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Article 1

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As with many industries, the pharmaceutical industry is becoming a global enterprise both in marketing prescription drugs and in conducting the human research necessary to establish the safety and efficacy of those drugs. The industry makes a significant contribution to health care: most important new drugs in the past forty years have come from private pharmaceutical companies.[1] However, the current regulatory system for pharmaceuticals presents a number of problems for many nations. The costs to pharmaceutical companies of duplicative research trials and unnecessary regulation results in higher prices, delays in treatment, or the unavailability of some drugs in some markets. At the same time, pharmaceutical regulation is intended to protect consumers from unsafe and ineffective drugs. How do nations achieve this goal yet still ensure that research costs are not prohibitive? The trend has been to move beyond national borders in order to find solutions to this dilemma. The current international focus on "harmonizing" drug regulations as a way to reduce the costs of drug development and provide earlier access to innovative therapies is a necessary step. However, the focus should be broadened to a global perspective.

Protection for human subjects of biomedical research has also become a global concern. When research was a purely local endeavor, local regulations for the protection of human subjects were adequate. For example, the United States has a very advanced and comprehensive set of laws for protecting its population during the investigation and distribution

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1. MILTON SILVERMAN ET AL., BAD MEDICINE: THE PRESCRIPTION DRUG INDUSTRY IN THE THIRD WORLD 187-88 (1992) [hereinafter BAD MEDICINE] (also describing the Soviet Union's, China's and Cuba's approaches, which prohibit profits, as "almost a total failure" at encouraging the discovery of important new drugs).

of pharmaceuticals.[2] However, research is no longer a local endeavor. The U.S. pharmaceutical industry is the largest in the world;[3] yet only 7.5% of the 1,771 new drugs marketed in the United States between 1961 and 1987 were marketed *first* domestically.[4] In 1986, approximately 18% of research funded by U.S. companies was conducted abroad.[5] Moreover, the current trend to "harmonize" pharmaceutical regulations, by increasing acceptance of research studies conducted abroad, so called "foreign data," or by adopting a mutual recognition procedure, will only increase the need for regulations extending beyond national borders to protect human subjects. Without such regulations the populations of developing countries may be particularly subject to exploitation.

We have reached a period in history in which we must formulate our laws with a global focus. We can no longer focus solely on local, state or national regulatory schemes that do not "tak[e] into account the significant role played by transnational forces embodied in multinational corporations, global capital markets, and rapidly advancing technologies and new scientific discoveries."[6] The lead article in a new law review dedicated to the study of globalization observed that "[t]oday, the line between domestic and international is illusory . . . [so that] we need . . . the kinds of domestic legal reforms necessary to mesh with or respond to global economic and political forces."[7]

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2. *See* Anne E. Wells, Comment, *Regulating Experimental AIDS Drugs: A Comparison of the United States and France*, 13 LOY. L.A. INT'L & COMP. L.J. 393, 399 (1990); FINAL REPORT OF THE ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION, Appendix C, Report of the Subcommittee on Medical Devices, Radiological, Health & Biomedical Research C18 (May, 1991) [hereinafter EDWARDS COMMITTEE REPORT] (indicating that the "FDA is the world leader in consumer protection"); Henry G. Grabowski, *Regulation and the International Diffusion of Pharmaceuticals*, in THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM 5, 7 (Robert B. Helms ed., 1980) (indicating that "[r]egulatory controls over new pharmaceuticals began much earlier in the United States than in Europe, and . . . consistently have been more stringent in scope and intensity than those abroad); Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace*, 48 FOOD & DRUG L.J. 577, 578 (1993) (indicating that "the [FDA] has enjoyed the luxury of world leadership regarding the regulation of new drug development, review, and postmarket surveillance."); Anne E. Wells, Comment, *Regulating Experimental AIDS Drugs: A Comparison of the United States and France*, 13 LOY. L.A. INT'L & COMP. L.J. 393, 399 (1990) (citing INSTITUTE OF MEDICINE-NATIONAL ACADEMY OF SCIENCES, CONFRONTING AIDS: UPDATE 1988, at 137 (1988)).

3. Kathleen Johnson, *United States*, *in* INTERNATIONAL PHARMACEUTICAL SERVICES: THE DRUG INDUSTRY AND PHARMACY PRACTICE IN TWENTY-THREE MAJOR COUNTRIES OF THE WORLD 603, 616 (Richard N. Spivey et al. eds., 1992) [hereinafter INTERNATIONAL PHARMACEUTICAL SERVICES].

4. *Id.* at 617. The FDA has made significant improvements in its drug approval process and has significantly reduced drug approval times, particularly in reviewing applications for "new molecular entities," those which represent new drug products as opposed to reformulations, new combinations, or new dosages of previously approved products. Peter H. Rheinstein, *Significant FDA Approvals in 1995*, 53 AMER. FAM. PHYS. 1871 (1996), *available in* LEXIS, News Library, ASAPII File.

5. Johnson, *supra* note 3, at 617.

6. Alfred C. Aman, Jr., *Indiana Journal of Global Legal Studies: An Introduction*, 1 IND. J. GLOBAL LEGAL STUD. 1, 2 (1993).

7. *Id.*

This Article will concentrate on two aspects of human rights implicated in the regulation of pharmaceuticals: first, the effect of the regulatory process on the availability to consumers of safe and efficacious drugs, and second, the use of human subjects for clinical drug trials or investigational research.[8] The need to distribute potentially beneficial drugs to the sick as expeditiously as possible and the need to protect research subjects are competing forces.[9] In Part I, this Article will describe the interdependency of world health care and the globalization of the pharmaceutical market, and will advocate that pharmaceutical products be regulated with a global focus. Part II of this Article will describe the international movement to harmonize pharmaceutical regulations, its origins, and goals. Part III will recommend that, in keeping with global human rights concerns, including the need to ensure that safe and efficacious drugs are available to consumers on a global basis, "total harmonization" should not be the goal of harmonization efforts. Part IV will address the effects of harmonization on human subjects in international research, and will advocate greater international protection for subjects through the development of binding, minimum standards, which should include obtaining informed consent and proceeding with human subject research only after oversight by representatives of the scientific and lay communities.

I. Pharmaceutical Regulation and World Health as Global Concerns

The need for a globalized response is evident in the pharmaceutical industry. A global focus is needed not only because of the significant presence of multinational companies[10] and the world-wide market for industry products,[11] but also because of the inter-relationship among nations in combatting diseases such as the world-wide AIDS epidemic.[12] The most

8. The human rights addressed in this Article may also be affected by patent hostility and price controls if they decrease drug availability or cause pharmaceutical companies to withdraw from some particular markets or to engage in less innovative research. *See* BAD MEDICINE, *supra* note 1, at 52; Clive Cookson, *Health-Cost Cuts Are a New Inhibition–Regulation*, FIN. TIMES, July 23, 1991, at IV. Sometimes, human rights may also be implicated in the work environment due to exposure to toxic substances, but this activity is governed by an entirely different regulatory mechanism. *See* Occupational Safety and Health Act of 1970, 29 U.S.C. §§ 651-78 (1988 & Supp. IV 1992).

9. Wendy K. Mariner, *AIDS Research and the Nuremberg Code*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 286, 294 (George J. Annas & Michael A. Grodin eds., 1992) [hereinafter NAZI DOCTORS].

10. Shoji Kodama, *Pharmaceutical Firms Revising System to Monitor Drugs*, NIKKEI WKLY., Jan. 18, 1992, at 8 (describing multinationals as especially well positioned "to benefit" from harmonization).

11. *Id.* (describing pharmaceuticals as high-tech products which, like electronics equipment, have "vast global potential"). *See also* Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations Among the United States, the European Community, and Japan*, 16 HOUSTON J. INT'L L. 665, 707 (1994).

12. *See* Evelynn M. Gentemann, Comment, *After* School Board of Nassau County v. Arline*: Employees with AIDS and the Concerns of the "Worried Well,"* 37 AM. U. L. REV. 867, 870 n.7 (1988). *See also* BAD MEDICINE, *supra* note 1, at 6.

"globalized" responses to date are the industry-led efforts to harmonize the requirements for registration of pharmaceuticals.[13]

When dealing with an emerging legal concept, it is important to ensure that a common nomenclature is in place. If "globalization" means the extension of the operations of firms in "developing, producing and selling goods and services outside their home country,"[14] then the pharmaceutical industry is well on its way to globalizing.[15] Instead, if speaking of the juridical or regulatory level, and if globalization means something other than internationalization,[16] then globalization[17] of pharmaceutical regulation has not yet occurred. Indeed, some argue that there is no globalization of law and that the world is currently facing disintegrative forces that equal or exceed the integrative forces.[18] Internationalization "refers to cooperative activities of *national* actors, public and private, on a level beyond the nation-state but in the last resort under its control" like matters "made the subject of bi- or multilateral cooperation."[19] "[G]lobalization as distinct from internationalization denotes a process of *denationalization* of clusters of political, economic and social activities."[20] While the process of harmonizing pharmaceutical regulation is an international endeavor, the very idea of mutual recognition of a drug's approval is a move toward denationalization. Whether or not globalization can and will occur, the present international harmonization effort can be seen as a strong integrative step.

In fact, the industry's continued globalization and the trend of international legal activities will only serve to heighten global concerns and the need to adopt global solutions to address these concerns.[21] Regional agreements such as NAFTA and international agreements such as the General Agreement on Tariffs and Trade are expected to increase globalization in the drug marketplace,[22] and correspondingly to increase the need for regulatory agencies to consider the "international health and safety implications"[23] of these agreements.

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13. *See infra* text accompanying footnotes 42-47.

14. Claudio C. Tarabusi & Graham Vickery, *Globalization and Pharmaceuticals*, OECD OBSERVER, Dec.-Jan. 1993, at 41 n.2, *available in* LEXIS, News Library, Curnws File.

15. *Id.*

16. Jost Delbrück, *Globalization of Law, Politics, and Markets–Implications for Domestic Law–A European Perspective*, 1 IND. J. GLOBAL LEGAL STUD. 9, 10-11 (1993).

17. *Id.*

18. Benjamin R. Barber, *Global Democracy or Global Law: Which Comes First?*, 1 IND. J. GLOBAL LEGAL STUD. 119, 119-24 (1993) (describing international law as "soft law," i.e., composed of non-binding legal principles which are not accepted as obligatory, and lacking in effective enforcement mechanisms because power is always exercised by individual nations).

19. Delbrück, *supra* note 16, at 11.

20. *Id.* at 10-11.

21. *Id.* at 11 ("[I]deally, globalization is to serve the *common good of humankind*, e.g., the preservation of a viable environment or the provision of general economic and social welfare.").

22. *Positive Outlook for OTC's in Latin America*, MARKETLETTER, Nov. 15, 1993, *available in* LEXIS, News Library, Curnws File.

23. FINAL REPORT OF THE ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION 52 (May, 1991) [hereinafter EDWARDS COMMITTEE REPORT].

Many of the issues raised by the current industry practice and regulation raise global concerns; health is a global concern. The problems caused by drug shortages, use of inferior, expired or misprescribed drugs, and inadequate or ineffective medical supervision are not merely local problems. For instance, antibiotics in developing countries are frequently used in inadequate dosages and for too short a treatment period, resulting in inadequate treatment for the local population and creating drug-resistant strains of bacteria.[24] These bacteria become impossible to treat as they invariably spread throughout the world.[25] Physicians and patients in the United States also contribute to the development of drug resistant strains of bacteria, *inter alia*, by misusing antibiotics for viral infections.[26]

Another example of how the health concerns of nations are interrelated is in the therapeutic value of medicinal products made from local flora and fauna, most of which are to be found in the Third World.[27] In addition, the failure of the existing pharmaceutical systems to cure preventable and treatable diseases of the Third World[28] has health care implications for citizens of the developed world who travel abroad as tourists, diplomats, business people, or soldiers.[29] Finally, the lesson we are learn-

24. BAD MEDICINE, *supra* note 1, at 7, 45.

25. *See* Lawrence K. Altman, *Mechanism Explained for Drug Resistance in Some TB Strains*, N.Y. TIMES, Jan. 18, 1994, at C4; *Exotic Diseases Waiting to Burst on the World*, DAILY TELEGRAPH, Sept. 4, 1993, at 8 (reporting on drug resistance to bacteria, including those present in pneumonia, gonorrhea, urinary tract infections, wound infections, and TB).

26. Michael D. Lemonick, *The Killers all Around*, TIME, Sept. 12, 1994, at 63, 67; Richard Saltus, *Return of the Germ*, 13 AM. HEALTH 72, 1994 WL 13047876, at *3-4, *14. *See also* Joan Stephenson, *Fighting Infectious Disease Threats via Research: A Talk with Anthony S. Fauci*, 275 JAMA 173, 174 (1996) (discussing whether external restraints should be imposed on physicians because "[m]any infectious disease experts have warned about overuse and misuse of antibiotics by physicians, which has encouraged the emergence of resistant strains of microbes.").

27. Shayana Kadidal, Note, *Plants, Poverty, and Pharmaceutical Patents*, 103 YALE L.J. 223, 223-25 (1993) (describing drugs developed from a Madagascar plant which have helped to increase the remission rates in various cancers, and the signing of the Convention on Biological Diversity as a means of providing compensation in exchange for the country's protection of these "biodiversity sources"). *See also* Michael J. Huft, Comment, *Indigenous Peoples and Drug Discovery Research: A Question of Intellectual Property Rights*, 89 NW. U. L. REV. 1678 (1995).

28. *See* BAD MEDICINE, *supra* note 1, at 4, 7, 161-75 (describing the situation as due to several factors, not just multinational corporate concerns with the bottom line, and generally improving as of the mid-1980s when Ciba-Geigy responded to the health crisis in the Dominican Republic through its Servipharm program). The industrialized nations, representing 25% of the world's population, consume 86% of the total drug supply, while the 75% of the population in the Third World accounts for the remaining 14% of the available drug supply. *Id.* at 4. Although the situation is improving slightly, except in Africa. *Id.* at 5. AIDS is perceived as a serious threat to world health, yet more people die each month from any one of several treatable or vaccine-preventable diseases such as malaria, measles, whooping cough, diphtheria, and polio. *Id.* at 6.

29. Of course, the global problem of contagious diseases cuts both ways; developing countries may also be subject to contagion brought from abroad. Ren-Zong Qiu, *What Has Bioethics to Offer the Developing Countries*, 7 BIOETHICS 108, 125 (1993) (attributing the current AIDS pandemic partly to importation from foreign tourists attracted to the "sex industry" of the host country).

ing in examining national health care delivery systems about the old adage that an ounce of prevention is worth a pound of cure is equally applicable to global health care needs.[30] We can pay some now to improve global health care delivery systems, or we can pay a lot more later.[31] In order to solve these problems we need a greater level of international cooperation than has existed.[32] Given that the pharmaceutical industry needs a global market to obtain a return on investment,[33] and that the regulations of other countries affect the domestic interests of producer and consumer nations, our perspective on pharmaceutical regulation must be global if we are to adequately protect human rights.

