a drug's safety or efficacy.").

[60] *See* RITA RICARDO-CAMPBELL, DRUG LAG: FEDERAL GOVERNMENT DECISION MAKING 20 (1976) (describing— in 1976—the trend of pharmaceutical companies moving clinical studies abroad in order to circumvent the IND requirements).

[61] U.S. DEP'T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY: ACCEPTANCE OF FOREIGN CLINICAL STUDIES 2 (Mar. 2001), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm.

[62] *See id.* at 1–2 (summarizing the specific FDA regulations that govern the standards for FCTs as they relate to U.S. standards, and the interplay between these regulations and the Helsinki Declaration).

[63] *See id.*

3.2. Analysis of the Movement Abroad

In the 1980s, there was a large migration of clinical studies leaving the United States.[64] The exodus was especially pronounced for studies investigating compounds in the early stages of research.[65] Three of the most important regulatory factors that contributed to the movement abroad were: (1) the restrictive regulations imposed by the FDA on clinical studies conducted under an IND;[66] (2) the recently promulgated FDA legislation that confirmed FCTs not performed under an IND could be used to support an NDA or future IND;[67] and (3) the lax regulatory approach of certain foreign governments.[68] Purportedly in an attempt to stem the movement, the FDA fought to streamline its drug marketing approval process.[69] The streamlining provisions eventually promulgated were limited, however, shortening the marketing application process by six months *at best* and allowing FCTs to be the sole support for an NDA.[70] More likely, the FDA was attempting to ameliorate some of the restrictiveness of the 1962 Kefauver-Harrison Amendments, which created unpopular delays in the approval process.[71] Moreover, no amount of administrative streamlining could offset two crucial non-regulatory factors that pushed clinical studies abroad: the extreme

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[64] FOOD AND DRUG LAW, *supra* note 6, at 650.

[65] *Id.*

[66] *Id.*

[67] *See* Ricardo-Campbell, *supra* note 60, at 20.

[68] *See, e.g.*, FOOD AND DRUG LAW, *supra* note 6, at 650; Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT'L L. 513, 532–33 (2002) (describing a medical "race to the bottom," in which many African countries minimize regulations to attract outside medical research); Yevgenia Shtilman, *Pharmaceutical Drug Testing in the Former Soviet Union: Contract Research Organizations as Broker-Dealers in an Emerging Testing Ground for America's Big Pharma*, 29 B.C. THIRD WORLD L.J. 425, 427 (2009) (noting how citizens in developing countries, whose governments oppose stricter regulation on experimental drug trials, make attractive subjects for clinical researchers).

[69] FOOD AND DRUG LAW, *supra* note 6, at 650.

[70] *HSS Completes Work on Rules to Speed Approval Process of New Drugs*, WASH. POST, Dec. 12, 1984, at A4.

[71] Gorski, *supra* note 55, at 330–32 (outlining the controversy surrounding the relatively slow drug approval process in the United States).

reduction in cost achieved by conducting studies in less-developed countries;[72] and the larger pool of willing participants.[73]

Current analysis indicates that a study conducted outside the United States can reduce the price tag of drug trials to one half[74] or even one tenth[75] of what the same study would cost to run inside the United States. Differing costs for facilities, raw materials, employee wages, and government licensing are possible causes for this extreme discrepancy. Additionally, subject recruitment may be faster in developing countries.[76] This last factor serves a dual benefit to the Sponsor because a larger, more willing subject population means that larger studies become feasible[77] and that studies can be completed expeditiously. Rapidly completed studies also lower costs by shortening the period when facilities and employees are needed, while simultaneously increasing revenue by bringing the new drug to market earlier.[78]

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[72] FOOD AND DRUG LAW, *supra* note 6, at 650.

[73] Gregory Lopes, *Drug Makers Look East For Testing; Lower Costs, More Patients in Asia to Help Speed Approval*, WASH. TIMES, Dec. 8, 2007, at A1; Hathaway et al., *supra* note 53, at 674.

[74] *See* Lopes, *supra* note 73 (discussing the reduced cost of drug trials in developing countries).

[75] *See* Glickman et al., *supra* note 6, at 816 (describing the rapid increase in the number of clinical trials being conducted outside of the United States and possible causes for the trend).

[76] *Compare* Jennifer Kahn, *A Nation of Guinea Pigs,* WIRED MAGAZINE, Mar. 2006, http://www.wired.com/wired/archive/14.03/indiadrug.html (describing how a vulnerable population in India proved highly receptive to clinical drug testing) *with* Sonia Shah, *Globalization of Clinical Research by the Pharmaceutical Industry*, 33 INT'L J. HEALTH SERVICES 29, 29 (2003) (stating that 1 in 350 Americans are willing to participate in clinical research). *See also* Samiran Nundy & Chandra M. Gulhati, *A New Colonialism? – Conducting Clinical Trials in India*, 352 New ENG. J. MED. 1633, 1634 (2005) (discussing reasons why clinical trials are being conducted outside of Western countries and the implications of this trend); Hathaway et al., *supra* note 53, at 674.

[77] *See* Kahn, *supra* note 76 (comparing drug approval during the 1980s, when approximately 1,300 volunteers was enough to get approval, with the mid-1990s, when it was necessary to recruit approximately 4,200 volunteers). Kahn rightly notes that part of the cause for rising enrollment numbers was the need to show increased efficacy as drugs became more effective. *Id.*

[78] Lopes, *supra* note 73. *See* SONIA SHAH, THE BODY HUNTERS 5 (2006) ("[E]very day a new drug remains locked up in development bleeds companies of up to $1 million in potential sales income.").

Data regarding the trends in FCTs during the 1980s and 1990s was troublesome to compile because the FDA "[did] not track NDA information by the location where research was conducted."[79] Additionally, many FCTs are not conducted under an IND, so the FDA does not know of their existence.[80] Thus, data compiled on FCTs during those decades comes from Sponsors who voluntarily conducted their FCT under an IND.[81] These studies may represent only a small portion of overall FCTs during that time. In an attempt to shed light on this uncharted subject, the Department of Health and Human Services Office of the Investigator General ("OIG") released a 2001 report titled *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, which gave the United States a limited idea of the expanding FCT industry. The OIG documented a sixteen-fold increase between 1990 and 1999 in the number of foreign clinical investigators conducting studies under an IND.[82] "In 1980, just 41 foreign clinical investigators conducted drug research under an IND. By 1990, that number grew to 271, and by 1999, to 4,458."[83] The report also noted a substantial increase of studies located in "emerging sites"—so designated because of the limited experience these countries had conducting clinical research—which included Latin America, Eastern Europe and East Asia.[84] Studies in these regions were linked with increased use of contract research organizations[85] ("CROs") by study Sponsors.[86]

In its 2001 report, the OIG listed five major concerns regarding the increase in FCTs: (1) the FDA has minimal information on the performance of foreign IRBs; (2) not all foreign investigators who conduct research that is submitted in an NDAs sign an attestation

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[79] GLOBALIZATION OF CLINICAL TRIALS, *supra* note 27, at 6.

[80] *Id.*

[81] *Id.*

[82] *Id.* at i.

[83] *Id.* at 6.

[84] *Id.* at 8. Study Sponsors confirmed that an increasing number of trials were being conducted in "emerging sites." *See id.*

[85] *Id.* at 9 ("Contract research organizations are entities with whom drug sponsors often contract to manage trials in foreign countries, particularly those in which sponsors have no offices.").

[86] *Id.*

that they will uphold human subject protections; (3) the FDA experiences challenges inspecting investigators at foreign sites; (4) the FDA has limited information on the people and entities involved in foreign research; and (5) the FDA typically does not review or discuss with Sponsors the study designs and monitoring plans of NDA research that was not conducted under an IND.[87] The OIG also made five recommendations to the FDA in light of these concerns: (1) examine ways to obtain information on the performance of foreign IRBs who oversee clinical trials used to support an NDA; (2) help inexperienced IRBs build their capacity; (3) encourage Sponsors to obtain a signed attestation clause from each foreign clinical investigator, promising to uphold human subject protections; (4) encourage Sponsors to monitor foreign studies more closely; and (5) develop a database to track growth and location of FCTs.[88] The FDA viewed most of these recommendations as favorable. However, the FDA disagreed with implementing the attestation clause and tracking of FCTs, due to their lack of authority outside of the United States and the financial costs of data collection, respectively.[89]

3.3. Current Law Governing FCTs

When a study is conducted under an IND but is located outside of the United States, the study still must comport with all relevant FDA regulations as if it were being conducted within the United States.[90] A Sponsor is not required to conduct an FCT under an IND in order to use it as support for an NDA or IND.[91] The rules governing the submission of an FCT not conducted under an IND are codified in 21 C.F.R. 312.120, which was last amended in 2008.[92]

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[87] *Id.* at 12–15.

