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Ethics in a Global Biopharmaceutical Environment

Michael J. Malinowski*

I. Introduction

Pharmaceuticals and biologics (biotech products) have integrated into biopharmaceuticals, sharpening the focus on genomics (gene function) and proteomics (protein function) in drug development.¹ Moreover, the forefront of the “genomics revolution” has advanced: scientists now are grappling with the challenge of making medical sense out of the completed map of the human genome.² The means to meet this challenge is bioinformatics — the combination

* Ernest R. and Iris M. Eldred Endowed Professor of Law. The author wishes to express his gratitude to June Carbone, a friend and valued colleague, and organizer of the live symposium from which this article originated, “The Globalization of Pharmaceutical Development: Race, Markets, and Ethics, Santa Clara University School of Law, Mar. 16-17, 2006. The author also would like to thank his LSU Law Center colleagues for their valued thoughts, suggestions and care delivered in a faculty forum when this article was simply a presentation. The comments of Lucy McGough, Jim Bowers, Alberto Zuppi, and Lee Ann Lockridge have been directly incorporated into this article. This article also is part of a presentation made to the DePaul University College of Law and has been enriched by the comments received during that lively exchange.

1. *See generally* Centennial Symposium: *Proceedings of “The Genomics Revolution? Science, Law and Policy,”* 66 LA. L. REV. 1-143 (2005). For a law-policy report on the general state of biotechnology in the U.S., see generally Michael J. Malinowski & Radhika Rao, *Legal Limitations on Genetic Research and the Commercialization of Its Results*, 54 AM. J. COMP. LAW 45-65 (2006).
2. *See generally* JAMES D. WATSON, *DNA: THE SECRET OF LIFE* (Alfred A. Knopf ed., 2003); *THE GENOMIC REVOLUTION: UNVEILING THE UNITY OF LIFE* (Michael Yudell & Robert DeSalle eds., 2002) (concluding, “The knowledge gained [from Human Genome Project] could cure cancer, prevent heart disease, and feed millions. At the same time, its improper use can discriminate, stigmatize, and cheapen life through frivolous enhancement

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of information technology and biotechnology.³ Bioinformatics accelerated the rate of completion of the map of the human genome by multiples during the final phase of the Human Genome Project (HGP)⁴ and, subsequently, capabilities have increased exponentially. These bioinformatics capabilities and the quest to make medical sense out of the human genome are creating a potentially insatiable demand for access to human biological samples and accompanying medical information.⁵ In fact, demand has spilled over the borders of developed economies and is pouring into the world of developing economies.⁶

Part II of this article surveys the forefront of biopharmaceutical research and development (“R&D”) with emphasis on the broadening reach into the global setting to gather human biological samples and accompanying medical information.⁷ Part III presents a case study involving a genetic research

technologies.”); Allen Guttmacher & Francis Collins, *Welcome to the Genomic Era*, 349 NEW ENG. J. MED. 996-98 (2004), available at <http://www.nejm.org>; *Climbing the Helical Staircase: A Survey of Biotechnology*, THE ECONOMIST, Mar. 29, 2003, at 1-24.

3. See generally ESSENTIALS OF GENOMICS AND BIOINFORMATICS (C.W. Sensen ed., 2005). For discussion of HGP, see generally 291 SCIENCE 1145 (Feb. 16, 2001) (issue entitled “The Human Genome”); 409 NATURE 745 (Feb. 15, 2001) (issue dedicated to the release of a draft map of the human genome). Timely information about the genomics revolution may be obtained from the National Human Genome Research Institute (NHGRI), available at <http://www.nhgri.nih.gov>.
4. *Id.*
5. See Paula Yoon, *Risk Prediction for Common Diseases*, 66 LA. L. REV. 33, 40 (2005). See generally *Symposium: Regulation of Biobanks*, 33 J. L. MED. & ETHICS 1-188 (Mark Rothstein & Bartha Knoppers eds., 2005). See also Malinowski & Rao, *supra* note 1, at 57-58. For discussion of the added dimension of ethical considerations associated with population genetics, including the concept of group consent, see generally Henry T. Greely, *Informed Consent and Other Ethical Issues in Human Population Genetics*, 35 ANNUAL REV. GENET. 785-800 (2001).
6. “The globalization of medical research is, in effect, quickly outpacing the development of internationally accepted ethical guidelines for the conduct of research. For many medical researchers working in resource-poor countries, ethical decision-making is like sailing in the days before modern navigation; one is never quite sure where one is, or in what direction one is headed.” Daniel W. Fitzgerald & Angela Wasunna, *Away from Exploitation and Towards Engagement: An Ethical Compass for Medical Researchers Working in Resource-Poor Countries*, 33 J.L. MED. & ETHICS 559, 559 (2005).
7. Although this article focuses primarily on basic research, much of its content also applies to clinical research, and the U.S. has been increasingly exporting human clinical trials to the world’s developing economies for some time. See generally Finnuala Kelleher, *Note: The Pharmaceutical Industry’s Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J. L. & SOC. PROBS. 67 (2004); Ruqaiyah Yearby, *Good Enough to Use for Research, But Not Good Enough to Benefit From the Results of that Research: Are the Clinical HIV Vaccine Trials in Africa Unjust?*, 53 DEPAUL L. REV. 1127 (2004). For discussion of how recruiting subjects is easier, quicker, and cheaper outside of the U.S., see generally William Dubois, *New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT’L L. 161 (2003); Joanne Roman et al., *Note: U.S. Medical Research in the*

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undertaking in China by US interests — Millennium Pharmaceuticals, a Cambridge, MA-based biotech company, and Harvard University.⁸ This case study, though hopefully atypical,⁹ illustrates the extent to which meaningful, reliable protection of human subjects does not exist in the global biopharmaceutical arena. Part IV presents the governing law and policy, which is essentially questionable reliance on pilings of ethical guidelines in the absence of a bedrock of compulsory, enforceable law. Part V introduces a range of proposals to sure up protection of human subjects in contemporary global biopharmaceutical R&D, including a proposal that works within the neoclassical economic theory

Developing World: Ignoring Nuremberg, 11 CORNELL J.L. & PUB. POL'Y 441 (2002); Mary Pat Flaherty, et al., *Testing Tidal Wave Hits Overseas; on Distant Shores, Drug Firms Avoid Delays—and Scrutiny*, WASH. POST, Dec. 18, 2000, at A1; Margaret Wertheim, *Medical Sweatshops: The Third World Is Providing a Cheap Source of Subjects for Research into AIDS and Other Conditions*, GUARDIAN (LONDON), Oct. 5, 2000, at 3. See also *infra* note 81.

