Regulation of Drug Treatments for HIV and AIDS: a Contractarian Model of Access

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The HIV/AIDS epidemic has provoked a reexamination of U.S. drug testing and approval policies. The traditionally conservative posture of the Food and Drug Administration (FDA) has resulted in the development of a highly protective and lengthy drug approval process that denies consumers early access to experimental drugs. While this paternalistic approval process may be warranted in most cases, it can deprive HIV/AIDS patients and others suffering from similarly life-threatening diseases of their only hope for effective treatment. Professor Salbu examines the shortcomings of both the paternalistic model employed by the FDA and the open access model proposed by AIDS activists in light of the conflicting interests of the individual, the pharmaceutical industry, and the state. Professor Salbu offers a contractarian model that would limit government intrusion and allow individuals to assume the risk of taking untested but potentially promising drugs. This article recommends a specific policy that recognizes the primacy of individual autonomy while protecting the more limited interests of both industry and the state.

Introduction 402

I. History of the FDA Approval Process 406
   A. *Regulation of Drugs Prior to AIDS* 406
   B. *Recent Developments in Drug Regulation* 410

II. Options for Drug Access Policy: Paternalism, Open Access, and Contractarianism 418

III. A Contractarian Model for the Development of Ethical, Humane,

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and Effective Access to HIV+/AIDS Drugs 422
A. *Protection of the Rights and Interests of the Individual* 423
B. *Preservation of Corporate Autonomy* 429
C. *Promotion of the State Interest in Public Health* 430
1. *Enhancing Clinical Trials* 432
2. *Other Approaches to Data Collection* 434
D. *The Utility of the Contractarian Model in Balancing Interests* 439

IV. Implementing the Contractarian Model 440

Conclusion 453

Introduction

The world has lived with Acquired Immune Deficiency Syndrome ("AIDS") for over fifteen years.[1] By late 1993, the number of deaths attributable to AIDS in the United States alone surpassed 200,000.[2] AIDS is presently the leading cause of death among both men and women between the ages of 25 to 44 in many cities.[3] Although homosexual men comprised forty-eight percent of AIDS diagnoses in 1993, the incidence of AIDS is increasing most rapidly among other groups, including women,[4] racial and ethnic minorities,[5] and intravenous drug users.[6] Projections by the Centers for Disease

1. The first sign of AIDS to receive worldwide attention was a concentration of Kaposi's sarcoma cases observed among male homosexuals in the United States in 1979. It is possible that AIDS-related illnesses pre-date these earliest observations but were simply not recognized as having a shared viral source.

2. Anne Rochell, *AIDS Deaths in U.S. Top 200,000; Next 14 Months to Claim at Least 130,000 More*, ATLANTA CONSTITUTION, Oct. 29, 1993, at A1.

3. Richard M. Selik et al., *HIV Infection as Leading Cause of Death Among Young Adults in U.S. Cities and States*, 270 JAMA 2991 (1993).

4. For a detailed argument that the construction of AIDS as a gay male disease has impaired research and treatment of AIDS among women, see GENA COREA, THE INVISIBLE EPIDEMIC: THE STORY OF WOMEN AND AIDS (1992).

5. Some suggest that the danger of AIDS among racial and ethnic minorities must be addressed more aggressively. *See, e.g.*, Catherine Woodard, *Minorities Often Hit By AIDS Infections; Struck More by Fatal Pneumonia*, NEWSDAY, Oct. 10, 1993, at 59 (referring to efforts by the Gay Men's Health Crisis to provide services and outreach programs for minorities, in the absence of adequate government attention). Others have contended that reports of high incidence among blacks and Hispanics are racist. *See, e.g.*, Tony Brown, *Tony Brown's Journal: Report Blames Blacks and Hispanics for AIDS*, ETHNIC NEWSWATCH, Jan. 21, 1993, at 5b. For a psychological and sociological analysis of AIDS among blacks, *see* Wayne L. Greaves, *The Black Community*, *in* AIDS AND THE LAW 281 (Harlon L. Dalton, et al. eds., 1987).

Control ("CDC") suggest that AIDS-related deaths will continue to mount rapidly in the foreseeable future.[7] While a number of treatments for AIDS are available,[8] there is presently neither a vaccination nor a cure.

