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The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Knowledge Is the Best Medicine

Michelle D. Miller, R.N., M.P.H.*

Introduction

Consider the following medical experiments: “live cancer cells” injected into twenty-two chronically ill patients without their knowledge,¹ prison inmates’ testicles irradiated without their consent,² hospitalized patients injected with plutonium without their knowledge,³ and 400 people with syphilis “treated” with placebos for decades so that the United States Public Health Service could trace the natural course of the disease.⁴ These human rights abuses did not occur in Nazi Germany. Rather they occurred in the United States, in many cases in contravention of the Nuremberg Code, which was created by an American tribunal in the aftermath of World War

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1. Robert D. Mulford, Note, *Experimentation on Human Beings*, 20 *STAN. L. REV.* 99, 99 (1967). This became known as the Jewish Chronic Disease Hospital experiment. *Id.*

2. ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT 3 (1995). The Atomic Energy Commission funded this research on prison inmates in Washington and Oregon to gain information to be used in government programs. *Id.*

3. *Id.* at 2. University scientists in Berkeley, California, Chicago, Illinois, and Rochester, New York, conducted the experiments at the direction of the federal government. The government expected the data to provide information on how to limit the dangers faced by workers building the atomic bomb. *Id.*

4. JAMES H. JONES, *BAD BLOOD* 1-2, 5 (1993). The United States Public Health Service (PHS) started the study in 1932 in Macon County, Alabama, to learn more about the natural course of syphilis. The subjects, all black men, were never told that they had syphilis. The doctors only said that they were being treated for “bad blood.” In reality, these men were never treated for syphilis. They were given inducements, such as a free physical exam, free treatment for minor ailments, and a burial stipend for their survivors, to continue to allow the PHS doctors to draw their blood periodically. As of 1969, at least 28, and as many as 100, of these men had died as a direct result of syphilis, a disease treatable with antibiotics since the 1940s. *Id.* at 1-6.

II to delineate ethical requirements for medical experimentation.⁵

The Nuremberg Code is that part of the judgment against twenty Nazi doctors and three Nazi medical administrators (the *Doctors' Trial*)⁶ which details the legal requirements of permissible medical experimentation.⁷ The judges emphasized the importance of informed consent⁸ in human-subjects research, describing it as "absolutely essential."⁹ Given this explicit declaration that informed consent is necessary, how is it possible that the aforementioned experiments could take place in the United States? Perhaps such experimentation could occur because the idea that the individual possesses the right to make all decisions relating to what is done to her body has traditionally been subordinated by the medical profession to the notion that the power to make all treatment decisions rests with the physician.¹⁰ Yet informed consent to medical experimentation and treatment is necessary to uphold the ideal of self-determination, a principle at the very foundation of American society.¹¹

One area of medical research that requires the use of humans as test subjects is pharmaceuticals research. The Food and Drug Administration (FDA), a department of the Public Health Service located within the U.S. Department of Health and Human Services (HHS), regulates the pharmaceutical industry. The FDA requires research on human subjects as a prerequisite to drug approval in an effort to avoid placing potentially harmful

5. See generally THE NAZI DOCTORS AND THE NUREMBERG CODE (George J. Annas & Michael A. Grodin eds., 1992) [hereinafter THE NAZI DOCTORS].

6. George J. Annas & Michael A. Grodin, *Introduction*, in THE NAZI DOCTORS, *supra* note 5, at 3, 4. Although the War Crimes Tribunal was multinational, the United States was responsible for the *Doctors' Trial*. 1 TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, at 8 (1950) (Military Tribunal Case 1, United States v. Karl Brandt et al.). The judges sitting at the *Doctors' Trial* were appointed by President Truman. They were: Walter B. Beals (presiding), Justice of the Supreme Court of Washington; Harold L. Sebring, Justice of the Supreme Court of Florida; Johnson T. Crawford, former Justice of the Oklahoma District Court; and Victor C. Swearingen (alternate member), former assistant attorney general of Michigan. THE NAZI DOCTORS, *supra* note 5, at 113 (photo caption).

7. Anthony Szczygiel, *Beyond Informed Consent*, 21 OHIO N.U. L. REV. 171, 194 (1994) (stating that the "Code set the 'absolutely essential' prerequisite of a voluntary, competent, informed, and comprehending consent for human experiment subjects"). In his opening statements for the prosecution, Gen. Telford Taylor detailed examples of experimentation on concentration camp inmates. Examples include: sterilization via irradiation, submersion for hours in ice cold water, injection with malaria or typhus, exposure to mustard gas, and the collection of skulls for racial comparisons. Telford Taylor, *Opening Statement of the Prosecution, December 9, 1946*, in THE NAZI DOCTORS, *supra* note 5, at 67, 71-86. See *infra* notes 27-29 and accompanying text.

8. The U.S. Department of Health and Human Services requires an investigator to obtain "the legally effective informed consent of the subject or the subject's legally authorized representative . . . under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of concern or undue influence." 45 C.F.R. § 46.116 (1996). See *infra* note 50 for the specific required elements of informed consent.

9. THE NAZI DOCTORS, *supra* note 5, at 102.

10. Jay Katz, *Informed Consent—Must It Remain a Fairy Tale?*, 10 J. CONTEMP. HEALTH L. & POL'Y 69, 73-74 (1994). It is only within the last 35 years that physicians have become legally obligated to share decision-making with their patients. *Id.* at 72.

11. See *infra* note 313.

products on the market.¹² An interesting aspect of the FDA's work in this area is the evaluation of clinical data from foreign countries. Historically, the FDA has been reluctant to accept data from foreign countries as the primary proof of drug efficacy and safety.¹³ Thus, a domestic investigator must replicate foreign experiment results.¹⁴ The pharmaceutical industry has criticized this duplication as being too expensive and of doubtful benefit,¹⁵ while doctors and economists have complained that the practice causes unnecessary delays in the availability of effective drugs.¹⁶

In an effort to address some of these problems, the FDA joined Japan and the European Union (EU) in founding the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1989.¹⁷ The primary goal of the ICH is to standardize the pharmaceutical development practices and procedures of the three parties.¹⁸ As part of this effort, the ICH is attempting to harmonize the various protocols used by the participating countries to regulate human-subjects research. To this end, the ICH has recently completed draft guidelines for "Good Clinical Practice" (ICH-GCP), which include requirements for informed consent in pharmaceuticals research.¹⁹

This Note examines the definition of informed consent proposed by the ICH. Given the vast cultural differences between the parties to the ICH concerning the nature and importance of self-determination, is it possible

12. S. REP. No. 87-448, at 8 (1961).

13. Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 337 (1989). See *infra* note 263 and accompanying text.

14. Jerome A. Halperin, *From Investigation to Marketplace: Moving Drugs Through the System*, 36 FOOD DRUG COSM. L.J. 166, 169 (1981).

15. Mark A. Kassel, Note, *Getting There First with the Best: The Need to Shorten the Prescription Drug Approval Process*, 27 VAL. U. L. REV. 95, 123 (1992). Redundant replication of foreign data is wasteful. However, replicating a foreign study in such a way as to discover new information, such as the drug's effect at different dose levels or on new populations, would be extremely useful. Louis Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 369, 369 (1986).

16. See, e.g., Barrett Scoville, *Shifting the Burden: Restructuring the Drug Review Process*, 49 CLINICAL PHARMACOLOGY & THERAPEUTICS 229 (1991); GEN. ACCOUNTING OFFICE, *FDA DRUG APPROVAL—A LENGTHY PROCESS THAT DELAYS THE AVAILABILITY OF IMPORTANT NEW DRUGS*, GAO REP. NO. HRD-80-64 (1980); WILLIAM M. WARDELL & LOUIS LASAGNA, *REGULATION AND DRUG DEVELOPMENT* 45-47 (1975).

17. Joseph G. Contrera, Comment, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 939-40 (1995). See *infra* Part II.

18. Stuart L. Nightingale, *The International Harmonization of Drug Standards: The Status of the International Conference on Harmonization Initiative 3* (Aug. 3, 1995) (on file with the FDA) (Dr. Nightingale is the Associate Commissioner for Health Affairs at the U.S. Food and Drug Administration). See *infra* Part II.A.

19. International Conference on Harmonization: *Draft Guidelines on Good Clinical Practice*, 60 Fed. Reg. 42,948 (1995) (proposed Aug. 17, 1995) [hereinafter *Draft Guidelines*]. "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects." *Id.* Each party to the ICH possesses its own Good Clinical Practice guidelines. The ICH-GCP represents an attempt to standardize these individual guidelines.

or even desirable to standardize the disparate approaches to informed consent in pharmaceuticals research? This Note asserts that the ICH process fails to protect participants of pharmaceuticals research adequately. Arguably, the political pressure on the FDA to streamline its drug approval process threatens the safety of the people the FDA purports to safeguard. In a rush to prove that it can respond effectively to criticism of its lengthy drug approval process, the FDA may diminish U.S. informed consent standards in the name of harmonization. Alternatively, the FDA may be tempted to overlook cultural differences in the role of informed consent on human-subjects research for the sake of quickly achieving agreement. However, an agreement which ignored the existence of these disparate viewpoints would fall far short of actual harmonization. In that case, although U.S. citizens will continue to be protected by rigorous informed-consent standards, the United States will be accepting pharmaceuticals research from nations that do not enforce strict standards of informed consent. This position is potentially dangerous for U.S. citizens who purchase foreign pharmaceuticals, as well as morally untenable for a nation dedicated to respecting human rights.

Part I of the Note presents a brief survey of the tradition of informed consent to medical research²⁰ in the United States, the European Union, and Japan. Part II introduces the ICH, including a discussion of its goals and processes. In addition, this Part explains the ICH structure as a form of international regulatory negotiation. Part III.A. of the Note analyzes how the regulatory negotiation used by the ICH may provide incentives for the FDA to loosen its current informed-consent standards. Even if the FDA does not diminish U.S. informed-consent standards, accepting research data from countries which fail to protect subjects' rights to self-determination as vigilantly as the United States may still lead to negative consequences. Therefore, Part III.B. focuses on the dangers inherent in ignoring important cultural differences in the name of harmonization. Finally, Part IV makes recommendations for protecting the subjects of pharmaceuticals research within the context of harmonizing international pharmaceutical development.

I. A Cultural Comparison of Informed Consent

A. Informed Consent in the United States

This section begins with a general discussion of informed consent in biomedical research in the United States. Although pharmaceuticals research belongs to this larger tradition, it implicates unique considerations. Consequently, this section also specifically addresses this subset of biomedical research.

20. This Note focuses primarily on informed consent to medical research rather than to medical treatment. However, since experimental drugs are usually taken as part of a treatment protocol there is often very little practical difference. See *infra* notes 38-43 and accompanying text.

1. Informed Consent in Biomedical Research

Before World War II, the American public was largely unaware of the legal issues surrounding medical experimentation.²¹ The few cases addressing the subject defined medical experimentation as a deviation from standard medical practice that could only be justified by a positive outcome.²² No court raised the issue of requiring informed consent until the 1930s.²³ In that case, *Fortner v. Koch*, the Supreme Court of Michigan explained that doctors could only perform human experimentation with the knowledge and consent of the patient.²⁴ The issue received relatively little attention prior to World War II, as only two other courts followed reasoning similar to that of the *Fortner* court.²⁵

The revelation of the experiments performed on concentration camp inmates by Nazi physicians in the name of medical science dramatically forced the issue of informed consent to the attention of Americans.²⁶ In the *Doctors' Trial*, the U.S. Military Tribunal No. 1 noted that medical experimentation must remain within certain well-defined bounds in order to comply with acceptable norms of medical ethics.²⁷ According to the Tribunal, medical researchers must observe ten basic principles. These ten principles became known as the Nuremberg Code.²⁸ Given that the judg-

21. Maria Woltjen, Note, *Regulation of Informed Consent to Human Experimentation*, 17 *LOY. U. CHI. L.J.* 507, 509 (1986). The Nuremberg *Doctors' Trial* depiction of unethical Nazi experimentation on concentration camp inmates initiated the first widespread public debate in the United States on the subject of human-subjects research. *Id.* at 510-11.

22. George J. Annas, *The Nuremberg Code in U.S. Courts: Ethics Versus Expediency*, in *THE NAZI DOCTORS*, *supra* note 5, at 202 (citing *Owens v. McClearey*, 281 S.W. 682, 685 (Mo. 1926)).

23. *Fortner v. Koch*, 261 N.W. 762 (Mich. 1935).

24. *Id.* at 765. The court recognized the importance of experimentation to medical progress, but cautioned that medical experimentation should not vary greatly from accepted medical practice. *Id.*

25. *Stammer v. Board of Regents*, 29 N.Y.S.2d 38 (1941), *aff'd*, 287 N.Y. 359 (1942) (reversing the revocation of a physician's license after he experimented with a new cream for facial cancer and noting that such experimentation is within the scope of a doctor's practice as long as he obtains informed consent from his patient); *Bonner v. Moran*, 126 F.2d 121 (D.C. Cir. 1941) (holding that a physician must obtain the informed consent of a minor's parents where a 15-year-old boy underwent a skin graft to benefit a cousin).

26. *See supra* note 7.

27. *THE NAZI DOCTORS*, *supra* note 5, at 102.

28. Because it is part of a judgment by an American tribunal in an international setting, the Nuremberg "Code is part of international common law and may be applied, in both civil and criminal cases, by state, federal and municipal courts in the United States." GEORGE J. ANNAS ET AL., *INFORMED CONSENT TO HUMAN EXPERIMENTATION: THE SUBJECT'S DILEMMA* 21 (1977). The Code is "[t]he most complete and authoritative statement of the law of informed consent to human experimentation . . ." *Id.* at 1. The Nuremberg Code is comprised of ten basic principles:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to

ment originated from a U.S. trial complete with U.S. judges, prosecutors, and criminal procedure,²⁹ an objective observer might have expected that U.S. courts would use the Nuremberg Code as the legal standard for medical experimentation. However, it was not until 1973, more than twenty-five years later, that any court cited the Code.³⁰ The delay may be partially attributable to the extreme nature of the Nazi experiments³¹—no court wanted to compare an American doctor to a Nazi physician. As Professor

enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted when there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

II TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW No. 10, at 181-82 (1950) (Military Tribunal Case 1, United States v. Karl Brandt et al.) [hereinafter Nuremberg Code].