8. See *infra* Part III and accompanying text. This case study was one of several human subjects controversies in global biopharmaceutical R&D reported in “The Body Hunters,” a six-part Washington Post series published in December 2000 following an 11-month investigation by a team of journalists, which triggered more investigative journalism and popular press coverage of controversies in global biopharmaceutical R&D, and a 28-page responsive report published by Pfizer, Inc. on its website (<http://www.pfizer.com>). See Joe Stephens, Mary Pat Flaherty, Deborah Nelson, *The Body Hunters*, WASH. POST, Dec. 2000, available at <http://washingtonpost.com/wp-dyn/world/issues/bodyhunters>; Joe Stephens, *Overseas Testing: Drug Firms Avoid U.S. Watchdogs by Using World's Most Desperate*, 24 IRE J. 22 (June 30, 2001); David Warsh, *Where the Germs Are*, BOSTON GLOBE, Jan. 2, 2001, at C1. The controversies included Pfizer's test of an unapproved antibiotic in seriously ill Nigerian children in the midst of a serious meningitis epidemic, use of placebos in AIDS studies in Thailand, and forged consent forms and patient deaths in a heart study done at the Naval Hospital in Buenos Aires. See *id.* For more coverage of such controversies, see also Fitzgerald & Wasunna, *supra* note 6, at 561-565; Flaherty, *Testing Tidal Wave*, *supra* note 7, at A1; Wertheim, *Medical Sweatshops*, *supra* note 7, at 3.
9. The team of reporters responsible for “The Body Hunters,” *supra* note 8, compiled a database of applications to the State Department to conduct federally funded clinical trials at overseas sites. This database is being maintained by the Fogarty International Center at NIH. See Stephens, *Overseas*, *supra* note 8. (For information about the Fogarty International Center, visit its internet site at <http://www.fic.nih.gov/>.) The Fogarty International Center resources provide some transparency in global clinical research. The more comprehensive Bioresearch Monitoring Information System File, however, is limited to domestic trials known to the FDA; reporting is voluntary for overseas trials, and FDA only lists them in the database if researchers/sponsors submit resulting data to support a new drug application. Stephens, *Overseas*, *supra* note 8. For broader documentation of this pattern of exploitation, see Joe Stephens, *Where Profits and Lives Hang in Balance: Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market*, WASH. POST, Dec. 17, 2000, at A1. For discussion of the need to establish a conclusive registry, see generally Jennifer M. Gold & David M. Studdert, *Clinical Trials Registries: A Reform that is Past Due*, 33 J. L. MED. & ETHICS 811 (2005).

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promoted forcefully by the US in the enactment and implementation of the Trade Related Intellectual Property Rights (TRIPS) provisions of the General Agreement on Tariffs and Trade (GATT).¹⁰ The article concludes that the US has the responsibility and capability to realize reliable human subject protections in international biopharmaceutical R&D as a complement to the patent regime baseline established by GATT/TRIPS.

II. The Global Forefront of Biopharmaceutical R&D

A major theme of the Human Genome Project (HGP) was genetic sameness: we are all 99.9 percent the same in terms of the billions of base pairs — the As, Cs, Gs, and Ts that form our DNA¹¹ — that constitute the basic molecular formula for each of us.¹² Perhaps the most important finding of HGP to date is that all human diversity is attributable to just 25,000 or less active genes.¹³ Yet, one need only ride the New York City subway a few stops or people watch in Time Square to witness just how diverse we are, especially for such a young species. So, how do we resolve our genetic sameness with tangible human diversity?

The answer is that genes multitask with dimensions of complexity a universe beyond the appreciation of most at the commencement of HGP.¹⁴ So, ironically, the awesome accomplishment of HGP is extremely humbling. Nevertheless, by opening up a gateway of understanding and vision, HGP has brought human health science to a new beginning:

Reminiscent of Galileo pointing his telescope into the sky and discovering celestial “new lands,” contemporary scientists are using bioinformatics to peer into the human genome. They are beginning to truly comprehend the extent to which the human genome is a universe that encompasses voluminous multitasking and innumerable layers of dynamic intricacy. Consequently, the science community and pharmaceutical and biotechnology

10. See *infra* notes 84-91 and accompanying text.

11. These letters stand for the nucleotides adenine, thymine, cytosine, and guanine. Information about the basics of DNA is available at the internet sites of the National Institutes of Health, <http://www.history.nih.gov/exhibits/genetics/sect1.htm>, and the National Human Genome Research Institute, and see The Human Genome Project, *Timeline: 1953 – DNA Double Helix*, <http://www.genome.gov/Pages/Education/Kit/main.cfm?pageid=31> (last visited Nov. 4, 2006).

12. Prof. Troy Duster, Dinner Presentation, “The Globalization of Pharmaceutical Development: Race, Markets and Ethics” (Mar. 16, 2006) (addressing the “shift from genetic sameness to individuality” pre- and post-HGP) (copy on file with author).

13. J. Michael McGinnis, *Population Health and the Influence of Medical and Scientific Advances*, 66 LA. L. REV. 9, 10 (2005).

14. *Id.* at 10. (Estimates prior to the final phase of HGP generally ranged from 100,000 to 150,000 genes.)

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sectors are more fully appreciating, and realizing, the difficulty of crafting market-scale medical applications from genetic knowledge.¹⁵

In hindsight, HGP was a potential “white elephant” at its commencement, for the enabling technology necessary for its completion was an information technology revolution beyond existing capabilities.¹⁶ Fortunately, information technology accomplishments in the mid and late 1990s made HGP achievable years ahead of schedule.¹⁷ Subsequently, silicon microchip technology has advanced so as to allow researchers to fit the entire human genome on a single piece of silicon held easily in the palm of a human hand.¹⁸ Scientists are utilizing this capacity to make voluminous, timely sample comparisons to translate the map of the human genome into medical meaning.¹⁹ Appreciation of the intricacies of the human genome coupled with bioinformatics capabilities has created ravenous demand for human biological samples and accompanying medical information. As observed by Dr. Paula Yoon at the CDC’s Office of Genomics and Disease Prevention, “[w]e need large-scale, population-based collaborative research because, when you start looking at multiple genes and multiple environmental factors to stratify risks, you need big numbers to find meaningful associations.”²⁰ The result is global demand for samples, biobanking, the organized collection of human biological samples and accompanying medical information, is burgeoning in response.²¹

15. Michael J. Malinowski, *Taking Genomics to the BioBank: Access to Human Biological Samples and Medical Information*, 66 LA. L. REV. 43, 45 (2005).

16. *Id.* at 45.

17. “In 1997, HGP was half-way through its 15-year duration and 90% of the project’s funding had been spent just to sequence accurately 2.68% of the human genome.” Michael J. Malinowski, *Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities, and Lost Opportunities*, 41 JURIMETRICS J. 23, 26 (2000). The author was working for the Massachusetts Biotechnology Council and then in private practice at this time in Boston and, ironically, from an investment competition perspective, information technology was the arch nemesis of biotechnology.

18. Robert Wells, *Intellectual Property/Ownership Issues*, 66 LA. L. REV. 69, 73 (2005).

19. *See generally id.*

20. Yoon, *Risk Prediction*, *supra* note 5, at 40.

21. *See generally Symposium, Biobanks*, *supra* note 5; Malinowski, *BioBank*, *supra* note 15.