[88] *Id.* at 17–20.

[89] Kelly Huegel, *FDA Not Keeping Pace with Foreign BiMo Audits, Urged to Inspect IRBs, Push Sponsors to Do Better Monitoring*, 1 BIORESEARCH MONITORING ALERT 222, Oct. 1, 2001.

[90] 21 C.F.R. § 312 (2012).

[91] 21 C.F.R. § 312.120 (2012).

[92] *See generally* 21 C.F.R. § 312.120 (2008). On August 2, 2012, Rep. Edward Markey (D-Mass.) introduced to the U.S. Congress the Trial and Experimental Studies Transparency (TEST) Act, H.R. 6272, 112th Cong. (2012). The TEST Act, in its proposed form, mandates that the Secretary of Health and Human Services, within one year of enactment of the Act, amend 21 C.F.R. 312.120 "to require that

Prior to 2008, FCTs not conducted under an IND could be submitted if the study adhered to the principles stated in the 1989 Declaration of Helsinki or the laws and regulations of the country in which the study was being conducted, whichever provided greater protection for participants.[93] In their 2008 amendments, the FDA discarded the Declaration of Helsinki/Host Country standard and in its place instituted a standard called Good Clinical Practice ("GCP").[94]

> For the purposes of [21 C.F.R. 312.120], GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.[95]

The FDA justified its shift away from the principles embodied in the Declaration of Helsinki by explaining that industry members could be confused as to which version of the Declaration was in force at a given time, and the FDA did not want to bind the industry or itself with a document outside its control.[96] It would also be fair to speculate that the FDA was prompted by new provisions in the 2000 version of the Declaration that discouraged the use of placebo studies, a mainstay of U.S. clinical research.[97]

In order to verify that a study abided by GCP, a Sponsor must provide a supplement explaining the steps taken to ensure

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clinical trial information for such a foreign clinical study be submitted for inclusion in the registry and results data bank . . . as a condition for acceptance of such study as support for an IND . . . or application for marketing approval . . . ." *Id.* § 4. The Test Act was referred to the House Subcommittee on Health on August 3, 2012 and remains there as of this writing. *See Bill Summary & Status 112th Congress (2011–2012) H.R. 6272*, LIB. CONG., http://thomas.loc.gov/cgi-bin/bdquery/z?d112:h.r.06272: (last visited Feb. 20, 2013).

[93] Robyn S. Shapiro & Julie M. Rusczek, *Client Alert: The FDA's New Rule on Foreign Drug Trials*, DRINKER BIDDLE & REATH LLP, June 2008, at 1.

[94] 21 C.F.R. § 312.120(a)(1)(i) (2012).

[95] *Id.*

[96] *See Regulation of Overseas Clinical Trials Is Growing*, DRUG INDUSTRY DAILY, Nov. 17, 2008.

[97] *Id.*

conformity with GCP.[98] The FDA provides a list of items that should be incorporated into this supplement including, but not limited to, information about the investigator's qualifications, information about the facility, and a description of how the clinical investigator obtained the informed consent of participants.[99] Sponsors are also required to show that their FCT was reviewed, approved, and monitored by an Independent Ethics Committee ("IEC"),[100] which an IRB could satisfy.[101] Additionally, the FDA requires that it be able to validate data from a study through on-site investigations, if the FDA deems it necessary.[102]

If an FCT not conducted under an IND fails to meet some of the regulatory requirements of GCP, the Sponsor can apply for a waiver.[103] The FDA will grant a waiver if the Sponsor can satisfy one of the following conditions: (1) explain why their compliance with a requirement is unnecessary or unachievable; (2) explain how the purpose of a missed requirement was satisfied through an alternative means; or (3) provide an adequate reason to grant a waiver.[104] FCTs not conducted under an IND which fail to meet the requirements of 21 C.F.R. 312.120 can still have their data examined by the FDA—usually for the data's bearing on how a new drug may be administered safely[105]—although the data cannot be used to support an IND or NDA.[106]

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[98] 21 C.F.R. § 312.120(b) (2012).

[99] *Id.*

[100] 21 C.F.R. § 312.120(a)(1)(i) (2012); *see also* 21 C.F.R. § 312.3 (2012) (defining Independent Ethics Committee as a panel adequately constituted to protect the rights and safety of human subjects).

[101] 21 C.F.R. § 312.3(b) (2012).

[102] 21 C.F.R. § 312.120(a)(1)(ii) (2012).

[103] 21 C.F.R. § 312.120(c) (2012).

[104] *Id.*

[105] Shapiro & Rusczek, *supra* note 93, at 3.

[106] 21 C.F.R. § 312.120(a)(2) (2012). For non-binding FDA guidance on submission of FCTs not conducted under an IND, see generally U.S. DEP'T OF HEALTH & HUMAN SERV., GUIDANCE FOR INDUSTRY AND FDA STAFF: FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND FREQUENTLY ASKED QUESTIONS (Mar. 2012), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf. This Guidance does not alter or conflict with any recommendations of this Article.

4. PROBLEMS ASSOCIATED WITH CLINICAL STUDIES CONDUCTED IN LESS-DEVELOPED COUNTRIES

While many applaud the use of FCTs as a means to speed up the marketing approval process for new drugs,[107] others have been skeptical and sometimes staunchly opposed to their use. In 1982, after the 1975 amendments to the FD&C Act and initial appearance of the 1980s FCT boom, Representative L. H. Fountain of North Carolina began holding congressional hearings on proposals that would allow a new drug to be approved for marketing based solely on studies conducted abroad.[108] During the hearings, Fountain cited to "several FDA documents that revealed serious problems with testing in other countries, particularly those that bar agency medical officers from checking test data."[109] Fountain also questioned the wisdom of an FDA comment made at that time. In its comment, the FDA stated that it would continue auditing all major U.S. human studies offered to support new drug applications, while at the same time limiting audits of foreign human studies to only when there was concern about the validity of the data.[110] Fountain feared that this would effectively create a double standard where foreign studies were considered more reliable than U.S. studies, as well as give drug companies another incentive to conduct their research away from the FDA's oversight.[111]

In the 1990s, there was large public backlash against the pharmaceutical industry in the wake of FCT mishaps, two examples of which are the Trovan trials in Nigeria[112] and the AZT

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[107] Two prominent groups lobbying for faster drug marketing approval are drug manufacturers and advocates for the terminally ill. *See* Washburn, *supra* note 49, at 16, 17–18 (attributing the initiatives to expedite the approval process of new drugs through FCTs to the collective efforts of AIDS activists and the Pharmaceutical Research and Manufacturers of America—PhRMA).

[108] Morton Mintz, *Administration Seeks to Speed Approval of New Drugs*, WASH. POST, Oct. 19, 1982, at A2. This proposal was later accepted and is currently codified in 21 C.F.R. § 314.106 (2012).

[109] Mintz, *supra* note 108, at A2.

[110] *Id.*

[111] *Id.*

[112] *See* William DuBois, *New Drug Research, the Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161, 163–64 (2003) (describing the Trovan clinical trials conducted in Africa,

vaccine trials that took place in Uganda.[113] The public's interest in the behavior of pharmaceutical companies culminated in certain stirring publications during 2001, including the *Washington Post*'s six part series "The Body Hunters," the OIG's report *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, *supra*, and the blockbuster novel *The Constant Gardener*, which was later adapted to cinema. Even FDA officials at this time were openly skeptical of FCTs. Antoine El-Hage of the Center for Drug Division of Scientific Investigation went on record saying that the FDA was not aware of the existence of most FCTs prior to submission because they were not being conducted under an IND.[114] El-Hage also stated that the problem was further complicated because even if an issue was discovered in an FCT not conducted under an IND, the FDA could only disqualify the study data, not the foreign investigator who conducted the study.[115] This undermined the FDA's authority by limiting its ability to ensure that submitted studies were being run by competent, truthful individuals.[116] El-Hage ended his interview by saying, "Some countries, I won't say which ones, have limited clinical research experience. Some physicians represent themselves as a principle investigator or as study-coordinator, and they supervise 20 or 30 different sites."[117] The statement implied that the combination of inexperience these countries had as regulators of clinical trials and the absurdity that a single investigator could effectively manage so

during which eleven children died, and that travesty's effect on the public and FDA).

[113] *See* Meier, *supra* note 68, at 517–21 (describing briefly the AZT AIDS vaccine trials in Uganda).

