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An Extraterritorial FDA: Could the Food and Drug Administration Apply Its Informed Consent Requirement Abroad Consistent with International Law?

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Abstract

This paper addresses the regulatory challenges wrought by the increasing amount of human subject drug testing conducted in developing countries in support of new drug applications to the Food and Drug Administration. Specifically, it examines the difficulty of enforcing the “informed consent” requirement for ethical scientific research performed in foreign territory. In poorer regions, a lack of government oversight, lower regulatory standards, and barriers to communication have too frequently resulted in allegations of human experimentation performed without its participants’ informed consent. In order to solve this problem, some commentators have suggested that the FDA could apply its human subject protections to foreign clinical research, and enforce them through injunctions or criminal prosecutions. However, the international legal limits on states’ prescriptive jurisdiction may prohibit this exercise of extraterritoriality. After analyzing the proposed extraterritorial regulation of foreign drug testing under the traditional bases and limitations of prescriptive jurisdiction, this paper concludes that such regulation would likely violate international law. However, because nonconsensual clinical research has previously been regarded as a crime against humanity, the FDA might be able to bring criminal prosecutions under the principal of “universal jurisdiction” against investigators or sponsors who conducted studies without their subjects’ informed consent. This analysis offers both positive and normative conclusions regarding the international legal system and the human rights regime.

An Extraterritorial FDA: Could the Food and Drug Administration Apply Its Informed Consent Requirement Abroad Consistent with International Law?

I. Introduction

The modern pharmaceutical industry has become a “global enterprise.”¹ So too has the clinical testing process for new drugs. Pharmaceutical companies based in developed countries increasingly use the citizens of the developing world as their human test subjects.² “[R]ich countries have the drugs and hypotheses, while poor countries have vast numbers of patients.”³

When the U.S. Food and Drug Administration (FDA) first promulgated its regulatory framework for new drug testing in 1962,⁴ government officials hesitated to accept the results of foreign research trials, and so pharmaceutical companies rarely sponsored clinical studies abroad.⁵ But the FDA has since liberalized its position on foreign research.⁶ In response,

¹ 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, 245 (1997).

² 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, 167 (2003).

³ Mary Pat Flaherty & Doug Struck, *Life by Luck of the Draw*, WASH. POST, Dec. 22, 2000, at A1.

⁴ See 27 Fed. Reg. 7990 (Aug. 10, 1962), 28 Fed. Reg. 179 (Jan. 8, 1963).

⁵ PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 650 (3d ed. 2007). See also Office of Inspector General, Department of Health and Human Services, *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, Sept. 2001, at 6, available at

pharmaceutical companies have moved their clinical testing overseas, attracted by the more permissive regulation of human experimentation and lower research costs abroad.⁷ Thus, in 1999, nearly 27 percent of new drugs approved for sale in the United States were first tested in foreign countries,⁸ and by 2008, that number had more than doubled to 80 percent.⁹ In fact, the FDA approved ten new drug applications in 2008 based *entirely* on foreign data – without a single clinical study conducted in the United States.¹⁰

The globalization of clinical testing for new drugs has generated an array of problems for

<http://oig.ils.gov/oei/reports/oei-01-00-00190.pdf> (“Until recently, almost all of the clinical drug research submitted in support of NDAs was conducted at sites within the U.S.”).

⁶ In 1975, the FDA announced that it would not discriminate between foreign and domestic clinical studies, *see* 38 Fed. Reg. 24220 (Sept. 6, 1973); 40 Fed.Reg. 16053 (Apr. 9, 1974), and in 1994 the agency specified that it would accept new drug applications based entirely on foreign data. *See* 21 C.F.R. § 314.106(b)(1) (1994).

⁷ *See* Mary Pat Flaherty et al., *Testing Tidal Wave Hits Overseas*, WASH. POST, Dec. 18, 2000, at A1. Pharmaceutical companies increasingly conduct these foreign studies in developing regions like India, Africa, Eastern Europe, and Latin America. *See* Yevgenia Shtilman, *Pharmaceutical Drug Testing in the Former Soviet Union*, 29 B.C. THIRD WORLD L.J. 425, 434 (2009).

⁸ *Id.*

⁹ Gardiner Harris, *Concern Over Foreign Trials for Drugs Sold in U.S.*, N.Y. TIMES, June 21, 2010, at A14. Seventy-eight percent of the human subjects involved in those trials were enrolled in research sites abroad. *Id.*

¹⁰ *Id.* Consider that such an application would have been automatically rejected only 14 years earlier.

the United States, home to the largest pharmaceutical industry in the world.¹¹ Concern over whether researchers abroad properly obtain patients' "informed consent" poses one such challenge.¹² The principle of informed consent, dating back to the Nuremberg Trials after World War II,¹³ forms one of the "basic ethical protections for research involving human participants."¹⁴ It requires that "a subject/patient willingly verifies his/her willingness to participate in a particular treatment, after having been informed of all aspects which are pertinent to that treatment and relevant to the subject's participation."¹⁵ Thus, in 1962, in the same bill

¹¹ See Dominguez-Urban, *supra* note 1, at 245.

¹² Of course, ethical concerns are not the only problem wrought by globalized clinical testing. For instance, foreign governments may allow for less rigorous experimental methodologies, which in turn could produce less reliable data by which to evaluate a drug's safety or effectiveness. See John Carroll, *HHS report underscores big shift to foreign drug trials*, FIERCEBIOTECH (June 22, 2010, 11:39 AM), <http://www.fiercebiotech.com/story/hhs-report-underscores-big-shift-foreign-drug-trials/2010-06-22>. Moreover, if certain drugs produced different reactions in different ethnic groups, or were especially sensitive to differing dietary or lifestyle factors, then they might provoke unexpected side effects when tested abroad but consumed in the United States. See Dominguez-Urban, *supra* note 1, at 263 – 64.

¹³ See Jennifer J. Couture, *The Changes in Informed Consent in Experimental Procedures: The Evolution of a Concept*, 1 J. HEALTH & BIOMEDICAL L. 125, 127 - 29 (2005).

¹⁴ Maxwell J. Mehlman & Jessica W. Berg, *Human Subjects Protections in Biomedical Enhancement Research*, 36 J. L. MED & ETHICS 546, 552 (2008).

¹⁵ Couture, *supra* note 13, at 126 n. 6. States prescribe varying processes for obtaining a research subject's informed consent. See generally *id.*

where Congress first mandated that new drugs be clinically tested prior to marketing,¹⁶ Congress also instructed that this newly required human experimentation occur only with the “informed consent” of its subjects.¹⁷ Senator Jacob Javits of New York, sponsor of the informed consent amendment, noted the absence of state statutes covering informed consent in human subject research,¹⁸ and explained the importance of such a requirement:

I am for experimentation. I feel deeply that some risks must be assumed in experimentation. But we must hold the balance between personal dignity and personal responsibility and the right of the individual to know how his life is being disposed of, at least with his consent, and the virtues of the experimentation.¹⁹

In the absence of an informed consent requirement, Senator Javits asked, “[W]here is the dignity, the responsibility, and the freedom of the individual?”²⁰

Yet a series of headline cases recently revealed that pharmaceutical companies seeking FDA approval of new drugs repeatedly failed to obtain patients’ informed consent in the course of conducting clinical trials in developing countries.²¹ In these less developed regions, where an

¹⁶ Pub.L. No. 87–781, 76 Stat. at 780 (amending, *inter alia*, 21 U.S.C. § 355(d)(7)).