Today, two of the most compelling goals of current AIDS policy—the need to engage in effective scientific and medical research and the challenge of meeting the current medical needs of those who are HIV-positive and those who have AIDS (hereinafter "HIV+/PWA"[9])—are in potential conflict[10]. At first glance, these crucial goals appear largely compatible. We place our faith in scientific and medical research to deliver us from the epidemic through the development of an effective vaccination, cure, or treatment.[11] In this sense, decisions that support the quality and quantity of AIDS research today and tomorrow will redound to the benefit of untold numbers of persons in the more distant future. Yet while the interests of current research and the needs of future patients are congruous, a tension exists between the goals of current research and the needs of existing patients who face imminent suffering and death.[12]

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6. *AIDS is Top Killer Among Young Men*, N.Y. TIMES, Oct. 31, 1993, at A19.

7. The CDC estimates that 500,000 Americans will be diagnosed with AIDS by 1995. *AIDS Deaths Mount More Slowly*, WASH. TIMES, Jan. 15, 1993, at A2.

8. While only a few AIDS treatment drugs, such as AZT and ddI, target HIV infection itself, a number of treatments have been developed for the many opportunistic infections and other medical complications that are common to individuals with HIV-related illness and AIDS. These include foscavir (for the prevention of CMV retinitis) and aerosolized pentamidine (for the treatment of pneumocystic carinii pneumonia).

9. It will often be necessary to refer simultaneously in these pages to both persons who are HIV-positive and persons with AIDS. When an observation herein refers to both groups, the term "HIV+/PWAs" has been adopted as a shorthand form intended to achieve clarity and avoid rhetorical clumsiness.

10. Persons with extremely debilitating, terminal illnesses such as AIDS may have little patience with the norms of scientific rigor, and are often willing to assume responsibility for, and risks associated with, the use of promising but untested experimental drugs.

For example, Paul Monette's autobiographical account discusses AIDS using a martial metaphor, describing in detail the battle he, his lover, and his friends fought against the progress of the disease. PAUL MONETTE, BORROWED TIME: AN AIDS MEMOIR (1988). He describes an AIDS underground information network of patients whose observations, though anecdotal, may provide the earliest clues regarding potential treatments and effects. The conditions Monette describes are the conditions of war, complete with the threat of imminent suffering and death. It is not surprising that many PWAs see governmental regulation of drugs as a safeguard too luxurious to serve their health care needs.

11. Research in these areas may become more highly integrated, because the prospect of "therapeutic vaccines" is considered increasingly promising by the scientific community. Therapeutic or treatment vaccines are those that "not only protect healthy people against infection but might also serve as a form of therapy for those already infected." Jon Cohen, *Lobbying for an AIDS Trial*, 258 SCIENCE 536, 536, (1992).

12. Dr. Alastair Clayton, director general of the Federal Center for AIDS in Ottawa, Canada, has argued that "[t]here are not that many individuals who have AIDS and not that many with symptomatic infection, so we have to encourage them to go on trials rather than getting the drugs through emergency drug release because then we don't learn as much." In contrast, Timothy McCaskell, chair of AIDS Action Now in Toronto, focuses on the availability of drugs regardless of source: "Whether people have access to a particular treatment through a trial or through emergency drug release or through some other mechanism, we really don't care." Nora Underwood, *A New War on AIDS: Activists are Gaining More Access to Drugs*, MACLEANS, Sept. 18, 1989, at 62.

The conflict between scientific research programs and the interests of those seeking immediate treatment is a function of the role of the HIV+/PWA as both research subject and patient.[13] While patients expect and deserve to be treated as ends in themselves, experimental subjects inherently serve as means to extrinsic ends. The goal of research is primarily the achievement of knowledge rather than the improvement of any one patient's health. In the role of patient, the HIV+/PWA looks for treatment in accordance with personal privacy, autonomy, dignity, and respect.[14] In the role of experimental subject, the HIV+/PWA is handled as a data source from which knowledge is to be derived. The roles of patient and subject are compatible only insofar as two conditions are met. First, knowledge received during investigation must be channeled into more effective treatment of the patient-subjects. Second, the patient's ability to control the direction of treatment must not be forfeited as a condition of participation.

The tension between the roles of the HIV+/PWA as patient and as subject is exacerbated by the traditionally conservative posture of the Food and Drug Administration ("FDA") in the drug approval process. Treatments approved for marketing in other countries are frequently unavailable in the United States.[15] Historically, this disparity in drug availability has been a function of FDA regulatory processes that are lengthy and bureaucratically rigid relative to those of other nations. Prior to reform in the 1980s, the time frame from initiation

13. While this Article concerns AIDS drugs, many of its conclusions and recommendations are applicable to treatments for other life-threatening diseases. The tension between individual as patient and individual as research subject existed before AIDS, but gained greater public attention through HIV and AIDS advocacy. AIDS is indistinguishable for the overall purposes of this discussion from other diseases that are terminal, for which there is no known cure or effective treatment that is unaccompanied by serious risk or potential side effects. While this Article addresses AIDS as a particular example in analyzing the intricacies of FDA regulation, the conclusions are generally applicable to the regulation of treatments for any diseases meeting the definitive criteria.