[114] Dan Whipple, *FDAer Sees No Recognition of Foreign BiMo Audits Yet*, 1 BIORESEARCH MONITORING ALERT 2 (Sept. 1, 2001).

[115] *Id.*

[116] *See United States: FDA Should Improve Oversight of Foreign Drug Trials*, TENDERSINFO NEWS, June 22, 2010 (quoting Dr. Kevin Schulman of Duke University, saying, "Where data is questionable most of the time, that doesn't become public . . . . If someone in Eastern Europe is fabricating data there's no database to say 'Don't use them for a different clinical trial.' There's no way to know."). *See also* Laura Strickler, *Report Raises Concern over Foreign Drug Trials*, CBSNEWS (June 22, 2010, 7:34 PM), http://www.cbsnews.com/8301-31727_162-20008510-10391695.html.

[117] Whipple, *supra* note 114, at 2.

many sites should raise suspicion about the data's validity and whether the studies were conducted in an ethical manner.

In 2010, two years after the FDA's most recent amendments to their FCT regulations, the OIG released its report *Challenges to the FDA's Ability to Monitor and Inspect Foreign Clinical Trials*[118] ("OIG 2010 Report") as a follow-up to its 2001 report. The OIG 2010 Report took data submitted in 2008 and compiled the information into a startling analysis of the rapid growth within the FCT industry and their increasing prevalence in NDA submissions.[119] The OIG 2010 Report estimated that forty to sixty-five percent of all clinical trials involving FDA regulated products were being conducted abroad,[120] and seventy-eight percent of all subjects who participated in clinical trials were enrolled at foreign sites.[121] Of all the drugs approved for sale in 2008, eighty percent included data originating from FCTs,[122] and ten medicines approved in 2008 were tested entirely abroad without using a single U.S. subject.[123] While most participants of FCTs were located in Western Europe—which is known for applying clinical oversight similar to what the United States applies[124]—more than twenty-five percent of participants were enrolled in Central and South American sites.[125] The consolidation of study participants in Central and South America was unusual because the regions contained only seven percent of all known foreign clinical sites in 2008.[126] This led to the realization that clinical sites in Central and South America were enrolling three times as many subjects per site compared to their Western European counterparts.[127]

Evidence of the long-term nature of this trend overseas was offered by the OIG in terms of the number of foreign investigators

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[118] *See generally* CHALLENGES TO THE FDA, *supra* note 54.

[119] *Id.* at i–ii.

[120] *Id.* at i.

[121] *Id.* at 10.

[122] *Id.* at ii.

[123] Gardiner Harris, *Concern Over Number of Foreign Clinical Trials for Drugs Sold in U.S.*, N.Y. TIMES, June 22, 2010, at A14.

[124] *Id.*

[125] CHALLENGES TO THE FDA, *supra* note 54, at 11–12.

[126] *Id.* at 12.

[127] *Id.*

conducting trials abroad—under an IND, which more than doubled between 1998 to 2008.[128] Another trend not cited by the OIG but which buttresses this conclusion is that while the number of foreign clinical investigators has been increasing, the number of domestic clinical investigators has been decreasing.[129]

Despite the large portion of clinical studies being conducted abroad, the OIG 2010 Report found that the FDA only inspected 0.7% of all foreign clinical sites in 2008, compared to 1.9% of all domestic clinical sites. The cost to audit a foreign clinical site is approximately $40,000, which does not promote an increased number of investigations.[130] Additionally, previous study designs utilizing a single large subject population at one site are giving way to using a multisite approach with several sites and smaller subject populations at each site, making FDA inspections more troublesome and less useful.[131] While not clear, this trend may be in part due to the increased likelihood of an FDA inspection at sites with larger subject populations.[132]

In connection to the FDA's low inspection rate for foreign clinical sites conducting studies under an IND, the OIG reiterated the cautionary call from its 2001 report; the FDA is not aware of the existence of foreign studies not conducted under an IND and "therefore cannot conduct inspections while the trials are in progress."[133] Following dissemination of the OIG 2010 Report there was public astonishment at the findings and their implications;[134] however, to date no changes have occurred.

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[128] *Id.* at 13–14.

[129] Alan L. Buchman, *The State of Clinical Research in America*, AM. FED'N FOR MED. RESEARCH (2010), *available at* http://www.afmr.org/multimedia/2009/Clinical-Research-Conference/jim200311.pdf.

[130] Harris, *supra* note 123.

[131] *Id.*

[132] CHALLENGES TO THE FDA, *supra* note 54, at 16.

[133] *OIG: FDA's AE Protocol Still Needs Improvement*, FDA NEWS: DEVICES & DIAGNOSTIC LETTER, Mar. 28, 2011.

[134] *See* Harris, *supra* note 123 (explaining how the OIG 2010 Report caused public concern when it revealed that a majority of drugs approved for sale in the United States are tested in foreign countries without adequate controls). Harris quotes U.S. Rep. Rosa DeLauro (D-Conn.) as saying the report "highlights a very frightening and appalling situation. By pursuing clinical trials in foreign countries with lower standards and where the FDA lacks oversight, the industry

Currently, the problems most associated with FCTs in developing countries are: (1) the FDA's lack of knowledge of most FCTs because they are not being conducted under an IND;[135] (2) the minimal experience and few resources that many of the countries being used to host these studies can devote to the regulation such studies require; (3) the human rights violations resulting from inadequate informed consent[136] and exploitation of vulnerable populations;[137] and (4) the concerns over data validity as a result of lax oversight and conflicts of interest.[138]

4.1. Ethical Concerns

Most of the criticism levied against FCTs comes from a fear that human rights violations are being committed when these studies are performed in less-developed countries. These concerns are most commonly expressed as follows: (1) subjects of FCTs are being taken advantage of by the companies running the FCTs; (2) subjects of FCTs are exposed to heavy risks with minimal benefits; and (3) subjects in FCTs are not adequately informed about the risks associated with their participation.

The allegation that FCT participants in less-developed countries are treated like guinea pigs, while theatrical, is not outlandish.[139] Many new drugs tested in less-developed countries pertain to ailments afflicting industrialized societies who already have their basic healthcare needs met; diseases that affect the day-

is seeking the path of least resistance toward lower costs and higher profits to the detriment of public health." *Id.*

[135] Whipple, *supra* note 114.

[136] *See* Meier, *supra* note 68, at 517–21, 530–35 (explaining how studies conducted in foreign countries carry human rights implications relating to informed consent and inadequate regulation because of poor legal enforcement and lack of financial resources); Laughton, *supra* note 8, at 208–09 (exploring the ethical issues and difficulties involved in obtaining informed consent when performing scientific studies in developing countries).

[137] *See* Laughton, *supra* note 8, at 208-09 (stating that vulnerable populations often feel financially coerced into participating in scientific studies for compensation). *See also* Kahn, *supra* note 76 (describing how a vulnerable population in India was highly receptive to clinical drug testing).

[138] *See supra* note 68 and accompanying text.

[139] *See, e.g.*, SHAH, *supra* note 78, at 62–76 (describing the historical exploitation of human participants in clinical trials); Kahn, *supra* note 76.

to-day lives of the impoverished local inhabitants are researched less frequently.[140] When the prominent medical concerns of their own country are not being investigated, neither the participants, nor the countries' other inhabitants, are benefitted in a meaningful or lasting way by the research. Moreover, even if an experimental drug could fill a healthcare need in the less-developed country where it is being tested, pharmaceutical companies have no duty, and in some cases have a disincentive,[141] to sell the drug locally at a price indexed for the country's purchasing power. Thus, while a new drug could benefit local inhabitants, it might not be available to them because of the high price that pharmaceutical companies must charge in order to cover their research and development costs.[142]

Another way less-developed countries may be harmed by FCTs is by exposing the participants to excessively high risks[143] without adequate follow-up medical attention.[144] Just as the inhabitants of less-developed countries are infrequently the direct beneficiaries of drug research conducted within their borders, ethicists assert that

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[140] Glickman et al., *supra* note 6, at 819 (detailing that clinical studies conducted in developing nations are not representative of the illnesses that are most prevalent in those countries); Shah, *supra* note 76, at 30 (quoting African bioethicist Dr. Solomon Benatar as saying "[t]he diseases that are of most interest are mainly the degenerative diseases—arthritis, obesity, heart disease—the diseases of people in the developed world . . . .").

[141] When a drug company sells its product for less, or supplies it for free, it runs the risk of creating a black market for its product. This is because the recipients receiving the lower price may choose to sell the product to individuals in wealthier countries at a price that creates a profit to the seller and a savings to the buyer. This is of particular concern where the initial recipient is a distributor and not the end user.