III. The Harvard University-Millennium Pharmaceuticals Controversy

In 1996, China passed a law to promote sterilization or, alternatively, life-long birth control for individuals with “genetic disease(s) of a serious nature.”²² Just a month later, Harvard University, through its affiliates, the Harvard School of Public Health and Brigham and Women’s Hospital in Boston, Massachusetts, coupled with Millennium Pharmaceuticals, the Massachusetts Mental Health Center, and the Government of China and Chinese field researchers to launch a genetic research study in Anhui, a rural province in China.²³ This population was especially appealing for genetic research because poverty and geography has kept the people isolated for over 2,000 years.²⁴ This study encompassed a bouquet of health conditions ranging from obesity to schizophrenia.²⁵

In 1999, Gwendolyn Zahner, a psychiatric epidemiologist and former assistant professor at the Harvard School of Public Health, filed a fifteen-page complaint with the US Office for the Protection of Human Research Participants (OHRP) alleging that two occupational epidemiologists at the school had taken advantage of the subjects in this study.²⁶ OHRP launched an investigation in 1999, which lingered into 2002.²⁷ The investigation generated damning findings, foremost of which was that coercion was used to recruit subjects.²⁸ The report addressed nearly a dozen studies overseen by Dr. Ming T. Tsuang.²⁹ The Harvard-Millennium research study had been deemed a “thought works” project,³⁰ and

22. Joe Stephens, *Overseas Testing*, *supra* note 8; John Pomfret & Deborah Nelson, *An Isolated Region’s Genetic Mother Lode; Harvard-Led Study Mined DNA Riches; Some Donors Say Promises Were Broken*, WASH. POST, Dec. 20, 2000, at A1; Alice Dember, *Harvard-Affiliated Gene Studies in China Face Federal Inquiry*, BOSTON GLOBE, Aug. 1, 2000, at A1.
23. See Correspondence from Kristina C. Borrer, Compliance Oversight Coordinator, Division of Compliance Oversight, to Ming T. Tsuang, Head, Harvard Department of Psychiatry, Massachusetts Mental Health Center (Mar. 28, 2002) (copy on file with author). See also; Andrew Lawler, *U.S. Questions Harvard Research in China*, 296 SCIENCE 28, Apr. 5, 2002 (no author identified); Esther Chang, *Fitting a Square Peg Into a Round Hole?: Imposing Informed Consent and Post-Trial Obligations on United States Sponsored Clinical Trials in Developing Countries*, 11 S. CAL. INTERDISC. L.J. 339, 346-47; Pomfret & Nelson, *supra* note 22, at A1; Dember, *Studies in China*, *supra* note 22.
24. Stephens, *Overseas Testing*, *supra* note 8.
25. Dember, *supra* note 22, at A1.
26. *Id.* See also Lawler, *supra* note 23, at 28.
27. See generally Correspondence, *supra* note 23.
28. *Id.* Communication challenges were underscored, including language and cultural barriers. See also Chang, *supra* note 23, at 346-47.
29. Dember, *supra* note 22, at A1.
30. The legacy of thought works projects included penalties for refusal to participate — such as

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Chinese government officials organized local cadres to encourage the needed DNA collection.³¹ At the time of the study, China's free health care system had collapsed,³² and study participants were offered health care, including access to exams, test results, follow-up care, and "health cards" for discounts on future treatment.³³ People literally gave blood and medical information as a quid pro quo for this immediate care and the promise of long-term treatment ensured through coupons redeemable at local clinics.³⁴ Unfortunately, these local clinics never were funded, and the long-term care never was realized.³⁵

When the OHRP findings were revealed, the immediate concern was fear of genetic discrimination given China's policy on reproduction and genetic diseases juxtaposed with the government's role in the study and its dismal human rights legacy. An additional concern was the fact that much of the actual work in the study was carried out by citizens of China while the principal investigators resided thousands of miles away in Cambridge, Massachusetts.³⁶ The defense raised by the researchers was that the samples were encrypted, and the code to break the encryption was beyond the reach of China's government officials.³⁷ Nevertheless, concerns were heightened by the discovery that many of the subjects' written consent forms had been backdated; the dates on the forms were written in identical third-party handwriting.³⁸ Moreover, Brigham and Women's Hospital and the Massachusetts Mental Health Center had delegated oversight of human subjects protection to an oversight committee in China.³⁹ Brigham & Women's admitted

negative tax consequences, land divisions, and other pressures. Chang, *supra* note 23, at 346-47. Positive incentives also had been utilized — for example, in another one of Dr. Ming T. Tsuang's studies, to encourage participation in a study on reproduction that encompassed 1000 women working at a petrochemical plant in Beijing. *Id.* According to Dr. Ock Joo Kim, a Professor at the College of Medicine, Seoul National University, and a fellow panelist at this live symposium, this reproduction study also was headed by Dr. Ming. T. Tsuang. Presentation by Dr. Ock Joo Kim, Panel III: Ethics in a Global Pharmaceutical Environment, 5th Annual Biotechnology Conference — The Globalization of Pharmaceutical Development: Race, Markets and Ethics, Mar. 17, 2006.

31. Dember, *supra* note 22, at A1; Lawler, *supra* note 23, at 28.

32. Chang, *supra* note 23, at 346-347. See also Dember, *supra* note 22, at A1; Lawler, *supra* note 23, at 28.

33. Chang, *supra* note 23, at 346-47.

34. *Id.*

35. *Id.*

36. Dember, *Studies in China*, *supra* note 22, at A1; *U.S. Questions*, *supra* note 23, at 28.

37. Dember, *supra* note 22, at A1.

38. Lawler, *supra* note 23, at 28.

39. Dember, *supra* note 22, at A1.

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that they had been derelict in this delegation of oversight.⁴⁰

Harvard responded to the inquiry and to OHRP's findings by announcing a commitment to increase the monitoring of its staff and by issuing a formal reprimand of the two key researchers involved.⁴¹ To the disappointment of many, OHRP accepted this response as a resolution of the matter.⁴²

IV. Existing Law-Policy to Protect Human Subjects in Global R&D

What conditions allowed the Harvard-Millennium controversy to occur? The summary answer is that there is no compulsory, enforceable international law to protect human subjects.⁴³ Rather, there are ethical guidelines, the most influential of which are (1) the Nuremberg Code,⁴⁴ (2) the Declaration of Helsinki,⁴⁵ and (3) Guidelines for Medical Ethics in Biomedical Research issued jointly by the World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS).⁴⁶ The Nuremberg Code, issued in 1947 in response to the gruesome atrocities deemed "Nazi medicine,"⁴⁷ consists of ten principles that are

40. *Id.* See also Lawler, *supra* note 23, at 28.

41. Lawler, *supra* note 23, at 28. (The primary researcher, Dr. Tsuang, now is a member of the faculty of the University of California at San Diego, and his research continues. UCSD News, May 21, 2003, available at http://health.ucsd.edu/news/2003/05_21_Tsuang.html.)

42. Lawler, *supra* note 23, at 28.

43. See generally Yearby, *supra* note 7; Benjamin Mason Meier, *International Criminal Prosecution of Physicians: A Critique of Professors Annas and Grodin's Proposed International Medical Tribunal*, 30 AM. J.L. & MED. 419 (2004); Roman, *supra* note 7.

44. TRIALS OF WAR CRIMINALS BEFORE THE NUREMBURG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, 181-83 (U.S. Gov't Printing Office 1946-1949). See generally Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, in THE NAZI DOCTORS AND THE NUREMBURG CODE 183 (George Annas & Michael A. Grodin eds., 1992).