This Article will address the basic human right[34] concern of "freedom from harm,"[35] in this case, externally imposed harm. It is the same right which authorizes, and some would say demands,[36] that governments enact criminal laws and punish criminal offenders, in other words, it is the gov-

30. *See* Brent L. Davis & Michael J. Wagner, *Top 10 Trends to Expect from Clinton's Health Care Plan: Field of Insurers Will Narrow Further*, CORP. LEGAL TIMES, Mar. 1994, at 20.

31. Sue Baker, *Third World; Study Says Acts of Man Make Natural Disasters Worse*, UPI, Nov. 19, 1984, *available in* LEXIS, Nexis Library, Arcnws File (quoting from a Red Cross report which concludes that most disasters are unsolved development problems).

32. Ren-Zong Qiu, *supra* note 29, at 125.

33. David W. Jordan, Note, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L L. 471, 500 n.197 (1992).

34. For a more thorough discussion of the source, definition, and scope of human rights, see generally HUMAN RIGHTS IN OUR TIME (Marc F. Plattner ed., 1984) (providing several essays defining and examining human rights); MYRES S. MCDOUGAL ET AL., HUMAN RIGHTS AND WORLD PUBLIC ORDER 211 (1980). Although the Article posits and supports the existence of this basic human right, it is not intended to provide a comprehensive demonstration of the existence, scope or source of this right. Professor James A.R. Nafziger suggested in a personal communication that the author might find support for the existence of this right in Article 3 of the Universal Declaration of Human Rights, The Universal Declaration of Human Rights (Article 3), G.A. Res. 217, U.N. GAOR, 3rd Sess., U.N. Doc. A/810 (1948), which states that "[e]veryone has the right to life, liberty, and security of person," or in Article 12 of the United Nations' Covenant on Economic, Social and Cultural Rights, which includes the "right of everyone to the enjoyment of the highest attainable standard of physical and mental health," International Covenant on Economic, Social and Cultural Rights, Dec. 12, 1966, 993 U.N.T.S. 3, G.A. Res. 2200, U.N. GAOR, 21st Sess., Supp. No. 16, U.N. Doc. A/6316 (1966). Even in the absence of such a right, each nation should reach the same conclusions about protecting its own citizens–as consumers and as research subjects–on the basis of sound public policy. Moreover, the global nature of health problems–particularly infectious diseases–and of the pharmaceutical industry require sound public policy include consideration of the citizens of other countries.

35. *See* Joan Claybrook & David Bollier, *The Hidden Benefits of Regulation: Disclosing the Auto Safety Payoff*, 3 YALE J. ON REG. 87, 121 (1985).

36. M. Cheriff Bassiouni et al., *An Appraisal of Human Experimentation in International Law and Practice: The Need for International Regulation of Human Experimentation*, 72 J. CRIM. L. & CRIMINOLOGY 1597, 1666 (1981) (stating that "[t]he obligation of states to regulate their activities in order to prevent and suppress unlawful conduct and to express the universal human concern with a category of activities whose potential for abuse is revealed by history and the uncertainties of modern medical science and technology is uncontestable"). *See also* New Orleans Gas Co. v. Louisiana Light Co., 115 U.S. 650, 663 (1885) ("The wants of the public are often so imperative that a duty is imposed on the government to provide for them.").

ernment's authority to regulate for the "public health, safety and welfare."[37] This right extends to protection from harm by other private citizens, as in the case of criminal laws or protective regulation. It also extends to protection from government activity which causes harm to citizens, such as torture.[38] Thus, in this Article the term "human rights" is used to refer to the need of the public to be protected from harm in the health care area, particularly in the regulation of pharmaceuticals.

Focusing on the human rights impact of national and international pharmaceutical regulation is apropos because of the significant current international developments in the regulation of pharmaceuticals, as well as recent renewed international interest in the ethical issues raised by human experimentation,[39] and the growing interest in ethical issues relating to research on minority populations and research conducted in developing countries.[40] In addition, since developing countries are expected to present a significant, growing market for pharmaceutical products, the actions of the developed countries involved in the harmonization process will have a significant impact beyond their borders.[41] Thus, pharmaceutical regulation implicates the need to examine the global, human rights impact of international harmonization efforts on the availability of safe and effective medicines, as well as the adequacy of human rights protection for subjects of biomedical research in light of increasing international pharmaceutical research.

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37. The authority arises out of the "police power," the power "to place restraints on the personal freedom and property rights of persons for the protection of the public safety, health, and morals or the promotion of the public convenience and general prosperity." BLACK'S LAW DICTIONARY 1041 (5th ed. 1985). *See* State v. Mosley, 708 P.2d 1022, 1025 (Nev. 1985) (stating that "the authority to provide for health, safety and welfare of the citizen is inherent in the police power of the State without any express statutory or constitutional provision").

38. Carnes Lord, *Human Rights Policy in a Nonliberal World*, *in* HUMAN RIGHTS IN OUR TIME 125, 133. *See* United States v. Stanley, 483 U.S. 669, 709-10 (1987) (O'Connor, J., concurring in part and dissenting in part); *Stanley*, 483 U.S. at 686 (Brennan, J., concurring in part and dissenting in part) (disagreeing with the majority's holding that active duty serviceman could not sue government for money damages for injuries arising from his being an unwitting participant in secret Central Intelligence Agency LSD experiments, in violation of the Nuremberg Code).

39. *See generally* INTERNATIONAL SUMMIT CONFERENCE ON BIOETHICS, TOWARDS AN INTERNATIONAL ETHIC FOR RESEARCH WITH HUMAN BEING (1987) (Ottawa, Canada) [hereinafter TOWARDS AN INTERNATIONAL ETHIC]. *See also WHO Guideline on GCP*, PHARMACEUTICAL BUS. NEWS, Feb. 8, 1993, *available in* LEXIS, News Library, Arcnws File (describing World Health Organization Efforts to set "globally applicable standards" for biomedical research on humans).

40. *See, e.g.*, *infra* text accompanying notes 120-139.

41. CENTRE ON TRANSNATIONAL CORPORATIONS, UNITED NATIONS, TRANSNATIONAL CORPORATIONS IN THE PHARMACEUTICAL INDUSTRY OF DEVELOPING COUNTRIES 135-36 (1984) [hereinafter TRANSNATIONAL CORPORATIONS]; *Optimization of Global R & D Strategy*, MARKETLETTER, Apr. 2, 1992, *available in* LEXIS, News Library, Arcnws File (listing Latin America and Southeast Asia). *See also* BAD MEDICINE, *supra* note 1, at 231-32 (predicting little growth in the pharmaceutical market of developed countries and describing the Third World market as untapped).

II. International Harmonization of Pharmaceutical Regulations

The present efforts to harmonize drug regulation laws began in 1990 with an agreement between the Commission of the European Communities, the United States Food and Drug Administration (FDA), the Japanese Ministry of Health and Welfare, the European Federation of Pharmaceutical Industry Associations, the United States' Pharmaceutical Manufacturer's Association, and the Japanese Pharmaceutical Manufacturers Association to jointly sponsor an International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[42] This unprecedented undertaking brought together the regulatory agencies and regional pharmaceutical associations representing a majority of the world's producers and consumers of pharmaceuticals.[43] The key objective of this industry-led conference was to reach agreement "on an action programme to complete international harmonisation (1991-1996) with a view to prevent[ing] unnecessary repetition of human and animal testing and to reduc[ing] pharmaceutical research and development costs."[44] The fourth ICH is planned for the week of July 16-18, 1997,[45] and all signs point to an on-going harmonization process extending well beyond 1997. Although complete harmonization is a remote possibility, participants such as the pharmaceutical companies and critics of the FDA would like it to happen. The ultimate goal of ICH is to put safe and effective drugs in the hands of consumers without undue delay.[46] Thus, the ICH effort responds to increased concern about the high and rising cost of research and development and its effects–including the possibility that drug availability and innovative research will be inhibited.

The problems of high drug development costs and duplicative testing requirements are not unique to the ICH participant countries. Pharmaceutical industry representatives also met recently to discuss the issue of regulatory harmonization in Latin America, and of truly world-wide harmonization.[47] The consensus was that harmonization should be pursued through regional alliances such as the Andean Pact, Mercosur and CARICOM.[48] Representatives from the Andean Pact nations and the Pan American Health Organization have met to discuss harmonization strate-

42. *Commission of the European Communities*, IP, May 10, 1990, *available in* LEXIS, News Library, Rapid File.

43. The EC, Japan and the United States account for 75% of world pharmaceutical production and 90% of world research and development activities. Jordan, *supra* note 33, at 492. The prescription drug market for the three is estimated to be 79%. Leigh Hancher, *Competition and the European Pharmaceutical Market*, 37 ANTITRUST BULL. 387, 387 (1992).

44. *Commission of the European Communities*, *supra* note 42. In Europe, "harmonization" is sometimes spelled "harmonisation;" this Article uses the American spelling except when the quoted material or citation uses the British spelling.

45. *ICH Steering Committee Expert Groups Meet*, MARKETLETTER, May 13, 1996.

46. Kodama, *supra* note 10, at 8.

47. *Positive Outlook for OTC's in Latin America*, *supra* note 22 (stating that Latin America presently has more than 20 drug regulatory systems, but great potential for harmonization).

48. *Id.*

gies.[49] Countries in other regional alliances, such as the Asia Pacific Economic Cooperation, have discussed regional harmonization of standards.[50] Still, to the extent that developing countries seek to develop, manufacture, and export pharmaceuticals, they will be affected by the harmonization activities at ICH. Moreover, research needs to be conducted in developing countries to resolve the pressing health needs of their citizens, which differ from the health priorities of developed countries, and which are not being addressed by existing research. Harmonized standards governing human research set by the ICH countries may discourage many of the world's scientists from conducting research abroad if the standards are too strict or burdensome.

A. The Total Harmonization Prescription

Just as visionaries in the 1970s thought the computer would herald the advent of a paperless society,[51] the prophets of drug harmonization envision a world where only one round of research trials is performed.[52] However, total harmonization requires overcoming obstacles created by different medical and cultural traditions, as well as opposition led by some national pharmaceutical industries.[53] There will always be some differences in clinical testing requirements due to wide differences in medical practice and social conditions.[54] In addition, the recent recognition that research trials performed on one population may not provide sufficient protection for the targeted patient population stands in contraposition to efforts to achieve total harmonization.[55]

One proposal, particularly favored by industry, entails a mutual recognition process whereby the drug is submitted for approval in one country. Subsequent approval by that country would be recognized by all others in

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49. *Id.* The CARICOM countries have already taken regional action on pharmaceuticals. *See Health Against Profits in Drug Abuse Battle*, LATIN AM. ECON. REP., Mar. 30, 1979, *available in* LEXIS, World Library, Allwld File (describing regional efforts to reduce prices and increase drug availability).

50. Peter Gill, *Australia: APEC Pact on Harmonisation of Standards*, AUSTL. FIN. REV., Apr. 14, 1993.

51. Andrew Beven, *Paperless Dreams Buried by Office Reams*, THE GUARDIAN, Oct. 7, 1992, at 15.

52. Cookson, *supra* note 8, at IV ("Total harmonisation would mean that a company would need to carry out only one set of scientific tests, animal experiments and human trials, in order to apply to register a new drug anywhere in the world."). *See also* Delthia Ricks, *In Pursuit of Drug 'Harmony,'* ORLANDO SENTINEL, Oct. 28, 1993, at A3 (reporting on the second International Conference on Harmonization held in Orlando). Article refers to the Conference's goal of "expediting the global availability" of new drugs so as to permit instant U.S. approval of "medications tested and approved abroad." *Id.*

53. Peter O'Donnell, *Many Trials on the Long Road to Harmony in Drug Testing*, FIN. TIMES, May 27, 1993, at 4.

54. Cookson, *supra* note 8, at IV. Still, some believe a country like Japan could insist that a new drug be tested on Japanese patients *only* when that special requirement is based on "rational criteria." *Id.*

55. National Institutes of Health Revitalization Act, Pub. L. No. 103-43, 107 Stat. 122, 133-35 (1993) (to be codified at 42 U.S.C. § 289a-20) (providing that NIH supported research must include women and members of minority groups unless doing so would be inappropriate). *See also infra* text accompanying notes 120-139.

the alliance.[56] This proposal, however, is criticized by consumer groups which generally view a mutual recognition process as presenting the danger that a company will choose the most lenient national regulatory system for introduction of a new drug; instead, they call for "upward harmonization"–use of the highest national standards.[57]

III. Pharmaceutical Regulation in ICH and Developing Nations – Regulating for Safety and Effectiveness

National regulation of pharmaceuticals has a long history. For example, England enacted the first law attempting to control drug quality in 1540.[58] The United States first took action against quack remedies and unlabelled products containing alcohol, cocaine, or opium in 1906.[59] However, it was the 1937 "sulfanilamide elixir" disaster which led to the Food, Drug and Cosmetic Act of 1938 (FDCA)–the first attempt to require drugs to be tested for safety and labelled for use.[60] Drugs sold pursuant to a doctor's prescription were exempted from these requirements by a 1951 amendment[61] until the thalidomide disaster led to the 1962 Kefauver-Harris amendments to the FDCA,[62] establishing the basic regulatory mechanism still used today to ensure drug efficacy and safety.[63] The ensuing publicity revealed that neither drug manufacturers nor prescribing physicians knew much about the effects of the drugs that patients were taking.[64] Prescribers then, as now, relied on information supplied by the manufacturers, information which sometimes was based on inadequate testing or on fraudulent claims.[65] The amendment subjected all *new* drugs to FDA approval before they could be imported, manufactured, distributed or sold

56. Louis H. Orzack et al., *Pharmaceutical Regulation in the European Community: Barriers to Single Market Integration*, 17 J. HEALTH POL. POL'Y & L. 847, 859-61 (1992).

57. *Id.* at 861.

58. M.F. Cuthbert et al., *The United Kingdom, in* CONTROLLING THE USE OF THERAPEUTIC DRUGS 99 (William M. Wardell ed., 1978).

59. JAMES ROBERT NIELSEN, HANDBOOK OF FEDERAL DRUG LAW 4 (2d ed. 1992).

60. *Id.* at 5-6 (covering drugs "introduced in interstate commerce"). In 1937 a small manufacturer decided to market one of the infection-preventing "sulfa" wonder drugs in a syrup base. Unfortunately for the 107 men, women and children who were reported to have died from ingestion of the "sulfanilamide elixir," the syrup base was composed of diethylene glycol, the same slightly sweet product used today for automobile antifreeze. *Id.*

61. *Id.* at 7-8.

62. Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C. § 355).