29. Annas, *supra* note 22, at 204.

30. *Id.* at 206, 220 n.21 (citing *Kaimowitz v. Michigan Dept. Mental Health*, Civil No. 73-19434-AW (Mich. Cir. Ct., Wayne Co., July 10, 1973)). The *Kaimowitz* court used the Nuremberg Code for guidance in its holding that an involuntarily committed mental patient could not legally consent to experimental psycho-surgery because he lacked the requisite mental competence. *Id.*

31. Annas, *supra* note 22, at 204.

Katz explained, “[i]t was a good code for barbarians but an unnecessary code for ordinary physician-scientists.”³²

In addition, the Nuremberg Code probably did not immediately become part of recognized law because the Tribunal misunderstood the content of standard medical practice relating to human-subjects research. Although the judges believed that the “basic principles” of the Nuremberg Code had long been accepted in Western medicine,³³ in actuality the American Medical Association did not fashion guidelines for the conduct of medical research until after the content of the Nazi concentration camp experiments became clear.³⁴ Ironically, the only Western nation which had pronounced an authoritative guarantee of research subjects’ rights before the Nuremberg Code was Germany.³⁵ This mistaken belief in the existence of a worldwide consensus on acceptable medical research practice caused the Tribunal to label the Nazi experiments an aberration, rather than just an extreme example from a long history of injuries inflicted on people in the name of medical science.³⁶ Following the Tribunal’s lead, American medical scientists avoided confronting their own questionable conduct by characterizing the Nazi abuses as different in kind, not just in degree.³⁷

As a result, the American medical community adopted a framework which distinguished between non-therapeutic experimentation, performed solely to test a hypothesis (e.g. the Nazi experiments), and therapeutic research, designed to help the subject patients as well as aid the scientist.³⁸ The medical community characterized therapeutic research as a form of

32. Jay Katz, *The Consent Principle of the Nuremberg Code: Its Significance Then and Now*, in *THE NAZI DOCTORS*, *supra* note 5, at 228. The American belief that the Nazis were not like Americans is partially responsible for the fact that U.S. courts have avoided invoking the Nuremberg Code even when it is directly applicable. Annas, *supra* note 22, at 218.

33. Katz, *supra* note 32, at 228. The testimony of two medical experts helped to convince the judges that, although there had been no official statement incorporating these basic principles, the medical community abided by them. In particular, the testimony of Dr. Andrew Ivy asserted that the hippocratic oath served to establish guidelines for the protection of patients. However, there is no mention in the oath about medical research. *Id.*

34. *Id.* Currently, the American Medical Association directs physicians to obtain “voluntary written consent” from any person participating in a clinical investigation designed either for treatment purposes or for the accumulation of scientific knowledge. AM. MED. ASS’N, CODE OF MEDICAL ETHICS: ANNOTATED CURRENT OPINIONS § 2.07(3)(B) (1992).

35. Katz, *supra* note 32, at 227. In 1931, the Reichminister of the Interior promulgated Regulations on New Therapy and Human Experimentation. *Id.* The American Medical Association patterned its post-war guidelines on the ethics of human experimentation after the earlier German pronouncements. *I TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10*, at 82-86 (1950) (Military Tribunal Case 1, United States v. Karl Brandt et al.) (testimony of prosecution witness Dr. Andrew C. Ivy).

36. Katz, *supra* note 32, at 228. See *supra* notes 1-5 and accompanying text.

37. Katz, *supra* note 32, at 228.

38. Annas, *supra* note 22, at 217-18.

therapy, rather than experimentation.³⁹ Therefore, by definition, the Nuremberg Code did not apply to it.⁴⁰ This distinction is reflected in the case law, as U.S. courts have only cited the Nuremberg Code in cases addressing non-therapeutic research.⁴¹ Unfortunately, the line between non-therapeutic research and therapeutic research is a formal distinction lacking substantive support.⁴² A person's right to self-determination, and therefore the need for informed consent, should not change with the label attached to the bodily invasion, whatever its goal.⁴³

In the 1960s, reports of abuses of human subjects in American medical research caused great alarm.⁴⁴ For example, in 1966, Henry K. Beecher published an article revealing ethical violations in twenty-two reported research studies.⁴⁵ The American public demanded government action.⁴⁶ In 1974, Congress passed the National Research Act which established the National Commission for the Protection of Human Subjects of Biomedical

39. *Id.* at 217. As medical experimentation became more scientifically valid, it moved into the medical mainstream and out of the realm of quackery. *Id.*

40. *Id.* at 218. Non-therapeutic medical experimentation came to be considered the only real medical experimentation. Therefore, the Nuremberg Code applied only to it. This distinction enables the medical and legal communities to ignore the necessity of a strong informed-consent standard for all medical experimentation. For example, U.S. soldiers have often been used unwittingly as research subjects to test the effects of such substances as LSD and radiation. *Id.* One author points out that while we were horrified to hear that a Nazi physician told a young colleague not to experiment on herself because "[w]e have concentration camps for that," we seem to see no contradiction when our military says, "[w]e have soldiers for that." *Id.*

41. *See, e.g.,* *United States v. Stanley*, 483 U.S. 669 (1987) (holding that active-duty U.S. Army servicemen could not sue the federal government for money damages for injuries resulting from LSD administered experimentally by the Army without the soldier's consent). The majority voiced a reluctance to interfere with military "discipline and decision-making." *Id.* at 683. The dissent, noting the existence of the Nuremberg Code, asserted that the decision amounted to giving military officials unqualified immunity for intentional infliction of injury on service personnel. *Id.* at 708. This is the only case in which the U.S. Supreme Court has referred to the Nuremberg Code.

42. *See* Szczygiel, *supra* note 7, at 194.

43. *Cf. Katz, supra* note 10, at 86 (arguing that individual self-determination should always trump medical progress when the two goals are incompatible). Placing individual autonomy in the ascendant position insures that doctors always respect their patients as people. *Id.* at 85. Until recently, the idea that individual patients must be respected as autonomous moral decision makers was foreign to the medical profession. *Id.* at 73.

44. John A. Robertson, *The Law of Institutional Review Boards*, 26 UCLA L. REV. 484, 486-87 (1979).

45. Henry K. Beecher, *Ethics & Clinical Research*, 274 NEW ENG. J. MED. 1354 (1966). For example, placebos were given to 109 military servicemen suffering from streptococcal respiratory infections as a control group, while another group with the disease were treated with Penicillin G. *Id.* at 1356. In another case, effective treatment for typhoid fever, by administering Chloramphenicol, was withheld from 157 hospital charity patients to determine the relapse rate without such treatment. *Id.* A third instance of medical experimentation involved institutionalized mentally retarded children who were purposely infected with infectious hepatitis to determine the infectivity of the virus. *Id.* at 1358.

46. Woltjen, *supra* note 21, at 511.

and Behavioral Research (the Commission).⁴⁷ The National Research Act directed the Commission to identify "the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects."⁴⁸

Based on the Commission's findings, the Department of Health, Education and Welfare (HEW) (now the Department of Health and Human Services) established regulations for all human-subjects research conducted or funded by the government.⁴⁹ The regulations list eight requirements for valid informed consent.⁵⁰ In addition, the regulations mandate that HHS will refuse to award a federal research grant to an institution unless an Institutional Review Board (IRB) reviews and approves the research protocol.⁵¹ IRBs are required to ascertain whether legally informed consent has been obtained and whether the rights and welfare of the subjects are adequately safeguarded.⁵² This policing function requires IRBs to monitor all research conditions periodically throughout the course of the project to ensure that no violations have occurred.⁵³ The law pertaining to human-subjects research is currently shaped by these regulatory requirements.

47. National Research Act of 1974, Pub. L. No. 93-348, 88 Stat. 348 (1974). See also Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, in *THE NAZI DOCTORS*, *supra* note 5, at 183, 187.

48. National Research Act of 1974, *supra* note 47, § 202(a)(1)(A).

49. 45 C.F.R. § 46.101(a) (1996).

50. The eight elements are as follows:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expanded duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which the confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

45 C.F.R. §§ 46.116(a)(1-8) (1996).

51. 45 C.F.R. § 46.103(b) (1996); 21 C.F.R. § 56.103(a) (1996). See also Glantz, *supra* note 47, at 188 (discussing Institutional Review Board regulations).

52. Robertson, *supra* note 44, at 491. The IRBs are mandated to ensure that research subjects receive all information that the members of the IRB judge relevant to the subjects' rights and welfare. 45 C.F.R. § 46.109 (1996).

53. Robertson, *supra* note 44, at 491.

2. Informed Consent in Pharmaceuticals Research

Human experimentation is a very important aspect of pharmaceuticals research. Until a drug is actually tested in human trials there is no way to be sure of its efficacy, for products that work in the test tube and on other animals do not always produce the desired results in the human body.⁵⁴ Although pharmaceuticals research shares common medical and legal standards with other forms of human-subjects research, it has a unique history. Until this century, the U.S. pharmaceutical industry was largely unregulated; *caveat emptor* was the philosophy of the day.⁵⁵ As a result, consumers became de facto research subjects, as there was no legal requirement that drugs be tested for safety or efficacy prior to reaching the market.⁵⁶ Many people were undoubtedly injured by ingesting poisons or narcotics marketed as safe medicine.⁵⁷

At the beginning of this century, Congress attempted to ameliorate the situation, but most of these efforts were either misguided, misdirected, or simply ineffectual. In 1906, for example, the Pure Food and Drug Act made misrepresentation of pharmaceutical content illegal.⁵⁸ A manufacturer was not required to disclose the contents of a product, but if it chose to do so, the government could monitor the accuracy of the claims.⁵⁹ In addition, the label had to display the presence of any narcotic content to the consumer.⁶⁰ The statute had limited effect.⁶¹ In 1911, the U.S. Supreme Court ruled that the law prohibited only false claims regarding ingredients, not false health claims.⁶² A year later, Congress attempted to

54. Cf. Kenneth L. Melmon et al., *Principles of Therapeutics*, in GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 40, 43 (Alfred Goodman Gilman et al. eds., 1980) (explaining the desirability for clinical trials in drug efficacy research).

55. Richard C. Litman & Donald S. Litman, *Protection of the American Consumer: The Muckrakers and the Enactment of the First Federal Food and Drug Law in the United States*, 36 FOOD DRUG COSM. L.J. 647, 647 (1981). Government regulation of pharmaceuticals dates to the colonial period. For example, in 1630, Nicholas Knopf was convicted of selling "a water of no worth or value" as a cure for scurvy. He was sentenced to pay a fine or be whipped. Wallace F. Janssen, *The U.S. Food and Drug Law: How It Came; How It Works*, 35 FOOD DRUG COSM. L.J. 132, 132-33 (1980). Notwithstanding this example of vigilance, legal action preventing the sale of nostrums (quack medicines) was the exception, rather than the rule until the twentieth century. *Id.*

56. *Id.* at 133.

57. See Litman & Litman, *supra* note 55, at 652. In fact, because European countries regulated drugs earlier than the United States, this country became a dumping ground for unsafe and contaminated European drugs in the nineteenth century. Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 422 (1981).

58. Pure Food and Drug Act of 1906, ch. 3915, 34 Stat. 768 (1906) (repealed 1938).

59. *Id.*

60. *Id.*

61. See Catharine E. Bednar, *A Constitutional Analysis of Federal Drug Marketing Regulations and Food and Drug Administration Implementation*, 13 Sw. U. L. Rev. 531, 543-46 (1983). For example, a newly named non-narcotic preparation, for which a producer chose not to reveal the contents, fell completely outside the scope of the law. *Id.* at 543 n.72.

62. *United States v. Johnson*, 221 U.S. 488, 495 (1911) (Holmes, J.) (holding that the defendant could not be prosecuted under the Pure Food and Drug Act of 1906, even

remedy the problem by passing the Sherley Amendment.⁶³ The Amendment prohibited fraudulent label claims about a drug's therapeutic effectiveness.⁶⁴ Unfortunately, the statute, as interpreted, required proof that the drug manufacturer had deliberately lied in order to defraud the public.⁶⁵ Consequently, the statute had little, if any, practical effect.⁶⁶

The Sulfanilamide⁶⁷ Elixir catastrophe of 1937 moved Congress to real action. In that year, at least 107 deaths resulted from the sale of an untested new medicine to the public.⁶⁸ On the theory that children prefer drugs in a liquid form, the manufacturer decided to dissolve it in a syrup.⁶⁹ The manufacturer chose di-ethylene glycol,⁷⁰ a key ingredient in anti-freeze.⁷¹ No one bothered to run any safety tests or even to research the solvent in chemistry text books, and tragedy followed.⁷² In response, Congress passed the Food, Drug, and Cosmetic Act of 1938.⁷³ The statute dramatically expanded the enforcement power of the FDA. It required companies to provide scientific proof of safety before a new product could be marketed.⁷⁴

Until 1959, the pharmaceutical industry enjoyed a cordial relationship with Congress regarding economic and corporate issues.⁷⁵ In that year, Senator Estes Kefauver, chairman of the Senate Subcommittee on Antitrust and Monopoly, began hearings on monopolistic pricing practices of the industry.⁷⁶ However, before the subcommittee reached a resolution, the

though he knew that his "Mild Combination Treatment for Cancer" would not produce the health effects claimed, because he had made no false ingredient claims).

63. Act of Aug. 23, 1912, ch. 352, 37 Stat. 416 (1912) (amending the Pure Food and Drug Act of 1906).

64. *Id.*

65. Janssen, *supra* note 57, at 428.

66. *Id.*

67. Sulfanilamide was used at the time to treat acute rheumatic fever and pneumonia. MILTON SILVERMAN & PHILIP R. LEE, *PILLS, PROFITS, & POLITICS* 6 (1974).

68. *Id.* The human body metabolizes di-ethylene glycol into oxalic acid, leading to a lingering, excruciatingly painful death from kidney failure. Many of the casualties were children. *Id.*

69. *Id.* at 86.