[142] Harold T. Shapiro & Eric M. Meslin, *Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries*, 345 N. ENG. J. MED. 139, 141 (July 2001) (describing the lack of access to adequate medicine in developing countries, even when clinical studies are conducted there).

[143] *See* DuBois, *supra* note 112, at 195 ("[T]he riskiest experiments are among the first to be sent abroad."); Mary Pat Flaherty et al., *Testing Tidal Wave Hits Overseas*, WASH. POST, Dec. 18, 2000, http://www.washingtonpost.com/ac2/wp-dyn/A11986-2000Dec15 (recounting that the FDA denied an American drug company's application to test its drug because of health risks, and the company sent the study to Russia and had it performed there).

[144] *See* Shapiro & Meslin, *supra* note 142, at 141 (recommending the establishment of protocols for post-study medical care as a way "to ensure that the study is responsive to the health needs of the host country").

it is unethical to place the dangers associated with untested medications on a population known by Sponsors to be vulnerable and more easily influenced. Incentives offered to participants in less-developed countries can be enticing to the point of being coercive,[145] and may encourage the impoverished to throw caution to the wind in order to receive compensation that can only provide their basic needs momentarily.[146] The coercive nature of some FCTs, coupled with potential medical complications, can lead to unfortunate results. Specifically, vulnerable members of a population may expose themselves to experimental substances for short-lived financial compensation despite the potential for long-lasting side effects. Looking to the Trovan case, *supra*, it is clear that obtaining necessary medical treatment following clinical trials can be difficult because of a country's healthcare infrastructure—or lack thereof—and because a pharmaceutical company may not be prepared to respond in a timely manner.[147] This issue is further complicated because pharmaceutical companies are removed from the situation due to an increased use of CROs.[148] Though some might claim that unforeseen medical complications are to be expected and should be addressed by legal recourse, the response

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[145] *See Payment to Research Subjects – Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators*, U.S. FOOD & DRUG ADMIN. (Sept. 18, 2010), http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm (advising IRBs to review the amount and timing of payment to research participants to ensure neither is coercive, in violation of 21 C.F.R. § 50.20).

[146] *See* Laughton, *supra* note 8, at 208; *but see* Kahn, *supra* note 76 (describing how Indians participating in a clinical trial are poor enough to make the medical treatment provided during the study, excluding the experimental drug, amount to a healthcare windfall); Meier, *supra* note 68, at 532 (explaining that some developing countries encourage medical research to supplement their country's meager health system); Shah, *supra* note 76, at 31 ("[C]onsumer health advocates say that clinical trials are the only way some poor patients can get any formal healthcare at all.").

[147] *See* Joe Stephens, *Where Profits and Lives Hang in the Balance*, WASH. POST, Dec. 17, 2000, http://www.washingtonpost.com/wp-dyn/content/article/2007/07/02/AR2007070201255_pf.html (recounting the story of a young Nigerian girl afflicted with meningitis who died while participating in a clinical trial of Trovan).

[148] *See* Miriam Shuchman, *Commercializing Clinical Trials – Risks and Benefits of the CRO Boom*, 357 N. ENG. J. MED. 1365, 1366 (Oct. 2007) (questioning CRO reporting methods and commenting on the industry's tendency to internalize problems).

fails to account for the lack of a comprehensive court system in less-developed countries. And, even with access to a semi-functioning legal system, it is unclear to what extent the governments of such countries will aid their citizens, since it is often the government who solicits pharmaceutical research.[149]

Lastly, there is a concern that subjects are inadequately informed about the risks associated with clinical trial participation.[150] Informed consent is required under 21 C.F.R. 312.120 if an FCT is not conducted under an IND. Yet, medical ethicists claim that clinical investigators often do not adequately convey the specific risks associated with participation in an FCT.[151] Informed consent has been a cornerstone of clinical research since the Nuremberg Code, which is widely recognized as the original international code for bioethics. Primary reasons cited for why adequate informed consent may not have been given are: the foreign investigators' lack of resources to perform their own background research on a drug; a desire to speed the approval process along;[152] the potential absence in a developing country of the norm of giving informed consent—to the U.S. standards; the low level of education in participant population;[153] and the fact that participants may speak a different dialect of a language than the

[149] *See* Stephens, *supra* note 147 (describing how Nigerian citizens were unable to seek their government's help following the Trovan trials in Nigeria for fear of government retaliation).

[150] *See* Laughton, *supra* note 8, at 207–08 (speculating whether consent is truly informed in the developing world due to the limited education of participants as well as linguistic and cultural barriers); *see also* Karen DeYoung & Deborah Nelson, *Latin America Is Ripe for Trials, and Fraud Frantic Pace Could Overwhelm Controls*, WASH. POST, Dec. 21, 2000, http://www.washingtonpost.com/wp-dyn/content/article/2008/10/01/AR2008100101182.html?sid=ST2008100101390 (describing an experiment that took place at a naval hospital in Argentina, where prosecutors allege that none of the 137 patients administered the drug actually gave consent to participate in the experiment).

[151] *See supra* notes 112, 113, 136 and accompanying text.

[152] *See* Laughton, *supra* note 8, at 207–09.

[153] *Id.* Also, note that in the United States, most informed consent forms must be written at a sixth grade reading level, thus reflecting a belief that participants should have at least an understanding equivalent to that of a sixth grader. *Id.*

clinical investigator, which can cause the participant to misunderstand the risks involved with taking a drug.[154]

4.2. Concerns of Validity

While the actual number of FCTs invalidated during and after the FDA's drug marketing approval process is unclear, a legitimate call for concern can still be raised simply by pointing to the possibility that invalid FCT data could be submitted without detection. This concern arises primarily because: (1) FCTs do not need to be conducted under an IND, which means that they lack FDA oversight or guidance; (2) foreign IRBs in less-developed countries may not be as well trained in how to monitor clinical trials; (3) less-developed countries can be lax in regulating clinical trials; and (4) there is a lucrative market for FCTs, which could promote reckless speed, deceptive reporting, or fraud.

The fact that most FCTs are conducted without the FDA's knowledge, despite their increasing appearance in the FDA's marketing approval process, is at the crux of the issue. Without adequate guidance from an experienced regulatory body and a realistic threat that a site may be audited for data validity *while the study is being conducted*, there is less assurance that adequate research techniques are being utilized to ensure validity.[155] Auditing a study years after its conclusion provides an incomplete picture of what took place and risks vital facts being lost or

[154] *See* George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL'Y 297, 314–16 (1995-1996) (explaining the importance of language choice when crafting an informed consent).

[155] *See* Glickman et al., *supra* note 6, at 818 (stating that a lack of oversight in FCTs leads to suspicion over the validity of their data). There are many cases of data fraud uncovered in FCTs. *See, e.g.*, DuBois, *supra* note 112, at 163–64 (describing allegations of fraud in the Trovan study in Nigeria, including failure to obtain consent and faulty record keeping); Shuchman, *supra* note 148, at 1366 (describing the drug trials for Ketek, which was tested abroad, and the fraud that was unearthed by the FDA); Maureen Martino, *Clinical Trial Fraud Accusations Rock MannKind ($MKND) Stock*, FIERCEBIOTECH (Nov. 5, 2010), http://www.fiercebiotech.com/story/clinical-trial-fraud-accusations-rock-mannkind-mknd-stock/2010-11-05 (reporting allegations that MannKind fabricated patient data at Russian and Bulgarian testing sites for Afrezza, an inhaled insulin drug).

forgotten.[156] Taking into account the sometimes suspiciously high occurrence of positive results in clinical trials, the necessity of having all facts available becomes much clearer. [157]

Another factor that could undermine data produced in developing countries is the lack of a functioning healthcare system. Many research inquiries involving side effects revolve around whether a participant sought medical attention while taking the experimental drug. This line of inquiry arose in more-developed countries where individuals have relatively easy access to affordable hospitals and would seek medical attention when necessary. In less-developed countries, however, seeking professional medical attention may not be feasible because resources are lacking or a participant may be unable to afford the consultation. Compounding the issue, participants may not want to seek medical attention or disclose problems to the clinical investigators because of a fear—which is well founded—that they will be removed from the clinical trial and forgo their future compensation for participating. These systemic problems could minimize the reporting of side effects experienced in a clinical study, which could result in the continuation of a study that is unsafe for participants or marketing approval for a drug that is harmful to consumers.