63. NIELSEN, *supra* note 59, at 8. Thalidomide had been available abroad as a sleeping pill until the discovery that use during early pregnancy frequently resulted in severe deformities to the fetus. A pregnant woman who had purchased the drug abroad left the United States to have an abortion rather than risk giving birth to a "deformed child." *Id.* Prior to 1962, use of thalidomide was still under investigation by the FDA in the United States; only a few infants were injured because of the drug's availability as physician samples. *See id.*; BAD MEDICINE, *supra* note 1, at 210.

64. NIELSEN, *supra* note 57, at 8. *See also* DAVID J. ROTHMAN, STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING 86-87 (1991) (regarding the discovery that physicians were administering experimental drugs without informing patients).

65. NIELSEN, *supra* note 59, at 8.

in the United States.[66]

As Justice Felix Frankfurter indicated, the policy behind this extensive regulatory mechanism is based on the fact that drugs "touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection."[67] Through the first half of this century, concern for human rights concentrated on the consumer. The primary concerns about therapeutic drug use are that it might prove to be directly harmful or that it might prove to be ineffective and thus result in time and money wasted by sick individuals who might forego alternative treatments.[68] Recently, attention has also focused on the human "cost" of delays in drug approval.[69]

A. Indications for Harmonization

A "Single Market" has been readily established for most products in the European Union, but not for pharmaceuticals.[70] The European Union ("EU") began moving toward a harmonized drug regulatory policy in 1965.[71] Despite continuing attempts to create either a mutual recognition procedure or a single regulatory mechanism for approval of pharmaceuticals, the EU member states have acted under disparate, autonomous regulatory mechanisms.[72] However, in 1993 the EU did establish a centralized system for evaluating medicine through a newly created superordinate agency which began operating in 1995.[73] The centralized system exists

66. *Id.* at 3.

67. United States v. Dotterweich, 320 U.S. 277, 280 (1943).

68. 1 JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13.01 (2d ed. 1993).

69. *See, e.g.*, John Patrick Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 934-38 (1991); Dale Gieringer, *Twice Wrong on AIDS: The F.D.A. Frustrates Victims*, N.Y. TIMES, Jan. 12, 1987, at A21. There is a great deal of dispute about the extent of this cost. *See, e.g.*, BAD MEDICINE, *supra* note 1, at 211-13 (suggesting that drastic estimates of the cost of regulatory delay are largely hyperbole). *See also id.* at 213 (listing a number of drugs which have had to be recalled and describing Great Britain's faster drug approval process as requiring many more product withdrawals). There is also some disagreement with the view that the United States is the slowest of the "sophisticated" drug producing nations. *See, e.g.*, Rosemary P. Wall, Comment, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317, 328 (1984) (indicating that Japan has the most stringent regulatory process because foreign drugs are not available in Japan until they have been approved in the country of origin and must in any event be re-tested in Japan).

70. *E.C. Commentaries*, Coopers & Lybrand, Mar. 3, 1994, at 1- 2, *available in* LEXIS, World Library, Allwld File. This report attributes the delay to cost control and national public health measures. *Id.* at 1.

71. Leigh Hancher, *The European Pharmaceutical Market: Problems of Partial Harmonization*, 15 EUR. L. REV. 9, 12 (1990).

72. *Id.* at 12-17.

73. *EMEA Reports Successes in Inaugural 1995*, MARKETLETTER, Feb. 5, 1996, *available in* LEXIS, News Library, Curnws File; *E.C. Commentaries*, *supra* note 70, at 7. Most pharmaceutical manufacturers will be able to proceed under either this centralized system or under a re-vamped de-centralized mutual recognition procedure. *Id.* There is some indication though that while the EU has in theory finally reached accord on a workable harmonized regulatory scheme, in practice, at least in the view of industry officials, the trend is in the opposite direction–toward imposition of more individualized

alongside a decentralized mutual recognition system which is supervised and arbitrated by the same agency.

While the regulatory systems in some European countries are generally considered to be faster at approving drugs and to place greater emphasis on post-marketing surveillance, it is not clear that patients are better off.[74] Although the U.S. system seems to delay the introduction of some efficacious drugs, the number of drugs whose marketing approvals in Europe have been withdrawn after severe adverse reactions, including deaths, is used by supporters to defend the FDA's slower regulatory system.[75] However, a harmonized and centralized European drug approval process may exacerbate the so-called "drug lag;" pharmaceutical companies may initially bypass the United States and submit their new products to the European Agency for the Evaluation of Medicinal Products (EMEA) in order to bring the product to market quickly and recoup their development costs.[76]

In Japan, a purely national focus presents its own barrier to the marketing of new pharmaceutical products to Japanese consumers. The Japanese drug approval process has been described as seemingly "designed to protect local pharmaceutical companies as much as Japanese patients"[77] because of its insistence on extensive testing in Japan.[78] After the SMON affair[79] Japan enacted stringent drug approval requirements.[80] However, like the United States,[81] Japan is also becoming more receptive to the use of foreign data.[82]

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and unique requirements by the member countries. *See Pharma Industry's Need to Regain Credibility*, MARKETLETTER, Mar. 15, 1993, *available in* LEXIS, News Library, Arcnws File; *EC Single Market "Hype" Warning*, MARKETLETTER, Mar. 9, 1992, *available in* LEXIS, News Library, Arcnws File.

74. *Testing Time for Drugs*, ECONOMIST, Aug. 7, 1982, at 69, *available in* LEXIS, News Library, Arcnws File.

75. *See id.* (listing such a situation with the anti-arthritic drug, Opren).

76. *See* Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace*, 48 FOOD & DRUG L.J. 577 (1993). *See also* Elizabeth M. Rutherford, *The FDA and "Privatization"–The Drug Approval Process*, 50 FOOD & DRUG L.J. 203, 223 (Anniv. Ed. 1995) (indicating that the "threat [to] the FDA's [regulatory] preeminence" posed by European regulatory competition will spur agency efforts to harmonize drug regulations and avoid needless duplication); Comment, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2021 (1995) (indicating that the result may be "an even greater 'drug lag'").

77. Clive Cookson, *Drug Industry Still Healthy*, FIN. TIMES, Nov. 21, 1990, at 37.

78. Clive Cookson, *Prescription for Success*, FIN. TIMES, Dec. 3, 1990, at VII. The industry is described as becoming more accomodating in view of the overseas expansion of Japanese companies. *Id.*

79. *See infra* notes 134-136 and accompanying text.

80. Wall, *supra* note 69, at 328.

81. *See infra* note 129 and accompanying text.

82. Cookson, *supra* note 77, at 37. As of 1990, the Ministry of Health and Welfare was described as "becoming more willing to accept toxicity tests and preclinical data from overseas" but still "insist[ing] on Japanese clinical data before it will consider any new drug." *Id.* The Article noted that one sign of progress was the upcoming approval of the contraceptive pill for use in Japan after three decades of use in the United States and Europe. *Id.*

The pharmaceutical regulations of the more than one hundred developing countries with their diverse governments, laws, and cultures need not be fully described here.[83] However, it is significant that most developing countries apparently rely on the regulatory processes of the developed countries through use of a certifcation scheme which permits the drug's use in the developing country if the drug has been approved for use in the country of manufacture.[84] This certification scheme, adopted to combat the dumping of untested, ineffective or dangerous products on the markets of developing countries,[85] is not an ideal solution. When a consumer country lacks facilities to monitor pharmaceutical use, promulgation of pharmaceutical products under a safe-until-proven-otherwise presumption can be a significant problem;[86] the certification scheme encounters difficulties with pharmaceuticals from nations whose regulations are too lax (ineffective or dangerous drugs marketed) or too stringent (effective treatments delayed or unavailable). Furthermore, reliance on a certification scheme may exacerbate a situation about which developing countries have long complained–the lack of treatments geared to the health needs of developing countries.[87] A manufacturer may have no incentive to test a drug and subject it to the regulatory process of a country where the drug is unlikely to have much of a market.[88] Instead, certification will tend to provide consumers in developing countries access to drugs marketed to meet the needs of, and tested on, consumers in developed countries. Consumers in developing countries with their own regulatory approval process may be no better off if pharmaceuticals must be subjected to yet another review process with its own idiosyncratic requirements.

Although pharmaceutical products are developed and marketed internationally, if not globally, they are currently regulated only at the national level. The focus of these national regulations has been on establishing the safety and effectiveness of new products. The FDA, in particular, has been lauded for its role in protecting consumers from unsafe and ineffective products. National regulations can reduce the possibility that unsafe or ineffective products are introduced into a particular country. However, national regulations can also create significant barriers to pharmaceutical

83. The state of the pharmaceutical industry and of drug regulation in developing countries varies widely. TRANSNATIONAL CORPORATIONS, *supra* note 41, at 11. The most advanced countries engage in manufacture of active ingredients, processing of raw products, and conduct research for developing new drugs. *Id.* Those countries, which can meet a substantial portion of their own drug requirements and sometimes export to other countries, include Argentina, Brazil, Cuba, Egypt, India, Mexico and South Korea. BAD MEDICINE, *supra* note 1, at 44. Yet many developing countries lack the financial resources and technical skills to set up the necessary testing facilities. Ellen N. Cone, Note, *International Regulation of Pharmaceuticals: The Role of the World Health Organization*, 23 VA. J. INT'L L. 331, 348 (1983).

84. Cone, *supra* note 211, at 349-50 (describing the development and functioning of the WHO recommended scheme).

85. Wall, *supra* note 69, at 329.

86. TRANSNATIONAL CORPORATIONS, *supra* note 41, at 31.

87. Wall, *supra* note 69, at 329.

88. *Id.* at 329-30.

availability. Until recently, new pharmaceuticals were required to be tested and approved in every major market where the drug was to be sold.[89]

B. Patient Warnings–Drug Availability and Human Rights

The duplication of effort and requirement of compliance with diverse national regulations increase the costs of new drugs to the consumer and may result in delays of product entry into countries with more stringent drug approval mechanisms or small markets.[90] Although the treatment of human subjects in pharmaceutical research has long been recognized as a human rights issue,[91] until recently little attention was paid to the human rights issues created by the regulatory process. In the United States, the FDA perceives its regulatory role to be based on "good science and consumer protection."[92] However, there is an inherent tension between requiring safety and developing new, effective drug therapies.[93] This tension has led the terminally ill to challenge both the delays in the process and the legitimacy of government regulation altogether.

In the 1980s, for example, the FDA's regulatory process came under attack because of the lack of available treatment for AIDS, the FDA's perceived contributions to the drug lag, and the high cost of drug development.[94] For the first time, unexplained or unnecessary delays in the drug approval process were seen as human rights issues. In response to public pressure, the FDA changed its regulations to allow terminal patients greater access to promising drugs, even though the required scientific testing and regulatory review processes had not yet been completed.[95] AZT was one of the drugs which received this fast track treatment because the initial studies suggested it was effective in combatting AIDS.

The AZT story, however, also reveals the need to conduct research in a systematic and scientific manner. Overemphasizing the needs of the individual patient for promising treatments can ultimately be detrimental to society and to that class of patients[96] because the purpose of the investigation–determining whether the drug is effective–may be compromised. The findings in the AZT study about the drug's true effectiveness are questionable because the study was contaminated by outside factors, such as members of the placebo group obtaining AZT on their own.[97] Blurring the line

89. Kanusky, *supra* note 11, at 667 and *passim*; Nancy E. Pirt, *The Regulation of the Export of Pharmaceuticals to Developing Countries*, 25 DUQ. L. REV. 255, 267 (1994).

90. Kanusky, *supra* note 11, at 667, 703-07 (1994).

91. *See infra* text accompanying notes 137-58.

92. Ronald Podraza, *The FDA's Response to AIDS: Paradigm Shift in New Drug Policy?*, 48 FOOD & DRUG L.J. 351, 351 (1993).

93. Klaus von Grebmer, Commentary, *in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM 59, 61-62 (Robert B. Helms ed., 1980).

94. *See generally* Podraza, *supra* note 92.

95. *See Id.* at 361-67.

96. *See* Podraza, *supra* note 92, at 356 (describing the tension between the patient's right of self-determination and the collective interests of all patients).

97. Linda Marsa, *Toxic Hope: Widely Embraced, the AIDS Drug Is Now Under Heavy Fire*, L.A. TIMES MAG., June 20, 1993, at 14. Research subjects are not required to take the placebo instead of seeking treatment since they can withdraw from the study at any

between research and treatment can also be detrimental to patients themselves when they put their hopes on one drug as "*the* cure" despite serious side effects from that drug, and when science is unable to verify their beliefs because the experiment is not properly controlled.[98] Later evidence revealed that AZT, a highly toxic drug with very severe adverse effects, is not tolerated by many AIDS patients and may provide only transitory benefits because the virus develops a resistance to AZT.[99] Moreover, only four out of every hundred patients achieve the anticipated benefit of a slower progression of the disease.[100] Thus, relaxing the regulatory process by allowing AIDS patients access to AZT may have led many to rely on a drug that was nowhere near as effective as it initially promised to be.

The AZT story also contains a warning about the dangers to consumer safety of streamlining the regulatory process too much. With AZT, the usual toxicity studies were not completed and the clinical trials were halted early when AZT demonstrated some benefit, despite reports of methodological problems with these studies.[101] Thus the FDA's allowing AZT to be widely available to patients before completion of the regulatory process may have been a mistake for reasons of safety *and* effectiveness.

While inefficiencies in the regulatory process and a continuing re-evaluation of the endorsed research protocols are legitimate areas of focus, a complete abrogation of pharmaceutical regulation is not in the best interests of individuals or society. If experimental drugs are widely available, it will be "impossible to determine which drugs do and do not work" because controlled research will be impossible.[102] While some individuals will have fortuitously come across the "right" drug, many others will not, and they will have wasted time on ineffective or harmful drugs. If, as with AZT, most patients place their hopes on the first drug which shows promise, they may forego other new treatments and new innovations altogether. Without a significant subject population to test new treatments, the safety and effectiveness of other potential cures will not be established unless the initial treatment is proven to be ineffective. No one will be able to identify the safe and effective drugs, and society will be worse off.[103] "Most people are not in a position to evaluate the risks and benefits of an experimental substance, especially when science is uncertain about them. Thus, society has an obligation to identify therapeutic measures and to prevent exploitation of and harm to its members."[104]

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time. In this case the patient-research subjects put what they thought were their own interests ahead of society's need to know whether the drug is effective, without dropping out of the study.

98. *See id.* at 28.

99. *Id.* at 32-33.

100. *Id.* at 33.

101. *Id.* at 28.