70. *Id.* The choice of di-ethylene glycol appears to have been motivated by the drug's poor solubility in normal solvents, such as water and alcohol. The manufacturer added coloring and raspberry flavoring to complete the mixture. *Id.*

71. Arthur H. Hayes, *Food and Drug Regulation After 75 Years*, 246 *JAMA* 1223, 1224 (1981).

72. SILVERMAN & LEE, *supra* note 67.

73. Federal Food, Drug, and Cosmetic Act, ch. 675, § 1, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-394 (1988)).

74. *See id.* § 505, 52 Stat. at 1052. In addition, the Act provided the FDA with specific authority to inspect pharmaceutical production plants, eliminated proof of fraud as a requirement to enjoin false drug claims and authorized federal courts to restrain violations of the Act via injunction. *Id.* *See also* Janssen, *supra* note 57, at 429.

75. Lasagna, *supra* note 13, at 323-24.

76. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 *ARIZ. ST. L.J.* 581, 584 (1982). These hearings covered the pricing practices of the steel, automobile, bread, and drug industries. *S. REP. NO.* 87-448, at 1 (1961). The investigation of the pharmaceutical industry alone spanned 26 months and generated 12,885 pages of testimony. Lasagna, *supra* note 13, at 324.

Thalidomide tragedy struck. Thalidomide is a sedative that had been marketed as safe and effective in Europe in the late 1950s and early 1960s.⁷⁷ In the United States, the drug was in the final stages of FDA-required testing when obstetricians discovered its harmful side effects. As part of testing, 3,897 pregnant women were given the sedative.⁷⁸ Nine of those women gave birth to children suffering from phocomelia,⁷⁹ a birth defect which causes the infant's extremities to resemble the flippers of seals.⁸⁰

Congress reacted by passing the Kefauver Drug Amendments Act of 1962.⁸¹ The Act required "experts using . . . drugs for investigational purposes" to inform anyone to whom they administered the drug of its experimental nature and to obtain her consent, unless, in the expert's professional judgment, such knowledge would be detrimental to her interests.⁸² Prior to this enactment, neither state nor federal law required doctors to inform their patients that a prescribed drug was experimental.⁸³ Unfortunately, the statutory phrase, *detrimental to the person's interests*, appears to have served as a loophole for researchers. Consequently, the Act failed to achieve its major goal of requiring adequate informed consent.⁸⁴

To cure this imperfection, the FDA promulgated specific informed-consent regulations.⁸⁵ The current version of the FDA regulations requires that a physician provide her patient with the following:⁸⁶ 1) an explanation of the purpose of the research and notification that the procedure to

The hearings focused on economic concerns rather than drug safety. By 1958, the pharmaceutical industry's annual budget was estimated at \$140 million. While it appears small when compared to today's expenditure of \$6 to \$7 billion per year, it was considered large at the time. Lasagna, *supra* note 13, at 323.

77. SILVERMAN & LEE, *supra* note 67, at 94. Thalidomide produces a "refreshing sleep" without grogginess. It was widely given to "fretful infants." Physicians and pharmacists thought the drug was free from side effects. *Id.*

78. Hayes, *supra* note 71, at 1224.

79. *Id.* In Europe, it was estimated that by 1962, 3,500 to 5,000 cases of phocomelia would result from pregnant women's ingestion of Thalidomide. S. REP. NO. 87-1744, at 40 (1962).

80. SILVERMAN & LEE, *supra* note 67, at 95.

81. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C.A. §§ 301-394 (West Supp. 1992)).

82. *See id.* § 103(b) 76 Stat. at 783 (amending Federal Food, Drug, and Cosmetic Act, § 505(i), 52 Stat. at 1040 (codified as amended at 21 U.S.C. § 355(i) (1988))).

83. Glantz, *supra* note 47, at 186.

84. *Id.*

85. *Id.*

86. Protection of Human Subjects, 21 C.F.R. §§ 50.20-50.27 (1996). These regulations are similar to those promulgated by HHS for institutions receiving federal funds for non-drug-related medical experimentation. *See supra* note 50. There are two important differences between the sets of regulations. First, the FDA regulations require the physician to inform the subject that the FDA may inspect her records. 21 C.F.R. § 50.25(a)(5) (1996). Second, the written informed-consent requirement may be waived when the FDA determines that the research poses no more than a "minimal risk." 21 C.F.R. § 56.105 (1996). *Minimal risk* is defined as a risk not greater than that ordinarily encountered in daily life, or during routine physical or psychological examinations. 21 C.F.R. § 56.102(i) (1996).

be followed represents a departure from established practice;⁸⁷ 2) a description of the risks and discomforts which may reasonably be expected;⁸⁸ 3) a description of any benefits to the subject or to others which may reasonably be expected;⁸⁹ 4) a statement describing the extent to which confidentiality of the subject's records will be preserved;⁹⁰ 5) a statement of whether any alternative treatments exist;⁹¹ 6) a description of the availability of medical therapy or compensation in case injury results from the experiment;⁹² 7) an opportunity to ask questions concerning the experiment;⁹³ and 8) an assurance that the subject is free to refuse to participate or to withdraw her consent and discontinue participation at any time without penalty or loss of benefits to which she is otherwise entitled.⁹⁴

After many decades of virtually ignoring the human rights issues inherent in medical experimentation,⁹⁵ the FDA regulations reflect a commitment by the United States to protect those interests, at least at the federal level.⁹⁶ The requirements for informed consent manifest that resolve. All federally sponsored research must include a procedure to provide potential subjects with sufficient information to determine for themselves whether or not they will participate in the experiment.⁹⁷

B. Informed Consent in the European Union⁹⁸

The Directive of the Commission of the European Communities addressing analytical, pharmacotoxicological and clinical standards and protocols in testing medicinal products, provides the most current expression of Good

87. 21 C.F.R. § 50.25(a)(1) (1996). Informed consent shall include identification of any procedures which are experimental. *Id.*

88. 21 C.F.R. § 50.25(a)(2) (1996).

89. 21 C.F.R. § 50.25(a)(3) (1996).

90. 21 C.F.R. § 50.25(a)(5) (1996).

91. 21 C.F.R. § 50.25(a)(4) (1996).

92. 21 C.F.R. § 50.25(a)(6) (1996).

93. 21 C.F.R. § 50.25(a)(7) (1996).

94. 21 C.F.R. § 50.25(a)(8) (1996).

95. See *supra* notes 1-5, 45 and accompanying text.

96. Only three states, California, New York, and Virginia, have statutes specifically addressing informed consent in the context of medical experimentation. In all three states researchers must provide the following information in order to obtain legal informed consent from their subjects: an explanation of the procedures, drugs, or devices to be used in the experiment; a disclosure of alternatives; a description of potential risks and benefits; an offer to field any questions the subject may have; and the instruction that the subject may voluntarily withdraw from the experiment at any time. Both New York and Virginia require the creation of an Institutional Review Board for any institution proposing to do research involving human subjects. See CAL. HEALTH & SAFETY CODE § 24172 (West 1984); N.Y. PUB. HEALTH LAW § 2441 (McKinney 1985); VA. CODE ANN. § 32.1-162.16 (Michie 1984); Woltjen, *supra* note 21, at 518-23.

97. See 45 C.F.R. § 46.101(a) (1996), *supra* note 49 and accompanying text.

98. The term *European Union* (EU) superseded *European Community* (EC) when the Maastricht Treaty took effect in 1992. Treaty on European Union, Feb. 1, 1992, art. a, 31 I.L.M. 247, 255 (1992).

Clinical Practice for the EU (EU-GCP).⁹⁹ The EU-GCP directive points the reader to the current version of the Declaration of Helsinki¹⁰⁰ for ethical guidance concerning the completion of clinical trials.¹⁰¹ In addition, the directive states, “[i]n principle, the freely given informed consent of each trial subject shall be obtained and documented.”¹⁰²

The World Medical Assembly (WMA) adopted the Declaration of Helsinki in 1964.¹⁰³ The WMA Committee on Medical Ethics subsequently revised the Declaration in 1975 and again in 1989.¹⁰⁴ The Declaration is comprised of twelve basic principles.¹⁰⁵ Unlike the Nuremberg Code, which began with an exhortation on the essential nature of informed con-

99. Commission Directive 91/507/EEC, 1991 O.J. (L 270) 32, 48 [hereinafter Commission Directive]. This particular directive falls into the category of “[a]cts whose publishing is not obligatory” for the member states. *Id.*

100. World Medical Association, *Declaration of Helsinki IV (1989)*, reprinted in *THE NAZI DOCTORS*, *supra* note 5, at 339 [hereinafter *Helsinki IV*].

101. Commission Directive, *supra* note 99, at 48. A clinical trial is “[a] carefully designed and executed investigation of the effects of a drug administered to human subjects.” *TABER’S CYCLOPEDIA MEDICAL DICTIONARY* 341 (15th ed. 1985).

102. Commission Directive, *supra* note 99, at 48.

103. Sharon Perley et al., *The Nuremberg Code: An International Overview*, in *THE NAZI DOCTORS*, *supra* note 5, at 149, 159. The WMA Committee on Medical Ethics first submitted a resolution for a code of ethics regarding human experimentation to the WMA’s 15th General Assembly in September 1961. *Id.* The World Health Organization, the branch of the United Nations responsible for directing international public health initiatives of member nations, adopted the Helsinki Declaration in 1964. Katz, *supra* note 32, at 233.

104. *Helsinki IV*, *supra* note 100.

105. The principles of the Helsinki Declaration are as follows:

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed

sent, the Declaration begins by stressing the importance of medical progress. In fact, the Declaration relegates informed consent to a numerically subordinate position. Principle 9 asserts that “[i]n any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail The physician should then obtain the subject’s freely-given informed consent, preferably in writing.”¹⁰⁶

While the drafters may not have intended the numerical order of the principles to establish a hierarchy denoting importance, it is interesting to note that the original draft of the Declaration opened with a statement regarding the importance of informed consent in a section entitled “General Principles and Definitions.”¹⁰⁷ However, even that version qualified its commitment to informed consent in the very next section, “Experiments for the Benefit of the Patient.”¹⁰⁸ In that section, physicians were endowed with great discretion to conduct therapeutic research without consent, so long as the experiment was not performed for the sole purpose of acquiring knowledge.¹⁰⁹ The grant of such potential power to physicians emphasizes the paternalistic notion that doctors know better than patients whether the latter should participate in experimental treatment.

to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject’s freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor’s consent must be obtained in addition to the consent of the minor’s legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

Id.

106. *Id.*

107. Katz, *supra* note 32, at 233 (citing Ethical Committee of the World Medical Association, *Draft Code of Ethics on Human Experimentation*, 2 BRIT. MED. J. 1119 (1962)).

108. *Id.*

109. Katz, *supra* note 32, at 233.

Nevertheless the Declaration of Helsinki does require informed consent. It appears, however, that the EU-GCP does not necessarily mandate such consent. That document, while directing the reader to the Declaration for ethical guidance, immediately diminishes the impact of that document by modifying the informed consent requirement with the critical phrase, “[i]n principle.”¹¹⁰ This qualification seems to indicate that the acquisition of informed consent is not necessarily required in practice.

The English tradition highlights the differences between the EU and the U.S. treatment of informed consent.¹¹¹ Prior to the 1970s, the United States utilized the professionally oriented standard of disclosure,¹¹² which determines what constitutes adequate informed consent by reference to standard medical practice.¹¹³ Thus, if a doctor has conformed to the expected standard of care, as established by expert medical testimony,¹¹⁴ then she is not liable for medical malpractice regardless of whether the patient feels he was adequately informed of the risks of treatment.¹¹⁵

During the 1970s, an increasing number of U.S. states gravitated toward a reasonable-patient standard.¹¹⁶ Currently, twenty-five states retain the former standard, twenty jurisdictions (including the District of Columbia) use a reasonable-patient standard, two states use a subjective-patient standard, and four states use a mixed approach.¹¹⁷ A good example of the early reasonable-patient standard is provided in *Canterbury v. Spence*.¹¹⁸ In that case, the U.S. Court of Appeals for the District of Columbia Circuit decided that the medical profession should not determine the degree of disclosure necessary to constitute adequate informed consent. Instead, the court held that disclosure should depend on what “material” factors would be necessary for the hypothetical “reasonable person” to decide whether or not to undergo treatment.¹¹⁹

110. Commission Directive, *supra* note 99, at 48.

111. It is beyond the scope of this Note to address the history and tradition of informed consent in every EU member state.

112. See *Canterbury v. Spence*, 464 F.2d 772, 783 (D.C. Cir. 1972). The majority opinion details the distinction between the professionally oriented standard and the reasonable-patient standard.

113. *Id.*

114. *Id.* at 783 n.38.

115. *Id.*

116. JUDITH AREEN ET AL., *LAW, SCIENCE AND MEDICINE* 384 (1984).

117. Szczygiel, *supra* note 7, at 209-10. A subjective-patient standard focuses on what the patient in the particular case believes to be adequate disclosure, rather than what a hypothetical reasonable person would find adequate. *Id.*

118. 464 F.2d at 787. In this case Dr. Spence performed a laminectomy on a nineteen year old man suffering from back pain. A laminectomy is the excision of the posterior portion of a vertebra. On the first day after the surgery, the man fell from his bed while unattended. Consequently, he experienced difficulty breathing and became paralyzed below the waist. Eventually he regained the use of his legs, but permanently required crutches to walk and had difficulty with bowel and bladder incontinence. The patient sued the doctor for failing to apprise him of the risks involved in the operation. *Id.* at 776-78.

119. *Id.* at 787.

In contrast to the development of the reasonable-patient standard in the United States, the House of Lords in the United Kingdom asserted that the physician should have more discretion in prescribing medical treatment.¹²⁰ Given this attitude toward professional discretion, it follows that the United Kingdom and her fellow EU members would rely on the Declaration of Helsinki for guidance. The Declaration places informed consent in the context of medical experimentation subordinate to physician discretion, thus narrowing the scope of the former for the sake of the latter.

Alternatively, the Nuremberg Code makes informed consent "absolutely essential."¹²¹ Although the Code has not been widely followed in the United States,¹²² almost half of all American jurisdictions base their informed-consent standards on patient self-determination, rather than medical practice.¹²³ Moreover, any entity receiving federal funds for biomedical research must meet stringent informed-consent requirements.¹²⁴ Clearly, there is a marked difference between U.S. and EU perspectives on the issue of informed consent in medical experimentation.