The use of an IEC is currently a requirement in order for an FCT to be considered by the FDA for support of an IND or NDA. However, there is no way for the FDA to effectively evaluate the competency of the foreign IECs, and the supplemental form that Sponsors are obligated to provide would appear to offer little evidence for this point. Particularly in countries where there is less

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[156] *See* Donald L. Bartlett & James B. Steele, *Deadly Medicine*, VANITY FAIR, Jan. 2011, http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101 ("By [the time a foreign study is submitted] the [FDA] has lost the ability to see whether the trials were managed according to acceptable standards, and whether the data collected was manipulated or fabricated.").

[157] *See* Shah, *supra* note 76, at 30 (reporting on a review that stated "99 percent of controlled trials published in China bestowed positive results upon the treatment under investigation"); Carl Elliott, *The Deadly Corruption of Clinical Trials*, MOTHER JONES, Sep.–Oct. 2010, http://www.motherjones.com/environment/2010/09/dan-markingson-drug-trial-astrazeneca?page=3 ("A 2006 study in *The American Journal of Psychiatry*, which looked at 32 head-to-head trials of atypicals, found that 90 percent of them came out positively for whichever company had designed and financed the trial.").

experience in regulating clinical research, IECs may provide less than adequate assurance of a trial's integrity. For instance, investigation into a recent study conducted in China found that the study's design for cardiac research was not effective despite having been through a local IRB.[158] In countries, like China, where the government typically does not require a study to be reviewed by an IRB, a lapse in oversight can be expected because the monitoring boards have limited experience with their task prior to being contracted by foreign researchers. The lack of experience, the lack of formal duties, and the lack of an established protocol for IRBs, or their IEC equivalent, likely lead to significant shortcomings in the review process of clinical trials.

Finally, there is an obvious financial incentive for less-developed countries, foreign investigators, and CROs[159] to continually acquire new clinical trials.[160] As Dr. Marcia Angell, former editor of the *New England Journal of Medicine* noted:

> There is no substitute for a researcher who is disinterested in the outcome because it is too easy to bias the results either consciously or unconsciously. What we are seeing now is the disappearance of impartial researchers and institutions . . . . As the economic ties between researchers and industry become virtually ubiquitous and manifold, you have to worry about the quality of the research.[161]

The financial bias problem can create a research culture where speed, low costs, and obtaining the "right data" from a study can take precedence over good clinical practice.[162] For developing countries, this can take the form of pandering to Sponsors with

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[158] *See generally* Wendy Stough et al., *Globalization of Cardiovascular Clinical Research: The Balance Between Meeting Medical Needs and Maintaining Scientific Standards*, 54 AM. HEART J. 232 (2007) (describing the COMMIT study).

[159] *See* Shuchman, *supra* note 148, at 1365 ("Annual CRO-industry revenues increased from about $7 billion in 2001 to an estimated 17.8 billion [in 2007] . . . .").

[160] *See* Shtilman, *supra* note 68, at 434–35 n.45 (stating that many CROs and physicians have a financial interest in the outcomes of drug studies due to licensing agreements with pharmaceutical companies over scientific discoveries).

[161] Washburn, *supra* note 49, at 20.

[162] *See supra* notes 6 and 78 and accompanying text (discussing the financial investment in a new drug and the potential profit to be made by bringing a new drug to market).

promises of minimal regulatory interference, even though some of those regulations may be necessary to ensure data quality.[163] For foreign investigators, recruitment compensation for a single study can be more lucrative than years of ordinary wages,[164] creating a strong incentive to continually land clinical contracts.[165] While these accusations of fraud are highly inflammatory to the medical community, the merit of the suspicion is strengthened when recalling that domestic scientific fraud is attempted even under the more intrusive regulatory conditions of the United States. The fen-phen drug fraud case,[166] and the case of Dr. Robert Fiddes—who notoriously enrolled nonexistent patients into more than two hundred clinical trials in the United States—[167] are just two recent incidences that come to mind.[168]

CROs should also be mentioned in this discussion, as they have an ever-increasing global presence. CROs, just like any other service provider, are in competition to land more contracts in their industry. The competitive atmosphere may create a "race to the

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[163] Shah, *supra* note 76, at 30 (quoting drug expert Kenneth Kaitin from Tufts University as saying the governments of China, India, and Taiwan bend over backwards to get drug companies to conduct research and manufacture the product in their country by providing tax breaks and facilities among other things); Kahn, *supra* note 76 (describing the Indian government's efforts to attract more clinical research by advertising the quality of its doctors and the poor health of its citizens); James Cekola, *Outsourcing Drug Investigations to India: A Comment on U.S., Indian, and International Regulation of Clinical Trials in Cross-Border Pharmaceutical Research*, 28 Nw. J. Int'l L. & Bus. 125, 126 (2007) (reporting that India collected $70 million in revenue from clinical trials in 2003, and was projected to reach $1.5 billion by 2010).

[164] Bartlett & Steele, *supra* note 156, at 60 ("An executive at a contract-research organization told the anthropologist Adriana Petryna, author of the book *When Experiments Travel*, 'In Russia, a doctor makes two hundred dollars a month, and he is going to make five thousand dollars per Alzheimer's patient' that he signs up.").

[165] DeYoung & Nelson, *supra* note 150.

[166] *See generally* Elliott, *supra* note 157 (discussing the company Wyeth and their attempt to fraudulently hide negative side effects from their fen-phen trials).

[167] *See generally* Sandy Robertson, *Tainted Trials*, MED. POST, June 22, 1999, *available at* http://web.archive.org/web/20040221075202/http://www.medicalpost.com/mpcontent/article.jsp?content=/content/EXTRACT/RAWART/3524/25.html.

[168] For a general discussion of clinical trial fraud in the United States, see Marc Buyse et al., *The Role of Biostatistics in the Prevention, Detection, and Treatment of Fraud in Clinical Trials*, 18 STAT. MED. 3435 (1999).

bottom" mentality that values results over quality.[169] This potentially dangerous combination is further exacerbated by confusion, regarding whether the CROs should report certain issues directly to the FDA, or to drug manufacturers only.[170] The legal uncertainty has created tension between the three parties and has probably resulted in some issues going unreported. Additionally, a lack of minimum credentials for CROs, and a lack of oversight of these organizations by the Sponsors contracting them, could create the potential for abuse, in terms of inappropriate clinical conduct or outright fraud.[171]

5. RECOMMENDATIONS ON HOW TO MINIMIZE PROBLEMS ASSOCIATED WITH CLINICAL STUDIES CONDUCTED ABROAD

There will always be some minimum amount of time necessary to properly and ethically research the safety and effectiveness of a drug. Yet, the FDA must be diligent and efficient in guiding experimental drugs to the market. To this end, establishing a better framework for FCTs would accomplish all three of these goals: safety, speed, and proven effectiveness. This Article proposes five initiatives to make FCTs safer and the drug marketing approval process more efficient: (1) the FDA should promulgate rules that encourage Sponsors to submit a "letter of possible intent" for FCTs not conducted under an IND; (2) the FDA should join forces with foreign counterparts to create a more comprehensive regulatory regime; (3) the FDA should aid in the creation of an international registry for clinical investigators, IRBs,

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[169] *See generally* Shuchman, *supra* note 148 (noting that, while CROs specialize in speed and efficiency, their lack of oversight results in questionable qualifications, accountability, and ethics); Kahn, *supra* note 76 (stating that India removed certain regulatory barriers that were in place for the subject's safety in order to better court pharmaceutical companies); *see also supra* note 68 and accompanying text.

[170] Shuchman, *supra* note 148, at 1366 (stating that CROs typically report concerns to their drug-company clients, and reporting on two cases where the drug-companies did not report these issues to the FDA: one involving suppression of fraudulent results in light of a pending FDA approval application, and another where the CRO was actively discouraged from contacting the FDA about a study stating their drug increased risk for several illnesses).

[171] *Id.* at 1367 (discussing the incentives for CROs to encourage the speedy completion of clinical trials and the hiring of under-skilled and under-experienced employees to complete the trials).

CROs, and clinical trials; (4) the FDA should amend their regulations for disclosure of a clinical investigator's financial interest; and (5) the FDA should coordinate with the United States Department of Justice ("DOJ") to pursue violations of the Foreign Corrupt Practices Act ("FCPA") by U.S. corporations who encourage or purposefully facilitate bribery of foreign officials.