¹⁷ Pub.L. No. 87–781, 76 Stat. at 780 (amending, *inter alia*, 21 U.S.C. § 355(i)(4)).

¹⁸ 108 CONG. REC. 17,395 (1962) (statement of Sen. Javits), *reprinted in* 22 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG & COSMETIC ACT AND ITS AMENDMENTS, at 323 (1979).

¹⁹ 108 CONG. REC. 17,397 (1962) (statement of Sen. Javits), *reprinted in* 22 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG & COSMETIC ACT AND ITS AMENDMENTS, at 325 (1979).

²⁰ *Id.*

²¹ *See, e.g.*, Karen De Young et al., *Latin America Is Ripe for Trials, and Fraud*, WASH. POST., Dec. 21, 2000, at A1 (reporting on the criminal investigation surrounding a study sponsored in

increasing amount of human experimentation occurs, government regulators are “generally ill-equipped to oversee, much less manage, the clinical trials being held within their borders.”²²

Moreover, poorer countries have “strong incentives to encourage leniency in national and local oversight of the research” in order to attract drug companies.²³ The “resulting ‘regulatory vacuum’ makes it difficult for these countries to ensure the welfare of trial participants,”²⁴ and allows researchers to violate, whether intentionally or accidentally, the fundamental ethical

Argentina by drug manufacturer Hoechst Marion Roussel, in which researchers forged consent forms in order to administer the experimental drug cariporide to patients without their consent, resulting in the deaths of several participants); John Pomfret & Deborah Nelson, *An Isolated Region’s Genetic Mother Lode*, WASH. POST., Dec. 20, 2000, at A1 (describing a study sponsored in China by U.S. pharmaceutical company Millennium Pharmaceuticals, Inc., in which researchers made false promises of free healthcare to impoverished Chinese participants, without properly explaining the purpose of the experiment, in order to draw their blood for genetic study); Sharon LaFraniere et al, *The Dilemma: Submit or Suffer*, WASH. POST., Dec. 19, 2000, at A1 (recounting American pharmaceutical company Pfizer, Inc.’s clinical trial of the anti-psychotic drug Zeldox at a Bulgarian mental institution, in which researchers failed to inform participants that the FDA had expressed concern over the drug’s effect on hearth rhythms and had refused to approve the drug until more safety tests had been conducted).

²² See Shtilman, *supra* note 7, at 434 – 36.

²³ See *id.*

²⁴ See *id.* at 436.

principle of informed consent.²⁵ In fact, pharmaceutical companies sometimes conduct drug trials abroad precisely to avoid the more stringent U.S. regulations on human experimentation.²⁶ Additionally, language barriers and cultural differences make it difficult for researchers to adequately explain the risks of the experimental process and ensure that participants have autonomously consented.²⁷ Even when obvious ethical violations do not occur, local variations in acceptable experimental procedures still invite accusations of exploitation.²⁸ Recently, the U.S. Embassy in Beijing went so far as to “warn[] U.S. medical researchers against working in impoverished, rural areas of China,” where “health care is poor and people are unable to protect their rights.”²⁹

²⁵ See Dominguez-Urban, *supra* note 1, at 270 - 71. To appreciate the scale of these violations, consider a 1996 study by the Catholic University medical school in Santiago, Chile, which revealed that nearly half of the 44 clinical trials conducted in the country that year suffered from “ethical problems,” most commonly a lack of patients’ consent. See LaFraniere et al, *supra* note 21.

²⁶ See Dubois, *supra* note 2, at 168.

²⁷ See LaFraniere et al, *supra* note 21.

²⁸ See Dubois, *supra* note 2, at 168. For instance, American pharmaceutical company Bristol-Myers sponsored a clinical study in Budapest of an anti-psychotic drug tested on mental patients confined to locked wards – a standard practice in Hungary that would not have been acceptable if performed in the United States due to the fear of coercing consent. See LaFraniere et al, *supra* note 21.

²⁹ Pomfret & Nelson, *supra* note 21 (internal quotation marks omitted). Indeed, the lack of healthcare in poor countries may undermine the entire concept of “informed consent,” as

There are currently no effective mechanisms to enforce the informed consent requirement worldwide. No international treaties regulate human experimentation.³⁰ The international codes of ethics that protect human test subjects – the Nuremberg Code³¹ and the Declaration of Helsinki³² – both require patients’ informed consent, but lack any sanctions or enforcement mechanisms.³³ The FDA does not use injunctions or criminal proceedings to enforce its informed consent requirement abroad. Instead, the FDA simply refuses to accept data submitted in support of new drug applications if it originated from foreign research conducted without the subjects’ informed consent.³⁴ This purely ex post approach does not protect the victims, nor

participants could be so desperate for medical care that they would agree to any experimental procedure. *See* LaFraniere et al, *supra* note 21. George J. Annas, head of the health law department at the Boston University School of Public Health, explained, “I’d argue you can’t do studies ethically in a country where there is no basic healthcare... You can tell a person there that this is research, but they hear they have a chance to get care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?”

Id.

³⁰ *See* Dominguez-Urban, *supra* note 1, at 273.

³¹ *The Nuremberg Code*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 3 (George J. Annas & Michael A. Grodin eds., 1992).

³² *Declaration of Helsinki Recommendations Guiding Doctors in Clinical Research*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 331 – 42 (George J. Annas & Michael A. Grodin eds., 1992).

³³ *See* Dominguez-Urban, *supra* note 1, at 273 – 74.

³⁴ *See* Dominguez-Urban, *supra* note 1, at 275 - 76.

does it hold the perpetrators accountable. It is further limited by the fact that FDA regulators often only inspect a foreign research site *after* the company has submitted its new drug application, “often years after the trial ceased.”³⁵

Just as Senator Javits once called for a federal mandate on research ethics due to the lack of state regulation, commentators have similarly proposed that the FDA extraterritorially extend its domestic human subject protections to apply to *foreign* research.³⁶ Under an extraterritorial

³⁵ Harris, *supra* note 9.

³⁶ See Dubois, *supra* note 2, at 165. Cf. Dominguez-Urban, *supra* note 1, at 245 (“How do nations achieve this goal [ensuring safe and effective drugs] yet still ensure that research costs are not prohibitive? The trend has been to move beyond national borders in order to find solutions to this dilemma.”). More generally, activists have called for states to use their influence extraterritorially in order to prevent human rights abuses abroad. See Christen Broecker, “*Better the Devil You Know*”: *Home State Approaches to Transnational Corporate Accountability*, 41 N.Y.U. J. INT’L L. & POL. 159, 180 – 81 (2008). Other proposed solutions include the imposition of civil liability through the Alien Tort Claims Act on companies that fail to obtain patients’ informed consent, see Samantha Evans, *The Globalization of Drug Testing: Enforcing Informed Consent Through the Alien Tort Claims Act*, 19 TEMP. INT’L & COMP. L.J. 477 (2005), the creation of an international body to enforce binding ethical standards on a global scale, see Ruqaiijah Yearby, *Good Enough to Use for Research, But Not Good Enough to Benefit from the Results of that Research*, 53 DEPAUL L. REV. 1127, 1150 (2004), or the use of market exclusion in lucrative markets to deter unethical research. See Fazal Khan, *The Human Factor: Globalizing Ethical Standards in Drug Trials Through Market Exclusion*, 57 DEPAUL L. REV. 877, 902 (2008).