102. Mariner, *supra* note 9, at 295.

103. *Id.*

104. *Id.* at 296. Some, however, would abolish entirely such "paternalistic" measures as drug regulation and automobile safety standards. *Id.*

Before achieving total harmonization, the ICH nations must grapple with the issue of how much testing is required before a conclusion can be reached that a drug is safe and effective and should become available as a treatment. Currently, ICH participants hold widely divergent views on this issue. For instance, not only does France not require a randomized, controlled study, French researchers view placebo-controlled studies as "cruel and inhumane" since the patients receiving the placebo have "no chance of surviving."[105] In contrast, American scientists do not believe a drug's efficacy can be proven until after such a randomized controlled study has been carried out.[106]

The French view of controlled studies also presupposes that, at least with respect to terminal patients, those receiving the drug (the treatment group) are better off. A recent clinical trial which resulted in several deaths among the treatment group underscores the fact that automatically assuming the treatment group is better off may be overly simplistic.[107] Determining how much testing should be required is partly a policy issue, but it is primarily a question for science. The prevailing scientific view is that without randomized controlled studies, causality cannot be proven.[108] Other

105. Wells, *supra* note 2, at 403.

106. *Id.* at 412. Randomized controlled studies are designed to determine whether a drug's seeming effectiveness is caused by some factor other than the drug, particularly the psychological effect known as the placebo effect whereby patients who believe they are taking an effective drug will in fact feel better. Michael D. Green, *Legal Theory: Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation*, 86 Nw. U. L. Rev. 643, 646-47 (1992).

107. Lawrence L. Altman, *Fatal Drug Trial Raises Questions About 'Informed Consent,'* N.Y. Times, Oct. 5, 1993, at C3.

108. Stephanie C. Austin et al., *The History of Malariotherapy for Neurosyphilis: Modern Parallels*, 268 JAMA 516, 518 (1992) (claiming that because randomized controlled trials (RCT's) were never carried out no one knows whether malariotherapy is efficacious in the treatment of neurosyphilis); Mary M. Dunbar, *Shaking up the Status Quo*, 46 Food Drug. & Cosm. L.J. 673, 680-81 (1991) (indicating that for some researchers RCT's are necessary to a determination of drug efficacy, while for others they are the "gold standard"); Kenneth F. Schulz et al., *Assessing the Quality of Randomization from Reports of Controlled Trials Published in Obstetrics and Gynecology Journals*, 272 JAMA 125, 126-27 (1994) (indicating that "[r]andomized controlled trials provide the most valid basis for the comparison of interventions in health care. . . . Thus, for readers to have justifiable confidence in the internal validity of a trial, the report should demonstrate adequate randomization."); Kenneth F. Schulz, *Subverting Randomization in Controlled Trials*, 274 JAMA 1456, 1456 (1995) (supporting JAMA's emphasis on RCT's and indicating that empirical evidence "supports the importance of adequate randomization"); Paul D. Stolley & Tamar Lasky, *Malaria Therapy: The Value of the Randomized Controlled Trial, Reply to Criticism*, 269 JAMA 211, 212 (1993) (indicating that presently efficacy of a treatment cannot be demonstrated without a randomized control trial). *See also* Charles Marwick, *Philosophy on Trial: Examining Ethics of Clinical Investigations*, 260 JAMA 749, 749-50 (1988) (interviewing John Fletcher who suggests that randomization is not only ethically permissible, but may be ethically required under the justice principle because it produces the most scientifically valid results and distributes the risks and benefits of the study "as fairly as possible over the whole population of those participating.").

Randomized controlled trials are the best method to prove causation, whether it be proving that the drug causes the beneficial effect anticipated, i.e., is effective, or that the drug causes other unanticipated and harmful effects, i.e., is not safe. Unless a cause and effect relationship is demonstrated, it will not be clear whether the observed effect

types of research can only give correlational information which would require a much longer time frame before a decision on drug effectiveness could be reached at the same comfort level as under a randomized study. We should not abandon controlled studies unless doing so would be in the interests of good science–a determination which has not yet been made.

The U.S. drug approval process has been described as biased towards an assurance of safety prior to marketing approval.[109] Some of the European regulatory systems are "more flexible" in pre-marketing regulations, but regulate more heavily in the post-marketing phase.[110] One benefit of a post-marketing regulatory phase is its ability to catch adverse reactions that show up only with prolonged use, or, like the DES tragedy,[111] manifest themselves only years later.[112] Whatever the duration of pre-marketing clinical research requirements, there will always be some adverse reactions that are not discovered in the research phase; thus, total safety cannot practicably be achieved. Moreover, the longer the research phase, the longer the delay in the drug's availability to the public. There may also be some negative information on drug efficacy, such as drug tolerance, which can only be discovered through post-marketing surveillance.

Therefore, one way to reduce the time needed before a drug is approved, and still ensure safety and effectiveness, would be for the FDA to reduce pre-marketing research requirements, and employ post-marketing surveillance more effectively, as is done in Europe. In essence, the drug's marketing phase would become another long-term study of a wider, more varied population.[113]

(whether harmful or beneficial) was caused by the drug or some other factor. Moreover, all drugs cause some side effects and every decision to approve a new drug requires a risk-benefit analysis in which the drug's apparent effectiveness is weighed against its apparent safety. *See infra* notes 141-42 and accompanying text. Thus, basic information about the drug's safety is needed prior to approval. However, not every adverse effect that will result from wider use of the product can be detected in the clinical trials; thus safety cannot be assured entirely through pre-market testing. David Kessler, *Introducing MEDWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 JAMA 2765, 2765 (1993). Thus conducting randomized controlled trials is important for reasons of effectiveness *and* safety, but this type of pre-market testing is implicated more in concerns over a drug's effectiveness.

109. *See* Jordan, *supra* note 33, at 484-88 (describing various factors which play a role in this systemic bias). The mechanisms for drug approval in the United States and various countries, have been described elsewhere. See Wall, *supra* note 69, at 323-30 (describing processes in the United States, Great Britain and Japan); Johnson, *supra* note 3, at 619-20.

110. *See* Grebmer, *supra* note 93, at 59-61 (describing an incident in which the German newspaper, *Der Spiegel*, published an article attacking a drug company for continuing drug trials when the trials had indicated the drug reduced mortality).

111. In the case of DES (diethylstilbestrol), safety problems were not discovered until women whose mothers took the drug while pregnant developed vaginal cancer. *See, e.g.*, Sindell v. Abbot Laboratories, 607 P.2d 924, 925-26 (Cal. 1980), *cert. denied sub nom.* E.R. Squibb & Sons, Inc. v. Sindell, 449 U.S. 912 (1980).

112. Wall, *supra* note 69, at 325.

113. *A Faster Track for New Drugs*, FIN. TIMES, Dec. 9, 1991, at 20, *available in* LEXIS, News Library, Arcnws File; *Testing Time for Drugs*, *supra* note 74, at 65.

If time and cost savings are to be achieved, this would entail, at the very least, reducing the duration of randomized controlled studies. If safety is to be assured, the regulatory process would have to be capable of withdrawing drugs from the market speedily after undesirable adverse reactions are identified.[114] However, the prospects in some countries for a harmonized regulatory policy that places greater emphasis on post-market surveillance are less than ideal. In the United States, few doctors report adverse reactions to the authorities, and, as a result, a post-marketing surveillance system would be ineffective[115] absent a national paradigmatic shift. It is not clear which system would be more cost-effective, as a number of factors come into play. While post-market surveillance might be cheaper for the regulatory agency (and the pharmaceutical firm), a shift to more post-market oriented regulation might shift the costs of research to patients, their insurers and other health care payors (which may well be the government).

For many developing countries, post-marketing surveillance is not feasible. For those countries which lack basic health care resources and have very few doctors for large segments of the population, such post-marketing regulation is nearly impossible.[116] For those countries which rely entirely on the producer nations' regulatory decisions to allow marketing, there would be less protection from unsafe and ineffective drugs with a system balanced in favor of post-marketing surveillance. Some of the ICH participants have recognized the special needs of developing countries.[117] A solution to the regulatory problems of these countries cannot be achieved without a global focus on harmonization activities and international cooperation.

Similarly troublesome are the prospects of harmonizing drug approval through a mutual recognition system without a uniform system of regulation. Mutual recognition would provide less protection for those countries which continue to emphasize pre-marketing approval. First, pharmaceutical firms would likely seek approval in the countries with the least pre-marketing surveillance and then simply seek recognition of the approving

114. *See A Faster Track for New Drugs*, *supra* note 113, at 20.

115. *Id.*

116. Health expenditures in the Third World are "appallingly low." BAD MEDICINE, *supra* note 1, at 4. WHO sources estimate that half a billion people are suffering from tropical diseases and live in countries with an average per capita income under $400 and average annual government health care expenditures of $4 per person. *Id.* For a description of the lack of health care personnel and resources in many developing countries, see generally *id.* at 1-8. There's also some indication that some physicians in developing countries report positive results without following research protocols. *See infra* note 170.

117. *See Japan Orphan Drug Promo System*, MARKETLETTER, Oct. 4, 1993, *available in* LEXIS, World Library, Allwld File (describing statement of Japanese official that developing countries have responsibilities towards the rest of the world). *See also* BAD MEDICINE, *supra* note 1, at 237 (quoting then FDA associate commissioner, Stuart Nightingale).

country's decision in all other nations.[118] Second, all countries without effective post-marketing surveillance would have to rely on the post-marketing surveillance system of the approving country. This approach is unlikely to detect genetic, dietary and other local differences.[119] A centralized approval system would either prolong the testing process in order to take these differences into account, or it would similarly need to rely on a uniform system of post-marketing surveillance being in place. Therefore, in order to adequately protect humans from harm, adoption of a mutual recognition or centralized regulation process requires a harmonized regulatory system with an agreed-upon emphasis on pre- and post-marketing surveillance in place throughout the world.

C. Contraindications to Total Harmonization–Ethnic and Other Factors

Recently, attention has focused on the tendency of pharmaceutical research conducted in the United States to rely on homogeneous subject populations, primarily "middle-aged white men" in carrying out clinical trials.[120] As a result of this practice, when drugs are approved for human consumption, physicians must "guess whether new findings can be extrapolated to the rest of their patients."[121] "[F]or most classes of drugs, no one knows if ethnic variations in drug metabolism exist, or where they have been seen, as with β-blockers and antidepressants, what the full extent of their clinical relevance might be."[122] Similarly, some male-only studies of heart disease resulted in dietary recommendations which actually increased the risk of heart disease for women.[123]

If differences exist in the way different ethnic groups react to certain drugs, then a research protocol which excludes that group may miss not only the side effects of that particular drug, but may result in a significant positive effect being missed altogether (i.e., a false-negative result). These issues raise equity or justice concerns,[124] but to the extent that the effect of inadequate pre-marketing research essentially becomes post-marketing experimentation,[125] which is likely without proper disclosure, the situa-

118. Comment, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2024 (1995) (indicating that dominance of the pharmaceutical companies on the world health market may lead regulatory agencies in a mutual recognition system to "engage in a competitive 'race to the bottom' of the regulatory pool").

119. *See infra* notes 120-139 and accompanying text.

120. Paul Cotton, *Is There Still Too Much Extrapolation from Data on Middle-aged White Men?*, 263 JAMA 1049, 1049 (1990).

121. *Id.* The situation leaves some physicians wary of prescribing these drugs altogether. *Id.*

122. *Id. See also* Rebecca Dresser, *Wanted: Single White Male for Medical Research*, 22 HASTINGS CENTER REP. 24, 26 (Jan.-Feb., 1992) (stating that "normal" lithium dosages when given to African-Americans produce toxic reactions due to physiological differences); Comment, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2024-25 (1995).

123. Dresser, *supra* note 122, at 27.

124. *Id.* ("The justice principle mandates fair distribution of the benefits and burdens of biomedical research.").

125. *See* Sue V. Rosser, *Re-visioning Clinical Research: Gender and the Ethics of Experimental Design*, 4 HYPATIA 125, 129 (1989). *See also* R. Alta Charo, *Protecting to Death:*

tion raises concerns about both beneficence[126] and autonomy based principles. The problem of pharmaceutical data based on a population which is not representative of the ultimate consumer is not unique to U.S. based research.[127]

To the extent that drugs tested elsewhere will be marketed in the United States, the same issues will arise with respect to both efficacy and safety. Until recently countries including the United States and France required that regulatory approval be based on domestic data, i.e., research conducted on citizens of the country where regulatory approval is sought.[128] Although the FDA recently expanded the circumstances under which it would accept foreign clinical data, it recognized the need to require that the foreign data be "applicable to the U.S. population and U.S. medical practice"[129] because "medical, genetic, and cultural differences between countries" present "unique problems not associated with domestic data."[130]

That cultural, genetic, medical, dietary or lifestyle factors may affect drug interaction is suggested by recent international experiences with some drugs. For instance, a multi-nation epidemiological study of the controversial analgesic and anti-pyretic, dipyrone, which had been linked to the development of certain fatal blood diseases, found that use of the drug had no negative effect on patients in Israel and Budapest, but increased the risk of developing these fatal side effects by five times for patients in Milan and Sofia and by twenty to thirty times for patients in Ulm, Berlin and Barcelona.[131] These disparate results generated much controversy and criticism. However, the investigators were all respected scientists and the disparities were never fully explained, except for the possible occurrence of geographic and ethnic differences.[132] In some countries, dipyrone is dispensed more often than aspirin, over-the-counter, and without any indication of these side effects.[133]

In Japan, the development of a fatal nervous system disease was associated with prolonged use of clioquinol, an anti-diarrheal agent.[134]

Women, Pregnancy, and Clinical Research Trials, 38 ST. LOUIS U. L.J. 135, 152 (1993). Dresser states that the choice is not about "protect[ing] women and people of color from research risks. Instead the choice is whether to expose some consenting members of these groups to risk in the closely monitored research setting, or to expose many more of them to risk in the clinical setting without these safeguards . . . ." Dresser, *supra* note 122, at 27.

126. Dresser, *supra* note 122, at 27.

127. *See, e.g.*, Kodama, *supra* note 10, at 8 (describing Japanese concerns over the lack of clinical tests on the elderly despite an increasingly elderly patient population).

128. Wells, *supra* note 2, at 403.

129. 21 C.F.R. § 314.106(b)(1) (1994).

130. New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452 (1985). The issue is apparently still on the agenda for regulators involved in the ICH process. *See* Ricks, *supra* note 52, at A3 (noting that working groups want to ensure that the drug approval process includes testing of the drug's effects on different ethnic groups).

131. BAD MEDICINE, *supra* note 1, at 93-94.

132. *Id.* at 93-97.

133. TRANSNATIONAL CORPORATIONS, *supra* note 41, at 33.

134. *Id.* at 32.