5.1. Track FCTs Not Conducted Under an IND Using a "Letter of Possible Intent"

The OIG recommended that the FDA monitor trends in FCTs not conducted under an IND and encourage Sponsors to register their trials under an IND.[172] While this recommendation is well intended, tracking trends in FCTs not conducted under an IND has logistical problems. To date, there is little information about these trials precisely because the FDA does not know of their existence, and thus, cannot track them. The OIG offered no insight on how to incentivize voluntary participation by Sponsors, except to say that the FDA should consider implementing legislation to encourage Sponsors to conduct their studies under an IND.[173] Yet, as long as Sponsors can submit their FCTs without fear of rejection, it is unclear what incentives could be offered to offset the burdens associated with IND registration.

As an alternative, the FDA could encourage Sponsors to send a "letter of possible intent" prior to beginning an FCT that will not be conducted under an IND. This letter would merely provide some basic characteristics about the study, and state that the Sponsor is considering *possibly* submitting the study to the FDA at a later date. This would not bring the study under the FDA's authority, yet would still inform the FDA of the study's existence while it is running, and give the FDA the ability to provide non-binding suggestions. An incentive for providing the letter could be an expedited review of that study's data. Additionally, a higher level of scrutiny could be held for studies not submitted through the "letter of possible intent," or not accompanied by a supplement that explained good cause for the failure. This higher level of

[172] CHALLENGES TO THE FDA, *supra* note 54, at iii and 20–21.

[173] *Id.* at 21.

scrutiny could also require a fee from the Sponsor for its administration to help offset costs associated with the program.

5.2. Begin Collective Efforts Between the FDA and its Foreign Counterparts

Historically, the FDA has not been keen to accept or supply foreign regulatory bodies with information about FCTs. Due to the expansive nature of clinical globalization, and the inability for any one agency to handle the issue alone, efforts should be made to increase cooperation between the FDA and their foreign counterparts.[174] By doing so, a more comprehensive picture of the FCT situation can be drawn, and concerted efforts in monitoring can create efficient, rather than duplicative, results. Also, the fact that the United States is geographically far from sites in Western Europe and Asia makes monitoring by the FDA problematic—much the same way that Eastern Europe feels about monitoring clinical trials in South America. Consolidated efforts could therefore be used to solve the mutual problem of monitoring clinical sites located far from a country's geographic location.

5.3. Creation of an International Registry

Registries are crucial for monitoring clinical trials. Without registries, the FDA, its foreign counterparts, and applicable NGOs expend excessive amounts of energy performing redundant background research. Four registration categories that would be particularly useful to the organizations that monitor clinical trials worldwide are: clinical investigators, IECs/IRBs, CROs, and clinical trials. Preferably, this information would be maintained by an NGO like the World Health Organization, and made available to anyone interested in researching individuals within a category. The benefit of this type of reporting system would be the collaborative effort of multiple countries to keep track of the organizations and individuals engaged in clinical trials at different levels of the process. Regulatory bodies would be able to check information submitted by Sponsors in marketing applications

[174] *Id.*; *see GCP Cooperation Begins Between FDA, EMEA*, CLINICAL TRIALS ADVISOR, Aug. 6, 2009 (describing a pilot collaboration project between the FDA and its EU counterpart).

against the information provided in the registry, and would be able to submit their own notes on a registered person or company. A second benefit of the registry is that it would provide individuals with a forum to voice concern about poor scientific practices. A significant problem with FCTs is that watchdog groups, and individuals harmed by the studies, lack the means to effectively warn others. The registry could help resolve this shortcoming by providing a way to publicize specific scientific and ethical violations that can be substantiated by the facilitating NGO. This would be accomplished either by updating a registrant's entry when violations occur, or—if the entity is not a member—adding their name to a "black list." Sponsors would be hesitant to use entities with a history of misconduct, or entities who were "black listed," if they knew the FDA and its counterparts used the registry in conducting their due diligence.

Funding for the registry could be acquired through an annual registration fee for registrants, and grants from the United States, European Union, and Japan.[175] Instituting the registration fee could be accomplished by self-registration, whereupon the registrant would receive a registration ID. When including itself as part of a marketing application, the registrant could provide the ID to make background information readily accessible. If a person or organization submitted in a marketing application were unregistered, agencies like the FDA could charge an extra fee to the Sponsor for the cost of having to perform the research from scratch. The NGO would be responsible for updating registered member accounts with current information supplied by regulatory bodies. Entities may also be encouraged to register if the registry became a networking tool, where Sponsors looked through profiles to find future contractors that met their study's needs.

Clinical investigator,[176] IEC/IRB, and CRO registries would be useful for listing basic information (location, contacts, etc.), as well as the credentials of these groups, their professional associations, and any accusations of misconduct. In addition to facilitating

[175] *Cf.* Shah, *supra* note 76, at 30 (reporting that the United States, the European Union, and Japan represent eighty percent of the global drug market).

[176] Such a registry would be particularly useful because it is unclear whether the FDA can currently add clinical investigators to its ban list if the investigator is not conducting studies under an IND. *See supra* note 116 and accompanying text.

verification of credentials by regulatory agencies, groups that participate in organizing and running the clinical trials could use the registry to streamline their selection process. Sponsors could use the list to find CROs with the appropriate experience in certain geographic areas. Sponsors and CROs could use the registry as a resource when choosing their clinical investigators, in ensuring that the investigator has sufficient exposure to the subject matter, and in selecting the location where the FCT will take place. Clinical investigators could, in turn, use the registry as a means to check on CROs that are soliciting them for employment and see if the organization is associated with studies that did not adhere to standards of clinical conduct. While it would in no way be a guarantee for the Sponsor that a chosen clinical investigator, IEC/IRB, or CRO would not be flagged by a regulatory agency, it would at least provide another tool in researching the adequacy of their selection. The usefulness of this approach is evidenced by the FDA's recent creation of a domestic IRB registry.[177] Knowledge of existing clinical investigators, IECs/IRBs, and CROs, and creation of an international identity where deeds can be attached to a name, is the first step in properly regulating this industry.

Clinical trials may be the most important category of the registry[178] and also would have to function differently from its counterparts. Unlike the other categories, clinical trials would be a more fluid listing. They would remain on the registry while in progress and for two years after completion, to allow for study verification by regulatory agencies reviewing an NDA or its equivalent. It would also be wise to forego any sort of a registration fee for this category in order to promote as many listings as possible. The goal of this particular registry would be to promote concerted site inspections by regulatory agencies and NGOs—like the WHO and Doctors Without Borders—if

[177] *See generally* U.S. DEP'T OF HEALTH & HUMAN SERV., GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS (IRBS): FREQUENTLY ASKED QUESTIONS—IRB REGISTRATION (July 2009), *available at* http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm171256.pdf.

[178] An attempt to create a more comprehensive registry of clinical trials, including those under an IND and those not conducted under an IND, has recently been introduced to the U.S. Congress by Rep. Edward Markey (D-Mass.) in the Trial and Experimental Studies Transparency (TEST) Act, H.R. 6272, 112th Cong. § 4 (2012). *See supra* note 92.

authorization can be obtained. This would help alleviate two of the main causes of low site inspections by the FDA. First, collective efforts between regulatory agencies and NGOs would help raise the percentage of FCTs being inspected, while not increasing budgeting by the FDA. The cost of inspecting an FCT was listed as a primary reason more inspections are not conducted by the FDA. Concerted efforts by multiple organizations helps reduce this problem by ensuring that sites are not investigated multiple times, and by allowing organizations with closer geographic proximity to conduct the investigation, thus reducing costs. Second, a registry of clinical trials would inform relevant groups of their existence. If the FDA is aware of FCTs, they can begin to track information about them and utilize that information to inform and benefit their regulations.

A final nuanced benefit of a clinical trial registry is that it would bring to the public forum studies that may not have achieved favorable results for a drug. Drug trials that "fail" may not be published, nor their results made public, for fear that those results will weaken an applicant's efficacy or safety claims.[179] Many times, the publication of favorable results occurs after drug manufacturers carefully design their study to answer a discrete question—one that they believe will come out favorably for the company—and thereby limit the amount of negative information discovered.[180] In other instances, however, there is an outright attempt to prevent negative clinical findings from being

[179] Washburn, *supra* note 49, at 21 (casting doubt on the validity of data produced by private studies by referencing an article published in the *Journal of the American Medical Association*, which concluded nonprofit studies of cancer drugs are eight times more likely to find unfavorable results than private studies); Shah, *supra* note 76, at 30 (reporting on a review that stated "99 percent of controlled trials published in China bestowed positive results upon the treatment under investigation.").

[180] Elliott, *supra* note 157. As Dr. Richard Smith, the former editor of the *British Medical Journal*, notes: "The companies seem to get the results they want not by fiddling the results, which would be far too crude and possibly detectable by peer review, but rather by asking the 'right' questions." *Id.* Elliott further notes: "A 2006 study in *The American Journal of Psychiatry*, which looked at 32 head-to-head trials of atypicals, [also] found that 90 percent of them came out positively for whichever company had designed and financed the trial." *Id.*

published.[181] International knowledge that a drug is being tested would provide greater incentive to fully disclose all studies in a marketing application.