FDA, human research in foreign territory conducted in order to market drugs in the United States would not only be subject to host country regulations, but also to the FDA's *domestic* standards for informed consent. An extraterritorial FDA would not simply reject bad data, but would subject foreign sponsors and researchers who sought to its obtain approval for new drugs to the same liabilities, including injunction proceedings and criminal prosecutions, as domestic investigators.³⁷ This approach would mirror previous U.S. attempts to fill gaps in international law with extraterritorial domestic statutes.³⁸ Moreover, in regulating foreign clinical trials, the FDA would comprise just a part of an overall trend towards “transnational regulatory litigation,”³⁹ in which U.S. officials and agencies have increasingly applied American regulations to conduct occurring abroad.⁴⁰

Scholars have previously examined whether, under American law, the FDA could extraterritorially regulate pharmaceutical testing conducted overseas in order to market a drug

³⁷ Such a strategy would avoid unpredictable and potentially frivolous ATCA lawsuits, require far less time than establishing and legitimizing an international body, and provide a greater degree of accountability for violators than mere market exclusion. *See supra* note 36.

³⁸ *See* Austen L. Parrish, *Reclaiming International Law from Extraterritoriality*, 93 MINN. L. REV. 815, 841 – 42 (2009) (the author is critical of this development).

³⁹ Hannah L. Buxbaum, *Transnational Regulatory Litigation*, 46 VA. J. INT'L L. 251, 255 (2006).

⁴⁰ *See* Parrish, *supra* note 38, at 847 – 49. This trend toward extraterritorial application of U.S. domestic law has occurred in areas as diverse as antitrust, intellectual property, securities, corporate governance, crime, labor, and the environment. *Id.*

within the United States.⁴¹ However, no scholar has yet examined whether the FDA could extraterritorially regulate this kind of foreign clinical research consistent with *international law*. Under international law, a state has a limited legal power to exercise legislative authority, primarily on the basis of territory and nationality.⁴² Current FDA policy, which makes adherence to its informed consent requirement a condition of acceptance for foreign research, does not violate these limits. It does not attempt to legislate in foreign territory, but merely articulates the FDA's own standards for admissible research. However, extraterritorial application of the FDA's clinical trial regulations to foreign research, enforced through injunctions or criminal prosecutions, *would* prescribe law to govern conduct by non-Americans in foreign territory, and thus might exceed the United States' legal power under international law.

So, even if *American* law permitted the FDA to regulate foreign research trials, would the application of the FDA's informed consent requirement abroad *still* violate the *international* legal prohibition on extraterritorial jurisdiction? Legal analysis of this question would not only determine the doctrinal validity of such a regulation, but also may help resolve the uniquely difficult policy issues posed by the regulation of foreign human experimentation. Opposition to the "exploitation of subaltern populations" by pharmaceutical companies would counsel in favor

⁴¹ See Dubois, *supra* note 2, at 189 – 94. This analysis involved the application of the "presumption against extraterritoriality" canon to the Federal Food, Drug, and Cosmetic Act, *id.* at 189 – 91, followed by an examination of whether the "effects test" exception included the specific drug safety and efficacy concerns addressed by the FDA. *Id.* at 192 – 94.

⁴² RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES pt. IV, ch. 1, subch. A, intro. note (1987).

of an extraterritorial FDA.⁴³ Yet one could equally object to extraterritorial regulation based on the centrality of public health policy to national sovereignty, and the danger of imposing culturally constructed conceptions of informed consent through “ethical imperialism.”⁴⁴

International law, which “has long recognized limitations on the authority of states to exercise jurisdiction to prescribe in circumstances affecting the interests of other states,”⁴⁵ could provide a first step toward unraveling these knots. Thus, this paper will examine whether, and to what extent, the FDA could enforce its informed consent requirement on human experimentation conducted abroad consistent with the international legal limits on prescriptive jurisdiction.

II. The International Law of Prescriptive Jurisdiction

According to the United Nations Report of the International Law Commission, “[t]raditionally the exercise of jurisdiction by a State was primarily limited to persons, property and acts within its territory.”⁴⁶ However, in the modern era, the exercise of “extraterritorial jurisdiction by a State with respect to persons, property or acts outside its territory has become an increasingly common phenomenon.”⁴⁷ International law provides the bases and limitations for a state’s “jurisdiction to prescribe” – the authority of a state “to make its law applicable to the

⁴³ Khan, *supra* note 36, at 878.

⁴⁴ Dominguez-Urban, *supra* note 1, at 280.

⁴⁵ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES pt. IV, ch. 1, subch. A, intro. note (1987).

⁴⁶ U.N. Int'l Law Comm'n, Report of the International Law Commission, Annex E, at 516, U.N. Doc. A/61/10 (2006).

⁴⁷ *Id.*

activities, relations, or status of persons, or the interests of persons in things.”⁴⁸ These bases and limitations “flow from the sovereign equality of states and the principle of non-interference.”⁴⁹

In most cases, a state has jurisdiction to prescribe law with respect to three kinds of conduct: conduct that takes place within its territory, the conduct of its nationals, and conduct outside its territory that has or is intended to have a substantial effect within its territory or that is directed against its security.⁵⁰ A state may also prescribe law with respect to the activities of

⁴⁸ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 401 (1987). The Restatement of the Foreign Relations Law of the United States describes the tenants of “international law as it applies to the United States.” *Id.* § 1. Although commentators have criticized certain provisions, *see, e.g.*, Kathleen Hixson, *Extraterritorial Jurisdiction Under the Third Restatement of Foreign Relations Law of the United States*, 12 FORDHAM INT’L L.J. 127 (1988), American courts have repeatedly cited the Restatement’s sections on prescriptive jurisdiction as an accurate articulation of international law. *See, e.g.*, Hartford Fire Ins. Co. v. California, 509 U.S. 764, 799 (1993); U.S. v. Vasquez-Velasco, 15 F.3d 833, 840 (9th Cir. 1994); U.S. v. Javino, 960 F.2d 1137, 1142 (2d Cir. 1992).

⁴⁹ Donald Francis Donovan & Anthea Roberts, *The Emerging Recognition of Universal Civil Jurisdiction*, 100 AM. J. INT’L L. 142, 142 (2006).