45. WORLD MED. ASS'N, WORLD MEDICAL ASSOCIATION THE DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS PRINCIPLE (adopted 1964, revised 2002), available at <http://www.wma.net/e/policy/b3.htm>.

46. COUNCIL FOR INT'L ORGANIZATIONS OF MEDICAL SCIENCES, INT'L ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Geneva: CIOMS, 1993), available at (3d ed. 2002), available at http://www.cioms.ch/frame_guidelines_nov_2002.htm (last visited Nov. 26, 2005). These guidelines were introduced with the hope of introducing pragmatic rules in lieu of the amorphous informed consent standards of the Code. See Roman, *supra* note 7.

47. JOHN J. MICHALCZYK, NAZI MEDICINE: IN THE SHADOW OF THE REICH (First Run Features 1997) (discussing the origins of eugenics movements in Germany and the Nazi doctors' experimentation on prisoners in the concentration camps). See generally INT'L AUSCHWITZ COMMITTEE, NAZI MEDICINE: DOCTORS, VICTIMS AND MEDICINE IN AUSCHWITZ (1986) (documenting the criminal experiments undertaken by the Nazi doctors); ROBERT JAY LIFTON, THE NAZI DOCTORS: MEDICAL KILLING AND THE PSYCHOLOGY OF GENOCIDE (1986) (examining the Nazi "biomedical vision" as evidenced by the doctors' cruel medical

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centered on the doctrine of informed consent.⁴⁸ The Code was never adopted by the United Nations as an instrument of international law.⁴⁹ Moreover, the reach of international criminal law extends only as far as the codification of victim rights by nations and international tribunals, and “[i]nternational law remains ambiguous in its prohibitions of physician participation in corporal and capital punishment or physician discrimination in the provision of health services.”⁵⁰ Similarly, the applicability of international tort liability in this context is a hazy shadow at best and, as a policing mechanism, tort liability places a tremendous burden on populations already extraordinarily overwhelmed with challenges.⁵¹

The Declaration of Helsinki, issued in 1964 and revised through 2000, is the medical profession’s effort to apply the Nuremberg Code to the practice of medicine and to generate some broad-reaching practical guidelines.⁵² The

experiments in the concentration camps); THE NAZI DOCTORS AND THE NUREMBERG CODE (George J. Annas & Michael A Grodin eds., 1992) (discussing the practices of the Nazi doctors that led to the Nuremberg trial and the implications of these practices on present day medical research and experimentation).

48. TRIALS OF WAR CRIMINALS, *supra* note 44.

49. See Kevin M. King, Note, *A Proposal for the Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT’L L. 163, 169 (1998).

50. Benjamin Mason Meier, *International Criminal Prosecution of Physicians: A Critique of Professors Annas and Grodin’s Proposed International Medical Tribunal*, 30 AM. J.L. & MED. 419, 421 (2004). As explained by one commentator, international criminal law is just beginning to crystallize in a potentially relevant context: “On July 17, 1998, representatives of more than 160 nations met in Rome, Italy and adopted an international treaty to govern a permanent international criminal court, the Rome Statute of the International Criminal Court (“Rome Statute”). The ICC, created by the Rome Statute, has subject matter jurisdiction over the so-called ‘core crimes’ of genocide, crimes against humanity, war crimes, and, once defined, aggression. Within this jurisdiction will fall crimes committed by physicians and non-physicians alike. This permanent criminal court, built upon the ad hoc tribunals of Nuremberg and beyond, came into effect in 2002 and has just begun to adjudicate its first case.” *Id.* at 420 (internal citations omitted). (Professors Annas and Grodin have proposed, since at least 1992, that an International Medical Tribunal be established to develop international criminal law in the field of medicine. See generally George J. Annas & Michael A Grodin, *Medical Ethics and Human Rights: Legacies of Nuremberg*, 3 HOFSTRA L. & POL’Y SYMP. 111, 119 (1999).)

51. The Bush Administration has argued vigorously that the vehicle for such liability, the Alien Tort Claims Act, interferes with the executive prerogative in foreign affairs, and that from a legal standpoint the statute grants federal courts jurisdiction but does not grant plaintiffs a private cause of action. See Lorelle Londis, *The Corporate Face of the Alien Torts Claims Act: How an Old Statute Mandates a New Understanding of Global Interdependence*, 57 ME. L. REV. 141, 143 (2005).

52. Helsinki II is widely received as the baseline set of principles for human subjects research. See Rebecca A. Finkenbinder, *New Recommendations on International Human Research: Can Minimum Standards Prevent the Exploitation of Vulnerable Human Subjects in Developing Countries*, 21 PENN. ST. INT’L L. REV. 363, 373 (2003).

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Declaration is the work product of the World Medical Association (WMA), which came into existence as the medical profession's response to Nazi Medicine and the threat of extensive regulation from outside of the profession.⁵³ The Declaration focuses on the duties and responsibilities of physicians engaging in research on human subjects, and it assumes a virtual common denominator: adherence to "generally accepted scientific principles."⁵⁴ An obvious question is "whose generally accepted scientific principles?" Also, the US has not signed onto the 2000 Declaration revisions, and these revisions are being challenged by the US Food and Drug Administration (FDA).⁵⁵ The FDA does not want standards that require researchers to give back to study participants or that require making study medicines available to all participants, including those outside of the US borders, once their effectiveness and safety are established beyond the placebo effect.⁵⁶

Perhaps the most meaningful guidance is the Guidelines for Medical Ethics in Biomedical Research issued in 1982 jointly by the WHO and the Council for International Organizations of Medical Sciences (CIOMS).⁵⁷ The goal in issuing the Guidelines was to introduce rules more specific than the Code's amorphous informed consent provisions.⁵⁸ However, the Guidelines are not legal text in content. Rather, they articulate three principles — respect for persons, beneficence, and justice — captured earlier in the US's Belmont Report, which emphasizes informed consent and the need for research to be responsive to the health needs and priorities of the community in which it is carried out.⁵⁹

53. Meier, *supra* note 50, at 423. ("In the aftermath of the Nazi horrors, physicians from thirty-two national medical associations met in London in 1946 to form the first international medical organization, the World Medical Association ("WMA"). The WMA has since burgeoned to become the world's preeminent physician organization.")
54. Declaration of Helsinki Principle I.1, II.2, II.3, in Office for Human Research Protections, Department of Health and Human Services, Institutional Review Boards (IRB) Guidebooks, App. 6 (1993).
55. John Barton, Keynote Address at the Santa Clara Univ. School of Law Annual Biotechnology Conference: The Globalization of Pharmaceutical Development: Race, Markets and Ethics (Mar. 17, 2006).
56. *Id.*
57. CIOMS was organized in 1949 by WHO and UNESCO. *See generally* Markus Schott, *Medical Research on Humans: Regulation in Switzerland, the European Union, and the United States*, 60 FOOD & DRUG L.J. 45, 50 (2005). (More information about CIOMS is available at <http://www.cioms.ch/>.)
58. *See* Schott, *supra* note 57, at 64.
59. *See* The Belmont Report, 44 Fed. Reg. 23192, 23192-93 (Apr. 18, 1979). The Belmont Report was issued in 1977 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research which was established in 1974 by the National Research Act. *See* Roman, *supra* note 7, at 456. The Guidelines incorporate the three Belmont Report principles: respect for persons, beneficence, and justice. *See* Yearby, *supra* note 7, at 1128.