C. Informed Consent in Japan

Significantly, the Japanese have no term that is the equivalent to the Western phrase *informed consent*.¹²⁵ Indeed, until recently, Japanese doctors rarely obtained informed consent before performing a medical procedure or conducting medical research.¹²⁶ Instead, for many years, the Japanese

120. See *Sidaway v. Bethlem Royal Hospital Governors*, 1 All E.R. 643 (H.L. 1985) (holding that professional judgment should determine what medical treatment risks are disclosed to patients). The plaintiff suffered spinal cord damage as the result of an operation. The physician had warned her in simple terms of some risks, but failed to mention possible damage to the spinal cord. *Id.*

The following story further illustrates the distinct approaches to the respective responsibilities of patient and physician. In the United States, an older man was admitted to a hospital with cardiac pathology. The diagnosis was explained to the patient, as were the competing alternatives available for treatment. He was then given a video explaining the two procedures and encouraged to watch the tape and discuss it with his family. The decision between by-pass surgery or angioplasty was left to him. In the United Kingdom, a man of similar age, having the same type of cardiac trouble visited a hospital. Leaving the man and his family at one end of the room, a group of doctors proceeded to huddle around his x-rays, occasionally glancing up at him. At the end of their discussion one of the doctors said to his patient, "Sir, here's what we're going to do for you." The doctors never gave the man any information upon which to base a decision. In fact, the man and his family were completely excluded from the decision-making process. Interview with David C. Lodmore, Editor-in-Chief, *Cornell Law Review* (Jan. 9, 1996) (the men in the account are his father-in-law and father, respectively).

121. Nuremberg Code, *supra* note 28.

122. See *supra* discussion accompanying notes 29-37.

123. Szczygiel, *supra* note 7, at 209-10.

124. See *supra* notes 86-94 and accompanying text.

125. Nobuyuki Honna, *Cultural Insights; Loan Words from English Have Important Roles to Play*, *DAILY YOMIURI*, July 31, 1995, at 8. Informed consent (i.e. explaining medical treatment issues to a patient and seeking her agreement) is not a concept that is easily expressed in Japanese. Direct translation would not convey the correct idea. *Id.*

126. *Gov't to Work Out Manual on Informed Consent*, *MAINICHI DAILY NEWS*, July 16, 1993.

have practiced an extremely paternalistic type of medicine.¹²⁷ For example, many Japanese physicians refuse to tell their patients that they have been diagnosed with cancer.¹²⁸ Historically, the Japanese populace supported this system; a 1989 public opinion poll found that only thirty-seven percent of the respondents believed that a person with cancer should be informed of her condition.¹²⁹

However, public opinion is beginning to change. A 1994 survey of 2,000 Japanese citizens revealed that sixty-four percent of the respondents would want to be told if they had cancer.¹³⁰ Currently, Japanese doctors utilize a case-by-case approach, informing a patient when they believe the truth will not exacerbate the patient's condition.¹³¹ In contrast, full disclosure is currently the norm in the United States.¹³² As of 1977, ninety percent of U.S. doctors surveyed agreed that they would reveal a diagnosis of cancer to their patient.¹³³ This represents a dramatic shift in attitude; a 1961 poll had found that ninety percent of U.S. doctors would *not* tell a patient diagnosed with cancer of his condition.¹³⁴

In Japan, several patients and families have sued their doctors for failing to disclose a cancer diagnosis,¹³⁵ and at least one patient has sued her doctor for revealing the diagnosis.¹³⁶ Japanese courts have generally dismissed both types of cases on the ground that physicians legally have great

127. Masao Onishi, *Physician, Explain Thyself; Doctors Must Get Down from Pedestal*, DAILY YOMIURI, Dec. 15, 1992, at 9 (in a typical medical examination in Japan, the white-gowned doctor arrogantly dispenses whatever treatment he deems best to the apprehensive patient).

128. Norio Higuchi, *The Patient's Right to Know of a Cancer Diagnosis: A Comparison of Japanese Paternalism and American Self-Determination*, 31 WASHBURN L.J. 455 (1992). Historically, Japanese doctors have refused to reveal a cancer diagnosis to a patient because it amounted to a death sentence. *Id.* Although now cancer is often treatable, many Japanese doctors are still reluctant to inform patients, particularly when the prognosis is poor, since they believe the shock may worsen the patient's condition. *Id.* at 456.

129. *Id.* at 455.

130. Joy Onozuka, *Check It Out; The Bottom Line on Illness*, DAILY YOMIURI, Mar. 9, 1995, at 10.

131. Higuchi, *supra* note 128, at 456.

132. *Id.* Many Japanese doctors criticize American doctors for disclosing too much to patients. There is a suspicion that the American practice of full disclosure is motivated more by the desire to avoid legal liability than a respect for the patient's autonomy. *Id.* at 457. However, some American physicians assert that their Japanese counterparts are too paternalistic. They claim that giving doctors so much discretion fails to recognize a patient's right to self-determination. *Id.*

133. *Id.*

134. *Id.* The heightened awareness of informed-consent issues heralded by Beecher's exposé of unethical medical experimentation may explain this extraordinary change in attitude. *See supra* note 45 and accompanying text.

135. Higuchi, *supra* note 128, at 456 (citing Tokyo District Court Judgment, Dec. 21, 1981, 1047 HANJI 101; Yokohama District Court Judgment, Nov. 25, 1988, 1317 HANJI 114).

136. *Id.* at 456 (citing Nagoya District Court Judgment, May 27, 1983, 507 HANTA 282).

discretion in deciding what medical information to share with a patient.¹³⁷ However, a recent case, *Makino v. Red Cross Hospital*,¹³⁸ broached the subject of patient *jiko-kettei-ken* (self-determination) for the first time.¹³⁹ This case involved a fifty-year-old nurse who went to the hospital complaining of stomach pain.¹⁴⁰ After making a tentative diagnosis of cholecystic (gall bladder) cancer, the doctors advised her to schedule surgery as soon as possible.¹⁴¹ They told her only that her gall bladder was swollen; the word *cancer* was never mentioned.¹⁴² Makino scheduled an appointment for the surgery for after her vacation. But, feeling better during the trip, she neglected to keep the appointment. Two months later, she collapsed at work and was rushed to the hospital, but it was too late to treat the cancer effectively. She died within six months.¹⁴³ Her surviving family, a husband and three children, sued the hospital for breaching a duty to disclose the diagnosis of cancer.¹⁴⁴

The court held that the defendant doctors did not breach their duty of care, reasoning that they had not reached a definitive diagnosis.¹⁴⁵ However, the court held that even had the doctors reached a definitive diagnosis, they would still have had the discretion to decide how much information to convey to the patient and her family.¹⁴⁶ In this regard, the decision appears unnoteworthy. However, for the first time, the court, albeit in dicta, asserted that doctors have a general duty to inform the patient or his family of the nature of the illness, any appropriate procedure, and the intended effects of the therapy.¹⁴⁷ The court explained that this duty is based on the patient's right of self-determination.¹⁴⁸ Although a Japanese court used self-determination language for the first time, the scope of the reform was limited by qualifying language granting doctors the discretion to determine the extent of information to provide to the patient. Therefore, physicians in Japan still have an immense amount of discretion in deciding when, to whom, and what to disclose about medical treatment.

The discretion protecting medical treatment decisions extends into the realm of medical experimentation. In the absence of government regulation, Japanese pharmaceutical companies and doctors can test investiga-

137. *Id.* The courts rely on the importance of physician discretion in making the "delicate" medical determination of whether particular information may worsen a patient's condition. *Id.*

138. *Id.* at 458 (citing *Makino v. The Red Cross Hospital*, Nagoya District Court Judgment, May 29, 1989, 1325 HANJI 103).

139. *Id.* at 460-61.

140. *Id.* at 458.

141. *Id.* at 459.

142. *Id.* at 458-59.

143. *Id.*

144. *Id.*

145. *Id.* at 460.

146. *Id.* The court explained that in Japan a doctor would never be required to disclose a diagnosis of cholecystic cancer to a patient, since it is virtually incurable. *Id.*

147. *Id.*

148. *Id.* Self-determination is limited when the doctor decides that disclosure would have possible adverse effects on therapy. In such a situation the physician may decide to whom, when, and how much information he should divulge. *Id.*

tional drugs on unsuspecting patients.¹⁴⁹ Experimental drugs are tested on thousands of patients without their knowledge, with pharmaceutical companies paying up to \$2,600 per research subject to hospitals.¹⁵⁰ In the past forty years there have been at least eleven major drug disasters in Japan, affecting up to 20,000 people and killing several hundred.¹⁵¹

The most recent scandal involved the drug Sorivudine. In the 1980s, the Japanese pharmaceutical company Nippon Shoji began plans to develop a "smash-hit" drug which it hoped would increase the value of its shares during a planned stock offering in 1991.¹⁵² The drug company decided to market Sorivudine, an anti-viral agent previously rejected in Europe as too dangerous.¹⁵³ When used in combination with certain chemotherapy agents, the drug injures or kills most patients.¹⁵⁴ During clinical trials in Japan, Nippon Shoji replicated these negative results. Three patients died within days of treatment with Sorivudine.¹⁵⁵ Two of these deaths were kept secret, because, as a former company executive explained, "[i]t is normal (in the pharmaceutical industry) to close your eyes to bad data . . . it would be a big problem if a drug which cost billions of yen to develop was not approved."¹⁵⁶

Researchers reported one of the deaths, as well as an animal trial in which every rat died, to the Health and Welfare Ministry's Medical Deliberation Committee, the Japanese equivalent of the FDA.¹⁵⁷ Nevertheless, the Health and Welfare Ministry approved Sorivudine¹⁵⁸ and Nippon Shoji released the drug with great fanfare. The drug was prescribed at a dosage of three pills a day, at a cost of \$29.54 per pill. Nippon Shoji made \$13 million in the first ten days.¹⁵⁹ The packaging contained a small warning label advising patients not to combine Sorivudine with anti-cancer

149. Akihiko Nishiyama, *New Rules Will Shake Drug Firms*, NIHON KEIZAI SHIMBUN (JAPAN ECONOMIC JOURNAL), Sept. 22, 1990, at 25.

150. Ben Hills, *Japan: Prescription for Disaster*, SYDNEY MORNING HERALD, July 30, 1994.

151. *Id.* For example, Enteroviroform, an anti-diarrheal drug, killed many people and may have blinded as many as 3,000 others. In addition, many Western parents in Japan take their children to the United States or Hong Kong for vaccinations because defective Japanese vaccines have killed children. *Id.*

152. *Id.*

153. *Id.*

154. *Id.*

155. *Id.*

156. *Id.* (quoting a former Nippon Shoji executive).

157. *Id.*

158. *Id.* Given the pressures on the Ministry, a denial of approval of the drug would have been unlikely. First, the Japanese Committee has only two inspectors to verify the validity of clinical data, as compared with the FDA's 100 inspectors, while Japan ingests twice as many medical drugs per year as the United States. In addition, Nippon Shoji spent \$13,000 entertaining each government official involved. Finally, if officials approve drugs, they can expect to be offered lucrative positions on a pharmaceutical company's executive board when they take early retirement in their fifties. *Id.*

159. *Id.* Nippon Shoji's president, Takakazu Hattori, claimed in private that Sorivudine was the most expensive drug on the market. The value of the company's shares soared as a result of the profits generated by the drug. *Id.*

drugs.¹⁶⁰ Many doctors did not even see the warning.¹⁶¹ However, a larger warning would probably have made little difference. In Japan, patients are generally not informed of the medications they receive and, as such, a patient's medication history can be difficult for doctors, and impossible for patients, to track.¹⁶² The problem is exacerbated by the fact that doctors rarely make appointments, so patients often see a different doctor on each visit.¹⁶³

Within two weeks of the drug's release the first death was reported to both the company and the Health and Welfare Ministry.¹⁶⁴ Eight days later the death toll was up to eight.¹⁶⁵ The Ministry finally issued a warning fifteen days later, after eight more people had died.¹⁶⁶ Although many patients survived their experience with the drug, some sustained lasting injuries, including keloids (painful scarring of the face and body), swollen extremities, and difficulty urinating.¹⁶⁷ The chairman and president of Nippon Shoji both resigned, and the Japanese government prosecuted other company executives for insider trading.¹⁶⁸

Following the Sorivudine scandal the Japanese government focused on improving the drug-approval process¹⁶⁹ by proposing an informed-consent requirement.¹⁷⁰ Although the Sorivudine disaster was an important catalyst, it did not single-handedly awaken concern about informed consent. As early as 1992 a number of citizens' groups started campaigning for a patients' rights law.¹⁷¹ Mr. Kondo, founder of the citizen action group

160. *Id.* The warning label did not contain a description of the potential for death or severe injury resulting from the combination of Sorivudine and anti-cancer drugs. *Id.*

161. *Id.*

162. *Sorivudine Should Not Have Been Approved*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Nov. 28, 1994.

163. James Sterngold, *Japan's Health Care: Cradle, Grave and No Frills*, N.Y. TIMES, Dec. 28, 1992, at A1. Consider the story of 70-year-old Genji Ito as an illustration of a typical visit to the doctor in Japan. Mr. Ito traveled 20 minutes by bicycle to get to the Toho University Hospital. He arrived at 7:30, an hour before the doctors start seeing patients. Because he was so early he was 69th in line. After waiting on a vinyl-covered bench until noon, he saw the doctor briefly for his heart medication. In Japan, crowded clinics and impersonal visits are the order of the day. On the positive side, Mr. Ito pays just 900 yen (\$7.25) a month for health care. *Id.*

164. Hills, *supra* note 150.

165. *Id.* Minutes from a meeting at Nippon Shoji headquarters prove that company executives knew of the mounting death toll. The company expected the deaths to remain a "secret within the company." *Id.*

166. *Id.* The belated warning saved company employees money. The day of the Health Ministry's warning 175 employees of Nippon Shoji dumped their shares on the market, personally saving millions of dollars. "After the announcement, [the company] shares plummeted from \$47 per share to \$22" per share. *Id.*

167. *Id.*

168. *Id.*

169. *Id.*

170. *Pharma Japan Statistics; Ethical Drug Market Trends*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Nov. 13, 1995.