Although isolated cases have been reported throughout the world, Japan was the only country faced with an epidemic: 10,000 people were stricken by 1970.[135] The disease, dubbed subacute-myelo-optico-neuropathy (SMON) often led to paralysis of the legs, acute gastrointestinal problems, blindness, and even death.[136] Many of the patients had been taking clioquinol regularly. Although the evidence for other patients was contradictory or incomplete, the outbreak in Japan ended shortly after clioquinol products were withdrawn from the market.[137] The product is considered a "public menace" in Japan and has been withdrawn in the United States, the United Kingdom and the Caribbean.[138] Other countries, including Brazil, Colombia, Egypt, India, Indonesia, Mexico, and Venezuela, consider the product safe and essential for public health.[139] The dramatically different experiences with clioquinol use have never been fully explained.

For all the foregoing reasons, harmonization in the regulation of pharmaceuticals cannot be achieved in a manner consistent with protecting human rights throughout the world unless the proper balance between the rights of the patient and society is achieved. Nations and regulators must determine the degree of scientific testing required before a legitimate conclusion can be reached about a drug's safety and effectiveness. Proposals for harmonization also raise the need to determine something we know very little about: how local and genetic differences affect drug interactions and how these differences can be recognized in a harmonized procedure. Since the problem is greater for developing nations relying on studies conducted in developed countries, these nations need to take a more active role in the developments at ICH.[140]

D. The Prudent Harmonization Prescription

There is no such thing as an effective drug without side effects.[141] Consequently, a "safe" medicine is one which has a positive benefit to risk ratio. That benefit to risk analysis varies over time, from country to country, and from region to region within any given country.[142] The analysis will also depend upon the needs of the society and of the individual patients suffering from the ailment for which a cure is sought. Given that these tensions are inherent in the analysis, determining what degree of testing is required

135. The accounts began with two Argentine physicians in 1935 who reported that patients they had treated with clioquinol had developed severe nerve damage. BAD MEDICINE, *supra* note 1, at 192-193.

136. *Id.* at 193.

137. *Id.* at 193-94.

138. *Id.* at 21.

139. *Id.* at 21-23. An Egyptian investigation of the SMON situation could not find a single case of SMON despite heavy clioquinol consumption in the country. *Id.* at 23.

140. A related concern, the limited applicability of data tested on younger subjects for an increasingly older patient population, has already been addressed at ICH. *See The Community, the US and Japan Participate in Conference on Harmonisation in the Pharmaceuticals Sector*, AGENCE EUROPE, Nov. 15, 1991, *available in* LEXIS, World Library, Allwld File.

141. TRANSNATIONAL CORPORATIONS, *supra* note 41, at 31.

142. *Id.*

to establish a particular risk to benefit assessment will involve both scientific and policy questions. In all events, policy decisions must be based on a scientifically valid and workable regulatory system.

Until the FDA began accepting foreign data to support applications for approval of new pharmaceutical products, there was little likelihood of harm to consumers from unsafe and ineffective drugs. On the other hand, unnecessary delays and duplication of costs are also harmful to consumers if they delay consumers access to safe and effective drugs. Harmonization efforts seek to reduce the harms of delay and duplication but present other potential sources of harm.

Some ICH participants and observers have called for total harmonization.[143] Total harmonization would involve one of two schemes, a centralized approval procedure or a mutual recognition procedure. A centralized approval procedure would have to rely on either protection through premarketing approval, as the FDA does, or protection through post-marketing surveillance, as in some European systems. A system based on the FDA's regulatory scheme would ensure safety and effectiveness, but would result in delayed approval for new pharmaceutical products in all ICH countries. A system emphasizing post-marketing surveillance would provide speedier access to new pharmaceutical products, but could not guarantee safety and effectiveness unless effective surveillance could be achieved.

In the United States, a significant barrier to effective post-marketing surveillance is the failure of the medical establishment to follow up and report on effectiveness and adverse reactions.[144] There may also be gaps resulting from a failure of patients to communicate with their physicians. This practice would have to be changed and a mechanism for gathering and analyzing post-market data would have to be implemented. The FDA currently has no power to require physicians to report on drug response or adverse reactions. The health care market is extremely decentralized and is primarily regulated by the states. FDA enforcement is based on the agency's ability to withhold or withdraw marketing approval from the man-

143. *See supra* note 52 and accompanying text.

144. Gerald A. Faich, *Adverse Drug Reaction Monitoring*, 314 NEW ENG. J. MED. 1589, 1591-92 (1986) (indicating that "[t]he rate of adverse-reaction reporting in the United States is far below that in many other developed countries" and that physicians have a moral duty to report suspected adverse reactions); Doug Podolsky, *Dangerous Drugs: What You–and Maybe Your Doctor–Don't Know About Your Prescription's Side Effects Could Hurt You. Or Even Kill You.*, U.S. NEWS & WORLD REP., Jan. 9, 1995, at 48, 51-52 (indicating that physicians "come up short at reporting adverse drug reactions, despite prodding by FDA chief David Kessler"). "[One] factor inhibiting physician reporting is that it is not an ingrained practice–it is not in the culture of U.S. medicine to notify the FDA about adverse events or product problems. In other countries such as the United Kingdom, adverse drug reporting is more frequent." Kessler, *supra* note 108, at 2765 (citing a study which reported that only 1% of serious events are reported to the FDA and emphasizing the importance of postmarket reporting of adverse effects to ensure product safety since many adverse effects probably will not be identified during premarketing investigations). The MEDWatch program, 59 Fed. Reg. 54,046 (1994), has improved reporting of adverse reactions, but at a 10% reporting rate is still only "scratching the surface." Linda Marsa, *Hey, Who Needs a Prescription?*, L.A. TIMES MAG., Sept. 29, 1996, at 10, 30.

ufacturer. Effective post-market surveillance would have to be achieved through either concerted action by individual states or national action to control the practices of health care entities, particularly prescribing physicians. One possible solution would be to alter the FDA's regulatory process so that after positive pre-marketing clinical studies, the FDA can provide conditional marketing approval to a pharmaceutical. The initial marketing phase would serve as a post-market "field study." As a condition of marketing the drug, the pharmaceutical company would have to require physicians to report drug response, dosages, adverse reactions, complications, and the like. The pharmaceutical industry and the medical community would have to recognize that preliminary marketing of the drug is experimental and that proper informed consent must be obtained from patients.

For many developing countries which are not participants in the ICH process, but are affected by it, post-marketing surveillance may be economically impossible in light of scarce resources and the significant health care needs of their populations. These countries would have to rely on the post-marketing surveillance of ICH participating countries. Reliance on post-marketing surveillance by other countries may be ineffective in detecting ethnic, dietary, or cultural differences.

These differences may result in adverse drug reactions by the consumers of developing countries which are not manifested in the consumers of developed countries. Ethnic differences may also result in the failure to identify a drug which would provide an effective remedy to one ethnic population, because testing in a different ethnic population masked favorable results.

A mutual recognition procedure would only exacerbate ethnic differences. Mutual recognition could also lead to wholly inadequate pre-market testing if pharmaceutical developers are allowed to seek approval in the countries with the most lax regulatory oversight. Thus, to ensure that safe and effective drugs are speedily made available to consumers a prudent and thoughtful approach which takes into consideration the effects of harmonization on the protections provided to all citizens of the global health care market is needed. All regulatory bodies must act in concert under equivalent standards in order to prevent the "dumbing down" of regulatory review. These standards must take the possibility of ethnic differences into account in the pre-marketing phase in order to protect consumers in poor countries. These decisions must be based on good science and good policy.

IV. Pharmaceutical Regulation–Protection of Research Subjects

Even if the science and policy issues of protecting consumers can be worked out, human rights issues raised by pharmaceutical experimentation remain. The pharmaceutical industry already conducts research abroad. The recent trend toward greater acceptance of foreign data and the efforts to harmonize drug regulations can only lead to more research being

conducted abroad. As is the case with manufacturing and regulatory capacity, developing countries have limited capabilities for conducting research.[145] Pharmaceutical research is the predominant type of research using human subjects.[146] Considering the global dimensions of health and pharmaceutical research and marketing, to what extent can the countries involved be assured that this research is being conducted ethically? Presently, national regulations have very little extra-territorial effect, and international guidelines have not been widely accepted[147] and have no enforcement mechanisms.

Current regulations for protecting human subjects have roots in the Nazi war-time experiments and the resulting "Doctor's Trial" at Nuremberg.[148] Still, attention in the United States turned to the human rights of research subjects only in the 1960s and 1970s.[149] In 1966, the FDA and NIH responded quickly to the publicity generated by the disclosure of unethical conduct during a cancer study at Jewish Chronic Disease Hospital,[150] and the published exposé by Henry Beecher, a respected physician and researcher at Harvard Medical School, of widespread, unethical

145. TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 69 (statement of José Barzelatto of the WHO, noting that the problem of lack of research on tropical diseases can only be solved through international efforts to expand the research capabilities of developing countries).

146. *Id.* at 39.

147. *Id.*

148. *See generally* NAZI DOCTORS, *supra* note 9; George J. Annas, *Mengele's Birthmark: The Nuremberg Code in the United States Courts*, 7 J. CONTEMP. HEALTH L. POL'Y 17 (1991).

149. Although the health agencies in the federal government, the Public Health Service and the National Institute of Health, had considered the need for regulating human subject research as early as 1945, nothing was done for two decades. JAMES H. JONES, BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT 188 (1981). This was due partly to the fact that the Nazi experiments were perceived to be the isolated and aberrant actions of deranged individuals. *Id.*

150. *See* JAY KATZ, EXPERIMENTATION WITH HUMAN BEINGS 9-65 (1972). In July, 1963, three physicians, with the approval of the director of medicine at Brooklyn's Jewish Chronic Disease Hospital, injected live cancer cells into twenty-two chronically ill patients. *See* Hyman v. Jewish Chronic Disease Hospital, 248 N.Y.S.2d 245 (N.Y. Sup. Ct. 1964), *rev'd*, 251 N.Y.S.2d 818 (N.Y. App. Div. 1964), *rev'd*, 206 N.E.2d 338 (N.Y. 1965) (affirming the trial court's decision to order disclosure of the records). The subcutaneous injections of these non-cancerous, but otherwise debilitated, patients were intended to demonstrate that the slower rejection rates of cancer patients similarly injected was due not to their debilitated state, but to their cancer. The experiment, conducted under the auspices of the Sloan-Kettering Institute and financed by the U.S. Public Health Service, created controversy among the hospital's physicians, three of whom chose to resign rather than to be seen as endorsing the experiment. Another physician reported the matter to the medical board of the hospital and eventually to the board of directors. There were allegations that the 18 patients were unable to consent because they were mentally incompetent and that informed consent had never been sought. When the board of directors took no action on the matter, a dissenting board member sued to obtain disclosure of the hospital's records alleging that the board's action was unlawful and that it exposed the hospital and himself as a director to liability. As a result, a disciplinary board eventually concluded that the physicians had not obtained consent and had acted improperly. KATZ, *supra.*

research practices at the highest levels of American science.[151] Both institutions promulgated guidelines governing human research in 1966. The FDA's guidelines were based partly on the 1964 Declaration of Helsinki, with some emphasis placed on obtaining informed consent.[152] NIH's contribution was to move from a system where ethical decision-making was left to the individual conscience of the physician-investigator to a system of compulsory collective review.[153] Initially, however, the forerunner of the institutional review board (IRB) was basically a peer review committee.[154]

Within the next decade, matters changed dramatically. Revelations about the Tuskegee Syphillis study[155] and other research scandals led to intense congressional scrutiny, which in turn led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[156] The Secretary of the Department of Health Education and Welfare (now Health and Human Services) was to select eleven members "from among 'the general public and from individuals in the fields of medicine, law, ethics, theology, biological science, physical science, social science, philosophy, humanities, health administration, government, and public affairs'" with no more than five of them being researchers.[157] The Secretary chose five scientists, three lawyers, two ethicists, and one individual from public affairs.[158] The National Commission identified the basic ethical principles which were to govern human research and promulgated regulations based on those principles.[159] Under a "forcing clause," the Secretary was required to accept the Commission's recommendations or publicly disclose the reasons for their rejection.[160] Many of the recommendations were accepted[161] and became the

151. ROTHMAN, *supra* note 64, at 70-84, 86-93 (1991). *See generally* M.H. PAPPWORTH, HUMAN GUINEA PIGS: EXPERIMENTATION ON MAN (1967) (exposing similar abuses in the United Kingdom).

152. ROTHMAN, *supra* note 64, at 89, 93. Final adoption of the 1964 Declaration of Helsinki was itself influenced by the prospect of the FDA's move to standardize research trials. Annas, *supra* note 148, at 25-26.

153. ROTHMAN, *supra* note 64, at 90.

154. *Id.*

155. *See generally* JONES, *supra* note 149. For forty years, the United States Public Health Service had studied 400 syphilitic poor black men from rural Alabama without informing them about the true nature of the study (to study the untreated course of syphilis in the black male, originally intended to confront the beliefs of the medical profession in the 1930's that the course of syphilis was different in blacks and whites) and had even dissuaded or prevented many of the men from obtaining treatment. Despite various reports of the study being made in the medical literature from time to time, the study came to public scrutiny and was terminated only after a former employee of the Public Health Service disclosed the information to an Associated Press reporter who broke the story in July of 1972. *Id.* at 188-219. As of 1965, only one physician had objected to the study on ethical grounds. *Id.* at 190.

156. ROTHMAN, *supra* note 64, at 168-88.

157. *Id.* at 188.

158. OFFICE OF TECHNOLOGY ASSESSMENT, BIOMEDICAL ETHICS IN U.S. PUBLIC POLICY—BACKGROUND PAPER 11 (1993) (Doc. No. OTA-BP-BBS-105) [hereinafter BACKGROUND PAPER].

159. *Id.*

160. *Id.*

161. *Id.*

current regulations[162] governing federally sponsored human research. The FDA regulations adopt the same ethical principles.

The FDA now accepts clinical research data from trials conducted abroad in support of an application for drug approval, provided that the research is conducted "in accordance with ethical principles acceptable to the world community."[163] The FDA accepts data that conforms to the Declaration of Helsinki or "the laws and regulations of the country in which the research was conducted, whichever represents the greater protection for the individual."[164]

The EU has likewise adopted the Declaration of Helsinki as its code of ethics for research trials.[165] Apparently, Japan only recently (in 1985) promulgated clinical practice standards "to pay due ethical consideration to the rights of persons who undergo clinical tests."[166] However, a recent article on the harmonization process describes Japan's introduction of "high clinical practice standards" as lagging behind Europe and the United States.[167] The article indicates that patients serving as research subjects "are supposed to be adequately informed."[168] The wording of this phrase suggests that they may not always be so informed. While most industrialized nations have some ethical review standards or mechanisms in place, many developing countries, where the majority of the world's population and hence potential research subjects live, do not.[169]

A. Ethical Malaise in International Research.

The current regulatory climate leaves room for the possibility that pharmaceutical companies and other researchers will be testing drugs on humans in countries where protection for human subjects is nonexistent or enforcement is lax. Some commentators believe that drug companies bypass existing regulatory mechanisms to persuade individual physicians to conduct clinical trials on new and untested products in situations where even the physician's institution is unaware.[170] These are cases that are difficult to monitor or trace, and in which it is entirely unknown whether informed consent was obtained.[171] Some cases have come to light that suggest inves-

162. 45 C.F.R. §§ 46.101-46.117 (1993).