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The net effect of international law is that the protection of human subjects in global biopharmaceutical R &D depends upon national law — the law of the jurisdiction in which the research is conducted⁶⁰ and the law of the homeland of those conducting the research study.⁶¹ Commentators have recognized the following regarding the law of the jurisdiction in which the research is conducted:

With biomedical research becoming increasingly global, research volunteers in resource-poor countries may be at a heightened risk of exploitation. As the number of new drugs and products entering clinical trials grows, so does the need to find clinical sites capable of conducting research quickly and inexpensively. Therefore, research sponsors may be attracted to resource-poor countries where a large population of people with high disease burden may serve as research volunteers, where access to patients may be easier due to fewer competing clinical trials and lax regulation, where patients may not have access to medications and hence may be drug naive, and where lower personnel costs may make the research less expensive. Potential research volunteers in resource-poor countries, who are poor, illiterate, and unfamiliar with their rights as research volunteers may thus be vulnerable to exploitation by international medical researchers and research sponsors.⁶²

In the context of the Harvard-Millennium controversy, the government of China with its preexisting eugenics policy, legacy of human rights violations, and aggressive promotion of genetic research within its borders, was not a reliable source of meaningful human subjects protection.⁶³ Thus, the OHRP investigation focused on “the extent to which the Harvard-Millennium controversy violated national US law.”

The primary bodies of US law created to protect human subjects are the Common Rule⁶⁴ and Food and Drug Administration regulations.⁶⁵ The Common

60. See Dubois, *supra* note 7, at 190. See generally Dubois, *New Drug Research*, *supra* note 7. It is commonplace for countries to relax US standards, making trials abroad usually quicker and cheaper.

61. Lisa R. Pitler, *Ethics of AIDS Clinical Trials in Developing Countries: A Review*, 57 *FOOD & DRUG L.J.* 133, 152 (2002). See generally Roman, *supra* note 7; Barbara A. Noah, *Racial Disparities in the Delivery of Health Care*, 35 *SAN DIEGO L. REV.* 135 (1998). (National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, available at <http://www.georgetown.edu/research/nrcbl/nbac/clinical/execsum.html>).

62. Fitzgerald & Wasunna, *supra* note 6, at 559-60 (2005) (footnotes omitted).

63. Dember, *supra* note 23, at A1.

64. 45 C.F.R. Part 46 (2005).

65. The relevant FDA regulations are 21 C.F.R. Part 56 (2006) (IRB rules); 21 C.F.R. Part 50 (2006) (informed consent rules). For guidance on both the Common Rule and FDA regulations, see generally CARL H. COLEMAN, ET AL., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* (2005). Excellent, pragmatic “decision trees” and other guidance for applying U.S. regulations to protect human subjects are available at NIH’s internet site, www.nih.gov.

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Rule applies to all federally funded research and often is stretched to cover all research undertaken by institutions that receive federal funding — meaning institutions such as Harvard University, which routinely ranks among the top recipients of National Institutes of Health (NIH) funding.⁶⁶ To comply, institutions must establish institutional review boards (IRBs), policies, and implementation procedures to ensure that requisite oversight and prescribed requirements are realized.⁶⁷ Moreover, institutions must report the same to OHRP to obtain an Assurance of Compliance, a prerequisite for receiving federal funding, and provide periodic updates.⁶⁸

The FDA, gatekeeper to the US market for food and medicinal products, allows and oversees limited access to the population entrusted to its watch to enable research with the purpose of establishing safety and efficacy for potentially marketable products.⁶⁹ Independently of the Common Rule but in a parallel fashion, the FDA makes compliance with its human subjects regulations a condition on the research it permits to take place via an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE).⁷⁰ Moreover, confirmation of compliance is a condition for acceptance of data in support of applications for market access.⁷¹ The FDA also conditions acceptance of data

66. Harvard ranked 12th in 2005 NIH grants to domestic institutions of higher education. Available at <http://grants2.nih.gov/grants/award/trends/dheallinst05.htm>.

67. COLEMAN, *supra* note 65, at 169-202.

68. 45 C.F.R. Part 46, §103(a). Registration must be updated every thirty-six months. *Id.* See COLEMAN, *supra* note 65, at 169-202.

69. For information about the FDA and its regulations, visit www.fda.gov.

70. COLEMAN, *supra* note 65, at 142-60.

71. The Common Rule requires the sixteen participating agencies to confirm that institutions conducting the research they fund, including institutions outside of the US, comply with the human subject protections it prescribes or one of the following: INT'L CONFERENCE ON HARMONISATION, GUIDELINES FOR GOOD CLINICAL PRACTICE E6(R1), CONSOLIDATED GUIDELINE (1996), available at <http://www.ich.org/LOB/media/MEDIA482.pdf>; COUNCIL FOR INT'L ORGANIZATIONS OF MEDICAL SCIENCES, INT'L ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1993), available at <http://www.codex.uu.se/texts/international.html>. Updated version available at http://www.cioms.ch/frame_guidelines_nov_2002.htm; MEDICAL RESEARCH COUNCIL OF CANADA, TRI-COUNCIL POLICY STATEMENT ON ETHICAL CONDUCT OF RESEARCH INVOLVING HUMANS (2005), available at <http://www.pre.ethics.gc.ca/english/pdf/TCPSintroductione.pdf>; INDIAN COUNCIL OF MEDICAL RESEARCH, ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN SUBJECTS (2000), available at <http://www.icmr.nic.in/ethical.pdf>; or other "internationally recognized standards." See Department of Health and Human Services, 45 C.F.R. § 46 (2005). Sponsors of market applications for new products are technically required to identify all clinical investigators who conducted clinical trials of the product (including employees and non-employees of the company) and to submit a certification that discloses any of the following financial arrangements: compensation affected by the outcome of the

gathered outside the US on compliance with US regulations or the International Conference on Harmonisation Guidelines for Good Clinical Practice.⁷² However, in reality, the US tends to defer heavily to the laws and regulations of the country in which the research is conducted.⁷³ Moreover, the “U.S. has no clear enforcement mechanisms for its research guidelines”⁷⁴ and the “FDA currently lacks any way to track the total number of experiments conducted abroad, nor can it determine the number of new drugs that are approved on the basis of foreign clinical research.”⁷⁵

In addition to these standard human subject protections, the Common Rule compels IRBs to police conflicts of interest (CIs), and specific Public Health Services and FDA regulations directly address CIs and require the same.⁷⁶ Accordingly, in addition to IRBs, many federally funded research institutions have committees that focus on conflicts of interest and operate in conjunction with IRBs. Moreover, today, collaboration often is synonymous with meaningful research. The Harvard-Millennium controversy is representative of many contemporary research undertakings in that multiple institutions were involved, including a commercial sponsor removed from US federal funding and related requirements. Also, as illustrated by the Harvard-Millennium case study and substantiated by Brigham & Women’s admission, it is too easy for an institution to remain compliant, technically, with OHRP requirements, but delegate oversight to a collaborator.⁷⁷

study, significant equity interest in the sponsor of the study, proprietary interest in the tested product, and significant payments of other types from the sponsor. 21 C.F.R. § 54.4(a)(3)(i-v)(2006).