The most salient example of a pre-AIDS drug access issue concerned laetrile, a controversial cancer treatment that was unapproved in the United States but available in Mexico during the 1970s. In *United States v. Rutherford*, the plaintiffs sought access to laetrile despite the absence of FDA approval. The 10th Circuit Court of Appeals was sympathetic to the arguments of terminally ill patients, observing that the FDA's concepts of safety and effectiveness "have no reasonable application to terminally ill cancer patients." 582 F. 2d 1237, 1236 (10th Cir. 1978). The Supreme Court reversed, recognizing an expansive FDA mandate to ensure safety and effectiveness of all drugs, including those sought by terminally ill patients. 442 U.S. 544, 552 (1979).

14. For more elaborate discussion of privacy, autonomy, dignity, and respect in the treatment of HIV+/PWA, *see infra* part III.A.

15. The culture of FDA approval procedures has been characterized as "deadly over-caution." Carolyn Lochhead, *"Deadly Over-Caution": FDA Assailed for Slow Testing of New Drugs*, SAN FRAN. CHRON., Oct. 26, 1992, at A1 (quoting unidentified critics of the FDA).

Low tolerance levels for FDA approval time frames are exacerbated by suggestions that the process is needlessly dilatory. One study indicates that average FDA approval periods are substantially longer than comparable periods in the United Kingdom. Kaitin et al., *The Drug Lag: An Update of New Drug Introductions in the United States and the United Kingdom, 1977 through 1987*, 46 CLIN. PHARMACOLOGY & THERAPEUTICS 121 (1989).

of investigation to FDA approval of drugs averaged approximately twelve years.[16] While a number of legal and regulatory modifications discussed in this Article have reduced average approval periods considerably,[17] a number of regulatory hurdles remain. These impediments to the expedient availability of HIV/AIDS treatments should be carefully scrutinized. Those that are unjustified should be expunged.

This Article proposes workable contract-based[18] reforms of the FDA drug approval process that are designed to improve HIV+/PWA access to experimental AIDS drugs, either within or outside the context of experimental participation. The analysis incorporates the legal, ethical, and policy considerations that justify a movement from quasi-contractarian regulatory amendments, promulgated beginning in 1987, to a more purely contractarian stance.

Under this regulatory scheme, pharmaceutical companies engaged in developing drugs for AIDS treatment would be permitted, but not required, to sell experimental drugs to HIV+/PWAs who choose not to participate, or are unable to participate, in clinical trials. While the terms elected by mutually consenting supplier and buyer will vary from case to case, contractual arrangements could potentially include two important provisions. HIV+/PWAs seeking extra-experimental access could be required by manufacturers to pay a reasonable price for the drugs they receive; they could also be required to sign waivers of informed consent, exonerating the pharmaceutical supplier and prescribing physician from any and all liability associated with using the drug.[19] These proposed regulations are framed to balance concern for individual autonomy and choice, governmental and public interest in eradicating AIDS, and corporate incentives for developing new AIDS treatments. The Article argues that a contractarian model best achieves a balance of these concerns.

Part I discusses the history of pharmaceutical regulation in the United States and the processes used by the FDA to approve drugs. This part also outlines the most recent Congressional and FDA proposals for future regulatory reform. Part II examines three regulatory models of drug access: paternalism, open access, and contractarianism. Part III argues in favor of a contractarian approach, balancing the interests of patients, private corporations, and the state. This part includes an examination of privacy and autonomy interests of patients

16. *See* David Rotman, *The Price of Doing R&D Soars*, CHEMICAL WEEK, June 13, 1990, at 46 (citing findings from Tufts University Center for the Study of Drug Development).

17. The findings of one study suggest that this average has been reduced from twelve years to just over six years. *Id.*

18. Contractarianism augments the use of contract to supplant regulatory functions. For a detailed discussion, analysis, and critical examination of contractarianism, *see* Jean Braucher, *Contract Versus Contractarianism: The Regulatory Role of Contract Law*, 47 WASH. & LEE L. REV. 697 (1990).