171. Kaoruko Aita, *Citizens' Groups Seek Bill to Protect Patients' Rights*, JAPAN TIMES WKLY. (International Edition), Oct. 19, 1992, at 14. The group wants to create a system to review medical malpractice claims. About 350 new malpractice claims are filed each year. Plaintiffs rarely win these cases in court, even though the citizens' group asserts

Nagano, explained that it is unusual for Japanese doctors to tell patients anything about their illnesses or treatments.¹⁷²

Another group, *Kanja no kenriho wo tsukurukai* (Association to Create Patients' Rights) has held symposia to discuss questions people should ask their doctors about their diagnoses and treatments.¹⁷³ The group consists of lawyers, nurses, welfare workers, and patients who believe that the legal system must help protect patients' rights.¹⁷⁴ Membership has grown from fifty to five hundred in just a year.¹⁷⁵ Doctors have also become involved in the movement. The 24th General Assembly of the Japan Medical Congress in 1995 focused on the "human side of medical treatment," rather than more traditional subjects, such as the progress of medical science.¹⁷⁶ In years past, the physicians had relegated informed consent to a subordinate position in discussions. In 1995, by contrast, there was a dramatic increase in attendance at the seminar on informed consent.¹⁷⁷

In keeping with these trends, government regulation of informed consent in Japanese pharmaceuticals research is on the rise. In September 1989, the Ministry of Health and Welfare (MHW) announced Good Clinical Practice (GCP) standards for Japan.¹⁷⁸ As of late 1990, the MHW no longer accepted research protocols not in conformance with the GCP standards.¹⁷⁹ However, the GCP standards focusing on informed consent specify only that "written documentation is desirable."¹⁸⁰ The GCP also suggested the use of Institutional Review Boards (IRBs) for any entity seeking approval of drugs.¹⁸¹ Despite the proactive work by the MHW, the GCP informed-consent standard serves only as a guideline in Japan.¹⁸² The MHW's Committee on the Study of Matters Related to Informed Consent considered legally mandating adherence to written informed-consent standards as suggested by the GCP, but concluded that such action would

that 70% to 80% of the medical records used by doctors to defend against malpractice claims are altered. In fact, medical records are considered to be the doctor's property and patients cannot access their own records. The citizens' group seeks to decrease malpractice by requiring doctors to obtain informed consent for all medical procedures. *Id.*

172. *Id.*

173. Akiko Fukami, *Informed Consent: Doctor Says Patients Have Right to Know*, JAPAN TIMES WKLY. (International Edition), Aug. 17, 1992, at 8.

174. *Id.* The group proposes an informed-consent requirement, as well as a non-judicial check system to investigate malpractice claims. *Id.*

175. Aita, *supra* note 171.

176. Kazuo Maeno & Futoshi Kataoka, *Medical Congress Discusses 'Humane' Treatment*, DAILY YOMIURI, Apr. 17, 1995, at 3.

177. *Id.*

178. *Japan: GCP to Be Implemented in Fall 1990*, CHEMICALS BUS. NEWS BASE, Dec. 1, 1989.

179. *Id.*

180. *National Cancer Center Introduces New Clinical Trial Method for Anticancer Agents*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Apr. 24, 1995.

181. *Study on Proper Clinical Trial Methods to Start Soon*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Jan. 30, 1995. See *supra* notes 51-53 and accompanying text.

182. *Id.*

be "inappropriate."¹⁸³

At a 1994 meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, a majority of the members of the New Drugs Subcommittee reported that problems with the pharmaceuticals approval system persisted.¹⁸⁴ Specifically, they indicated in the questionnaire that the pharmaceutical industry continues to place too little emphasis on informed consent.¹⁸⁵ Indeed, a physician at the Osaka City General Hospital performed a survey in 1992 in which only sixty-one percent of physician respondents claimed that they explain clinical trials to the subjects involved.¹⁸⁶ Other approval problems exist as well. For example, an investigation by the deputy director of the Pharmaceuticals and Cosmetics Division of the MHW's Pharmaceutical Affairs Bureau discovered that pharmaceutical companies attempted to circumvent the IRB requirements.¹⁸⁷ "In many [drug] companies, the head of the r[esearch] and d[evelopment] section serve[d] as the IRB chairperson."¹⁸⁸ Because IRBs function as watchdogs of the research and development divisions of pharmaceutical companies, having the head of the division serve as the IRB chairperson is like having "a fox guarding the chicken coop."¹⁸⁹ In response, the government has stressed the importance of an independent chairperson.¹⁹⁰

Currently, the Pharmaceutical Affairs Bureau inspects all pharmaceutical manufacturers and medical facilities conducting clinical trials on new drugs to determine whether they are adhering to GCP standards.¹⁹¹ The Bureau also continues to encourage practitioners and drug companies to obtain written informed consent.¹⁹² To date, even when doctors obtain informed consent, they provide simplistic explanations and receive only verbal consent.¹⁹³ In fact, in a recent survey of clinical investigators, only 48.9% agreed that a researcher should always obtain informed consent in

183. *Informed Consent—Integral Part of Clinical Trials on New Drugs*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., July 3, 1995.

184. *The 15th General Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Dec. 26, 1994.

185. *Id.* The questionnaire addressed pharmaceutical approval-process topics, including approval application fees, review procedures, clinical trial methodology, and clinical trial guidelines. *Id.*

186. *Most Cancer Patients Want to Be Fully Informed*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Mar. 6, 1995. See *supra* note 101 for a definition of *clinical trial*.

187. *Importance of IRB Independence Stressed*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Sept. 25, 1995.

188. *Id.*

189. *Id.* (quoting Kazuhiko Mori, deputy director of the Pharmaceuticals and Cosmetics Division of the Pharmaceutical Affairs Bureau).

190. *Id.*

191. *Japan: GCP Inspections Started on Full Scale in Japan*, CHEMICALS BUS. NEWS BASE, June 4, 1993. The inspections emphasize clinical-trial contracts, informed consent, preservation of records, and institutional review boards. *Id.*

192. *Japan: PAB to Place Greater Importance on Informed Consent in Clinical Trials*, CHEMICALS BUS. NEWS BASE, Oct. 13, 1994.

193. *Yomiuri Shimbun, Cancer Center to Implement 'Informed Consent' System*, DAILY YOMIURI, July 27, 1995, at 3.

writing.¹⁹⁴ Interestingly, the responses strongly support strengthening the other GCP guidelines.¹⁹⁵

In a recent incident, thirteen people died in a clinical trial for Irinotecan Hydrochloride, an anti-cancer agent.¹⁹⁶ This catastrophe sparked renewed efforts from the Pharmaceutical Affairs Bureau of the MHW.¹⁹⁷ Allegedly, all thirteen patients had given informed consent, but only six of them had done so in writing.¹⁹⁸ Mr. Tanaka, a spokesperson for the Bureau, asserted that "[t]op priority must be placed on patients' rights in clinical trials, and for this purpose, informed consent must be obtained in writing whenever possible according to the GCP manual."¹⁹⁹

The MHW's development of GCP standards and the public's demand for patients' rights indicate that Japan is beginning to believe in the importance of informed consent. However, the strength and nature of this commitment is yet to be fully defined. Over half of all Japanese doctors surveyed still believe it is not necessary to obtain formal, written, informed consent from research subjects.²⁰⁰ Indeed, a recent study found that only three out of twenty-six patients participating in clinical drug trials had been asked for written, informed consent.²⁰¹

Moreover, Japanese doctors still describe informed consent as a "doctor's 'explanation'" and a "patient's 'consent.'"²⁰² Under this model, patients are neither encouraged nor made to feel comfortable enough to ask questions.²⁰³ This system may not represent a great improvement over the old authoritarian method, as detailed explanations given without attention to actual patient understanding only serve to confuse the patients.²⁰⁴ Another danger of this cursory definition of informed consent is that patients are thought to be gaining ground in health care self-determination, but in reality, doctors still have the final word in medical treatment decisions.²⁰⁵

As an illustration of ongoing Japanese medical paternalism, consider the Medical Practitioners Law.²⁰⁶ Article 22 outlines the physician's duty

194. *Consensus Not Reached on Informed Consent in Clinical Trials*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Sept. 12, 1995 [hereinafter *Consensus Not Reached*].

195. *Role of Chief Investigators in New GCP Not Clear*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Sept. 12, 1995. In particular, the survey response indicated agreement among chief investigators for strengthening GCP inspections and for thorough monitoring. *Id.*

196. *Informed Consent Must Be Obtained in Writing: Mr. Tanaka of the PAB*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Nov. 14, 1994.

197. *Id.*

198. *Id.*

199. *Id.*

200. *Consensus Not Reached*, *supra* note 194.

201. Yomiuri Shimbun, Editorial, *Protecting Patients' Human Rights*, DAILY YOMIURI, Apr. 26, 1995, at 6.

202. Onishi, *supra* note 127.

203. *Id.*

204. *Id.*

205. *Id.*

206. Medical Practitioners Law (Civil Code), Law No. 201 of 1948 (Supp. 1991) (Japan).

to deliver a prescription directly to the patient or patient's caregiver.²⁰⁷ However, the mandate provides for a number of exceptions. For example, when a doctor believes that the prescription may make the patient "uneasy," he does not have to give the prescription to the patient.²⁰⁸

D. Informed-Consent Standards Compared

A comparison of the approaches to informed consent taken by the United States, the European Union, and Japan clarifies how disparate the cultures are in this respect. The three parties to the ICH appear to lie on a continuum with self-determination at one end and medical paternalism at the other. The United States is positioned at the self-determination end, emphasizing the right of individuals to make informed decisions about whether or not to participate in experimental medical treatment.²⁰⁹ Japan is found close to the medical-paternalism border. Only recently have Japanese citizens begun to agitate for patient rights, including the right to be fully informed before making medical decisions.²¹⁰ The European Union lies somewhere in the middle of the spectrum. As represented by the United Kingdom, these nations agree that informed consent is important, but focus at least as much on medical progress.²¹¹ Physicians still hold a great deal of discretion in medical decision-making, even of an experimental nature.²¹² It is in this setting of conflict that these three parties formed the International Conference for Harmonization to attempt, *inter alia*, to standardize their disparate informed-consent procedures.

II. The International Conference for Harmonization

In October 1989, a conference of regulatory officials from Japan, the United States, and the EU met in Paris with a representative of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).²¹³ The participants agreed to a joint meeting including all of the sponsoring regulatory agencies, thereby creating the ICH.²¹⁴ The ICH is a joint effort between the United States, Japan, and the EU to identify and reduce differences in the requirements for pharmaceuticals approval.²¹⁵

207. *Id.* art. 22 (Duty to Deliver Prescription).

208. *Id.*

209. *See supra* Part I.A.1.

210. *See supra* Part I.C.

211. *See supra* Part I.B.

212. *Id.*

213. P.F. D'Arcy & D.W.G. Harron, *Proceedings of the First International Conference on Harmonization Brussels 1991*, 1991 INT'L FED'N PHARMACEUTICALS MFRS. ASS'N 8-9 (1991). Located in Geneva, Switzerland, the IFPMA acts as an international consultant to the pharmaceutical industry on all issues relating to the research and manufacture of prescription medications. *Id.* at xxiii.

214. *Id.*

215. Nightingale, *supra* note 18, at 3. The work of the ICH is conducted by 1) Expert Working Groups, 2) the Steering Committee in charge of oversight and policy, composed of two members of the regulatory agency of each country, two industry representatives from each country, and one person from each of three observer groups from Canada, the European Free Trade Area, and the World Health Organization, 3) an ICH

The six sponsors include the European Commission,²¹⁶ the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the U.S. FDA (the Center for Drug Evaluation and the Center for Research and Biologics Evaluation and Research, divisions of the FDA), and the Pharmaceutical Research and Manufacturers of America.²¹⁷ A partnership between these three socio-political regions is logical since, taken together, they develop the great majority of all new drugs.²¹⁸

A. ICH Goals

The ICH was founded to standardize pharmaceutical development practices and procedures between the three participants.²¹⁹ It has two primary goals. The first goal is to decrease the costs of drugs to consumers by minimizing regulatory problems associated with the need to comply with the differing requirements of each country, thereby lowering research and development costs.²²⁰ The second goal is to increase the safety, efficacy, and quality of pharmaceuticals.²²¹ The FDA has characterized the public health benefits of these tripartite regulatory negotiations²²² as follows: 1) to decrease the spread of disease within and between countries, 2) to increase consumer access to safe and effective drugs, 3) to improve the quality, safety, and efficacy of imported pharmaceuticals, and 4) to improve information transfer between countries on public health issues.²²³ The FDA Commissioner also claims that ICH efforts have enormous potential to limit duplication in research and therefore, will result in a major breakthrough by making a common registration process a reality.²²⁴

B. ICH Process

One of the first items on the agenda at the first ICH conference was the formulation of the structure of the ICH and its process for creating harmo-

coordinator, which rotates depending on which nation is sponsoring the current conference, and 4) a Secretariat to coordinate the ICH process, provided by the IFPMA. *Id.* at 4.

216. The European Commission is the executive body of the EU. D'Arcy & Harron, *supra* note 213, at xxi.

217. Draft Guidelines, *supra* note 19, at 42948.

218. Nightingale, *supra* note 18, at 3. The countries hold a conference every two years in one of the member countries. *Id.* at 4. The first conference was located in Brussels, Belgium in 1991. In 1993, Orlando, Florida hosted the conference. Yokohama, Japan was the site of the most recent conference held in November 1995. D'Arcy & Harron, *supra* note 213, at 2.

219. *See supra* note 18 and accompanying text.

220. Contrera, *supra* note 17, at 928.

221. *Id.*

222. *See infra* Part II.C.

223. THE FDA TASK FORCE REPORT ON INTERNATIONAL HARMONIZATION, REPORT TO THE COMMISSIONER OF FOOD AND DRUGS OF DECEMBER 1992 (1992).

224. Dr. David A. Kessler, FDA Commissioner, Keynote Address at the Second International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (Oct. 27, 1993) [hereinafter Kessler Address].

nized standards.²²⁵ The ICH members established a five-step process which includes: 1) the prioritization of problems by Expert Working Groups (EWGs), 2) approval of the EWGs' recommendations by the Steering Committee and promulgation of draft guidelines, 3) review of the draft guidelines by each party, 4) acceptance of the final guidelines by the parties, and 5) incorporation of final guidelines into each nation's pharmaceutical production regulations.²²⁶

225. The ICH Steering Committee met in April 1990 to set the goals and structure of the ICH process. D'Arcy & Harron, *supra* note 213, at 9.