163. Foreign Clinical Studies Not Conducted Under an IND, 21 C.F.R. § 312.120(a) (1993).

164. *Id.* at § 312.120(c). The Declaration, which is set out in subsection (c)(4) of the regulations appears to be the Declaration of Helsinki of the World Medical Association as amended through the 41st World Medical Assembly, Hong Kong, September 1989.

165. John J. Gorski, *An FDA-EEC Perspective on the International Acceptance of Foreign Clinical Data*, 21 CAL. W. INT'L L.J. 329, 351 n.150 (1991).

166. Minori Tatsuno et al., *Japan, in* INTERNATIONAL PHARMACEUTICAL SERVICES, *supra* note 3, at 303, 320.

167. Kodama, *supra* note 10, at 8.

168. *Id.*

169. TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 39.

170. Ren-Zong Qiu, *supra* note 29, at 124. *See also* TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 70 (indicating that physicians in developing countries frequently use the drugs supplied by pharmaceutical companies for testing without doing proper follow-up; the physicians' reports are nonetheless used to obtain regulatory approval).

171. Ren-Zong Qiu, *supra* note 29, at 124.

tigators are conducting research in developing countries because it is easier to get approval.[172] Another incident in Africa suggests that substantial amounts of research can be conducted without seeking local regulatory approval.[173] Another reason why developing countries might be preferred is the decreased exposure to liability, e.g., product liability.[174] The current harmonization activities can only lead to an increase in research conducted in other countries.

Unethical research is possible even when racism, cruelty or greed are absent as motivating factors for the scientists involved in research. Experience teaches that the "greatest dangers to liberty lurk in insidious encroachment by men of zeal, well-meaning but without understanding."[175] The tendency of scientists "to assume there is a hierarchy of ethics with the scientific ethic at the pinnacle" and to minimize "competing social ethics" has long been documented.[176] Under this view "the end of knowledge justifies the scientific means" and science's contributions are best achieved when it is allowed to be carried on independent of political, social, and religious pressures.[177] Implicit in the Nuremberg trial of the Nazi physicians is the notion that humans are "most vulnerable to misuse when they are asked to submit to experiments in the name of science."[178] The presence of doctors in white coats in a therapeutic setting among patients may result in the misplaced notion that what is being done is for a patient's own good.[179] Residents of some developing countries are particularly susceptible because of the high degree of illiteracy and low level of education.[180] Payments to research subjects or even the provision of medical services not otherwise available may serve as inducements for poor citizens of developing countries to take risks we would find unacceptable in

172. *See* Peter Lurie et al., *Ethical, Behavioral, and Social Aspects of HIV Vaccine Trials in Developing Countries*, 271 JAMA 295, 296 (1994). In 1990, the WHO also investigated use of an AIDS treatment that was being tested for efficacy in Romania on HIV positive orphan babies and adults without prior in-depth animal or laboratory studies or studies of toxicity and safety conducted on healthy humans–something which was not possible "in the West." Steven Dickman & Peter Aldhous, *WHO Concern Over New Drug*, 347 SCI. 606, 606 (1990). The drug's previous testing in the East African state of Malawi resulted in conflicting reports about the scientific validity of its alleged positive effects. *Id.* Shortly after the WHO investigation, the drug trials were banned by Romanian officials despite their earlier claims that their own regulatory agency had found the drug safe and efficacious. *Romania Halts AIDS Drug Test*, N.Y. TIMES, Oct. 30, 1990, at C9.

173. *See Zimbabwe Accuses Doctor of Nazi-like Experiments*, TORONTO STAR, Mar. 5, 1993, at A3 (describing an official investigation of a British anesthetist who had experimented on 500 patients, without their knowledge and official approval, to determine the sensitivity of women under anesthesia to morphine).

174. Lurie et al., *supra* note 172.

175. Olmstead v. United States, 277 U.S. 438, 479 (1928) (Brandeis, J., dissenting).

176. KATZ ET AL., *supra* note 150, at 105 (quoting Ted R. Vaughan, *Governmental Intervention in Social Research–Political and Ethical Dimensions in the Wichita Jury Recordings*, *in* ETHICS, POLITICS AND SOCIAL RESEARCH 50, 60-75 (Gideon Sjoberg ed., 1967)).

177. *Id.* at 104-05.

178. Mariner, *supra* note 9, at 295.

179. KATZ ET AL, *supra* note 150, at 55, 60.

180. Ren-Zong Qiu, *supra* note 29, at 115.

developed countries.[181]

B. The Limited Remedy of Existing Research Controls and Side Effects of Harmonization

In the United States, the primary enforcement mechanism is the FDA's ability to refuse to consider domestic or foreign data which fails to meet the applicable guidelines. In addition, with respect to domestic data, the FDA has a number of administrative actions which it may take in response to an IRB or its governing institution's failure to comply with the regulations protecting human subjects. These include termination of ongoing studies, withholding of approval for new studies, and disqualification.[182] These administrative actions require on-site inspections by the FDA, which are difficult to achieve abroad.[183]

Under U.S. law, harmful conduct by one human being upon another is usually governed by the states through criminal laws.[184] However, very few states have laws governing research, largely because of the existence of federal regulations.[185] In fact, a great deal of research is federally regulated because of its federal funding or because it requires FDA approval.[186] How much research is conducted outside this scheme of federal regulation is unknown, but absent state laws, it is entirely unregulated.[187] The limits

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181. For example, organ trafficking in Uruguay and Argentina is widespread; one individual who had advertised a kidney for sale indicated that he had been out of work for a year and a half and that he considered the personal sacrifice necessary for the future of his children. *See* Maria L. Avignolo, *Children Robbed of Their Kidneys in Argentina*, SUNDAY TIMES (London), Dec. 8, 1991, *available in* LEXIS, News Library, Arcnws File. A similar situation has been widely reported to exist in Egypt. *See* Chris Hedges, *Egyptian Doctors Limit Kidney Transplants*, N.Y. TIMES, Jan. 23, 1992, at A5.

182. 21 C.F.R. §§ 56.120-56.124 (1993).

183. *See* Philip B. White, *International Memoranda of Understanding*, 49 FOOD & DRUG L.J. 171, 171 (1994) (describing how Memoranda of Understanding can reduce the costs and burdens of onsite inspections for FDA oversight of "good manufacturing practices"); Joseph G. Contrera, Comment, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious Will Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 948-49 (1995) (suggesting that a Memoranda of Understanding procedure to allow foreign inspectors to inspect for good clinical practices would avoid the "costly and time-consuming" requirement of verification of compliance by the FDA). The FDA continues to experience difficulties with verification of studies conducted abroad because of inadequate or incomplete records and fraudulent or concealed information. Keith C. Epstein & Bill Sloat, *Foreign Tests Don't Meet U.S. Criteria*, PLAIN DEALER, Dec. 17, 1996, at 1A, *available in* LEXIS, News Library, Curnews File. *See also* Gorski, *supra* note 165, at 342 (indicating that foreign laws which deny access to medical records can also present problems for the FDA).

184. George J. Annas & Michael A. Grodin, *Where Do We Go from Here?*, *in* NAZI DOCTORS, *supra* note 9, at 307, 312.

185. Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, *in* NAZI DOCTORS, *supra* note 9, at 183, 194.

186. *Id.* at 187. In addition, institutions which receive federal funds are required to ensure that research which is not federally funded also be "reviewed for ethical propriety;" most institutions apply the federal guidelines to all research rather than administer separate systems of review. BARRY R. FURROW ET AL., BIOETHICS: HEALTH CARE LAW AND ETHICS 387. The regulations for FDA approval and federally funded research are essentially the same. *Id.*

187. Glantz, *supra* note 185, at 194.

of federal regulation became abundantly clear in 1977 when a pharmaceutical company obtained approval from the Nevada legislature to sell the controversial "anti-aging" drug Gerovital in Nevada even though the drug had not been approved by the FDA.[188] The FDA admitted it was "powerless" to act if the company could keep all phases of the drug process (manufacture, distribution, and consumption) within the state's borders.[189] There have been isolated reports of questionable research conducted outside the scope of government review,[190] and while some allege that the current magnitude of the problem is small,[191] there is simply no way to know.[192] Similarly, there seem to be no enforceable regulations prohibiting unethical research conducted abroad so long as the drug's sponsor does not need to rely on that data for FDA approval.

There are no international treaties governing experimentation on humans.[193] As a result, the international documents dealing with research trials have little legal effect.[194] The most widely known international codes of ethics for the protection of human subjects are the Nuremberg Code and the Declaration of Helsinki. Both, however, have shortcomings. They direct themselves solely to the "integrity and judgment" of the investigator, although the Declaration of Helsinki, beginning in 1975, added ethical

188. Larry Kramer, *Gambling with the FDA in Nevada: State Approves Drug that Claims to Help the Elderly*, WASH. POST, Nov. 13, 1977, at F1.

189. *Id.* The FDA would be able to require the pharmaceutical company to register as a manufacturer and would be able to examine the manufacturing plant to investigate for quality control if interstate commerce was present. *Id.* In the United States, the authority for federal pharmaceutical regulation is and has been based on the Constitution's authorization for congressional control of interstate commerce. NIELSEN, *supra* note 59, at 4.

190. One extraordinary incident recently came to light five years after the unauthorized experiments were conducted. *See* Philip J. Hilts, *Researchers Admit Study with Drugs Had No O.K.*, N.Y. TIMES, Oct. 28, 1993, at B5. In 1987, two neurosurgeons, former N.I.H. researchers, injected terminal, brain tumor patients with a drug that had been approved by the FDA for a kidney cancer study conducted at the same institution by two other researchers. They were never prosecuted for any wrongdoing and the U.S. Attorney's office in Manhattan refused to reveal their names. Meanwhile, the surgeon who had diverted the surplus drugs to this unauthorized research was investigated by the U.S. Attorney; his name was forwarded for disciplinary action, although no charges were brought because "no apparent harm" was done to the dying patients. *Id.* The two neurosurgeons who actually conducted the study had sought FDA approval; after receiving an initial rejection from FDA (due to insufficient information on their application) and impatient to treat their waiting patients, the pair convinced the prominent cancer specialist to give them the drug to conduct their unauthorized study. The scientists then engaged in a five year cover-up of their activities. *Id.*

191. Marcia Angell, *Barbarism in the Name of Science: Data from Unethical Experiments Should Be Barred*, WASH. POST, July 10, 1990, at 6.

192. A recent exposé of British pharmaceutical research suggests that fraud and misconduct by academic researchers, drug companies, and especially general practitioners hired to conduct clinical trials for post-marketing surveillance, is on the increase. Rosie Waterhouse, *Exposure of Fraud in GP Drug Tests 'On the Rise,'* INDEPENDENT, Jan. 25, 1993, at 3.

193. Erwin Deutsch, *Medical Experimentation: International Rules and Practice*, 19 VICTORIA U. WELLINGTON L. REV. 1, 4 (1989).

194. *Id.* at 4.

review for "consideration, comment and guidance" by committee.[195] Both fail to provide an enforcement mechanism, or any sanctions, and have been criticized as too ambiguous, representing nothing more than "pious hopes" that physicians will behave ethically.[196] As the legislative findings of California's laws governing non-federally regulated research recognized, in the international context, "[n]either the Nuremberg Code nor the Declaration of Helsinki are codified under law and are, therefore, unenforceable."[197] Both the code and declaration have also been criticized as too tied to Western principles which are not necessarily applicable to other cultures.[198]

The latter concern was addressed in the Proposed Guidelines produced by a 1978 collaboration by the World Health Organization (WHO) and the Council of International Organizations of Medical Science (CIOMS) to assist developing countries to ensure that principles of medical ethics are observed in biomedical research.[199] The WHO/CIOMS Guidelines provide a more flexible approach to the problem of informed consent. While "the involvement of human subjects in biomedical research must be contingent whenever feasible, upon freely-elicited informed consent and upon liberty to withhold or withdraw collaboration at any stage without fear or prejudice," the Guidelines recognize that the goal may be unobtainable, and yet research may still be morally justified.[200] The focus of the Guidelines then becomes protecting the welfare of subjects in light of this limitation. Among the dilemmas addressed by the Guidelines are community-based research, such as water fluoridation (where individual informed consent is not obtainable) and research conducted in communally-oriented societies.[201] In the latter case, the Guidelines provide for consent through a trusted intermediary or community leader with the proviso that the community leader make clear to the subject that the subject's participation is not required and may be withheld or withdrawn at any time.[202] Placing too much emphasis on "informed consent" as the primary means of protecting research subjects can lead to insufficient protection.[203] Accordingly, the Guidelines emphasize the need for mandatory prospective ethical review of research protocols.[204] It is unclear to what extent the CIOMS Guidelines have been implemented, although there is some evidence to suggest they are in use.[205] On the international level, laws governing medical

195. Sharon Perley et al., *The Nuremberg Code: An International Overview, in* NAZI DOCTORS, *supra* note 9, at 149, 160. IRB's under the FDA regulations have authority to disapprove research proposals. 21 C.F.R. § 56.109(a) (1993).

196. Perley et al., *supra* note 195, at 160.

197. CAL. HEALTH & SAFETY CODE § 24171(b) (West Supp. 1997).

198. Perley et al., *supra* note 195, at 162.

199. *Id.* at 161. The Guidelines are based on the Declaration of Helsinki. *Id.* at 162.

200. *Id.* at 162-63.

201. *Id.* at 163.

202. *Id.*

203. *Id.* Subjects in developing countries "may not be sufficiently aware of the implications of participating in an experiment to give adequately informed consent." *Id.* at 162.

204. *Id.*

205. *Id.*

practice and harmful conduct by one human being upon another are usually the province of individual nations, yet the codes of conduct governing human experimentation are largely international.[206]

Considering the limited protection for human subjects in many areas, one possibility would be to prohibit research altogether unless the investigators can proceed under a recognized ethical code. However, this view fails to recognize that research does not always involve an experiment conducted to the detriment of the subject. Research brings with it many benefits. First, clinical drug trials may present the *only* available treatment for a particular disease.[207] Second, free medical treatment, increased monitoring, and the attention of specialists often accompany research. Third, as previously noted,[208] drugs do not have the same effect for all populations. If a drug is never tested in one country, scientists may fail to discover that it would have an effect on its population, and may dismiss it as ineffective.[209] A critical example where this may be the case is in the testing of AIDS drugs, particularly the vaccines that are about to enter the final stages of drug trials: the strains of AIDS prevalent in developing countries are different from those in the U.S. and Europe.[210] Finally, a drug that is regarded as safe and effective in a developed country cannot be presumed to be equally beneficent in a developing country that "lacks ancillary medical, nutritional, and distributional services."[211] Thus, failing to test a drug prior to marketing represents merely a shift to post-marketing experimentation and raises human rights issues of its own.[212] It is not satisfactory to say that research cannot be conducted where the human rights of potential subjects cannot be assured.