19. Under a contractarian model, exchange relations will be modulated by self-interest and self-protection, such that companies will ordinarily be unwilling to sell highly speculative products without adequate compensation and mitigation of risk.

and corporations, as well as the public interest in scientific and medical research progress. Part IV outlines proposed regulatory modifications to the existing FDA approval system. The Conclusion suggests that we adopt a regulatory policy that supports individual rights, relatively free from governmental coercion or intrusiveness. Under the proposed contractarian scheme, benefits would exceed costs, and costs would be borne by those individuals who chose to assume the risk of taking untested but perhaps highly promising drugs. The availability of an enforceable contractual liability waiver would ensure that those who claim the interests of freedom are also willing to assume a corresponding responsibility for their choices and actions.

I. History of the FDA Approval Process

This part examines the process and underlying rationale for both the ordinary FDA approval track and the accelerated track for certain investigational new drugs ("INDs"). It also examines the development of regulations that allow pre-approval prescription of experimental drugs ("treatment INDs") under a limited set of conditions. Finally, this part provides an overview of recent legislative and administrative proposals, some already adopted, including parallel track trials, the use of surrogate markers in the drug approval process, external review of IND applications, and proposals for enhanced reciprocity with foreign pharmaceutical regulatory agencies.

A. *Regulation of Drugs in the United States Prior to AIDS*

In the United States, new drugs cannot ordinarily be marketed without FDA approval.[20] The current approval process has developed out of a series of governmental reactions to intermittent crises and disasters over the past century. Without exception, Congress has increased regulatory authority over the approval of new drugs as a result of media coverage of either pervasive abuses or specific tragedies.

The Pure Food and Drug Act ("1906 Act"),[21] enacted in 1906 in response to criticism by the Progressive movement of widespread food and drug impurities,[22] established liability for the manufacture of adulterated[23] or misbranded[24] drugs. The 1906 Act was weak by today's standards. It required

20. *See infra* text accompanying notes 34-42.

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

22. For a discussion of the history of the Pure Food and Drug Act of 1906, see Peter Barton Hutt, *Development of Federal Law Regulating Slack Fill and Deceptive Packaging of Food, Drugs, and Cosmetics*, 42 FOOD DRUG COSM. L.J. 1, 1-2 (1987).

23. Pure Food and Drug Act, ch. 3915, §7, 34 Stat. at 769.

24. *Id.* § 8, 34 Stat. at 770.

a manufacturer to monitor its drugs for strength, quality, and purity,[25] and to provide complete and accurate labelling of drug contents.[26] However, in 1911, the Supreme Court ruled that while the language of the Act prohibited mislabeling of drug ingredients, it did not prohibit other kinds of fraudulent claims made on product labels.[27] Moreover, the 1906 Act failed to enumerate standards or specific methods of pre-market testing that would prevent adulteration, or to provide any mechanism for centralized regulatory approval of new drugs.[28] Finally, while the Act provided for criminal prosecution of manufacturers,[29] it did not establish liability for infliction of injury or death as a consequence of marketing adulterated or misbranded drugs.

In 1937, the shortcomings of the 1906 Act were demonstrated by the tragedy brought on by the use of Elixir Sulfanilamide, marketed by the drug manufacturer Massengill. While the "elixir" was merely a liquid version of a drug already available in pill form, the solvent used in the solution had not been tested for safety. Its toxicity resulted in 107 deaths.[30] Under the 1906 Act, Massengill was fined $26,100 for product mislabeling.[31]

Following the Elixir Sulfanamilide tragedy, lawmakers responded to public concern by strengthening regulatory control over pharmaceutical products.[32] They argued that the 1906 Act needed to be strengthened to avert future tragedies, and that the government should not simply rely upon the deterrent effects of fines. This goal could be achieved by preventing dangerous new drugs from entering the market.[33] Towards that end, Congress passed the Federal Food, Drug and Cosmetic Act ("1938 Act"),[34] which required safety testing and government approval of new drugs[35] prior to commercial

25. *Id.* §§ 1-12, 34 Stat. at 768-72.

26. *Id.*

27. *United States v. Johnson*, 221 U.S. 488 (1911). In 1912, to remedy this shortcoming, Congress passed the Sherley Amendment, which prohibited false or fraudulent claims made on drug labels. Act of Aug. 13, 1912, ch. 352, § 8, 37 Stat. 416.

28. The 1906 Act did authorize the Bureau of Chemistry of the Department of Agriculture to conduct compliance examinations of drugs. Pure Food and Drug Act, ch. 3915, § 4, 34 Stat. at 416. However, this provision did not require pre-marketing approval and served merely as an enforcement tool for spotting offenses in the marketplace.

29. *Id.* §§ 1-5, 9-10, 34 Stat. at 768-9, 771-2.