72. Int’l Conference on Harmonisation, GUIDELINES FOR GOOD CLINICAL PRACTICE E6(R1), CONSOLIDATED GUIDELINE (1996).
73. See generally Lisa R. Pitler, *Ethics of AIDS Clinical Trials in Developing Countries: A Review*, 57 FOOD & DRUG L.J. 133 (2002). See, e.g., Dubois, *supra* note 7, at 170.
74. Finkenbinder, *supra* note 52, at 387.
75. Dubois, *supra* note 7, at 168.
76. Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, 69 Fed. Reg. 26,393 (May 11, 2004); Food and Drug Administration, 21 C.F.R. § 54.4 (2003); IRB Member Conflicts of Interest, 45 C.F.R. § 46.107(e). See COLEMAN, *supra* note 65, at 207-39. Note, however, that the FDA waives conflicts of interest for members of its advisory committees where interests do not exceed \$100,000. See www.fda.gov/fdac/special/newdrug/advice.html.
77. See generally Roman, *supra* note 7.

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V. A Proposal to Do More

Research may prove a point of entry for countries left out of the genomics revolution, but “it is neither necessary nor desirable to relax our ethical standards in order to achieve this goal.”⁷⁸ As illustrated by the Harvard-Millennium case study and related controversies,⁷⁹ the global reach and existing research needs of biopharmaceutical R&D demand a baseline of compulsory, enforceable international human subjects protection regulations — meaning codification of shared global standards with an effective enforcement mechanism.⁸⁰

One option is to develop such law through the establishment and proceedings of an International Medical Tribunal, as proposed by Professors Annas and Grodin, beginning close to the commencement of HGP.⁸¹ Another is to build upon an already existing mechanism — the International Conferences on Harmonisation (ICHs), which have developed shared scientific standards for clinical data and good clinical practice.⁸² However, ICH is representative of global biopharmaceutical R&D, meaning that the world’s dominant commercial interests comprise half of its sponsors and more than half of its Steering Committee members.⁸³ Those interests are unlikely to voluntarily support the introduction of

78. Harold P. Shapiro & Eric M. Meslin, *Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries*, 345 NEW ENG. J. MED. 139, 141 (2001).

79. See *supra* notes 6-8.

80. See generally Symposium: *Emerging Issues in Population Health: National and Global Perspectives*, 314 J.L. MED. & ETHICS 473 (2003); Roman, *supra* note 7; Benjamin Mason Meier, *Int’l Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT’L L. 513, 514 (2002); Paul Farmer & Nicole Gastineau Campos, *Symposium: Looking Forward in Bioethics, New Malaise: Bioethics and Human Rights in the Global Era*, 32 J.L. MED. & ETHICS 232 (2003). WHO has responded by developing twenty standards to improve reporting on human subject testing of drugs and devices. See Lawrence K. Altman, *Science and Health*, N.Y. TIMES, May 19, 2006, at A10. For more information, visit the site of WHO at <http://www.who.int/enl>.

81. See *supra* note 50 and accompanying text.

82. *Id.* For information about ICH, visit the Official Web Site for ICH, <http://www.ich.org/cache/compo/276-254-1.html>. Six conferences have been held, and the ICH7 Conference was scheduled to take place March 29-30, 2006 in Vienna, Austria, but was cancelled.)

83. Presentation, Barton, *supra* note 55. (Both government and industry have been active participants in the ICHs. The US has been represented by both the FDA and the Pharmaceutical Researchers and Manufacturers of America (PhRMA), Europe has been represented by the European Medicines Evaluation Agency (EMA) and the European Federation of Pharmaceutical Industries Associations (EFPIA), and Japan has been represented by the Ministry of Health, Labor and Welfare and the Japan Pharmaceutical Manufacturers Association (JPMA). In addition, to the representatives of these six sponsors, the Steering Committee includes members of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and observers from Health Canada,

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meaningful additional regulatory requirements and associated liabilities.

A third option is to draw from recent experience establishing a global common denominator in intellectual property rights through the Technology Related Intellectual Property Rights (TRIPS) of the General Agreements of Tariffs and Trade (GATT), which has been implemented in phases since its enactment on January 1, 1995.⁸⁴ Commercial interests, including the biopharmaceutical sectors, drove the GATT/TRIPS efforts with the mantra of establishing a baseline of enforceable IP rights essential to break down market impediments, advance market access, and promote globalization.⁸⁵ GATT/TRIPS is the embodiment of neoliberal economic theory premised on the claim that economic liberalization will promote growth and reduce poverty in countries with developing economies.⁸⁶ To the extent that there is truth to the theory,⁸⁷ GATT/TRIPS should increase the presence of biopharmaceutical R&D in developing economies and should build upon the existing need for a shared, compulsory, and enforceable international standard for the protection of human subjects — a need already realized as illustrated by the Harvard-Millennium controversy and related controversies, as

the World Health Organization, and Swissmedic, Swiss Agency for Therapeutic Products. ICH Official Web Site, *supra* note 79.)

84. Countries deemed “developing” were given until January 2000 to comply, and “least developed countries” were given until 2005. Puleng LenkaBula, *The Social and Ethical Implications of Article 27 of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) on African Communities, Biodiversity and Indigenous Knowledge*, J. THEOLOGY S. AFR., vol. 36, July 1, 2005, WLNR 16456512. For discussion of the provisions of TRIPS, the protections it affords patent holders, and the negotiations leading to its adoption, *see generally* Vishal Gupta, *A Mathematical Approach to Benefit - Detriment Analysis as a Solution to Compulsory Licensing of Pharmaceuticals Under the TRIPS Agreement*, 13 CARDOZO J. INT'L & COMP. L. 631, 636-42 (2005); John Gladstone Mills et al., Patent Law Basics § 19:4.1 (2006) (a general discussion of the World Trade Organizations (WTO) TRIPS agreement and WTO dispute resolutions); Donald P. Harris, *TRIPS Rebound: An Historical Analysis of How the TRIPS Agreement Can Ricochet Back Against the United States.*, 25 NW. J. INT'L L. & BUS. 99, 101 (2004).
85. *See generally* Christopher K. Eppich, *Patenting Dilemma: Drugs for Profit Versus Drugs for Health*, 43 SANTA CLARA L. REV. 289 (2002); Bryan C. Mercurio, *TRIPS, Patents, and Access to Life-Saving Drugs in the Developing World*, 8 MARQ. INTELL. PROP. L. REV. 21 (2004).
86. *See generally* Mohammed Nuruzzaman, *Economic Liberalization and Poverty in the Developing Countries*, 35 J. CONTEMP. ASIA 109, 109 (Mar. 1, 2005); A. Berg & A. Krueger, *Lifting All Boats: Why Openness Helps Curb Poverty*, 39 FIN. & DEV. 16 (2002); Ian Vasquez, *Globalization and the Poor*, 7 INDEP. REV. 197 (2002).
87. For an argument that the theory is flawed based upon empirical data on the impact of economic liberalization on countries with developing economies, *see generally* Nuruzzaman, *supra* note 86.