226. *Id.* In the first step of the ICH process the Expert Working Groups (EWGs) prioritize the harmonization issues with which they are dealing. The probability of reaching a group consensus is factored into the priority decision. *Id.* at 9. Each of these issues represents a regulatory difference between two or more of the parties. When confronting a harmonization problem, the group first lists several general considerations that should be followed when promulgating a regulation governing pharmaceutical testing. *Id.* at 9. Drafting committees composed of representatives from each party's regulatory agency build draft guidelines around these considerations. Contrera, *supra* note 17, at 940 n.57 (citing INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, CLOSING REPORT, STATUS OF HARMONIZATION INITIATIVES, Annex 5, 17 (1993)) [hereinafter CLOSING REPORT]. FDA technical experts from both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research participate in these drafting efforts. Contrera, *supra* note 17, at 941 n.57 (citing Draft Memorandum from FDA on FDA/ICH Stages of Document Development 1 (Dec. 23, 1993)) [hereinafter FDA Memorandum]. In the United States, the proposed standards are then made available to the public for comment. The FDA Office of the General Counsel and the FDA Office of Policy approve the final FDA draft. *Id.* at 2. Eventually, the EWG adopts party consensus draft guidelines which are forwarded to the ICH Steering Committee. *Id.*

Step two of the ICH process involves the Steering Committee's approval of the EWG's recommendations. The Steering Committee first sends a copy of the consensus draft guidelines to each of the regulatory agencies for consultation pursuant to its internal consultation process. Each regulatory body reviews the guidelines for policy considerations and approves the draft. CLOSING REPORT, *supra*, at 17. At the FDA, the draft then goes back to the Office of General Counsel for final clearance before being published for public comment. The content of the draft guidelines and a request for public comment are published in the Federal Register. Contrera, *supra* note 17, at 940 n.57 (citing INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, REPORT OF THE STEERING COMMITTEE MEETING, March 9-10, 1993, Brussels 9 (1993) (ICH document Ref: ICH 2/14)) [hereinafter REPORT OF THE STEERING COMMITTEE].

Step three involves review of the comments and draft guidelines. In the United States, the FDA responds to public comments following publication of the draft guidelines in the Federal Register. The Office of General Counsel and the Office of Policy examine the revised guidelines after this round of notice and comment. After approval by these two offices, the FDA transmits the results to the appropriate EWG for its approval. The EWG then sends the tripartite guidelines to the Steering Committee for further approval. FDA Memorandum, *supra*, at 2.

Step four involves the ICH acceptance of the final tripartite guidelines. After receiving the final iteration of the draft guidelines, the Steering Committee either approves the draft or recommends changes. If approved the Steering Committee submits the harmonized tripartite guidelines to the regulatory agencies of each party for adoption according to the party's internal procedures. CLOSING REPORT, *supra*, at 17. In the United States, the FDA Steering Committee approves the document before the General Counsel and the Office of Policy see it once again. The FDA then publishes a notice of final rule in the Federal Register. FDA Memorandum, *supra*, at 3.

The fifth step of the ICH process concerns the incorporation of the guidelines into each party's pharmaceutical production regulations. CLOSING REPORT, *supra*, at 17. In

As part of the first step, the Steering Committee²²⁷ appoints EWGs²²⁸ composed of scientists recognized as experts in their fields.²²⁹ There are three general EWGs which focus on safety, efficacy, and quality respectively.²³⁰ These groups usually meet at the same time as the Steering Committee, although they sometimes participate in six-member drafting sessions in order to ensure progress on a specific guideline.²³¹ Only a meeting at which at least one member from each of the six sponsors is present constitutes an "official" meeting.²³² The goal of the Efficacy EWG is to enable the efficient development of new drugs worldwide.²³³ The four topics addressed by this EWG include clinical safety requirements, studies on the geriatric sub-populations of patients, design methods or requirements for dose-response trials, and definitions of good clinical practice.²³⁴

In August 1995, the FDA published draft guidelines created by the Efficacy EWG for "Good Clinical Practice."²³⁵ The purpose of the guidelines is to "define 'Good Clinical Practice' and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects."²³⁶ Requiring compliance with the standard is intended to assure the public that the rights, well-being, and confidentiality of persons participating in pharmaceuticals research will be safeguarded.²³⁷ These guidelines will not only standardize human-subjects research among the United States, Japan, and the European Union,

the United States, the FDA makes the requisite changes in the Code of Federal Regulations. If it becomes necessary to amend the regulation, the FDA reviews any further comments. FDA Memorandum, *supra*, at 3.

227. The Steering Committee oversees both the preparation for each ICH meeting and the development of the harmonization initiatives via the ICH process. REPORT OF THE STEERING COMMITTEE, *supra* note 226, at 9.

228. *Id.*

229. *Id.*

230. CLOSING REPORT, *supra* note 226, at 15.

231. *Id.*

232. *Id.*

233. D'Arcy & Harron, *supra* note 213, at 351. The Safety EWG concentrates on the toxicological aspect of pharmaceuticals. CLOSING REPORT, *supra* note 226, at 4-5. Toxicology is the study of a drug's harmful properties. GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 2 (Alfred Goodman Gilman et al. eds., 1980). The Quality EWG deals with stability testing, specifications for drug classification and dosage form, and standardization of pharmacopoeias. D'Arcy & Harron, *supra* note 213, at 39. Because this Note focuses on informed consent, only the Efficacy EWG will be discussed at length.

234. D'Arcy & Harron, *supra* note 213, at 351. Another example of draft guidelines produced by this EWG is Studies in Support of Special Populations (Geriatrics; Draft Guideline Availability), 58 Fed. Reg. 21,082 (1993). In addition, the Steering Committee has issued consensus draft texts from the Efficacy EWG to the larger group for consultation. These include: "Dose Response Information to Support Drug Registration," "Guidance on Clinical Safety Data Management—Definitions and Standards for Expedited Reporting," and "The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment." CLOSING REPORT, *supra* note 226, at 10-11.

235. Draft Guidelines, *supra* note 19.

236. *Id.* at 42,948.

237. *Id.*

but will also bring these countries in line with the already-standardized practices of Canada, the World Health Organization, Australia, and the Nordic countries.²³⁸ The guidelines address such specific considerations in human-subjects research as confidentiality, the reporting of statistical data, documentation, the involvement of vulnerable subjects, quality assurance, the use of Institutional Review Boards (IRBs), and informed consent.²³⁹

To determine whether the ICH Good Clinical Practice guidelines are sufficiently protective of pharmaceuticals research subjects' right to informed consent, it is necessary to explore further the process by which the guidelines were created. Specifically, it is important to evaluate how well the interests of potential research subjects were represented in the process.

C. ICH Use of Regulatory Negotiation

The ICH uses an international form of regulatory negotiation to formulate guidelines.²⁴⁰ Regulatory negotiation, also known as negotiated rulemaking, occurs when an administrative agency brings all interested parties together to create a proposed regulatory rule.²⁴¹ The goal is to reach a universally acceptable compromise. If all interested parties are satisfied with the proposed rule, a streamlined notice-and-comment procedure should result.²⁴² In addition, parties who participated in formulating the rule should be less apt to challenge it in court after it is finalized.²⁴³

238. *Id.*

239. *Id.* at 42,948-57.

240. Contrera, *supra* note 17, at 937.

241. PETER L. STRAUSS ET AL., ADMINISTRATIVE LAW 400-02 (1995). See generally Philip J. Harter, *Negotiating Regulations: A Cure for Malaise*, 71 GEO. L.J. 1, 42-52 (1982) (discussing requisite factors for the success of regulatory negotiation). Generally, a regulatory agency may create rules on the basis of its own knowledge and information. STRAUSS, *supra*, at 293. The proposed rule then enters the "notice-and-comment" process during which interested parties may suggest modifications. *Id.* at 292 (citing Administrative Procedure Act, 5 U.S.C. § 553(c) (1946)). Eventually, the agency adopts a final rule, taking into consideration the comments it received. *Id.* at 293. In contrast, regulatory negotiation requires the agency to negotiate the content of a proposed rule before it enters the notice-and-comment period. *Id.* at 400. Therefore, "Negotiated Rulemaking . . . permits affected interests to have greater control over the content of agency rules while ensuring fairness and balanced participation." Henry H. Perritt, Jr., *Negotiated Rulemaking Before Federal Agencies: Evaluation of Recommendations by the Administrative Conference of the United States*, 74 GEO. L.J. 1625, 1627 (1986). Its history reveals that regulatory negotiation is arguably successful. For example, none of the rules developed as a result of negotiated rulemaking and issued as final rules by the Environmental Protection Agency through 1987 has been litigated. Lee M. Thomas, *The Successful Use of Negotiated Rulemaking by EPA*, 13 ADMIN. L. NEWS 1, 3 (1987). But see Susan Rose-Ackerman, *Consensus Versus Incentives: A Skeptical Look at Regulatory Negotiation*, 43 DUKE L.J. 1206, 1206 (1994) (arguing that regulatory negotiation has been "oversold" as a reform).

242. Neil Eisner, *Regulatory Negotiation: A Real World Experience*, 31 FED. B. NEWS & J. 349, 371-73 (1984).

243. *Id.*

In determining whether regulatory negotiation is appropriate in a given situation, the agency head should ask the following questions: 1) will the rule significantly affect a limited number of readily identifiable interests; 2) can persons be identified who will adequately represent the significant interests; 3) are these persons willing to negotiate in good faith to reach a workable compromise; 4) is there a reasonable possibility that such a committee can reach a consensus within a relatively short period of time so that the procedure does not delay the rulemaking process; 5) is the agency willing and able to expend the necessary resources to provide adequate technical and organizational assistance to the committee; and 6) is the agency prepared to use the consensus as the basis for the proposed rule?²⁴⁴

Although the ICH promulgates guidelines rather than rules,²⁴⁵ the process can still be characterized as a type of regulatory negotiation.²⁴⁶ The interested parties, i.e. the pharmaceutical industries in each of the three regions and the drug-regulating bodies of each country, debate the issues in an attempt to create guidelines that increase the safety and effectiveness of drugs, while minimizing the research-and-development costs.²⁴⁷ Because the pharmaceutical industries and the governmental regulatory bodies are working together to find solutions, the rules resulting from the process should be acceptable to both.²⁴⁸ However, the ICH form of regulatory negotiation may fail because it excludes other important interests—specifically, the interests of potential research subjects.

III. Potential Implications for Informed-Consent Standards

By enabling the FDA to utilize foreign pharmaceuticals research, the ICH's standardization of Good Clinical Practice guidelines will aid the FDA in its quest to streamline its drug-approval process.²⁴⁹ Unfortunately, the FDA may be so eager to achieve this goal that it will overlook the potential negative outcomes to the ICH process. First, the FDA may be tempted to compromise the stricter informed-consent requirements of the United States in order to achieve standardization. Second, even if the FDA refuses to loosen American informed-consent requirements, it may accept the less protective requirements of the EU and Japan in the name of harmonization. The following section argues that both of these possibilities would lead to consequences of grave concern.

244. Negotiated Rulemaking Act of 1990, 5 U.S.C. § 563 (1990). Although this is an American statute, the ICH process is designed to work in a similar fashion. Contrera, *supra* note 17, at 938.

245. The general guidelines of an administrative agency serve to alert the regulated community of the agency's position on a given matter and are non-binding. In contrast, rules bind both the agency and the regulated industry to a substantive norm. See *Community Nutrition Institute v. Young*, 818 F.2d 943 (D.C. Cir. 1987).

246. Contrera, *supra* note 17, at 937.

247. *Id.* at 938.

248. *Id.*

249. See *infra* text accompanying notes 255-60.

A. Adoption of Less Stringent Standards

Thus far this Note has explored the differences in approaches to informed consent between the countries participating in the ICH effort to standardize pharmaceutical development. The ICH process fails to adequately account for these differences in its Good Clinical Practice guidelines. The result is an informed-consent standard insufficiently protective of human research subjects.

As the country most protective of a person's right to determine for herself whether or not to participate in medical experimentation, the United States has the most to lose from relaxed informed-consent standards. The following discussion explores the FDA's incentives to loosen informed-consent standards in the name of harmonization. Once the FDA subscribes to diminished informed-consent standards there is little recourse for potential research subjects. The ICH regulatory negotiation process gives this group no meaningful opportunity to disagree with the FDA since their interests are not represented in the process. In addition, judicial review provides no recourse for potential research subjects given the current state of beneficiary standing doctrine.²⁵⁰

The FDA faces great pressure to decrease the time and expense involved in the drug-approval process.²⁵¹ Harmonization would assist the FDA in its quest to expedite the process by eliminating the need to duplicate clinical-drug-trial data from other countries.²⁵² The present process is problematic because it developed as a response to a series of crises.²⁵³ During these crises the public was unwilling to support solutions which balanced safety with other considerations, such as cost.²⁵⁴ As a result, the United States arguably has created a procedure that is both more costly and time consuming than necessary.

Today the United States consistently lags behind other developed nations in the approval of new drugs.²⁵⁵ The current time lag between the synthesis of a new chemical entity and final FDA approval averages twelve years.²⁵⁶ It now costs an average of approximately \$231 million to take a new medicine from the laboratory to the pharmacy.²⁵⁷ Commentators blame FDA regulations for both the time delay and its attendant costs.²⁵⁸

250. See *infra* notes 281-89 and accompanying text.

251. Kassel, *supra* note 15, at 95 n.9.

252. Kessler Address, *supra* note 224.

253. See *supra* Part I.A.2.

254. Kassel, *supra* note 15, at 104.

255. *Id.* at 95.

256. Ann Gibbons, *Can David Kessler Revive the FDA?*, 252 *SCI.* 200, 201 (1991). The FDA is slower than the comparable agencies of other nations at every stage of the process. For example, in 1988, the average review interval for a newly developed drug was 15 months in the country of first approval. The FDA required an average of 29.7 months to review the same products. John C. Petricciani, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 *CLINICAL RES.* 701, 701 (1990).

257. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 *CHEMICAL & ENGINEERING NEWS* 28, 28 (1992).

258. Kassel, *supra* note 15, at 97. The time delays not only reduce early access for consumers, but also increase the cost of research and development. A one-and-a-half-

According to them, the FDA drug-approval process prevents Americans from obtaining innovative new drug therapies in a timely manner.²⁵⁹ For example, some critics estimate that the Beta Blocker, Timolol, used in the treatment of cardiovascular disease, could have prevented 100,000 American deaths had it been approved seven years earlier—the time at which it went on the market in Europe.²⁶⁰ In other words, critics argue, the FDA is causing needless deaths in the name of safety.

In an attempt to cure “drug lag,” under the Bush administration the President’s Council on Competitiveness promulgated eleven specific reforms in 1991.²⁶¹ The FDA rejected the Council’s proposal to expand the use of foreign data and to recognize foreign approvals.²⁶² Traditionally, the FDA has been wary of utilizing foreign studies because of a fear that they would not adequately safeguard consumer safety.²⁶³ Therefore, at least one domestic clinical investigation must be performed by a

year decrease in approval time can cut five years off the time needed to recoup research costs. Barry S. Roberts & Sara M. Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 405-06 n.13 (1989).

259. William Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 Through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 521 (1978).

260. Roberts & Bodenheimer, *supra* note 76, at 597. Former FDA Commissioner Hayes estimated that timolol would prevent approximately 17,000 deaths annually from secondary myocardial infarctions (i.e. heart attacks secondary to another disease or trauma). Anthony Hayes, *Current FDA Directives for Promoting Public Health*, 39 AM. J. HOSP. PHARMACY 427, 428 (1982).

261. Recommendations to Speed Drug Approvals Issued, [1990-91 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 42,603, at 43,617 (Nov. 18, 1991) [hereinafter Recommendations]. The recommendations were as follows:

- (1) use of external review,
- (2) expanded use of advisory committees,
- (3) an expanded role for Institutional Review Boards,
- (4) flexible interpretation of the efficacy standard,
- (5) accelerated approval,
- (6) expanded use of foreign data and recognition of foreign approvals in the United States,
- (7) enhanced computerization,
- (8) establishment of a classification system for application priorities,
- (9) use of internal systems of accountability,
- (10) reduction of excessive liability costs, and
- (11) direction of staff and financial resources toward new drug review.

Id. at 43,619-26.

262. *New FDA Approval Guidelines Set*, FACTS ON FILE, May 14, 1992, at 353. This recommendation would have required the FDA, in conjunction with foreign countries, to develop common standards for clinical studies, a common format for submission of drug approval applications, common sets of requirements for animal testing, criteria for plant inspections and good manufacturing practices, a reciprocity for approvals, and a process for the mutual acceptance of data. Recommendations, *supra* note 261, at 43,623-24.

263. Halperin, *supra* note 14, at 168. The agency is concerned with the following safety barriers implicated in accepting foreign data: the FDA’s lack of familiarity with foreign languages, Europe’s shorter historical commitment to high-quality clinical trials, discomfort with validating foreign data, poor design of foreign experiments, and a large number of statistical problems. Lasagna, *supra* note 13, at 370.

researcher recognized as competent by the FDA.²⁶⁴ Many scientists and leaders of the pharmaceutical industry argue that such replication is wasteful and unnecessary.²⁶⁵

Perhaps the FDA's participation in the ICH signals a new acceptance of standardization. Another possible interpretation is that the agency is experiencing so much pressure to reform its drug approval process, especially in light of public demands engendered by the AIDS crisis, that it is willing to ignore concerns about the differences in drug testing between the parties to the ICH. The FDA has long held that standardization is inadvisable because: 1) foreign research protocols traditionally are less detailed than American protocols in terms of judgment and measurement of efficacy, 2) foreign researchers are unaccustomed to being closely monitored through recorded data, 3) acclaimed foreign researchers are less amenable to guidance from their sponsors, 4) human interpretation of statistical norms and computer programs differ across cultures, 5) foreign companies do not believe FDA standards are truly necessary, and 6) trial report documents in other countries contain less data than in the United States.²⁶⁶ If the FDA is willing to compromise on these factors, it is certainly possible that it might also be amenable to lowering informed-consent standards. On the other hand, the FDA participation in the ICH may simply indicate an interest in pursuing *future* international standardization. This is an unlikely explanation, however, because the FDA has already signaled its intent to adopt the ICH-GCP by publishing it in the Federal Register and inviting public comment.²⁶⁷

A comparison between the FDA's current informed-consent standards²⁶⁸ and the ICH-GCP raises troubling issues. The FDA regulations delineate specific requirements for informed consent, including an explanation that the procedure is experimental, a description of the risks and benefits involved, a promise of confidentiality, a statement of alternative treatments, an explanation of medical therapy or compensation available in case of injury, an opportunity to ask questions, and an assurance that the subject is free to refuse to participate or to withdraw his consent at any time without loss of benefits.²⁶⁹ In contrast, the ICH guidelines are extremely vague, instructing researchers only to give a subject information that is "relevant" to his decision whether or not to participate.²⁷⁰ The definition of *informed consent* in the ICH-GCP is:

A subject's voluntary confirmation of willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written informed consent form that contains relevant information about the trial and that is signed and dated by the subject or the sub-

264. Halperin, *supra* note 14, at 169.

265. Lasagna, *supra* note 13, at 369.

266. *Id.* at 370.

267. Draft Guidelines, *supra* note 19, at 42,948.

268. See *supra* text accompanying notes 85-94.

269. 21 C.F.R. § 50.25(a)(1-8) (1985).

270. Draft Guidelines, *supra* note 19, at 42,949.

ject's legally acceptable representative.²⁷¹

If the FDA replaces its current regulations with the ICH-GCP, potential research subjects will have significantly less assurance that actual informed consent will be obtained. Ironically, the ICH regulatory-negotiation process will not allow these potential research subjects to advocate for a stricter ICH informed-consent standard, because they are not included among the groups represented at the ICH negotiations. Yet, surely an essential interest lies with potential research subjects—they should have been included. Indeed, the Negotiated Rulemaking Act²⁷² cautions the head of the agency to consider whether “there is a reasonable likelihood that a committee can be convened with a balanced representation of persons who can adequately represent the interests identified.”²⁷³ Because the ICH failed to invite this important interest to the bargaining table, the process cannot guarantee respect for the research subjects' needs.

Nor can research subjects rely on the FDA to protect their interests adequately. First, as this discussion indicates, the countervailing pressure of responding to “drug-lag” criticism casts doubt upon the FDA's motivation for participation in the ICH. Second, the FDA may have fallen victim to the peculiar group psychology of regulatory negotiation. In the process of regulatory negotiation, the agency becomes merely another part of the group, seeking consensus.²⁷⁴ This position denies the agency's role as representative of the public interest.²⁷⁵ This scenario is particularly problematic in the case of the ICH, because all of the non-governmental representatives are pharmaceutical companies.²⁷⁶ Indeed, a federation of these companies sponsors the ICH.²⁷⁷ It would be easy for the FDA to focus exclusively on the pharmaceutical manufacturers' interests, especially in the wake of pressure to streamline the drug-approval process.

On the other hand, the notice-and-comment period may adequately protect the public interest. The draft ICH-GCP specified that anyone could petition the FDA to continue to protect patients' rights via stringent

271. *Id.*

272. Negotiated Rulemaking Act of 1990, *supra* note 244, § 563.

273. *Id.* § 563(a)(3)(A). Of course, the ICH process is not subject to the requirements of the U.S. Negotiated Rulemaking Act since it is an international effort. However, as a form of regulatory negotiation, the ICH process implicates identical considerations to those addressed by the U.S. Act.

274. William Funk, *When Smoke Gets In Your Eyes: Regulatory Negotiation and the Public Interest—EPA's Woodstove Standards*, 18 ENVTL. L. 55 (1987).

275. *Id.* at 57. See also *Hudson Preservation Conference v. Fed. Power Comm'n*, 354 F.2d 608, 620 (2d Cir. 1965), *cert. denied*, 384 U.S. 941 (1966) (asserting that “the rights of the public must receive active and affirmative protection at the hands of the [agency]”). By deeming the agency merely another party to the agreement, regulatory negotiation limits the agency's responsibility for achieving consensus. As a result, the mandate of the statute may be subordinated to achieving consensus. This reliance on consensus for legitimacy is not problematic when all interests are represented. The fact that unrepresented interests do not participate in the notice-and-comment period or challenge the final rule in court does not indicate approval of the rule. Funk, *supra* note 274, at 57.

276. See *supra* part II.A.

277. Nightingale, *supra* note 18, at 4. See *supra* text accompanying note 213.

informed-consent requirements.²⁷⁸ The FDA has offered public workshops to discuss the draft guidelines.²⁷⁹ However, this access to the FDA is too limited to be effective.²⁸⁰ Indeed, the interests of future research subjects are extremely dispersed. No one knows when she may find herself in the position of having to decide whether or not to take an experimental drug. For this reason, most people who may someday become test subjects are unlikely to respond to the FDA's invitation to comment on rules that have no bearing on their current lives. Furthermore, notice is published in the Federal Register, which few Americans read regularly.

Furthermore, if the FDA adopts the ICH-GCP, research subjects will have no recourse until they are injured in a clinical trial performed with inadequate informed consent. Given current U.S. standing doctrine, a person will be unable to take the FDA to court prospectively to challenge the adequacy of new informed-consent standards. Standing is the "key to the courthouse door."²⁸¹ A party has standing to sue if she has sufficient stake in a controversy to create the need for judicial resolution of the issue.²⁸² Since standing is judge-made law,²⁸³ the definition of *sufficient interest* changes over time as courts reshape the concept. Currently, three U.S. Supreme Court decisions collectively establish stricter standing requirements for beneficiaries of agency action than for the industries directly regulated by the agency action.²⁸⁴

Lujan v. Defenders of Wildlife provides an explanation for this trend.²⁸⁵ In that case, the U.S. Supreme Court sharply curtailed the possi-

278. Draft Guidelines, *supra* note 19, at 42,948.

279. Nightingale, *supra* note 18, at 5 (describing public meetings held by the FDA to explain the ICH process).

280. For instance, because interests represented by consumer groups are likely to be well organized, they are able to make their voices heard. Yet, consumer groups' interests may be more aligned with the pharmaceutical companies than with research subjects because they demand that the FDA approve new drugs faster. See Kassel, *supra* note 15, at 95 n.9.

281. STRAUSS ET AL., *supra* note 241, at 1121.

282. *Sierra Club v. Morton*, 405 U.S. 727 (1972). In this case, the U.S. Forest Service accepted a bid by Walt Disney Enterprises, Inc. to build a ski resort in the Sequoia National Forest. Sierra Club sued the agency, seeking a declaratory judgment that the planned development contravened federal national park preservation law. The court held that although non-economic harm, such as loss of recreation in a national park, can constitute the "injury in fact" required for standing, the Sierra Club did not have standing because it had not made a showing that any of its members had sustained the alleged injury. *Id.*

283. STRAUSS ET AL., *supra* note 241, at 1121.

284. *Id.* at 1257. The cases are *Block v. Community Nutrition Institute*, 467 U.S. 340, 351 (1984) (holding that a consumer suit against the Secretary of Agriculture was precluded because congressional intent to exclude such suits was "fairly discernible in the statutory scheme"), *Lujan v. Defenders of Wildlife*, 504 U.S. 555 (1992) (holding that plaintiff conservation groups lacked standing to sue the Secretaries of Commerce and the Interior for promulgating regulations that misinterpreted the Endangered Species Act), and *Reno v. Catholic Social Services*, 509 U.S. 43 (1993) (O'Connor, J., concurring in the judgment) (acknowledging Lujan's stricter standards for beneficiary standing).

285. 504 U.S. at 555. The Court held that the "desire to use or observe an animal species, even for purely esthetic purposes" is a cognizable interest to support standing. *Id.* at 562. However, the plaintiffs had not shown that they had any plans to travel to

bility of standing for beneficiaries of administrative agency action.²⁸⁶ Writing for the Court, Justice Scalia explained that the likelihood of establishing standing “depends considerably upon whether the plaintiff is himself an object of the action (or foregone action) at issue.”²⁸⁷ If the plaintiff is not the direct object of the agency action, then causation for an injury suffered by the plaintiff depends on the response of a third party, namely the regulated industry.²⁸⁸ Because of the attenuated connection between the agency’s action—in this case, the regulation of the industry—standing will be “substantially more difficult” for the beneficiary to assert.²⁸⁹ Given this analysis, it is probable that the current Court would bar a research subject’s prospective challenge of the FDA’s acceptance of the narrower ICH informed-consent standards.

Indeed, if challenged in court, the FDA could argue that whether a research subject is injured by the relaxed informed-consent standard depends upon the researcher’s action. The FDA could claim that if the pharmaceutical industry follows the ICH-GCP correctly, a research subject should have sufficient knowledge to make an informed choice about whether or not to participate in a clinical trial. In other words, the argument asserts, it is the pharmaceutical company’s response to the guidelines that is critical, rather than the FDA’s promulgation of the guidelines. Of course, in actuality, while the behavior of the pharmaceutical company as research sponsor is certainly important, the public relies on the FDA to ensure pharmaceutical manufacturers’ compliance with minimal protective standards.²⁹⁰ Without the FDA holding them in check, these companies may find the pressure to market new drugs pushing them to compromise safety measures such as stringent informed-consent practices. Unfortunately, U.S. standing doctrine, combined with an ICH process that can afford to ignore patients’ rights issues, may lead to the FDA’s abdication of its public protection responsibility.²⁹¹

Egypt or Sri Lanka, where the animal species endangered by the projects partially funded by the Secretaries of Commerce and the Interior, were located. Therefore, the plaintiffs had demonstrated no “injury on fact.” *Id.* In addition, the Court argued that the citizen-suit provision of the Endangered Species Act violated the president’s power under Article II of the United States Constitution to execute federal law. *Id.* at 576.

286. *Id.*

287. *Id.*

288. *Id.* at 562.