⁵⁰ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 402 (1987). Additionally, there is an emerging “passive personality” basis for extraterritorial jurisdiction, under which states may apply their criminal laws to foreign acts if their nationals were victims of those acts. *Id.* § 402 cmt. g. However, because the passive personality principle has not yet been “generally accepted,” *id.*, this paper will not address it.

foreign branches of corporations incorporated under its laws.⁵¹ However, even when one or more of these bases for jurisdiction is present, a state still may not exercise prescriptive jurisdiction in matters connected to another state “when the exercise of such jurisdiction is unreasonable.”⁵² The determination of whether the exercise of jurisdiction is unreasonable requires evaluation of “all relevant factors,” including, where appropriate: (1) the link of the activity to the territory of the regulating state; (2) the connections between the regulating state and the party responsible for the regulated activity, or between the regulating state and those whom the regulation protects; (3) the character of the activity to be regulated, the importance of regulation to the regulating state, the extent to which other states regulate such activities, and the degree to which the desirability of such regulation is generally accepted; (4) the existence of justified expectations that might be affected by the regulation; (5) the importance of the regulation to the international system; (6) the extent to which the regulation is consistent with the traditions of the international system; (7) the extent to which another state may have an interest in regulating the activity; and (8) the likelihood of conflict with regulation by another state.⁵³ When it would not be unreasonable for two states to exercise prescriptive jurisdiction over particular conduct, but their regulations are in conflict, one state should defer to the other if it has the “clearly greater” interest.⁵⁴ Finally, in the case of regulatory statutes that prescribe both civil

⁵¹ *Id.* § 414(1).

⁵² *Id.* § 403(1).

⁵³ *Id.* § 403(2).

⁵⁴ *Id.* § 403(3).

and criminal liability, the presence of “substantial foreign elements” should “weigh against application of criminal law.”⁵⁵

“Universal jurisdiction” provides a special exception to the required bases for jurisdiction. Even absent any of the traditional bases, states may exercise universal jurisdiction to prescribe punishment for “offenses recognized by the community of nations as of universal concern, such as piracy, slave trade, attacks on or hijacking of aircraft, genocide, war crimes, and perhaps certain acts of terrorism.”⁵⁶ Historically, universal jurisdiction was intended to address offenses like piracy that defied traditional territorial jurisdictional principles, but in modern times it has also come to rely on “the sheer heinousness of certain crimes, such as genocide and torture.”⁵⁷ The offenses subject to universal jurisdiction comprise an “[e]xpanding class,” determined by “universal condemnation of those activities and general interest in cooperating to suppress them, as reflected in widely-accepted international agreements and resolutions of international organizations.”⁵⁸

III. Current FDA Regulation of Informed Consent in Human Clinical Testing

To obtain approval to market a new drug in the United States, a manufacturer must first submit a new drug application (NDA) to the FDA.⁵⁹ As part of this application, the manufacturer must provide “substantial evidence” on the basis of “adequate and well-controlled

⁵⁵ *Id.* § 403, cmt. f.

⁵⁶ *Id.* § 404.

⁵⁷ Donovan & Roberts, *supra* note 49, at 143.

⁵⁸ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 404, cmt. a (1987).

⁵⁹ *See* 21 U.S.C. § 355(a) (2008); *see also* HUTT ET AL., *supra* note 5, at 624.

investigations, including clinical investigations” that the drug is both safe and effective.⁶⁰

Clinical studies conducted within the United States in support of an NDA must proceed through the FDA’s extensively regulated investigational new drug (IND) process,⁶¹ which prescribes a set of responsibilities and experimental protocols for both the investigators performing the research and their corporate sponsors.⁶² Investigators must ensure that an institutional review board oversees and approves their research activities for compliance with community ethical standards and FDA regulations.⁶³ Moreover, an investigator working under an IND must obtain the informed consent of each human subject participating in the study.⁶⁴ The FDA requires that consent be sought under circumstances in which the subject has “sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”⁶⁵ As part of the informed consent process, researchers must provide each subject with up to sixteen elements of information regarding the study⁶⁶ “in language understandable to

⁶⁰ 21 U.S.C. § 355(d) (2008).

⁶¹ 21 C.F.R. § 312 (2010). The IND requirement for domestic clinical testing is premised on the FDA’s ability to exempt a manufacturer from the typical prohibition on shipping unapproved drugs for the limited purpose of clinical research. *See* 21 U.S.C. § 355(i) (2008).

⁶² 21 C.F.R. § 312.50 – 70 (2010).

⁶³ 21 C.F.R. § 312.66 (2010).

⁶⁴ *See* 21 U.S.C. § 355(i)(4) (2008); 21 C.F.R. § 50.20 (2010); *see also* 21 C.F.R. § 312.60 (2010).

⁶⁵ *Id.*

⁶⁶ *See* 21 C.F.R. § 50.25 (2010). These elements include, inter alia, a statement that the study involves research and an explanation of its purposes, a description of the procedures to be

the subject.”⁶⁷ Each subject’s consent must be documented in a signed form, and each subject must receive a copy of his or her form.⁶⁸ The FDA further requires that researchers take special account of whether child subjects are capable of providing assent, and that they obtain the permission of the children’s parents or guardians.⁶⁹ The sponsors of new drug research under an IND are held responsible for monitoring the progress of the clinical studies and ensuring that all FDA requirements, including the informed consent standards, are met.⁷⁰ The Federal Food, Drug, and Cosmetic Act classifies violation of the informed consent requirement as a “prohibited act,”⁷¹ against which the FDA has the power to bring an injunction proceeding⁷² or a criminal prosecution.⁷³

A manufacturer who intends to sponsor or conduct a clinical research study abroad in support of its NDA has two routes through which to submit the required data. First, the manufacturer can voluntarily submit to the IND process, “bringing the investigator, regardless of

followed, a description of any reasonably foreseeable risks, a description of any reasonably foreseeable benefits, a disclosure of appropriate alternative procedures, a statement that participation is voluntary, and an explanation of whom to contact for answers to questions about the research and the subject’s rights. *See* 21 C.F.R. § 50.25(a) (2010).

⁶⁷ 21 C.F.R. § 50.20 (2010).

⁶⁸ 21 C.F.R. § 50.27(a) (2010).

⁶⁹ *See* 21 C.F.R. § 50.55(b) & (e) (2010).

⁷⁰ *See* 21 C.F.R. § 312.56 (2010).

⁷¹ 21 U.S.C. § 331(e) (2008).

⁷² *See* 21 U.S.C. § 332 (2008).

⁷³ *See* 21 U.S.C. § 333 (2008).

the location of the research, under the federal regulations governing the conduct of research in the United States,” including the informed consent provisions.⁷⁴ Second, the manufacturer may avoid the IND procedure altogether and instead conduct its foreign clinical studies independently in accordance with local ethical and legal requirements.⁷⁵ Under this alternative process, the FDA does not regulate or oversee the research, nor does it assign responsibilities to investigators or their sponsors. Instead, the FDA simply requires as a condition for acceptance of the study⁷⁶ that it be “conducted in accordance with good clinical practice,” which includes “obtaining and documenting the freely given informed consent of the subject.”⁷⁷ The FDA will not accept as support for an NDA studies that fail to meet this informed consent requirement, although it will still “examine data from such a study.”⁷⁸ The term “good clinical practice” (GCP) refers to the guidelines for human experimentation promulgated in 1995⁷⁹ by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, an international conference convened by the United States, Japan, and the European Union in an

⁷⁴ Erin Talati, *An Open Door to Ending Exploitation: Accountability for Violations of Informed Consent Under the Alien Tort Statute*, 155 U. PA. L. REV. 231, 240 (2006).