30. Arthur Hull Hayes, *Food and Drug Regulation After 75 Years*, 246 JAMA 1223, 1224 (1981). For further discussion of the relationship between the Elixir Sulfanilamide tragedy and the 1938 Act, *see* David F. Cavers, *Food, Drug and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2, 20 (1939).

31. The manufacturers failed to list diethylene glycol, the toxic component of Elixir Sulfanilamide, on the label. Cavers, *supra* note 30, at 20; PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES at 42 (1980).

32. *See* TEMIN, *supra* note 31, at 43.

33. Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy*, 4 ADMIN. L.J. 589, 590 (1991).

34. Pub. L. No. 52-717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. §§ 301-392 (1988)).

35. Under the 1906 Act, drugs covered by adulteration and mislabeling provisions were restricted to those listed in two pharmaceutical registries: United States Pharmacopoeia and National Formulary. Ch. 3915, §§ 6-7, 34 Stat. at 769-70. Because this limitation proved unreasonably restrictive, particularly

marketing.[36] Under the provisions of the 1938 Act, prospective manufacturers were required to file applications for the sale of new drugs with the Secretary of Agriculture, describing drug components and composition, methods of production control, and proposed labeling language.[37] The 1938 Act also required that applicants supply copies of investigational safety reports, as well as samples of the drugs under consideration.[38] Unless the Secretary of Agriculture rejected or postponed consideration of the application within sixty days of filing, default approval was conferred by statute.[39] The 1938 Act also authorized the Secretary of Agriculture to promulgate regulations exempting INDs from this approval process.[40]

As the Elixir Sulfanilamide disaster inspired the 1938 Act, so the thalidomide tragedy[41] resulted in the Kefauver-Harris Amendments ("1962 Amendments").[42] The 1962 Amendments required more rigorous pre-approval drug testing than was required under the 1938 Act, instituting a series of clinical testing "phases" that comprise the norm under current law.[43] At present, the initial step in obtaining FDA approval entails testing on animals to determine whether the drug is sufficiently safe and promising to justify human experimentation.[44] Using evidence gathered in these preliminary tests to support

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in its failure to cover the new drugs most likely to require supervision, the 1938 Act required safety testing of new drugs. Ch. 675, § 505, 52 Stat. 1040, 1052-53.

36. The 1938 Act did not, however, require that a new drug be tested for effectiveness, nor that the effectiveness be reasonably proven as part of the approval process. Hoffman, *Defining "New Drugs": Recent Developments Affecting Prescription Drug Premarket Approval Requirements*, 37 FOOD DRUG COSM. L.J. 355; 356 (1982).

37. Ch. 675, § 505(b), 52 Stat. 1052 (1938) (codified at 21 U.S.C. §355(b) (1987 & Supp. 1989)).

38. *Id.*

39. Ch. 675, § 505(c), 52 Stat. 1040, 1052 (1938).

40. Ch. 675, § 505(i), 52 Stat. 1040, 1052 (1938).

41. Thalidomide, marketed as a sedative safe for usage by pregnant women, resulted in birth defects in thousands of infants. For discussion of the testing, marketing, and effects of thalidomide during the late 1950s and early 1960s, see HARVEY TEFF & COLIN R. MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH 1-10 (1976).

42. Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. §§ 301-81 (1982 & Supp. IV 1986)).

For the history of the 1962 Amendments and discussion of the problem of thalidomide in the context of this process, see VIEWS OF SENATORS ESTES KEFAUVER, JOHN A. CARROLL, THOMAS J. DODD, PHILIP A. HART, AND EDWARD V. LONG, S. REP NO. 1744, 87th Cong., 2d Sess. (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2898, 2905-07.

43. For discussion of the clinical testing phases, *see infra* text accompanying notes 47-50.

44. The value of animal testing of experimental drugs prior to human trials is controversial. Critics contend that differences among animals and humans in metabolizing substances renders results of animal testing questionable as applied to humans. Animal testing has been characterized as both underinclusive and overinclusive, in that promising treatments are eliminated and potentially dangerous treatments are allowed to proceed through the approval process. *See* John P. Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 938-39 (1991).

safety and efficacy claims, the drug sponsor files an IND application, seeking FDA authorization to begin the process of testing on humans.[45]

The current process of submitting INDs for clinical testing approval is relatively straightforward. An IND application serves as notification to the FDA that clinical trials are about to be initiated by the company, and permits tpthe FDA to engage in an initial assessment of the value of those trials on the basis of information provided by the applicant.[46] If the IND application is granted, the sponsor is permitted to begin clinical experimentation on human subjects, which is mandatory for final FDA approval of manufacture and distribution.