Concerning whether the FDA could legally rely on such a registry in evaluating marketing applications, it is evident that they could. The FDA certainly would not rely on this registry as the sole means of review for entities contained in a marketing application and would not be bound by any "decision" the NGO made about a particular entity. Therefore, the FDA could not be accused of unconstitutionally delegating its authority to another organization. Also, the FDA has authority from Congress under the Food & Drug Administration Modernization Act of 1997, Section 120, to outsource its safety review to third parties. Partial reliance on another organization would certainly fall within the scope of this provision allowing the FDA to enlist the assistance of an NGO for safety reviews. Moreover, utilizing such a registry would aid the FDA in protecting U.S. citizens from harmful drugs allowed to enter the stream of commerce, which is the mandate given to the FDA by Congress in the FD&C Act.

5.4. Amend Regulations Regarding Disclosure of a Clinical Investigator's Financial Interest

As of the time of writing, the FDA requires a Financial Disclosure form for clinical investigators participating in a "covered study"[182] as part of a marketing application.[183] The purpose of the disclosure is to uncover any financial bias that a clinical investigator may have had while conducting the study, related to his or her financial relationship with the Sponsor.[184] The disclosure requirement is satisfied by either submitting a form describing the presence of one or more of the financial interests

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[181] *See id.* (discussing the company Wyeth and its attempt to fraudulently hide negative side effects from its fen-phen trials).

[182] 21 C.F.R. § 54.2(e) (2012).

[183] 21 C.F.R. § 54.3 (2012).

[184] 21 C.F.R. § 54.1 (2012) ("One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study.").

listed in 21 C.F.R. 54.4(a)(3), or by submitting a certification attesting that none of the financial interests apply to a specific investigator.[185] A Sponsor must collect this information for studies conducted under an IND,[186] even if it is unclear whether the study will be used in a marketing application;[187] however, the Sponsor need not submit the information until the marketing application is sent to the FDA.[188] A Sponsor would also need to supply a financial disclosure or certification for foreign clinical investigators—regardless of whether their study was conducted under an IND—if the study is submitted in a marketing application.[189] However, there is an exemption available for a Sponsor who, despite due diligence, was unsuccessful in trying to acquire the information.[190]

The FDA should amend the Financial Disclosure requirement in three ways. First, the FDA should require that applications include the salary paid to the clinical investigator for conducting the study. The current language of the regulation does not require disclosure of salary information unless the compensation is tied to the results of the study.[191] However, excessive compensation could represent a significant source of bias for a clinical investigator, especially if the Sponsor repeatedly employs the investigator to run studies. While the FDA should not unnecessarily interfere with labor contracting, there is a point at which compensation can

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[185] 21 C.F.R. § 54.4 (2012).

[186] 21 C.F.R. § 312.53(c) (2012).

[187] FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR CLINICAL INVESTIGATORS, INDUSTRY, AND FDA STAFF: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS, E.5 (2013), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

[188] *See id.*

[189] FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR CLINICAL INVESTIGATORS, INDUSTRY, AND FDA STAFF: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS, F.3 (2013), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

[190] 21 C.F.R. § 54.4 (2012); FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR CLINICAL INVESTIGATORS, INDUSTRY, AND FDA STAFF: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS, F.2 (2013), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

[191] 21 C.F.R. § 54.4(a)(3)(i) (2012). Excessive compensation could have come in under disclosure requirement 21 C.F.R. § 54.4(a)(3)(ii), but the final regulation exempted compensation.

be recognized as so excessive that it will either purposefully or inadvertently bias the investigator. The FDA's examination of potential compensation bias should also take into consideration the respective economic realities of developing countries, in which a salary considered low by U.S. standards might be quite significant in a less-developed country hosting an FCT.[192]

Second, in light of the obvious disparity in purchasing power between more-developed and less-developed countries, the FDA should also adjust the term "significant payment"[193] as it appears in 21 C.F.R. 54.4(a)(3)(ii). The current definition of "significant payment" refers to any payments to the clinical investigator—other than payments for running the clinical trial or other clinical trials—during the study and for one year after its conclusion, the

[192] Interestingly, this recommendation is easier to implement domestically with the passing and implementation of the Physician Payment Sunshine Provision of the Patient Protection and Affordable Care Act of 2009. Within that provision there is an obligation that "any applicable manufacturer that provides a payment or other transfer of value to a covered recipient (or to an entity or individual at the request of or designated on behalf of a covered recipient), shall submit to the [Secretary of Health and Human Services]" a list of these transfers which could come from consulting, compensation for non-consulting services, gifts, travel, royalty or license, travel, and investments among other things. Patient Protection and Affordable Care Act of 2009, H.R. 3590, Pub. L. 111-148 § 6002(a)(1)(A) (2010). The proposed definition for "applicable manufacturer" has been broadly written to include all drug, device, biological, or medical supply manufacturers who are engaged in the production, preparation, propagation, compounding, or conversion of a covered drug, device, biological, or medical supply for sale or distribution in the United States or a U.S. territory, regardless of the location of manufacturing or incorporation. 76 Fed. Reg. 78743. Additionally, "covered recipient" received a broad definition proposal which would include all physicians except those employed by the reporting manufacturer or by a teaching hospital. 76 Fed. Reg. 78745. Since clinical investigators are not often employed by pharmaceutical companies, but rather are contracted to conduct clinical studies, it is unlikely they will meet the exemption as currently proposed. Applicable manufacturers will have to annually report all transfers over $10 to a covered recipient, unless the aggregate of gifts under $10 to a covered recipient exceeds $100 in a reporting year in which case those gifts will need to be included as well. Patient Protection and Affordable Care Act of 2009 § 6002(e)(10)(B)(i). These reporting requirements would make the FDA's verification of financial disclosure much easier. If similar requirements were created in other countries, it would substantially augment the collective capacity of various governments to uncover financial bias in clinical trials.

[193] 21 C.F.R. § 54.2(f) (2012) (providing the definition of a "significant payment").

cumulative effect of which exceeds $25,000.[194] The FDA should amend this regulation to reflect the reality that, while $25,000 is a relatively nominal sum for an American doctor, the same amount might represent more than the annual salary of a doctor in a less prosperous country and significantly more than a year's wages in a developing country.[195] If the idea behind this regulation is to root out potential sources of bias, the FDA should adjust this amount based on a sliding scale of where the clinical investigator is licensed to practice or where the study is conducted. The choice of whether to use the licensing country or the clinical-site country should be left for the FDA to decide on a case-by-case basis, so long as the FDA uses a method that most accurately reflects the potential for bias. In addition, the FDA should extend the reporting period in 21 C.F.R. 54 to include a one-year period prior to the study's start date in order to provide a more complete picture of the relationship between the clinical investigator and the Sponsor.

Lastly, the FDA should take care to review financial disclosures and limit the ability of Sponsors to exempt themselves from the requirement. In January 2009 the OIG released a report entitled *The Food and Drug Administration's Oversight of Clinical Investigator's Financial Information* ("Financial Information Report"). The report found that only one percent of all clinical investigators who had financial information submitted in an approved marketing application for 2007 listed a single financial interest.[196] This figure comes in stark contrast to a statement in the *Journal of American Medicine* that estimated twenty-three to twenty-eight percent of

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[194] *Id.*

[195] *See* CHRIS L. PETERSON & RACHEL BURTON, CONG. RESEARCH SERV., RL34175, U.S. HEALTHCARE SPENDING: COMPARISON WITH OTHER OECD COUNTRIES 18 tbl.2 (2007), *available at* http://assets.opencrs.com/rpts/RL34175_20070917.pdf (reporting that in 2011 general practitioners in the United States made an average annual salary of $161,000 USD, while their Mexican counterparts made $21,000 USD on average); David McCoy et al., *Salaries and Incomes of Health Workers in Sub-Saharan Africa*, 371 LANCET 675, 677 (Feb. 23, 2008) (reporting the average monthly income for a doctor in Ghana and Zambia in 2005 as approximately $1,200 USD and $1,400 USD respectively (annually $14,400 USD and $16,800 USD respectively)).