⁷⁵ See 21 C.F.R. § 312.120(a) (2010).

⁷⁶ 21 C.F.R. § 312.120(a)(1) (2010).

⁷⁷ 21 C.F.R. § 312.120(a)(1)(i) (2010).

⁷⁸ 21 C.F.R. § 312.120(a)(2) (2010).

⁷⁹ International Conference on Harmonization: Draft Guidelines on Good Clinical Practice, 60 Fed. Reg. 42,948 (1995). See also Michelle D. Miller, *The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 30 CORNELL INT’L L.J. 203, 233 – 34 (1997).

attempt to standardize their pharmaceutical development protocols.⁸⁰ The FDA also requires, as part of the GCP, that foreign research studies receive review and approval by an “independent ethics committee,”⁸¹ which operates much like an institutional review board.⁸²

The FDA’s informed consent regulations for research conducted under the guidance of an IND impose more stringent patient protections than does the GCP for foreign research conducted independently.⁸³ Although the FDA’s IND human subject protections claim to extend to *any* research filed in support of an NDA,⁸⁴ the language of the IND informed consent requirement,⁸⁵ and the fact that the FDA articulates a separate GCP standard for independent foreign studies, together suggest that the FDA regulations contemplate distinct informed consent standards for each research pathway. In the IND process, the FDA prescribes specific components of “informed consent,” including the language used, the precise information provided, and the circumstances under which consent may be given.⁸⁶ On the contrary, for independent foreign research, the GCP requires only that researchers inform each subject “of all aspects of the trial

⁸⁰ *See id.* at 205.

⁸¹ 21 C.F.R. § 312.120 (2010).

⁸² *See* Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 73 Fed. Reg. 22,805 (Apr. 28, 2008) (to be codified at 21 C.F.R. pt. 312).

⁸³ *See* Miller, *supra* note 79, at 235.

⁸⁴ *See* 21 C.F.R. § 50.1 (2010).

⁸⁵ *See* Shtilman, *supra* note 7, at 432 n. 33. *But see* Amy F. Wollensack, *Closing the Constant Garden*, 6 WASH. U. GLOBAL STUD. L. REV. 747, 769 (2007).

⁸⁶ *See* 21 C.F.R. § 50.25 (2010).

that are relevant to the subject’s decision to participate” and document his or her consent “by means of a written informed consent form.”⁸⁷ Under these “extremely vague” tenants, research subjects “have significantly less assurance that actual informed consent will be obtained.”⁸⁸ Moreover, the FDA subjects each pathway to different levels of enforcement, with different consequences for violation of the informed consent standard. The FDA is authorized to bring,⁸⁹ and has sent warning letters threatening to initiate,⁹⁰ injunction proceedings and criminal prosecutions against investigators and sponsors who conduct research under an IND and fail to fulfill its informed consent requirements. Yet FDA regulations present the GCP informed consent standard for independent foreign research as merely *a condition of acceptance* for the study,⁹¹ so that a violation of the requirement will merely disqualify its results from an NDA

⁸⁷ International Conference on Harmonization: Draft Guidelines on Good Clinical Practice, 60 Fed. Reg. 42,949 (1995) (proposed Aug. 17, 1995).

⁸⁸ Miller, *supra* note 79, at 235 – 36.

⁸⁹ See 21 U.S.C. § 331(e) (2008); 21 U.S.C. § 332 (2008); 21 U.S.C. § 333 (2008).

⁹⁰ See, e.g., Food and Drug Administration, *Avlon Industries 19-Jan-07*, U.S. FOOD AND DRUG ADMINISTRATION, (Jan. 19, 2007),

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076248.htm>; Food and Drug Administration, *International Association for Colon Hydrotherapy 21-Mar-03*, U.S. FOOD AND DRUG ADMINISTRATION, (Mar. 21, 2003),

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2003/ucm147378.htm>.

⁹¹ See 21 C.F.R. § 312.120(a)(1) (2010). The fact that the FDA “will [still] examine data” from research that violates this provision, 21 C.F.R. § 312.120(a)(2) (2010), further confirms that a violation merely disqualifies the study, rather than results in civil or criminal liability.

without the imposition of further penalties. Finally, foreign institutional review boards, lacking information and guidance, often fail to understand international research requirements and instead hold drug companies to a lower standard.⁹²

IV. International Legal Limits on the Extraterritorial Regulation of Human Experimentation

An extraterritorial FDA would apply its higher IND informed consent requirements to independent research conducted abroad in support of an NDA. Foreign investigators and sponsors who violated these standards – whether discovered upon submission of their data, through a whistleblower, or during an on-site inspection – would be subject to injunction proceedings and criminal prosecution in the United States. Alternatively, an extraterritorial FDA could continue to hold foreign researchers and sponsors to its lower GCP informed consent requirements, but, rather than simply reject flawed studies, instead actively enforce these standards through injunctions and criminal proceedings.

A. Bases of Jurisdiction

The FDA would have to premise its extraterritorial regulation of foreign clinical trials on one of the internationally accepted bases of jurisdiction to prescribe.⁹³ Of course, foreign research does not take place within United States territory and thus would not invoke the territorial basis for jurisdiction.⁹⁴ Nationality could provide a basis for the FDA to regulate the foreign clinical trials sponsored by American companies or conducted by American investigators

⁹² See Food and Drug Administration, *NIH Sees More Ethical Problems with Foreign IRBs; Steps Up Training*, FDA WEEK, Mar. 17, 2006.

⁹³ See RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES §§ 402, 414(1) (1987).

⁹⁴ See *id.* § 402(1)(a).

abroad.⁹⁵ The FDA might also be able to regulate research conducted or sponsored by foreign branches of American pharmaceutical companies. However, the nationality and foreign branch bases would not allow the FDA to regulate the many foreign research trials that are funded and performed by non-U.S. nationals.

To apply its informed consent requirements to *foreign* investigators or sponsors conducting human subject research abroad, the FDA would have to rely on the effect basis for jurisdiction.⁹⁶ In this case, the “effect” would be the FDA’s approval of the NDA and the marketing of the drug, researched in violation of the Federal Food, Drug, and Cosmetic Act’s informed consent requirement, within the United States. The sale of such a drug would violate the “sense of responsibility” Senator Javits suggested the nation feel in regards to the issue of informed consent,⁹⁷ and potentially make the American public morally complicit in the consumption of an unethically researched drug.⁹⁸ However, the FDA would face three principal difficulties in justifying its extraterritorial regulation on this basis – the discovery of flawed research before approval of the NDA, the nature of the “effect” of prohibited research within U.S. territory, and the degree of that “effect.”

⁹⁵ *See id.* § 402(2).

⁹⁶ *See id.* § 402(1)(c).

⁹⁷ 108 CONG. REC. 17,397 (1962) (statement of Sen. Javits), *reprinted in* 22 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG & COSMETIC ACT AND ITS AMENDMENTS, at 325 (1979).

⁹⁸ Other potential concerns the United States might have over foreign research conducted without participants’ informed consent – for instance, the loss of American credibility and esteem in the developing world or the threat to developing nations’ trust in medical research and public health initiatives – would not produce any “effect” *within* the United States.