The harmonization resulting from the ICH process also provides inadequate protection for human subjects. In August of 1995, the FDA published draft guidelines agreed to by the ICH participants which are intended to govern the conduct of research involving humans.[213] The draft Guideline on Good Clinical Practice is worded broadly enough to allow the FDA to continue to demand the same protection for human subjects required under existing regulations.[214] If the harmonization process amounts to nothing more than an agreement on basic requirements, then human subjects are placed at no greater risk through the adoption of these guidelines. If on the other hand, the harmonization process results in a mutual recognition procedure, the FDA may not be able to enforce the same high standards of protection for human subjects. The FDA's only

206. Annas & Grodin, *supra* note 184, at 313.
207. *See* Lurie et al., *supra* note 172.
208. *See supra* notes 120-33 and accompanying text.
209. *See id.*
210. *Id.*
211. Ellen N. Cone, Note, *International Regulation of Pharmaceuticals: The Role of the World Health Organization*, 23 VA. J. INT'L L. 331, 340 (1983).
212. *See supra* text accompanying notes 120-126.
213. International Conference on Harmonisation: Draft Guideline on Good Clinical Practice, 60 Fed. Reg. 42948 (1995).
214. 45 C.F.R. §§ 46.101-46.117 (1993).

weapon continues to be the ability to deny marketing approval for a pharmaceutical product. To exercise this weapon, the FDA will need to detect noncompliance with its requirements, and also to deny marketing approval under the mutual recognition agreement. To detect noncompliance, the FDA must monitor the requirements or be assured that another ICH participant is effectively monitoring the research.[215] It is not clear that FDA oversight is possible or economically feasible.[216] In addition to oversight, the FDA must have the right to deny marketing approval "for cause" where noncompliance is detected and the investigators fail to protect the rights of the human subjects in their research trials. The FDA has previously insisted on abidance by high ethical standards before accepting foreign data. It should continue to do so.

As presently worded, the Guideline on Good Clinical Practice "should be followed when generating clinical data that are intended to be submitted to regulatory authorities" in the ICH participant countries.[217] However, as far as the FDA is concerned, this interpretive rule is not binding on anyone, including the FDA.[218] It is not clear whether the guidelines, if finally agreed upon, will be made enforceable or mandatory for other ICH participating nations. However, no mechanism exists for any ICH participant (or third party) to enforce any aspect of harmonization on any other ICH participant which does not comply with or enforce an agreement.[219] Thus these guidelines present the same shortcoming in enforceability as the Nuremberg Code and the Declaration of Helsinki.

C. Prophylactic and Antiseptic Remedies–Prescription for Healthy Biomedical Research

A document of a binding character to which all the nations of the world may subscribe, such as a convention, is needed.[220] There are compelling reasons to promote the United Nations as the body to promulgate such a convention, including credibility.[221] Such a convention would require an enforcement mechanism to have any meaning. Enforcement might be

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215. Contrera, *supra* note 183, at 948-49.

216. *Id.* at 952-53 (citing budgetary constraints limiting FDA's international activities).

217. *Id.*

218. *Id.* (indicating that the guideline "does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind the FDA in any way").

219. Contrera, *supra* note 183, at 954-55.

220. *See, e.g.*, Bassiouni et al., *supra* note 36 (providing a draft of such a convention).

221. Annas & Grodin, *supra* note 184, at 312. CIOMS credibility has apparently been affected by its creation of "broad exceptions" to informed consent requirements and the World Medical Assembly's credibility has been affected by its failure to take a stance regarding Apartheid. *Id.* The World Medical Assembly's moral authority was also recently called into question by its election of a physician with a Nazi-SS past to the presidency. *See* Michael Franzblau, *Investigate Nazi Ties of German Doctor*, SAN FRANCISCO CHRON., Dec. 29, 1993, at A17 (he resigned as president when the AMA produced documents he had signed authorizing a patient's transfer to a center known for its euthanasia experiments).

through an international court such as a "permanent Nuremberg"[222] or a World Human Rights Court. Enforcement could also be achieved through the adoption of national laws (or uniform state laws) governing all research, and not just research which obtains government funding or requires government approval, that is conducted in that nation or by its nationals.[223]

1. For Immediate Relief–Adopting Minimum Standards

The European Union is presently working on a "Bioethics Convention" which would concern, *inter alia*, research in Europe.[224] The obstacles encountered by that process[225] would likely be repeated in an international effort to draft a bioethics convention. One possibility for minimizing delays would be to focus the convention narrowly on basic research principles and allow for later supplementation of principles governing more controversial areas of research, such as research on children, embryos, and fetuses. Except for a few controversial areas, there is a fairly wide "transcultural acceptance" of standards governing ethical research, although many cultural and national differences arise with respect to procedures for their implementation.[226] Another way to make the process of drafting such a convention feasible without producing a meaningless document is to concentrate on defining minimum universally acceptable standards.[227] As one delegate to the 1987 International Summit Conference on Bioethics pointed out, "[it is] odd that we have minimum standards for the experimental use of animals without something equivalent for the experimental use of human beings."[228]

Individual nations would then be free to tailor the enforcement mechanisms to the local culture and practice[229] or to adopt additional or more rigorous requirements. One of the approaches which has worked well for several nations in developing guidelines for a number of bioethics areas is illustrated by the work of the U.S. National Commission.[230] The U.S. Office of Technology Assessment (OTA) recently identified factors which appear to make government initiated biomedical ethics bodies (such as commissions, committees or ethics boards) successful. The OTA studied such bodies in the federal, state, and international arena. Predictors of success include "adequate staffing and funding," as well as commissions which were "relatively free of political interference, had flexibility in

222. Robert Drinan, *The Nuremberg Principles in International Law, in* NAZI DOCTORS, *supra* note 9, at 174, 176.
223. *See* Annas & Grodin, *supra* note 184, at 312.
224. *See* Arthur Rogers, *Europe: Ethical Diversity: European Community Fails to Establish Bioethics Policy*, 339 LANCET 861 (1992).
225. *Id.*
226. TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 51.
227. *Id.* at 53.
228. *Id.* at 70 (statement of Professor Gordon Dunstan).
229. *See id.* at 41 (describing committee review practices among some of the ICH nations).
230. *See supra* text accompanying notes 155-162.

addressing issues, were open in their process and dissemination of findings and were comprised of a diverse group of individuals who were generally free of ideology and had wide ranging expertise."[231] All of these factors may not apply to every country; however, when creating any working body to confront the tougher concerns raised by pharmaceutical regulation, such predictors should be given serious consideration, particularly those which consider the community's point of view. Given the vast amount of literature and scholarship available in this area, each nation's commission would not have to reinvent the wheel, but merely consider how to apply universal principles to local conditions, determine which procedural mechanisms will work most effectively, and establish any necessary additional protections for its population.

The more public the commission process is, the more it should help with the goals of the next important step in developing adequate protection for the rights of human subjects of research. In order to have an effective system of protection, there must be a high level of awareness of the ethical problems posed by pharmaceutical research on the part of scientists and those who will represent the interests of the public and the culture where the research is being conducted. Developing countries seem to be at a disadvantage in our increasingly smaller world and international cooperation needs to be strengthened to prevent developing countries from becoming exploited.[232] There is a need to train bioethicists from developing countries to teach, to do research, and to serve on IRB's.[233] Moreover, if scientists do not internalize the ethical norms, there will be no enforcement. First, as with any law, self-enforcement is the most effective mechanism. Second, often the only way unethical conduct is discovered is through whistle-blowers, i.e., persons within the scientific community who have inside knowledge of the facts and who feel a moral obligation to step forward. Among notable disclosures of potential ethics problems which would not have come to light were it not for an insider are the Jewish Chronic Disease Hospital cancer study,[234] the Tuskegee Syphilis Study,[235] and the recent disclosures by U.S. Energy Secretary Hazel O'Leary about government radiation testing.[236] Thus, an effective system would need to

231. BACKGROUND PAPER, *supra* note 158, at 18.

232. *See* Ren-Zong Qui, *supra* note 29, at 124.

233. *Id.*

234. *See supra* note 150 and accompanying text.

235. *See generally* JONES, *supra* note 149.

236. *See* Keith Schneider, *Secret Nuclear Research on People Comes to Light*, N.Y. TIMES, Dec. 17, 1993, at A1. After decades of government secrecy, Energy Department Secretary Hazel R. O'Leary disclosed in December of 1993 that numerous experiments exposing civilians to high levels of radiation were conducted for three decades after World War II. *Id.* Some of these experiments were conducted without obtaining the consent of the subjects. Although the disclosure was prompted by a newspaper's Freedom of Information Act request for more information regarding one research project conducted at Argonne National Laboratory, neither verification about that project nor the scope of radiation research activity on civilians would have come to light but for the Energy Secretary's decision to disclose and order a full scale investigation. *See id.* The disclosures generated disagreement about the ethical standards applicable at the time the experi-

(1) train philosophers, theologians, scholars, and others to represent the community and consumer interests; (2) train scientists to recognize ethical dilemmas and apply the appropriate principles;[237] and (3) encourage and protect whistle-blowers.

Recognizing the important function served by whistle-blowers in reporting scientific misconduct, the United States recently promoted government protection of whistle-blowers from retaliation by their employers.[238] Whether a system encouraging whistle-blowers should be promoted depends on the presence of some amount of public accountability by the government. Otherwise, a system encouraging whistle-blowers may be dangerous to the scientific community.[239] In this regard, widespread news coverage has been instrumental in the development of various governments' responses and protection for research subjects and the citizenry.[240]

Once these factors are in place, each nation will be able to provide its citizens at least a basic level of protection when they are involved in research. Over time and with continued international effort, the protection available to human subjects should increase. Some developing countries will be able to offer their citizens protection equivalent to that offered by developed countries. This is a necessary, but not a sufficient step, because some developing countries may be unable or unwilling to protect the human rights of all those found within their borders. Every developed country must also apply the international code to all research (1) funded by that country's government, (2) subject to government approval, (3) conducted in that country, or (4) conducted by its nationals abroad. Developed countries must censure research which fails to meet these minimum standards.[241] This will cover the existing gaps in the regulations governing

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ments were conducted. *See, e.g.*, Linda Feldman, *Ethicists Look at Radiation Tests*, CHRISTIAN SCI. MONITOR, Dec. 31, 1993, at 2.

237. *See* TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 54. The appropriate principles should include seeking ethical review. *See infra* text accompanying notes 266-277.

238. National Institutes of Health Revitalization Act, Pub. L. No. 103-43, 107 Stat. 122, 142 (to be codified at 42 U.S.C. § 289b) (1993).

239. In Argentina, for instance, it is widely speculated that the 1985 disappearance of a hematologist employed at the Montes de Oca psychiatric clinic outside of Buenos Aires was part of an effort to cover up the investigation into the human organ trafficking being conducted at that facility. *See Horror Story at Argentine Mental Hospital*, AGENCE FRANCE PRESSE, Mar. 10, 1992; Avignolo, *supra* note 181.

240. *See* Deutsch, *supra* note 193, at 4-8.

241. One possibility would be to not only prohibit the use of unethical research as support for an application for new drug approval, as the FDA does, but to penalize any application tainted by such research. Thus, where a company cannot demonstrate that studies conducted in a developing country meet the minimum ethical requirements, regulatory approval may be denied even though the application is supported by sufficient ethically conducted research. An alternative penalty would be to grant regulatory approval but provide for an alternative sanction, such as decreasing the time allowed on patent protection. Such a position would comport with the view that we must never profit from unethically gathered data. *See* Marcia Angell, *Editorial Responsibility: Protecting Human Rights by Restricting Publication of Unethical Research*, *in* NAZI DOCTORS, *supra* note 9, at 281-82; Jay Katz, *We Must Never Benefit from Evil in "Science,"* NEWSDAY,

human conduct. Developed countries can also promote higher standards of ethical conduct by requiring government sponsored research conducted abroad, including pharmaceutical research for which regulatory approval is sought, to meet whichever guidelines provide the most protection for subjects, that of the sponsoring government or that of the government where the research is conducted.[242] We are not at the point yet of "harmonizing" regulations protecting human subjects on a global basis. This necessarily requires some duplication of ethical review. However, nations should strive to reduce the amount of duplicative review required, otherwise this may also make development of pharmaceuticals, especially those targeted at the needs of the developing world, prohibitively expensive.

2. *Informed Consent: Malady or Treatment?*

In terms of the specific procedures or principles to regulate research on humans, there are a couple of areas which particularly need to be addressed by developing countries in both the global dialogue for establishing international standards and in the national process of regulation-setting. The most controversial of these areas concerns the necessity of obtaining the informed consent of all subjects. Recently, some commentators have suggested that exporting the doctrine of informed consent to developing countries which have a communitarian outlook and lack a concept of "self" or "personhood" amounts to "ethical imperialism" or an imposition of Western values on non-Western cultures.[243] In such a society, it may sometimes be appropriate to accept the community standard of consent—to seek consent on behalf of the individual from the head of the household or the community leader.[244] This is the approach adopted by the CIOMS Guidelines.[245] Moreover, seeking individual informed consent may not only be fruitless, it may undermine the nonindividualistic society's fabric.[246] Failure to accept the community standard also violates the principle of autonomy in that it fails to respect the integrity of the community.[247]

The West may place too much weight on the principle of autonomy, and thus correspondingly on the protection afforded by informed consent. Whether patient autonomy includes the right to demand a specific type of

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July 11, 1988, at 50; Isabel Wilkerson, *Nazi Scientists and Ethics Today*, N.Y. TIMES, May 21, 1989, at 1-34.

242. *See supra* text accompanying notes 163-164 (describing such a requirement by the FDA). The CIOMS Guidelines provide that the ethical standards should be "no less exacting" than if the research were performed in the sponsoring country. Nicholas A. Christakis, *The Ethical Design of an AIDS Vaccine Trial in Africa*, HASTINGS CENTER REP., June-July, 1988, at 31.

243. Christakis, *supra* note 242, at 34-35; Ross Kessel, *Commentary: Informed Consent in the Developing World*, HASTINGS CENTER REP., June 1984, at 23; Lisa H. Newton, *Ethical Imperialism and Informed Consent*, IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH, May-June 1990, at 10.

244. Newton, *supra* note 243.

245. *See supra* text accompanying note 202.