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well as the recent WHO response.⁸⁸ A reliable international common denominator for the protection of human subjects would be a natural R&D complement to the global IP baseline established by GATT/TRIPS. Moreover, such a standard would be consistent with specific GATT/TRIPS provisions, as well as its spirit and intent to promote globalization. The US was highly influential in establishing the basic patent regime criteria codified in TRIPS, but the US practice of minimizing morality considerations in patent prosecution was trumped by European IP standards that place a morality check on patentability. Specifically, Articles 27.2 and 27.3 of TRIPS allow for IP rights to be overridden “to protect the public order, morality, animal or plant health/life, the environment; may exclude diagnostics, therapeutics and surgical methods of treatment of humans and animals from patentability.”⁸⁹ Moreover, the TRIPS patent regime bends to allow nations to respond to health emergencies. Under Article 31, a WTO member may grant the use of the subject matter of the patent without the consent of the patent holder through compulsory licensing to meet urgent health care needs.⁹⁰ Perhaps, over

88. See *supra* Parts III & IV.

89. These provisions are consistent with Article 53(a) of the European Patent Convention and the European Biotechnology Directive. See Convention on the Grant of European Patents, Oct. 5, 1973, 13 I.L.M. 270, available at <http://www.european-patent-office.org/legal/epc/e/ma1.html>; Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213) 13, available at http://eur-lex.europa.eu/LexUriServ/site/en/oj/1998/l_213/l_21319980730en00130021.pdf.

90. Agreement on Trade Related Aspects of Intellectual Property Rights, art. 31, available at http://www.wto.org/english/tratop_e/trips_e/t_agm3_e.htm#7. Article 31 allows compulsory licensing where a government has attempted to negotiate with a patent holder on reasonable commercial terms for a reasonable period of time, the use of the patented technology must be to predominately supply the domestic market, and pays the patent holder adequate remuneration. However, when faced with a national emergency, other extreme urgency, or for public non-commercial use, this negotiation requirement may be waived. *Id.* See generally World Trade Organization Ministerial Conference, Declaration on the TRIPS Agreement and Public Health, para 5, available at http://www.globaltreatmentaccess.org/content/press_releases/01/111401_WTO_TRIPS_DE_CL.html; Anthony P. Valach, Jr., *TRIPS: Protecting the Rights of Patent Holders and Addressing Public Health Issues in Developing Countries*, 4 CHI.-KENT J. INTELL. PROP. 156, 156 (2005); Daniel J. Gervais, *Intellectual Property, Trade and Development: The State of Play*, 74 FORDHAM L. REV. 505, 508 (2005); Bradley Condon & Tapen Sinha, *Global Diseases, Global Patents and Differential Treatment in WTO law: Criteria for Suspending Patent Obligations in Developing Countries*, 26 NW. J. INT'L L. & BUS. 1 (2005). Although there is no general compulsory licensing provision in the US Patent Act, 28 U.S.C. § 1498 allows the US government to exercise its eminent domain authority by granting compulsory licenses covering patented inventions. Grace K. Avedissian, *Global Implications of a Potential U.S. Policy Shift Toward Compulsory Licensing of Medical Inventions in a New Era of "Super-Terrorism"*, 18 AM. U. INT'L L. REV. 237, 258 (2002). Under section 1498, when an invention protected by a US patent is used or manufactured by

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time, these provisions will become a vehicle to introduce an international human subjects protection standard directly through TRIPS/GATT. Presently, the influence of neoliberal economic theory and commercial interests and the fledging status of extensive GATT/TRIPS implementation suggest otherwise.⁹¹

A fourth option is to realize a compulsory international baseline standard for human subjects research as a common denominator essential to move global biopharmaceutical R&D forward through a freedom to contract, technology transfer model where incentives are introduced for adherence to international norms for human subject protections. This positive incentive approach has proven extremely effective in US regulation of biopharmaceutical R&D from encouraging pediatric testing⁹² to the development of “orphan drugs” for small disease populations.⁹³ One can at least imagine foreign countries following the example set by US universities which have harnessed their research resources to gain access to indigenous populations and their medical histories, the biodiversity in which they live, and their knowledge of the same⁹⁴ through contracts with researchers and

or for the US without obtaining a license from the patent holder, the patent holder’s sole remedy is to bring an action against the US for the recovery of reasonable compensation. 28 U.S.C. § 1498.

91. See generally Nuruzzaman, *supra* note 86.
92. See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408, available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_bills&docid=f:s1789enr.txt.pdf. In its 2001 report to Congress on the program, the FDA declared “the industry’s response has been vigorous and the public health benefits have been extensive.” U.S. FDA, Dep’t of Health & Hum. Servs., *The Pediatric Exclusivity Provision: Jan. 2001 Report to Congress at 8* (2001), available at <http://www.fda.gov/cder/pediatric/reportcong01.pdf>. See generally Michael S. Labson, *Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients*, 6 J. Health Care L. & Pol’y 34, 35 (2002); I.Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661 (2003); Lainie Friedman Ross & M. Justin Coffey, *Women and Children First: Applicable to Lifeboats? Applicable to Human Experimentation?*, 6 J. HEALTH CARE L. & POL’Y 14, 15 (2002); Lauren Hammer Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 136 (2003).
93. Orphan Drug Act, Pub. L. No. 94-414 § 526(a)(2), 96 Stat. 2049 (1982), codified as amended at 21 U.S.C. §360bb(2000), available at <http://frwebgate1.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=549585412272+0+0+0&WAIAction=retrieve>. For discussion of the Orphan Drug Act and interesting discussion of use of rewards-based biopharmaceutical R&D law-policy, see generally Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337 (2006).
94. A prime, timely example is the kambo, a poisonous tree frog. Paulo Prada, *Poisonous Tree Frog Could Bring Wealth to Tribe in Brazilian Amazon*, N.Y. TIMES, May 30, 2006, at C1, C6. The government of Brazil is supporting the plan of an indigenous tribe to

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research sponsors that encompass the desired human subjects protections.⁹⁵ Such an effort could be research sponsor-driven, academic research-driven, or some combination of the two. As articulated forcefully by Lita Nelson, Director of the Technology Transfer Office at the Massachusetts Institute of Technology, academic research institutions are organized through entities such as the Association of University Technology Managers and the Licensing Executives Society, and they have the means through technology transfer terms to make health care resources much more available to developing economies—for example, by not granting exclusive licenses without building in protections for developing countries' needs.⁹⁶ The US is particularly well-suited to push such an initiative into motion given the concentration of global biopharmaceutical R&D originating from inside its borders, the non-exclusive licenses the U.S. Government holds on all intellectual property stemming from the extensive research it funds, and the academic research community's dependence on Bayh-Dole and U.S. federal technology transfer policy.⁹⁷ Universal human subjects protection standards and a program to implement them could be developed by the International Monetary Fund-World Bank and the World Trade Organization in conjunction with the United Nations Educational Scientific and Cultural Organization (UNESCO) and the World Health Organization, and a meaningful effort would likely draw support from the international science and medical organizations, including the World Medical Association, CIOMS, and the International AIDS Vaccine Initiative (IAVI).⁹⁸ By drawing from the human subjects protection fabric recently woven through the International Haplotype Mapping Project,⁹⁹ CIOMS guidelines,¹⁰⁰ and other international biopharmaceutical R&D bioethics guidelines and experience, the flexible U.S. freedom to contract model for technology transfer could be