The first issue the FDA would face in premising its extraterritorial jurisdiction on the effect basis is that, if the FDA discovered the informed consent violations before approving the drug for marketing, the prohibited research would never have had any actual “effect” within the United States. However, the effect basis would still justify FDA jurisdiction over these cases. International law permits extraterritorial jurisdiction in cases involving intended but unrealized domestic effect.⁹⁹ So long as “the intent to commit the proscribed act is clear and demonstrated by some activity, and the effect to be produced by the activity is substantial and foreseeable, the fact that a plan or conspiracy was thwarted does not deprive the target state of jurisdiction to make its law applicable.”¹⁰⁰ For instance, the fact that a plan coordinated in Pakistan to bomb American commercial airliners “did not come to fruition” did not “wrest jurisdiction over the prosecution from [an American] court,” since the “alleged crimes clearly had intended effects on the United States and its citizens.”¹⁰¹ Similarly, flawed foreign research discovered before approval of the NDA would still have had an intended domestic effect – the intent of obtaining FDA approval and selling the tested drug in the United States. Thus, so long as foreign investigators and sponsors conducted their study with the demonstrable intent of supporting an NDA for marketing a drug within the United States, the FDA could legitimately exercise extraterritorial jurisdiction over the research.

The second concern – the unique nature of the domestic “effect” of foreign research conducted without its participants’ informed consent – poses a far more difficult obstacle to the

⁹⁹ See RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 402 cmt. d (1987).

¹⁰⁰ *Id.*

¹⁰¹ U.S. v. Yousef, 927 F.Supp. 673, 682 (S.D.N.Y. 1996).

FDA's extraterritorial jurisdiction. Although foreign drug research presents a number of potential regulatory challenges for the FDA,¹⁰² a clinical study in which foreign investigators failed to obtain their subjects' consent would have no material "effect" within the United States. As one scholar explained, "The health of U.S. consumers will not be affected by a lack of consent by a patient in a developing-country hospital. The U.S. marketplace suffers no harm if the potential side effects of a drug are not explained to research subjects."¹⁰³ Instead, the domestic "effect" of such research could only be characterized as a moral one – Americans would be consuming drugs proven safe and effective, and approved for U.S. marketing, on the basis of clinical studies conducted contrary to the nation's fundamental ethical values.

Yet the effect basis for extraterritorial jurisdiction did not originate, nor has it come to be accepted, as applicable to the kind of moral complicity inflicted through the unethical production of goods abroad for domestic consumption. Instead, the effect basis refers to tangible physical or economic effects. In one of the earliest cases to employ the effect principle,¹⁰⁴ the Permanent Court of International Justice held that Turkey had jurisdiction to charge a French sailor with manslaughter after he negligently collided his boat with a Turkish ship.¹⁰⁵ Under international law, each vessel was considered assimilated to the territory of the country whose flag it flew.¹⁰⁶ Yet the court held that, although the offense had "its origin on board the Lotus [the French

¹⁰² See *supra* note 12.

¹⁰³ Dubois, *supra* note 2, at 194.

¹⁰⁴ See John Eisinger, *Script Kiddies Beware: The Long Arm of U.S. Jurisdiction to Prescribe*, 59 WASH. & LEE L. REV. 1507, 1515 (2002).

¹⁰⁵ S.S. Lotus (Fr. v. Turk.), 1927 P.C.I.J. (ser. A) No. 9 (Sept. 1927).

¹⁰⁶ *Id.* at 25.

ship],” Turkish jurisdiction was legitimately implicated because “its effects made themselves felt on board the Boz-Kourt [the Turkish ship].”¹⁰⁷ It explained, in a widely adopted holding,¹⁰⁸ that “offences, the authors of which at the moment of commission are in the territory of another State, are nevertheless to be regarded as having been committed in the national territory, if one of the constituent elements of the offence, and more especially its effects, have taken place there.”¹⁰⁹ The domestic effect of regulated foreign conduct need not constitute direct violence, but also could comprise more general harm. For instance, the Ninth Circuit has repeatedly approved the extraterritorial application of U.S. statutes prohibiting the importation and distribution of controlled substances due to the detrimental effects such materials produce in the United States.¹¹⁰ Moreover, states may regulate foreign activities due to their domestic economic impact. Although a source of controversy,¹¹¹ “[m]ost other states of Western Europe...as well as Canada and Japan...have accepted the effects doctrine as applied to economic effects.”¹¹² As a

¹⁰⁷ *Id.* at 30.

¹⁰⁸ See Gary B. Born, *A Reappraisal of the Extraterritorial Reach of U.S. Law*, 24 LAW & POL’Y INT’L BUS. 1, 25 (1992).

¹⁰⁹ S.S. Lotus (Fr. v. Turk.), 1927 P.C.I.J. (ser. A) No. 9, at 23 (Sept. 1927).

¹¹⁰ U.S. v. Vasquez-Velasco, 15 F.3d 833, 841 (9th Cir. 1994) (citing Chua Han Mow v. United States, 730 F.2d 1308, 1312 (9th Cir. 1984); U. S. v. King, 552 F.2d 833, 851 (9th Cir. 1976)).

¹¹¹ See RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 402 reporters’ n. 2 (1987).

¹¹² *Id.* § 402 reporters’ n. 3.

result, “substantial litigation has arisen under the [effect basis] in the fields of antitrust, securities, and trademark.”¹¹³

Yet even under these broader readings of the effect basis for extraterritorial jurisdiction, the foreign conduct has always caused or enabled physical or economic harm within the regulating state’s territory – in contrast to the “moral” injury inflicted by the domestic marketing of drugs approved via unethical research. In an analysis of whether the regulation of foreign clinical studies would satisfy the United States’ domestic law version of the effect basis,¹¹⁴ one scholar noted simply, “There is no effects test basis for regulating the safety of human subjects.”¹¹⁵ International law likely compels the same conclusion. The material effect of experimentation without informed consent manifests only in the territory where the research occurs. The marketing of immorally produced goods in the United States creates no tangible effect that international law could recognize as validly implicating FDA jurisdiction over foreign research. Commentators have speculated that because the Restatement addresses extraterritorial antitrust and securities cases in separate provisions, “the general area of effects jurisdiction now stands free,” which could “substantially relax[] limitations on a state’s permissible exercise of effects jurisdiction.”¹¹⁶ Nevertheless, at best, an assertion that unethical foreign research produces a cognizable effect within United States territory by enabling the domestic sale of drugs tested in violation of the country’s moral values would be a novel take on international law.

¹¹³ Wade Estey, *The Five Bases of Extraterritorial Jurisdiction and the Failure of the Presumption Against Extraterritoriality*, 21 HASTINGS INT’L & COMP. L. REV. 177, 186 (1997).

¹¹⁴ See *United States v. Aluminum Co. of America*, 148 F.2d 416, 443 (2d Cir. 1945).

¹¹⁵ Dubois, *supra* note 2, at 194.

¹¹⁶ Hixson, *supra* note 48, at 147.

Especially considering the controversy that accompanied the expansion of the effect basis to cover economic impacts, the notion of a “moral effect” would be unlikely to survive the rigorous “unreasonableness” limitation discussed below.