[196] DEP'T. OF HEALTH & HUMAN SERV., OEI-05-07-00730, THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL INVESTIGATORS' FINANCIAL INFORMATION, 14 (Jan. 2009) [hereinafter OIG FINANCIAL INFORMATION REPORT].

academic investigators had a financial interest in medical companies,[197] suggesting that there may be more overlap. Equally problematic were the OIG's findings that forty-two percent of approved applications were missing some financial information, with twenty-eight percent of approved applications asserting the "due diligence" exemption for their failure to acquire the information, indicating an abuse of this exemption by Sponsors.[198] These figures, however, may simply be reflective of a larger systemic issue created by the FDA's apathy in monitoring the Financial Disclosures forms. In its Financial Information Report, the OIG noted that FDA investigators failed to document whether they reviewed financial information in thirty-one percent of approved marketing applications,[199] and took no action in twenty percent of applications where a financial interest was disclosed but no measures were implemented by the Sponsor to reduce the potential bias.[200] The results of the OIG's report indicate that FDA investigators should make a stronger effort to review potential financial conflicts in marketing applications and tighten the requirements for Sponsors' use of the "due diligence" exemption.

5.5. Pursue Violations of the Foreign Corrupt Practices Act

The FCPA was passed in 1977 in response to numerous allegations that U.S. companies and their affiliates were making

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[197] Justin E. Bekelman, et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 J. AM. MED. ASS'N. 454, 456 (2003).

[198] OIG FINANCIAL INFORMATION REPORT, *supra* note 196, at 17. Eighteen percent of those applications utilizing the "due diligence" exemption did not explain why they were unable to obtain financial information from clinical investigators. *Id.*

[199] *Id.* at 18. Of the marketing applications that lacked documented review of financial disclosures, more than one-third contained a clinical investigator who disclosed a financial interest. *Id.*

[200] *Id.* at 20. While taking remedial measures is not required until the FDA directs the applicant to do so, such measures are prominent—and seemingly important to the FDA—in this regulation. *See* 21 C.F.R. § 54.4(a)(3)(v) (2012) (requiring Sponsors to list any steps taken to minimize potential bias from a financial interest); 21 C.F.R. § 54.5(a) (2012) (listing the three factors that the FDA will consider when evaluating a financial interest: size of the interest, nature of the interest, and measures taken to minimize the potential bias created by the interest).

improper payments to foreign officials.[201] The legislation contains an anti-bribery provision that enables the DOJ to prosecute U.S. corporations and nationals who make "improper payments to foreign government officials for the purpose of obtaining or retaining business."[202] To successfully try a case under the anti-bribery provision of the FCPA, the DOJ must prove five basic elements:

1. A payment, either directly or through a third party, of anything of value
2. to any foreign official, political party, or candidate
3. through the use of an instrumentality of interstate commerce or by the actions of a U.S. person or domestic concern outside the United States or an act inside the United States by any other person (other than a U.S. national)
4. for the corrupt purpose of influencing an official act or decision of the recipient
5. in order to obtain or retain business or to secure an improper advantage.[203]

Within this framework, a U.S. corporation can be held responsible for the improper actions of contracted third parties.[204] This is particularly troublesome for pharmaceutical companies outsourcing FCTs because of the extensive number of third parties needed to run a study. CROs and clinical investigators are the most obvious of these contracted positions.[205]

As discussed above, one complaint against FCTs is that they circumvent the regulations of countries where they are being conducted. One way FCTs may get around regulations is by offering something of value to a politician or regulatory official in order to get licensing to perform the clinical study. Examples of

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[201] Drew A. Harker & Chad E. Miller, *The Foreign Corrupt Practices Act and Clinical Trials: A Trap for the Unwary*, 63 FOOD & DRUG L.J. 509, 509–10 (2008).

[202] *Id.* at 510.

[203] *Id.* at 510–11.

[204] *Id.* at 511, 514.

[205] *Id.* at 514 ("[T]he risk of FCPA violations grows markedly when a third-party agent is introduced.").

offers are money transfers to officials, employing officials as "consultants" for the study, or hiring persons upon recommendation of the official. These cases would most likely run afoul of the FCPA's provisions and could potentially be prosecuted by the DOJ. Other scenarios are not as cut-and-dry or obvious, yet still may present an opportunity to reprimand overreaching parties.

Where a member of a foreign IRB is also a foreign official, the FCPA could be implicated if the reviewing board as a whole, or the foreign official in particular, has been transferred something of value to induce an approval, continued approval, or to stem an investigation of a study. In this situation, the study would either be approved or allowed to continue despite conflict with a country's regulations for health and safety. The "something of value" offered could be money, gifts, trips, meals, or any assortment of things, if the intent was to circumvent regulatory action. There is even case law to suggest that offers of business exclusivity could also satisfy the transfer criteria.[206] In the present context, a CRO's promise to always seek approval from a specific for-profit IRB could be treated as an offer of business exclusivity.

Another place one may find a foreign official is in the laboratory or as an investigator at the clinical site. Inducements given by a CRO or Sponsor to laboratory personnel or clinical investigators so they will modify, falsify, or hide clinical data in order to prevent a study from being shut down—or to give better potential to a marketing application—could also be in violation of the FCPA. Here, the foreign official working on the study would be the recipient, and the manufacturing of fraudulent data would be the corrupt act. The last element of FCPA would either be satisfied by the continuation of the study—retaining business—or by gaining an unfair advantage in the marketing approval process. In addition, a foreign official working directly on the study could have negative consequences for the U.S. corporation if the employee induces another official to either give approval for the study, or prevent government action against a study that is

[206] *Id.* at 511, n.17.

violating domestic laws or regulations.[207] Foreign officials within the employ of a U.S. corporation are not immune from being a recipient of an inappropriate transfer, and they will count as a representative third party of the corporation if they choose to induce another foreign official to engage in misconduct.[208]

It should be noted that "payment or offer of something of value to a foreign official by a CRO, [clinical investigator,] or IRB, with the purpose of facilitating the success of a clinical trial may constitute an action that is taken to obtain or retain business, depending on the circumstances."[209] This could also include dissuading the government from prosecuting the FCT or persuading government officials to dismiss or otherwise block the civil suits of citizens against the FCT. In dissuading litigation, the business purpose is not as apparent; however, there is case law[210] to suggest that this may be in violation of the FCPA because the requirement of obtaining or retaining business will be read broadly by the courts.[211] Halting litigation that would likely have a beneficial effect on future drug sales and company stock prices certainly would appear to fall under this category.

The FDA lacks sufficient funding to effectively police bribery that may occur during FCTs.[212] DOJ prosecution under the FCPA offers a unique opportunity to both fight bribery and promote ethical practices in studies connected to U.S. corporations. With its

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[207] *Id.* at 517 ("[A] [principle investigator], who himself may be a foreign official and retained directly by the company to conduct a clinical study, may corruptly pay or offer to pay something of value to secure the action of another government official."). *See also United States v. Syncor Taiwan, Inc.*, No. CR 02-1244-SVW (C.D. Cal, Dec. 2002) (accepting a guilty plea by Syncor Taiwan for bribery of doctors employed in a state-owned hospital).

[208] Harker & Miller, *supra* note 201, at 517 (describing how payments between government officials do not immunize a corporation from FCPA liability simply because both parties worked for the foreign government).

[209] *Id.*

[210] *See U.S. v. Kay*, 359 F.3d 738 (5th Cir. 2004).

[211] Harker & Miller, *supra* note 201, at 516–17.

[212] *Id.* at 521. In 2006, a survey was given to one thousand FDA scientists asking about different performance aspects of the agency. Seventy percent believed that the FDA was unable to adequately perform its congressional mandate. *2006 UCS and PEER Survey of U.S. Food and Drug Administration Scientists*, *available at* http://www.ucsusa.org/assets/documents/scientific_integrity/fda-survey-questions-and-results.pdf.

greater resources,[213] the DOJ could make the probability of prosecution a true threat,[214] prompting fair competition and promoting better products.

6. CONCLUSION

In the upcoming years, experts expect an increase in the number of clinical trials being conducted in Eastern Europe, Central and South America, and China and India.[215] FCTs are, and will continue to be, an integral part of the FDA's marketing approval process. There is no inherent danger when using FCTs in the marketing approval process, and when taking into consideration their lower cost and potential to provide needed resources to less-developed countries, FCTs can be a laudable undertaking. However, the safety of those involved and the utility of the product produced must be ensured. This end can be accomplished through the collective efforts of the FDA, its foreign counterparts, and the pharmaceutical industry. A movement toward accountability occurred in the United States during the last century, and can be implemented at the global level to the benefit of all.

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[213] Harker & Miller, *supra* note 201, at 521.

[214] *Id.* at 519–20.

[215] CHALLENGES TO THE FDA, *supra* note 54, at 14.