246. Newton, *supra* note 243, at 11.

247. *Id.* at 10-11.

treatment (e.g., life-sustaining treatment without possibility of "medical benefit") is an issue that continues to be debated.[248] A similar instance occurs when some advocates of radical pharmaceutical reform demand that the FDA abandon its regulation of research and that drugs which have not been proven to be safe and effective be tested under a system where patient and physician make an "informed choice."[249] It is true that, simply because ethical rules based on our common western "traditions and heritage" work for us, does not necessarily mean they can be exported to the rest of the world.[250] "The underlying philosophy and heritage of Western Europe's civilization is intricately woven with the recognition of the inalienable and absolute rights of the individual."[251]

In the West, there may be too much emphasis on the formalities of "obtaining signatures on elaborate consent forms [which] can become a mechanical substitute for dialogue,"[252] that fails to convey to the potential subject information which is truly relevant to the subject's decision to participate in research.[253] Although there are at least seven requirements which must be met prior to research approval, review of research in the United States focuses largely on (1) whether "[r]isks to subjects are reasonable in relation to anticipated benefits"[254] and (2) whether the procedures for obtaining informed consent are adequate.[255] However, these are not reasons to abolish informed consent, but rather to redefine it.

As the Nazi war-time experiments demonstrated, meaningful, autonomous, informed consent is also necessary to serve as a check on society's use of the individual for its own ends. That is why abandoning informed consent in communitarian societies, which might favor the interests of society over those of the individual,[256] seems particularly troublesome.[257]

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248. *See* Judith F. Daar, *A Clash at the Bedside: Patient Autonomy v. A Physicians's Professional Conscience*, 44 HASTINGS L.J. 1241 (1993) (discussing a case honoring a family's request that an 87-year-old woman in an irreversible coma be kept on life support despite her physicians' belief that the treatment was futile); Ellen Goodman, *Do-It-Yourself Medicine No Cure for the System*, NEWSDAY, Oct. 28, 1993, at 123 (commenting on a case where an anencephalic infant's mother succeeded in keeping the brain-absent child on full life support).

249. *See, e.g.*, Beth E. Myers, *The Food and Drug Administration's Experimental Drug Approval System: Is it Good for Your Health?*, 28 HOUS. L. REV. 309, 334-36; Wells, *supra* note 2, at 411. For the reasons why such a system would not be in society's or the individual's best interests, see text accompanying *supra* notes 94-104.

250. Brian Walsh, *Protecting Citizens from Their Own Countries: How the European Court of Human Rights Affects Domestic Laws and Personal Liberties*, 15 HUM. RTS. 20, 22 (1988).

251. *Id.*

252. Harvey Teff, *Medical Models and Legal Categories: An English Perspective*, 9 J. CONTEMP. HEALTH L. & POL'Y 211, 218 (1993).

253. *See* Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 34-38 (1993).

254. 45 C.F.R. § 46.111 (1993).

255. BARRY R. FURROW ET AL., BIOETHICS: HEALTH CARE LAW AND ETHICS 387 (1991).

256. Christakis, *supra* note 242, at 35.

257. Abandonment of the informed consent requirement may lead to exploitation of communitarian societies by pharmaceutical researchers who may be tempted to perform research in these societies then try to use the results in developed countries or use them

Moreover, informed consent is needed in clinical trials, even though patients and investigators believe they have the patient's interest "uppermost in mind," because investigators may in fact have other personal and professional interests.[258] Informed consent serves as a check on these conflicting interests.[259] Informed consent involves two significant elements of ethical research. First, informed consent is substantive; it is one way to demonstrate respect for the individual's autonomy. Second, informed consent is a procedural device for the protection of the subject, which more often than not, tends to promote the interests of the subject. Even if we accept the view that informed consent is not the appropriate way to demonstrate respect for autonomy in a communitarian society, or can be overridden by the principle of nonmaleficence, we still need to be sure that sufficient procedural protections are in place.

Consent by head of the household or community leader may not provide sufficient procedural protection. First, there is the difficulty of researchers from outside the culture identifying the appropriate substitute decision-maker.[260] Second, relying on communitarian philosophy in the absence of informed consent/autonomy is problematic because individual research subjects may be exploited by a politician or community leader pretending to be carrying out the best interests of the whole society.[261] Finally, as demonstrated by the Tuskegee Syphilis Study, obtaining consent from more educated members of the same racial and ethnic group does not adequately protect the subjects from exploitation.[262] Consent by community leaders may be a necessary, but not a sufficient step to protect the rights of research subjects.

There are also reasons to question whether informed consent should be abandoned as a substantive element of autonomy. First, consent by the leader on behalf of the community requires a generalization that all members of the community subscribe to the communitarian outlook and have no concept of self. Moreover, some commentators have indicated that individual, informed consent is necessary because developing societies are becoming more urbanized, and the anthropological data on which the communitarian consent arguments are based are outdated.[263] Thus, the CIOMS Guidelines allowing substitute consent seem, at best, problematic, and at worst, inadequate.

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as an inexpensive way to conduct preliminary studies before proceeding with more rigorous research. *See supra* notes 159-62, 221 and accompanying text; *infra* notes 257-64 and accompanying text.

258. Katz, *supra* note 253, at 17.

259. *Id.* In fact, Katz suggests this is the *only* way to keep these non-therapeutic interests in check. *Id.*

260. Christakis, *supra* note 242, at 34.

261. Ren-Zong Qiu, *supra* note 29, at 121.

262. *See* Jones, *supra* note 149, at 196-200 (indicating that consent for the study had been obtained in 1969 from the mostly black Macon County Medical Society).

263. Carel B. Ijsselmuiden, *Research and Informed Consent in Africa: Another Look*, 326 NEW ENG. J. MED. 830, 831 (1992).

Another issue relating to autonomy and informed consent with which developing countries need to grapple is conveying the proper information and documenting informed consent when illiteracy, lack of education, or different conceptions of illness causation are prevalent.[264] Finally, investigators must be sure that neither the payment of fees to the subjects nor the provision of health care or other goods and services ancillary to the research become coercive.[265]

3. *Getting a Second Opinion–The Need for Independent Oversight*

It is difficult to legislate proper ethical conduct for all research protocols. The most workable approach to protect research subjects has been the use of independent/institutional review boards (IRB) or ethical committees.[266] IRB's primarily serve two functions. First, a peer review committee ensures that research protocols are "scientifically sound, well-planned and safe for human experimentation,"[267] and that the potential risks to the subjects are outweighed by potential benefits.[268] To carry out this function, the IRB must have sufficient scientific expertise to evaluate the research protocol and the competence of the researcher. Second, the IRB acts as the representative of the "broader local community in assessing community acceptance of the particular risk/benefit ratio."[269] Scientists cannot serve in this capacity because they are not "the appropriate person[s] to ask" to make a community assessment, just as a rabbi friend is not the appropriate person to ask to pick out an Easter ham.[270] The function of lay members of the IRB has also been described as watch-dogs, "to guard against a closed shop of the scientists."[271] To carry out this function, IRB's need to be "as open and representative of informed public interests as possible"[272] and "must relate intimately with the norms of the local population."[273] There has also been some discussion of the need to have a sufficient number of lay members so that they are not dominated by the scientists.[274] Denmark now requires a majority of lay members on each IRB.[275] All countries

264. Lurie et al., *supra* note 172, at 297-98.
265. *See* O.O. Ajayi, *Taboos and Clinical Research in Africa*, 6 J. MED. ETHICS 61, 62 (1980).
266. *See* TOWARDS AN INTERNATIONAL ETHIC, *supra* note 39, at 41-43.
267. Ajayi, *supra* note 265, at 63.
268. Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 105 (1993).
269. *Id.*
270. *Id.* at 106 (quoting Robert M. Veatch, *The National Commission on IRB's: An Evolutionary Approach*, 9 HASTINGS CENTER REP. 22, 26 (Feb. 1979)).
271. Deutsch, *supra* note 193, at 10.
272. David Taylor, *Prescribing in Europe–Forces for Change*, 304 BRIT. MED. J. 239, 242 (1992).
273. Ajayi, *supra* note 265, at 63.
274. Goldner, *supra* note 268, at 106.
275. *Id.* at 107. Not everyone believes that lay members need to number one-half or more of the committee in order to carry out this function and that they are not capable of determining "whether the study is scientifically valid" and therefore should not be allowed to block experimentation. *See* Deutsch, *supra* note 184. But the author also

should consider some type of local review process which can perform both peer review and community review. While a majority of lay IRB members may not be necessary, lay members should constitute a significant presence on the review committee.

In addition to their active functions, the existence of an IRB and the need for an investigator to appear before a review committee inspires the investigator's own "self-conscious and serious sense of reflection" which includes considering the points of view of the research subjects.[276] Being forced to confront competing viewpoints "may force a reconsideration" of the research means or sometimes alter research objectives as part of a scientist's recognition of ethical responsibility.[277]

Finally, another bioethics principle which is of importance to developing countries is the justice principle. The justice principle requires a sense of "fairness" in the distribution of the burdens and benefits of research.[278] When a community is called upon to serve as research subjects, the benefits ought to accrue to that community.[279] Moreover, the justice principle directs that subjects should be selected "for reasons related to the problem being studied" and not because of "their easy availability, their compromised position, or their manipulability."[280] This is a principle which ought to be embodied in an international code of research ethics. It has been recognized in other contexts. For example, the preamble of the Convention on Biological Diversity of the United Nations Conference on Environment and Development,[281] signed by 167 countries,[282] promotes the "fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including . . . by appropriate funding."[283] Further, Article 15 authorizes the signatories to take all necessary steps "to ensure that the benefits of research utilizing genetic resources are shared fairly with the nation of origin."[284] The justice principle would also require nations to consider whether research interests are fairly distributed or weighted against developing countries.[285]

Conclusion

Although the World Health Organization and a few countries are partici-

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indicates that the trend is towards "community review" and hence toward greater lay participation. *Id.*

276. KATZ ET AL., *supra* note 150, at 105.

277. *Id.*

278. Christakis, *supra* note 242, at 36.

279. Dresser, *supra* note 122, at 27.

280. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 5 (1974).

281. 31 I.L.M. 818 (1992).

282. Kadidal, *supra* note 27, at 225.

283. 31 I.L.M. 823 (1992).

284. *Id.* at 828.

285. *See supra* note 28 and accompanying text.

pating in the International Harmonization activities as observers,[286] greater attention by the other nations of the world is needed. Harmonization activities among the producer nations will have a significant impact on health care delivery for all nations.[287] While reducing unnecessary and duplicative procedures should lead to reduced costs and hence better health care for all, other outcomes can have potentially negative effects.

An increase in the acceptance of foreign data may lead to an increase in clinical research activities in countries which lack or are unable to enforce ethical regulations. The adoption by the producer countries of either a mutual recognition procedure or a centralized procedure that approves drugs at an earlier point in the research process will have to focus more resources on post-marketing investigation and regulation. For countries which rely on a certification scheme and those whose health care resources are already strained, such surveillance may be impossible. In addition, the recognition that genetic or local differences can have a significant effect on drug interactions suggests that testing which is not sensitive to these factors increases the chance that adverse effects may be missed or that drugs which would be efficacious for a different population have no apparent effect on the test population.[288]

Where should the balance between safe drugs and speedier access be struck? Some see the U.S. regulatory process in an international context as excessively procedural.[289] At present, each country makes a different value judgment about important life-sustaining drugs and acceptable risk levels based upon its culture.[290] Sometimes local conditions may have a legitimate effect on differences in individual countries' pharmaceutical needs,[291] and thus local regulatory approval may be justified in some cases. On the other hand, a harmonized regulatory process may benefit consumers by providing speedier access to effective therapies. Considering the global effect of regulatory activity by producer nations, the international harmonization process needs to shift to a global outlook, and greater attention needs to be paid to the harmonization process by all countries. Given the substantial, paradigmatic shift required by a harmonized policy, there should also be broader participation by representatives from the public and science.

Although developing countries may feel unable to participate in the harmonization process on an equal footing with developed countries, it is

286. *Global Harmonisation on Pharmaceutical Regulations a Step Nearer*, PHARMACEUTICAL BUS. NEWS, Nov. 15, 1991 (other observers include Australia, Canada, South Africa, Sweden, Russia and various EFTA member nations).

287. This factor only recently received some attention in the harmonization process. *World: Seminar on International Harmonization Held*, REUTER TEXTLINE–CHEMICALS BUSINESS NEWS BASE, Oct. 14, 1993, *available in* LEXIS, World Library, Allwld File.

288. Ethnic differences in drug evaluation will be the focus of the Third Conference, which is scheduled to take place in November, 1995 in Japan. *Pharma Harmonization "Helps Patients," Says ICH*, MARKETLETTER Nov. 15, 1993, *available in* LEXIS, News Library, Curnws File.

289. Wells, *supra* note 2, at 414.

290. *Id.*

291. TRANSNATIONAL CORPORATIONS, *supra* note 41, at 31.

vitally important that they do so. Developing nations may have limited resources and human power, but they represent more than three-quarters of potential pharmaceutical consumers. Latin America and the Caribbean are especially expected to present growing markets.[292] While uniting such a diverse group of nations may be difficult, regionalization may provide the key to the ability of developing nations to have a voice in global matters such as the pharmaceutical harmonization processes that affect their citizens.

Globalization does not require that all countries accept the judgment of another country that a drug is safe and efficacious. Because no drug can be completely safe and completely efficacious at the same time, a decision to approve a drug for marketing in a particular country involves achieving the proper balance between safety and effectiveness. Determining the acceptable level of adverse effects in light of the evidence of efficacy depends on various local factors, including the prescribing patterns in the country, self-medication practices, the availability of health care workers to monitor patient drug use, and an understanding of the health needs of the population. It also depends on ascertaining or investigating whether the drug's safety or efficacy is affected by local factors such as diet or genetics. Nonetheless, countries must recognize that human rights may be adversely affected both by approval of an unsafe or ineffective drug and by unnecessary regulatory delays or obstructions to drug availability.[293]

Globalization does require that we recognize the interconnectedness of world health and research on health, particularly in the area of pharmaceuticals. As with environmental pollution, diseases know no boundaries. Global health care must become a priority for all nations because we are all affected by the health care problems of the most troubled nations. If research is to be conducted in developing countries we must ensure that the benefits of that research are available to the citizens of that country.

The future will only increase the amount of research that is conducted abroad, particularly in developing nations. Some of that research is necessary for the health and well-being of the citizens of developing countries. Some of that research will be performed in developing countries only because regulatory loopholes make it possible. Without international cooperation, without concerted action by both developed and developing countries, those loopholes will remain. A viable and binding international agreement setting minimum standards for the conduct of research is needed now. In addition, local or national enforcement mechanisms need to be implemented in many developing countries and broadened in the developed countries. Otherwise we risk benefiting from and thereby encouraging unethical conduct on vulnerable populations.

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292. *See supra* note 39 and accompanying text.

293. *See, e.g.*, BAD MEDICINE, *supra* note 1, at 218 (describing the tendency of developing countries to delay drug approval until a local firm has begun competing production).