Finally, even if unethically conducted foreign research had a recognized moral effect within the United States, this effect might not be sufficiently “substantial” to justify FDA jurisdiction. The requirement that foreign conduct have a “substantial” effect within the regulating state’s territory¹¹⁷ checks a state’s ability to interpret the effect basis for extraterritorial jurisdiction too broadly.¹¹⁸ For instance, the French penal code adopts an “Effects Principle” with regard to extraterritorial jurisdiction.¹¹⁹ However, the United States District Court for the Southern District of New York found that French professional secrecy laws did not apply to a civil discovery request for the audit documents of an American company, initially produced at the request of French accounting firms, due to the trivial impact of such a disclosure on the French firms.¹²⁰ It is difficult, if not impossible, to quantify whether the moral effect of unethical foreign research submitted to market drugs in the United States would be sufficiently “substantial” to invoke FDA jurisdiction. Nevertheless, the non-material nature of the effect would appear fairly weak alongside the real world economic and political concerns urging against extraterritorial regulation. Thus, even if one accepted that unethical foreign research

¹¹⁷ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 402(1)(c) (1987).

¹¹⁸ Hixson, *supra* note 48, at 138.

¹¹⁹ *See In re Vivendi Universal, S.A. Securities Litigation*, 618 F.Supp.2d 335, 341 (S.D.N.Y. 2009).

¹²⁰ *See id.* at 342.

conducted in support of an NDA had a legitimate effect within the United States, the requirement that this effect be “substantial” would pose another daunting obstacle for the FDA.

B. “Unreasonableness” Limitation

Even if the FDA successfully grounded its extraterritorial application of the informed consent requirement on the nationality, foreign branch, or effect bases, it would still have to demonstrate that the exercise of this jurisdiction would not be “unreasonable.”¹²¹ In international law, this additional limitation serves as a “legitimizing principle,”¹²² since it qualifies extraterritorial jurisdiction through a mandate that “states must have a legitimate purpose for regulating acts that transcend their boundaries, and [that] they must exercise their powers proportionately.”¹²³ A “mere factual connection” between foreign drug testing and the United States established through the nationality, foreign branch, or effect bases is not enough. The FDA must legitimate its prescriptive authority by demonstrating that the exercise of its power to impose the informed consent requirement abroad would not be unreasonable.¹²⁴

¹²¹ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES §§ 403(1), 414(1) (1987).

¹²² Eleanor M. Fox, *Modernization of Effects Jurisdiction: From Hands-Off to Hands-Linked*, 42 N.Y.U. J. INT’L L. & POL. 159, 163 (2009).

¹²³ *Id.*

¹²⁴ Harold G. Maier, *Extraterritorial Jurisdiction at a Crossroads: An Intersection Between Public and Private International Law*, 76 AM. J. INT’L L. 280, 300 (1982). *See also* RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 403 cmt. a (1987)

Even interpreted in favor of the FDA’s extraterritorial jurisdiction, the majority of the factors that comprise the unreasonableness limitation weigh heavily against regulation of foreign research. The FDA might be able to satisfy the first three factors. The first factor, the link of the activity to the territory of the regulating state, examines the extent to which the activity takes place within the regulating state’s territory or has a “substantial, direct, and foreseeable effect” within its territory.¹²⁵ Although foreign clinical trials by definition do not occur in the United States, a lack of informed consent in foreign research, as already stated, could conceivably produce an abstract, moral effect within American borders. The second factor scrutinizes the connections, such as nationality, residence, or economic activity, between the regulating state and the person responsible for the regulated activity or those whom the regulation is designed to protect.¹²⁶ American investigators or American corporate sponsors who conduct overseas research would fulfill the first part of this factor. However, extraterritorial regulation of foreign drug testing would be principally designed to protect non-U.S. national test subjects, and would not satisfy the second part of this analysis. Under the third factor, states must consider the importance of regulation to the regulating state, the extent to which other states regulate such activities, and the degree to which the desirability of such regulation is generally accepted.¹²⁷ The FDA might regard extraterritorial regulation of human experimentation as an important moral imperative, especially considering the lack of such regulation in developing countries. The international codes on human experimentation reflect the general desirability of informed consent requirements.

¹²⁵ *Id.* § 403(2)(a).

¹²⁶ *Id.* § 403(2)(b).

¹²⁷ *Id.* § 403(2)(c).

However, the remaining five factors would pose an insurmountable barrier of “unreasonableness” for the FDA’s extraterritorial jurisdiction over foreign drug testing. The fourth factor examines the existence of justified expectations that might be protected or hurt by the regulation.¹²⁸ Considering the long history of strictly national regulation of human drug testing, the lack of international treaties on the issue, and the fact that drug companies conduct their tests overseas precisely to avoid the FDA’s stringent domestic testing regulations, it seems that pharmaceutical corporations and scientific investigators have justified expectations that they would be free to conduct their studies abroad without the FDA’s extraterritorial interference. Despite its moral desirability, extraterritorial regulation would also fail the fifth consideration, the importance of the regulation to the international political, legal, or economic system,¹²⁹ since testing without informed consent does not pose a global threat. The sixth factor, the extent to which the regulation is consistent with the traditions of the international system,¹³⁰ would similarly weigh against FDA authority, as there is no precedent in international law for the extraterritorial regulation of scientific research. The final two suggested factors would pose the most difficult obstacles. The seventh examines the extent to which another state may have an interest in regulating the activity.¹³¹ Public health is a traditional concern of the sovereign state,¹³² and foreign nations thus have a powerful interest in regulating the human clinical

¹²⁸ *Id.* § 403(2)(d).

¹²⁹ *Id.* § 403(2)(e).

¹³⁰ *Id.* § 403(2)(f).

¹³¹ *Id.* § 403(2)(g).

¹³² See Lawrence O. Gostin, *World Health Law: Toward A New Conception of Global Health Governance for the 21st Century*, 5 *YALE J. HEALTH POL’Y, L. & ETHICS* 413, 417 (2005).

research that occurs within their borders. By the same logic, the eighth factor, the likelihood of conflict with regulation by another state,¹³³ suggests that FDA jurisdiction over drug testing abroad would unduly interfere with foreign states' own regulations.

The Second Circuit previously reached a similar conclusion when it held that American firearm regulations could not apply to foreign weapon manufacturers, “[i]n light of the substantial interests that other countries have in regulating the manufacture of firearms within their own borders.”¹³⁴ Given the direct danger that a foreign-made firearm might pose to the United States, as opposed to the more abstract concern over unethical foreign research, it is extremely unlikely that extraterritorial regulation of drug testing abroad could be considered acceptable under international law. The additional weight applied against the extraterritorial application of criminal liability in situations with substantial foreign elements,¹³⁵ as is the case with foreign clinical research, creates a final obstacle that the FDA could not overcome. Even if legitimately premised on a nationality, foreign branch, or effect basis, the extraterritorial application of the FDA’s informed consent requirements to human subject research abroad would likely be considered unreasonable, and thus prohibited under international law, due to the unprecedented nature of such regulation and the substantial interests foreign states have in governing their own public health concerns.

¹³³ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 403(2)(h) (1987).

¹³⁴ U.S. v. Javino, 960 F.2d 1137, 1143 (2d Cir. 1992).