A three-phase process of testing on human subjects is now the FDA standard.[47] Phase I comprises initial safety testing, during which a relatively small sample of healthy, asymptomatic subjects receive the drug and are monitored for indications that the drug may be unsafe for human applications.[48] If the results of Phase I provide a preliminary indication that the drug is safe, the sponsor proceeds to Phase II, during which both the safety and efficacy of the drug are examined through controlled experimentation upon a larger sample of infected or symptomatic subjects.[49] If the results from Phase II are promising, a larger sample will be used in Phase III to further assess safety and efficacy.[50]

If the IND sponsor has gleaned promising results through Phase III, it may decide to continue seeking FDA approval by submitting a new drug application ("NDA"), which provides the FDA with information that includes the data collected and analyzed during experimentation.[51] Within 180 days, the FDA must either approve the application or notify the applicant of the opportunity to request a hearing on the merits of the application.[52] The FDA's approval is

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45. The filing of such application covers only the sponsor applicant's research team. Approval to proceed to clinical testing therefore permits only those listed as investigators to engage in experimentation with the IND. David A. Kessler, *The Regulation of Investigational Drugs,* 320 NEW ENG. J. MED., Feb. 2, 1989, at 281, 282. This limitation restricts clinical IND access to sponsored drugs.

46. The IND application contains, inter alia, names of parties responsible for the investigation, a statement of the investigational plan, a statement of the name of the drug to be tested and all its active ingredients, a summary of any previous human experience with the drug, a description of the overall plan for investigation, identification of phases of clinical investigation, a list of possible risks and side effects, a protocol for each planned study, and a summary of pharmacological and toxicological effects of the drug on animals. 21 C.F.R. § 312.23 (1988).

47. *Id.* § 312.21.

48. *Id.* § 312.21(a).

49. *Id.* § 312.22(b).

50. *Id.* § 312.22(c). In addition, a fourth and final phase follows drug approval. Phase IV consists of post-approval monitoring of drugs after they have been placed on the market. *Id.* § 312.85. Phase IV testing can be used by the FDA to measure the safety and efficacy of approved drugs on an ongoing basis, and to reevaluate drugs in light of developing scientific and medical knowledge. Since the focus here is on experimental drugs prior to FDA approval, Phase IV is of minimal relevance to the concerns raised in this Article.

51. The NDA contains data demonstrating "whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. §355(b)(1)(A) (1982 & Supp. IV 1986).

52. *Id.*

based on acceptable proof of the safety and efficacy of the drug when used for the purposes stipulated by the drug's sponsor.[53]

B. *Recent Developments in Drug Regulation*

The more stringent drug approval processes created by the 1962 amendments, while intended to protect the public, have contributed to a growing dissatisfaction over issues of consumer access.[54] AIDS has increased the level of discontent with the approval processes because of delays in access to drugs, and because of the conflict inherent in forcing HIV+/PWAs to become research subjects in order to receive experimental drug treatment. This section examines the present regulatory approach to drug access, with particular emphasis on recent amendments promulgated largely in response to AIDS. Although these amendments have been somewhat effective, they have not adequately addressed the tension between the treatment of HIV+/PWAs and the research value of those patients in the effort to eradicate AIDS.

During the 1980s and 1990s, HIV+/PWA organizations and groups in the gay community applied substantial pressure on Congress and the FDA to provide accelerated access to new AIDS drugs.[55] Largely as a result of these efforts, new rules and procedures were promulgated in 1987, 1988, 1991, and 1992. These rules and procedures have been intended to expedite access to experimental drugs for terminally ill patients.

A regulation promulgated in 1987 (the "1987 Amendment")[56] allows physicians to prescribe experimental drugs to patients as treatment INDs[57] provided that (a) the drugs are "intended to treat a serious[58] or immediately life-

53. The 1962 Amendments require "substantial evidence . . . consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . . . ." *Id.* § 355(d). Authorization of clinical testing can be revoked by the FDA if evidence arises suggesting that human drug testing is unsafe. *Id.* §§ 321(p), 355.

54. For criticism of the 1962 Amendments, see Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581 (arguing that "the increased burdens of regulatory compliance delayed the availability and discouraged the innovation of new drugs.")

55. Philip J. Hilts, *How the AIDS Crisis Made Drug Regulators Speed Up*, N.Y. TIMES, Sept. 24, 1989, at D5.

56. 21 C.F.R. § 312 (1988).