289. *Id.*

290. Lasagna, *supra* note 13, at 322.

291. The interaction between the ICH process and standing doctrine is important because an agency is less likely to ignore a party’s interests during the rulemaking process if that party is capable of hauling the agency into court to challenge the regulations at the end of the process. STRAUSS ET AL., *supra* note 241, at 1121. Because standing doctrine precludes potential research subjects from suing the FDA over relaxed informed-consent standards, the agency lacks this incentive to include their interests in the ICH negotiations.

B. Disregard for Important Cultural Differences

The FDA might continue to enforce current regulations in the United States and accept ICH informed-consent standards only for purposes of reviewing clinical trial data from the European Union and Japan. While a limited adoption would benefit American citizens participating in pharmaceuticals experimentation, whether the FDA should base drug approval on research from countries that are not as protective of patients' rights remains questionable. The European Union's adoption of the Helsinki Declaration as its standard for medical experimentation indicates that those countries are willing to emphasize medical progress at the expense of informed consent.²⁹² The EU directive defining Good Clinical Practice states that the member states support informed consent "in principle,"²⁹³ further calling into question the EU commitment to informed consent.

Japan's medical paternalism is of even greater concern. On one hand, the Japan Pharmaceutical Manufacturers Association supports the ICH-GCP, although it recognizes that the Japanese GCP must be modified to accommodate the new standards.²⁹⁴ On the other hand, a Japanese newspaper reported that the *only* difference between the ICH-GCP and Japan's informed-consent standards is that the former requires documentation.²⁹⁵ Considering the Japanese medical community's past tendency to ignore informed consent, this statement is disturbing.

If the Japanese believe that the only modification to their limited informed-consent standards necessitated by the ICH is written documentation, the ICH informed-consent requirements are very weak. During independent audits of compliance with Good Clinical Practice standards carried out in the first ICH conference, Dr. Frances Kelsey, of the FDA Division of Scientific Studies, discovered Japanese studies in which doctors had not obtained consent because they expected it would be denied.²⁹⁶ Indeed, informed consent is still a new idea in Japan, as evidenced by the lack of an equivalent expression in the Japanese language.²⁹⁷ It is unrealistic to believe that the Japanese will interpret the ICH definition of informed consent with rigor comparable to that of the United States.

There are a number of reasons why cultural differences may lead to substantial problems. The Japanese spend \$80 billion per year on pharmaceuticals.²⁹⁸ They take twice as much medication as Americans,

292. See *supra* part I.B.

293. See *supra* note 99 and accompanying text.

294. *Revised Japanese GCP Should Include IND Application System*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Nov. 7, 1995 (IND is an abbreviation for "Investigational New Drug"). See *supra* notes 178-83 and accompanying text.

295. *ICH-GCP Draft Clarifies Responsibility of Sponsors*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., July 31, 1995.

296. D'Arcy & Harron, *supra* note 213, at 473.

297. See *supra* note 125 and accompanying text.

298. Hills, *supra* note 150. The Japanese spend more on pharmaceuticals than on their defense budget, and they spend almost twice as much on medicines as they do on rice, their main food staple. *Id.*

and three times more than the British.²⁹⁹ There is even a phrase, *kusuri zuke shaki*, (drug-pickled society) for this particular social concern.³⁰⁰ One likely reason for the enormous amount of drugs taken is that doctors rely on kick-backs from the pharmaceutical industry—estimated to be up to a quarter of the \$80 billion spent annually on pharmaceuticals—to supplement their meager incomes.³⁰¹ Since informed consent is a controversial notion, doctors often prescribe drugs to their patients without even telling them what they are receiving.³⁰² Further illustrating the problem, the Japanese refer to their doctors with the title *sensei* (master).³⁰³ In Japan, patients rarely ask questions.³⁰⁴

This cultural milieu presents pharmaceutical companies with the perfect opportunity to make a great deal of money. Doctors and pharmaceutical companies make money from selling drugs, and, because patients rarely ask questions, there is ample opportunity to prescribe medication. There is also an incentive to market as many new pharmaceuticals as possible. Many companies market “*zoro-shin*” (“me-too” drugs)—products with small modifications from the original drug.³⁰⁵ The “new” but often worthless or dangerous medications provide doctors with even more drugs to prescribe to unsuspecting patients, increasing the money earned by both doctors and pharmaceutical companies.³⁰⁶ Japanese pharmaceutical manufacturers take this approach to create profits because they are “global minnows,” with virtually no sales outside Japan.³⁰⁷ Small market share is due, at least in part, to the refusal by other countries to accept Japanese clinical-trial data.³⁰⁸ Other countries consider Japanese drug research to be lacking in thoroughness, and rarely publish papers submitted to academic magazines by Japanese researchers.³⁰⁹

This situation gives the Japanese pharmaceutical industry an incentive to participate in harmonization efforts, but no good reason to genuinely

299. *Id.* The Japanese lead the world in pharmaceutical consumption. *Japanese Health Care; Keeping Well in Their Own Way*, ECONOMIST, July 7, 1990, at 38 [hereinafter *Japanese Health Care*]. See also Sterngold, *supra* note 163.

300. Hills, *supra* note 150.

301. *Id.* Japanese doctors are paid poorly under the national health care system. One doctor estimated that he would need to see 150 patients per day in order to make a living. The incentives for taking kickbacks from the pharmaceuticals companies is, therefore, strong. The kickbacks come in the form of secret discounts on the approved prices. *Id.* The MHW has attempted to end this practice, but the physicians comprise a powerful lobby in Japan. *Japanese Health Care*, *supra* note 299, at 38.

302. Hills, *supra* note 150. Doctors often remove labels from prescription drugs before giving them to a patient. Sterngold, *supra* note 163, at A1.

303. Hills, *supra* note 150.

304. See Onishi, *supra* note 127; Sterngold, *supra* note 163; *Japanese Health Care*, *supra* note 299.

305. *Japanese Society of Clinical Pharmacology and Therapeutics: Me-Too Drug Trials Pose Dilemma for Physicians*, COMLINE DAILY NEWS BIOTECH. AND MED. TECH., Nov. 27, 1995.

306. Hills, *supra* note 150.

307. *Id.*

308. Editorial, *Orient Clinical Tests to Patients*, DAILY YOMIURI, Dec. 3, 1995, at 5.

309. *Id.* Japanese clinical trial data is poorly rated by foreign countries because the research is known to lack thoroughness. *Id.*

strengthen informed-consent requirements. Surely such a state of affairs should give the FDA pause. Consider the Sorivudine disaster, in which fifteen people were killed and scores were injured when the drug was released without satisfactory research.³¹⁰ What might have happened after pharmaceutical testing requirements had been completely harmonized if Japan had developed the drug first? Instead of the dangerous drug being released on only an unsuspecting Japan, Europe and the United States would have marketed it as well. How many people would have been killed by one company's profit motives? Stringent informed-consent requirements would have prevented the disaster from occurring in the first place. If the subjects had been told of the risks, it is doubtful they would have agreed to test the drug. For example, the fact that every rat died during the animal trials³¹¹ would have indicated to potential research subjects that the experimental drug was highly dangerous.

In this way, true informed consent serves as a check on pharmaceutical manufacturers. If full disclosure results in a lack of research volunteers, then the drug may indeed be too dangerous to be marketed. The FDA should remain mindful of this protective aspect of informed consent. Consumer groups, economists, doctors, and pharmaceutical companies may chastise the FDA for taking too long to approve new drugs,³¹² but the same groups would blame the FDA if something like the Sorivudine disaster occurred in the United States.

Even if Japan's minimalist approach to informed consent would not lead to safety problems in the United States, the question remains: should Americans condone a system that ignores the individual's right to self-determination in matters of bodily integrity? This right has long been central to our concept of justice.³¹³ Although informed consent has been a foreign concept to the Japanese, Japanese citizens have now formed patients' rights groups with growing membership.³¹⁴ Because Americans believe that self-determination is a basic human right, we should consider

310. See *supra* notes 152-68 and accompanying text.

311. Hills, *supra* note 150.

312. Petricciani, *supra* note 256, at 701.

313. See *Schloendorff v. Society of New York Hosp.*, 105 N.E. 92, 92-93 (N.Y. 1914) (Cardozo, J.) ("[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."). Ironically, the plaintiff, who complained that her doctors had performed an operation to remove a fibroid tumor without her consent, lost the case. Judge Cardozo asserted that the hospital could not be held accountable for the actions of the private physicians who admitted patients. That is, there was no master-servant relationship between the hospital and doctors upon which to base hospital liability. *Id.* However, other informed-consent cases have cited the concept of self-determination represented by the case with approval. See e.g. *Canterbury v. Spence*, 464 F.2d 772, 786 (D.C. Cir. 1972), *cert. denied*, 409 U.S. 1064 (1972). As a necessary incident of self-determination, informed consent in the medical context is now widely accepted in the United States. See *Problems in Securing Informed Consent of Subjects in Experimental Trials of Unapproved Drugs and Devices: Hearing Before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business*, 103d Cong. 1 (1994) (opening statement of Chairman Wyden).

314. See *supra* notes 171-75 and accompanying text (discussing the growing patients' rights movement in Japan).

the moral implications of condoning informed-consent standards which impair the struggle of Japanese patients to obtain control over medical treatment decisions.

IV. Recommendations

Since participation by all significant interests is a requirement for successful regulatory negotiation,³¹⁵ the ICH process should be open to groups representing human research subjects' rights from each of the three parties to the ICH. However, direct involvement by groups representing human research subjects is not, by itself, enough to provide for adequate public participation. The issues surrounding human-subjects research is sufficiently important to all Americans to make participation in the notice-and-comment procedure readily accessible to the general public. To ensure the feasibility of such participation, the draft guidelines produced during the ICH process should be published more conspicuously. For example, physicians should distribute FDA pamphlets to their patients, explaining any ICH proposals that affect research subjects' rights. Another possibility is advertising notice-and-comment procedures through newspapers, radio, and television.

In addition to public participation, the stringent informed-consent standards that we currently enjoy in the United States should be protected via legislation. To this end, current HHS/FDA informed-consent regulations could be repackaged as a research subjects' and patients' rights statute passed through the bicameral-presentment process. The involvement of both houses of Congress, as well as the president, will ensure that all interests are represented through the political process.³¹⁶ This step is necessary because agency regulations can change easily with changes in the White House.³¹⁷ The legislation must also define the agency's mandate unambiguously to prevent each new FDA Director from re-interpreting the statutory requirements.³¹⁸ In the meantime, the FDA should advocate for rigorous ICH-GCP informed-consent guidelines so that a country reviewing pharmaceutical clinical trials from another country can ascertain whether or not the researchers obtained genuine informed consent.

315. See *supra* Part II.C.

316. In contrast to the political process in which all interests are represented by definition, regulatory negotiation is not democratically legitimate unless all interests are explicitly represented. Rose-Ackerman, *supra* note 241, at 1211.

317. *Motor Vehicles Mfrs. Assoc. of the U.S., Inc. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 2958 (1983) (Rehnquist, J., dissenting) (explaining that the agency's modification of regulations seemed to be in response to the election of a new president from a different political party).

318. See *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 (1984) (holding that the Environmental Protection Agency's interpretation of ambiguous statutory language is entitled to deference). The Court further held that an agency's construction of an unclear statute may rely upon the incumbent administration's policy views; however, an agency must give effect to the *unambiguously* stated intent of Congress. *Id.* at 843.

Conclusion

Historically, researchers have used humans in medical experimentation with little regard for their right of self-determination. The most notorious example of this fact is the experimentation carried out on concentration-camp inmates by doctors of Nazi Germany. However, Americans have also been treated like guinea pigs in the name of medical science, as incidents like the Tuskegee Syphilis Study illustrate. In response to this blatant disregard for individual freedom, the United States has gradually developed relatively stringent informed-consent requirements. These standards are necessary to ensure that persons involved in medical research receive knowledge of the risks and benefits material to a truly informed decision about their participation. Other countries have also stressed the importance of informed consent, but have not weighed the individual's right of self-determination as heavily against other considerations as has the United States. For example, the European Union supports informed consent "in principle," but seems to place the importance of medical progress in the ascendant position. The Japanese society is just beginning to recognize the validity of informed consent in the medical setting. Japan still represents an overtly paternalistic culture in which doctors make most of the treatment and research decisions.

Against the backdrop of these cultural disparities, the three participants formed the International Conference on Harmonization to standardize their pharmaceutical development processes. As part of the Good Clinical Practices fashioned by the ICH, the participants have developed a vague standard for informed consent. The lack of clarity stems partially from the need to define this value-laden concept in a manner acceptable to all three cultures. The danger is that, in a rush to respond to criticism from those who claim the FDA's drug-approval process is too slow, the FDA may relax U.S. informed-consent standards to better fit the ICH group consensus. If this is the case, potential medical-research subjects, very often patients with debilitating illnesses, will have inadequate protection against researchers who fail to comprehensively inform them of the risks involved.

The ICH process fails to protect potential research subjects' interests because they are not included in the negotiations over how best to harmonize pharmaceuticals research. In fact, the American public is only peripherally involved in the ICH process via the notice-and-comment period. This limited opportunity for involvement is insufficient to grant research subjects an effective voice in the process since the courts will be closed to anyone wishing to challenge the new standards prospectively, given the current trend away from beneficiary standing.

Even if the FDA does not replace the current informed-consent requirements with those detailed in the ICH-GCP, the question remains: should the U.S. condone potentially harmful medical paternalism by accepting clinical-trial data from countries with less stringent informed-consent standards? Two concerns are implicated. First, the less-protective informed-consent standards of other countries could injure American consumers if

the FDA accepts their clinical-trial data without question in the name of harmonization. Second, even if American consumers can be protected, arguably, the United States should not condone human-subjects research performed in other countries without the assurance that participants are fully informed of the potential risks.

In the United States, every individual is free to determine her life's path without the interference of the government, as long as she does not interfere with others' rights to do the same. This commitment to self-determination is no less an important part of our belief system in the medical sphere than it is in decisions regarding occupation or procreation. After all, the right to bodily integrity is basic to self-determination. That right is threatened when individuals are not given the opportunity to make fully informed decisions to participate in experimental medical treatment. If we believe that every human being is a morally autonomous decision maker, then we must encourage other nations with which we develop international standards to recognize the primacy of self-determination in medical research.