¹³⁵ RESTATEMENT (THIRD) OF THE FOREIGN RELATIONS LAW OF THE UNITED STATES § 403 cmt. f (1987).

C. Universal Jurisdiction

Although the FDA would lack the authority to apply its informed consent requirement abroad under the traditional bases and limitations on prescriptive jurisdiction, it may be able to bring criminal prosecutions against foreign investigators and sponsors, regardless of whether they intend to submit an NDA, through the principle of “universal jurisdiction.”¹³⁶ In order to do so, human experimentation without the participants’ informed consent would have to constitute a “universal offense,” which would be “subject to universal jurisdiction as a matter of customary international law.”¹³⁷ The Second Circuit recently addressed this very issue in a claim brought under the Alien Tort Statute (ATS).¹³⁸ The ATS grants the district courts subject matter jurisdiction over torts brought by aliens for violations of the “law of nations”¹³⁹ – a kind of universal civil jurisdiction¹⁴⁰ that allows federal courts to hear claims for violations of “well-established, universally recognized” norms of international law.¹⁴¹ In *Abdullahi v. Pfizer, Inc.*,¹⁴² the Second Circuit heard an ATS claim brought by a group of Nigerian children and their guardians against the American pharmaceutical company Pfizer, alleging that the company had conducted clinical studies of the antibiotic drug Trovan on children in Nigeria without disclosing

¹³⁶ *Id.* § 404.

¹³⁷ *Id.* § 404 cmt. a.

¹³⁸ 28 U.S.C. § 1350 (2008).

¹³⁹ *Id.*

¹⁴⁰ See Donovan & Roberts, *supra* note 49, at 146.

¹⁴¹ *Filartiga v. Pena-Irala*, 630 F.2d 876, 888 (2d Cir. 1980).

¹⁴² 562 F.3d 163 (2d Cir. 2009).

the experimental nature of the research or the risks involved.¹⁴³ Eleven children allegedly died as a result of the study, and many more were injured.¹⁴⁴ The Second Circuit found that the ATS granted it jurisdiction over the Nigerian plaintiffs' claim, as medical experimentation without patients' informed consent constituted a universal offense.¹⁴⁵ The court conducted a thorough review of the history of the informed consent standard in international law, beginning with the prosecution of Nazi doctors at Nuremberg who conducted medical experiments without their subjects' consent, moving through various international treaties that address human subject research such as the Fourth Geneva Convention and the International Covenant on Civil and Political Rights, and finally examining legislation in the United States and Europe that enforces the informed consent requirement.¹⁴⁶ It concluded, "the norm prohibiting nonconsensual medical experimentation on human subjects has become firmly embedded and has secured universal acceptance in the community of nations."¹⁴⁷

According to the Second Circuit's reasoning and historical analysis, nonconsensual human experimentation constitutes a sufficiently fundamental violation of international norms that the FDA could bring criminal prosecutions under universal jurisdiction against any investigator or sponsor who failed to obtain their subjects' informed consent during research abroad. Not only could the FDA bring prosecutions against foreign researchers and sponsors without regard for the territorial or nationality bases for jurisdiction, but also the unlimited nature

¹⁴³ *Id.* at 169.

¹⁴⁴ *Id.*

¹⁴⁵ *See id.* at 177, 187.

¹⁴⁶ *See id.* at 177 – 84.

¹⁴⁷ *Id.* at 183 – 84.

of universal jurisdiction would permit the FDA to criminally prosecute investigators and sponsors who had no intent of even submitting an NDA to market their drugs in the United States. The only constraint on the FDA's authority to prosecute these researchers under universal jurisdiction would be the severity of their violations. The Second Circuit emphasized that the Nigerian plaintiffs had alleged a "complete failure" on the part of the investigators to inform their subjects of the existence of the experiments.¹⁴⁸ The court noted, "we do not suggest that [the international prohibition on nonconsensual medical experimentation] would extend to instances of routine or isolated failures by medical professionals to obtain informed consent, such as those arising from simple negligence."¹⁴⁹ Thus, the FDA could not invoke universal jurisdiction for violations of its more stringent, domestic informed consent requirements, since the international norm that the Second Circuit identified does not demand such a strict standard. Instead, the FDA would have to rely on its lower GCP standard, as this more basic mandate that investigators simply obtain their subjects' consent and inform them of the study¹⁵⁰ coincides with the fundamental norm identified by the Second Circuit. Nevertheless, if one accepts the Second Circuit's declaration that human testing without the subjects' consent constitutes a crime against humanity, then the FDA could prosecute foreign researchers and sponsors who violated this fundamental requirement of international law through an assertion of universal jurisdiction.

V. Conclusion

The globalization of the pharmaceutical industry has increasingly incentivized drug companies to move their clinical research abroad. Particularly in the developing world, this

¹⁴⁸ *Id.* at 184.

¹⁴⁹ *Id.* at 185.

¹⁵⁰ *See supra* note 88.

change has made ethics oversight and human subject protection more difficult, and has resulted in disturbing reports of investigators conducting human experimentation without their participants' informed consent. Commentators have suggested that the FDA could extend its domestic informed consent requirements extraterritorially in order to regulate foreign drug testing. The international legal limits on states' prescriptive jurisdiction would prohibit such an exercise of FDA regulatory authority if it sought to enforce its stringent domestic informed consent requirements abroad. However, the FDA could invoke the principle of universal jurisdiction in order to bring extraterritorial criminal prosecutions against researchers and sponsors who utterly failed to meet internationally accepted informed consent standards.

The results of this analysis suggest two conclusions – one positive and one normative. In terms of positive law, the international legal order does not permit states to regulate foreign activities such as clinical research simply because they regard those activities as unethical and feel morally implicated as a result of their economic involvement. Although some commentators have called for states to impose extraterritorial human rights regulations on the multinational corporations headquartered within their territory,¹⁵¹ traditional international limits on prescriptive jurisdiction pose a legal obstacle to such an endeavor. Instead, the international community must unanimously condemn certain acts in order for states to bring extraterritorial criminal prosecutions under the principle of universal jurisdiction. In order to remain consistent with other tenants of international law, activists who seek to charge businesses with human rights responsibilities must begin with universally accepted human rights standards that would allow states more jurisdictional flexibility for their extraterritorial enforcement.

¹⁵¹ See Broecker, *supra* note 36, at 178 – 87.

The international law of jurisdiction may also suggest a normative position on the difficult policy question of whether Western governments should impose their own notions of medical ethics on developing countries. The preceding analysis demonstrated that the FDA may not impose its stringent IND informed consent requirements on research abroad, but could prosecute foreign investigators who failed to fulfill the more basic GCP standard under universal jurisdiction. Similarly, Western countries might consider insisting on some baseline human subject protections for foreign research, such as the Nuremberg Code or the Declaration of Helsinki, but also allow developing countries to implement those protections in accordance with their own unique cultural, political, and economic contexts. This approach would allow Western governments to respect foreign cultures, while also maintaining their fundamental commitment to human rights. Given the tension between the respect for states' sovereign authority and the protection of individual autonomy, FDA officials who seek to enforce the informed consent requirement abroad while staying within the bounds of international law may have to search for another means to ensure this principle of scientific ethics in the developing world.