commercialize secretions of the kambo for biotechnology R&D. *Id.*

95. We already have witnessed the technology transfer model being applied successfully in an analogous fashion through some biobanking experiences. *See generally* Michael J. Malinowski, *Technology Transfer in BioBanking: Credits, Debits, and Population Health Futures*, 33 L. MED. & ETHICS 54, 54-69 (2005).
96. *See generally* Lita Nelsen, *The Role of University Technology Transfer Operations in Assuring Access to Medicines and Vaccines in Developing Countries*, 3 YALE J. HEALTH POL'Y L. & ETHICS 301 (2003).
97. *See generally* MICHAEL J. MALINOWSKI, BIOTECHNOLOGY: LAW, BUSINESS, AND REGULATION (1999 & supplements.).
98. IAVI, established in 1996, funds R&D on HIV vaccines with the mission of linking industry and foreign countries. *See* Yearby, *supra* note 7, at 1148-1150. For more information about IAVI, visit their Internet site at <http://www.iavi.org/>.
99. For more information, visit the official site of the International Haplotype Mapping Project, at <http://www.hapmap.org/>.
100. *See supra* note 46.

applied in a manner that emphasizes sensitivity towards local culture, norms, customs and needs.¹⁰¹

Realistically, in the absence of a well-funded financial incentive based program through entities such as the World Bank¹⁰² and UNESCO,¹⁰³ the implementation of compulsory, enforced international standards is a prerequisite to effectively utilize freedom to contract in this context. It is simply unrealistic to expect countries with developing economies to self-police, especially when their populations suffer from unmet health care needs such as basic nutrition and diseases like malaria that are readily treatable in the developed world. It also is unrealistic to expect commercial biopharmaceutical interests under immediate R&D pressures to act philanthropically for some projected long-term gain.¹⁰⁴ Similarly, meaningful financial incentives are a prerequisite for realizing the recommendations made by the National Bioethics Advisory Commission (NBAC) active under former President Clinton.¹⁰⁵ These recommendations emphasize that countries sponsoring international research on human subjects must increase the capacity of host countries to self regulate.¹⁰⁶ However, host countries with developing economies

101. But “[t]he IMF-World Bank policy package has arduously tried to create American style institutions in the developing countries defying their distinct social institutions, cultural values, historical contextualities and local specificities.” Nuruzzaman, *supra* note 86, at 119.
102. It must be noted, however, that “[t]he World Bank failed to follow through on its pledges to spend up to \$500 million to combat malaria, let its staff working on the disease shrink to zero, used false statistical data to claim success and wasted money on ineffective medicines, according to a group of public health experts writing in the British medical journal *The Lancet*.” Celia W. Dugger, *World Bank Failed in Fight Against Malaria, Health Experts Say*, N.Y. TIMES, Apr. 25, 2006, at A5. However, subsequently, the World Bank appointed a new president, Paul D. Wolfowitz, and introduced a new finance monitoring system. *Id.*
103. Cf. JEFFREY D. SACHS, THE END OF POVERTY: ECONOMIC POSSIBILITIES FOR OUR TIME (2005) (appealing to nations with developed economies to introduce financial incentives to harness industry resources and close the science gap between developed and developing economies); Daphne Eviatar, *Spend \$150 Billion Per Year To Cure World Poverty*, N.Y. TIMES MAG., Nov. 7, 2004, 44-49.
104. *But see* Daniel W. Fitzgerald & Angela Wasunna, *Away From Exploitation and Towards Engagement: An Ethical Compass for Medical Researchers Working in Resource Poor Countries*, 33 J.L. MED. & ETHICS 559 (2005) (arguing that commercial entities are under an “ethical imperative to use their unique positions judiciously, and to the benefit of the host population” and proposing that a meaningful incentive is to build research capacity in host countries through the “creation of equitable working partnerships between wealth and poor countries”).
105. *See generally* NBAC, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/clinical/Vol1.pdf>.
106. *Id.* at I (Executive Summary).

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that are eager to promote research within their borders and open access to resulting medicines are unlikely to meaningfully self regulate in the absence of imposed requirements or significant financial incentives.¹⁰⁷

The most pragmatic approach may be to harness commercial forces to trigger a race to the top in human subjects' protection through enforcement and enhancement of domestic US law given the scope of biomedical R&D undertaken by US based interests.¹⁰⁸ Recent, well-documented human subjects' controversies are telling.¹⁰⁹ If the FDA and OHRP, drawing from the HapMap experience and Ethical, Legal and Social Implications Program (ELSI) fabric,¹¹⁰ were to generate workable standards for international population genetics and fully implement those standards with their enforcement powers, presumably major biopharmaceutical entities prosecuted would put pressure on the agencies to treat their competitors similarly. Consistent enforcement among US-based biopharmaceutical interests could, in turn, inspire demand by them for an international baseline so that US interests are not disadvantaged. In this manner, the same market forces that realized GATT/TRIPS could bring about an enforceable international standard for the protection of human subjects. The FDA and OHRP should implement the standards they are responsible for enforcing in the international context and force this overdue event into motion.

107. See generally Jennifer Kahn, A Nation of Guinea Pigs, WIRE MAG. Issue 14.03, Mar. 2006, at 142 (addressing "How India became the global hot spot for drug trials"). Many countries relax US standards, such as human clinical trial prerequisites and the administration of baseline treatments in conjunction with trials of potentially new medicines, and actively seek out study participation. See generally Esther Chang, *Fitting a Square Peg in a Round Hole? Imposing Informed Consent and Post-Trial Obligations on United States Sponsored Clinical Trials in Developing Countries*, 11 S. CAL. INTERDISC. L.J. 339 (2002). The raw health care needs of many countries with developing economies have been used as justification for "manipulat[ing] unacceptable U.S. research risks into acceptable risks in foreign contexts, especially where large disparities in health resources exist between the United States and the host country. Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853, 855 (1997). The end result is that "researchers involved in these experiments have exploited the inadequacies of the health-care systems in these developing countries to conduct research they would never even consider in the US. Roman, *supra* note 7, at 445.

108. For detailed support, visit the web sites of the two major U.S. trade organizations — the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO), at www.phrma.org and www.bio.org.

109. Stephens et al., *supra* note 8.

110. For information about the ELSI program, visit the site of the International Human Genome Research Institute at www.genome.gov, the National Institutes of Health site, www.nih.gov, and the Department of Energy site, www.doe.gov.

VI. Conclusion

Biopharmaceutical R&D is a global endeavor without a baseline rule of law to protect human subjects. A solid compilation of compulsory, enforced international human subjects protections is needed. This conclusion is illustrated graphically by the Harvard-Millennium controversy, the cluster of related controversies, and the voluminous ongoing appetite of researchers for access to human biological samples, related medical information, and human subjects in the shadow of the assembled map of the human genome. This article has identified a number of options for establishing a workable baseline of protection of human subjects that would move research forward to make medical sense out of HGP in a responsible manner. Let us jolt forward along the biopharmaceutical R&D path and without borders, but in a responsible, accountable manner.