57. For a practical guide to treatment INDs provided by the FDA, see Frank E. Young et al., *The FDA's New Procedures for the Use of Investigational Drugs in Treatment*, 259 JAMA 2267 (1988).

58. In the 1987 and subsequent FDA Amendments, the FDA has consistently used "serious" as a qualifier in tandem with the somewhat less ambiguous "life-threatening." In 1992, the FDA observed that seriousness "is a matter of judgment, but generally is based on . . . such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." 57 Fed. Reg. 13235 (1992). While this definition of seriousness does provide some degree of guidance in measuring the relative seriousness of an illness, it is imprecise in regard to specific thresholds.

threatening disease"; (b) there is "no... satisfactory alternative drug or other therapy available" for treatment; (c) clinical investigations have either been completed or are presently in progress; and (d) the drug's sponsor is seeking drug marketing approval with due diligence.[59] Treatment INDs can ordinarily be prescribed only during Phase III investigations under the 1987 Amendment.[60] Treatment INDs can also be dispensed during Phase II under "appropriate circumstances" but "ordinarily not earlier than Phase II."[61] In addition, the FDA is authorized to approve ad-hoc applications for emergency INDs on a patient-by-patient basis.[62] By early 1992, over twenty drugs had been distributed as treatment INDS for the treatment of specific diseases including AIDS, cancer, Parkinson's disease, obsessive-compulsive disorder, and neonatal respiratory distress syndrome.[63]

Under the 1987 Amendment, pharmaceutical manufacturers must apply to the FDA for authorization to charge patients for treatment INDs.[64] The FDA has thirty days to reject the application. If it does not do so within that time period, the application is automatically authorized.[65] Approval to charge patients for treatment INDs is granted only under the following conditions:

> (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence.[66]

The FDA treats the sale of INDs used in clinical trials ("clinical INDs") more strictly than the sale of treatment INDs. A request for approval to charge subjects for clinical INDs requires the sponsor to explain why "charging is

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The FDA has provided some examples of serious diseases, such as: AIDS, "all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, [and] cancer." *Id.* The agency also considers as serious "many chronic illnesses that are generally well-managed by available therapy" but which "can have serious outcomes." *Id.* The FDA has offered the following as examples of diseases in this category: "inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, [and] psychoses. . . ." The FDA acknowledges that these chronic illnesses may be considered serious for some but not all populations, or during some but not all phases. *Id.*

59. 21 C.F.R. § 312.34(b)(1)(i)-(iv) (1988).

60. *Id.* § 312.34(a).

61. *Id.*

62. 21 C.F.R. § 312.36 (1988). For a discussion of emergency INDs, see Ellen C. Cooper, *Changes in Normal Drug Approval Process in Response to the AIDS Crisis*, 45 FOOD DRUG COSM. L.J. 329, 334-35 (1990).

63. 57 Fed. Reg. 13,234 (1992).

64. 52 Fed. Reg. 19,476 (1987).

65. *Id.*

66. 21 C.F.R. § 312.7(d)(2) (1992).

necessary in order for the sponsor to undertake or continue the clinical trial."[67] This requirement suggests that there are legitimate and illegitimate purposes for selling clinical INDs. Patients may be charged to generate revenues that are necessary to defray the cost of ongoing clinical trials of the IND; they may not be charged for general commercial purposes that are not closely linked to the viability of those trials.

The 1988 Procedures[68] establish relatively "fast-track" drug approval of treatments aimed at life threatening and severely debilitating diseases.[69] Because they are viewed as provisional and temporary, and aimed largely at the challenges posed by AIDS, the 1988 Procedures are commonly referred to as interim provisions. According to the FDA, the procedures were adopted in recognition of the fact that "patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses."[70]

Drugs that qualify under these "fast-track" provisions can be approved in the absence of traditionally required Phase III clinical testing. According to FDA projections, this modification has the capacity to shave years off the ordinary lab-to-market time frame.[71] The 1988 Procedures provide numerous opportunities for companies seeking expedited approval to confer with FDA authorities while designing research protocols and preparing the IND application.[72] Under these procedures, the FDA may meet with sponsors prior to IND submission, as well as at the end of Phase I testing.[73] Following Phase II testing, the FDA evaluates applications for expedited approval by weighing the risks and benefits of the drug in light of the severity of the disease at issue and the availability of alternative therapies.[74]

In 1991, the President's Council on Competitiveness proposed a number of regulatory reform measures aimed at expediting FDA approval of INDs ("PCC Recommendations").[75] Some of the PCC Recommendations suggested

67. *Id.* § 312.7(d)(1).

68. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses, 53 Fed. Reg. 41,515 (1988) (codified at 21 C.F.R. §§ 312, 314).

69. The 1988 Procedures include related changes that go beyond the purview of this Article's analysis. For example, the procedures permit sponsors to engage in clinical testing without the use of placebo control groups when alternative effective therapies can be used for comparison and control. 53 Fed. Reg. 41,519 (1988).

70. 21 C.F.R. §312.80.

71. *FDA Announces Interim Regulations to Speed Marketing of Promising Drugs*, AIDS POL'Y & LAW, Nov. 2, 1988, at 1.

72. 21 C.F.R. §§ 312.82(a), 312.82(b) (1988).

73. *Id.*

74. 53 Fed. Reg. 41,523 (1988).

75. *Recommendations to Speed Drug Approvals Issued*, [1990-91 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 42,603 at 43,617 (Nov. 18, 1991).

official recognition and formalization of processes already in place, such as external review of IND applications[76] and expanded use of advisory committees and institutional review boards to advise research teams.[77] Other subsequently adopted PCC Recommendations include accelerated approval processes[78] and the use of surrogate markers as evidence of effectiveness.[79]

One reform measure contained in the PCC Recommendations that is still under consideration would enhance U.S. recognition of foreign drug approvals.[80] The PCC Recommendations suggest a number of measures for integrating international drug approval processes into the U.S. system to avoid redundancy and create regulatory efficiencies. These measures include automatic approval of drugs that have been approved by a country with which the U.S. has a reciprocity agreement[81] and the development of common research and drug approval standards across nations.[82] The most recent related proposals would allow use of animal test data from Japan and the EEC in FDA review processes,[83] and joint review of drugs by the FDA and foreign counterpart agencies in Japan, Australia, and the EEC.[84]

Early in 1992, the Public Health Service issued a Policy Statement ("PHS Policy") providing for expanded availability of INDs for the treatment of AIDS and other HIV-related diseases through a "parallel track" mechanism.[85] Parallel track studies[86] run concurrently with traditional studies. While traditional clinical trials require classical experimental control groups, parallel track studies can be conducted without the use of experimental controls.[87] The vehicle of sub-experimental quality trials expands access to experimental drugs to those who cannot be included in the limited number of slots available in the concurrent clinical investigation. While the parallel track trials were established primarily to expand access of AIDS patients to INDs,[88] physicians who provide

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76. *Id.* at 43,621.
77. *Id.*
78. *Id.* at 43,622.
79. *Id.*
80. *Id.* at 43,623.
81. *Id.* According to the proposal, reciprocity would be "negotiated on a country-by-country basis." The PCC Recommendations suggest beginning with two or three countries believed by FDA to have approval processes that meet FDA safety and effectiveness goals. *Id.*
82. *Id.*
83. Food Drug Cosm. L. Rep. ¶ 42,806 (Aug. 31, 1992).
84. Food Drug Cosm. L. Rep. ¶ 43,126 (Dec. 28, 1992).
85. 57 Fed. Reg. 13,250 (1992). While the logic of a parallel track probably applies to other diseases, the PHS Policy is initially limited to AIDS and other HIV-related diseases. The Policy suggests that expansion to other life-threatening diseases may be forthcoming. *Id.*
86. Parallel track studies were initiated in 1976 by the National Cancer Institute to grant expanded early access to some cancer treatment drugs. Under that program, the National Cancer Institute bore the cost of manufacture and distribution of associated drugs, and physicians were required to collect and submit data. For discussion of these studies, see David W. Barry, *A Perspective on Compassionate Parallel Track Category C Treatment Track IND Procedures*, 45 FOOD DRUG COSM. L.J. 347 (1990).
87. 57 Fed. Reg. 13,256 (1992).
88. 57 Fed. Reg. 13,250 (1992).

parallel track treatment are required to report safety and efficacy data to the drug's sponsor.[89] The parallel track thereby provides non-controlled information to clinical trial investigators. Sponsors are required to monitor both the safety and the data generation aspects of parallel track protocols.[90]

Sponsors must apply to the FDA for approval of expanded access via parallel track.[91] Parallel track proposals will ordinarily include detailed protocols of both the expanded availability and the controlled clinical trials.[92] The proposal review criteria include: (a) evidence of safety and efficacy; (b) sufficient data for recommending starting dosage; (c) preliminary pharmacokinetic and dose-response data; (d) indications that a described and defined population lacks a satisfactory alternative therapy; (e) assurance of manufacturer willingness and ability to support production at adequate levels to supply both controlled clinical trials and expanded availability studies; (f) FDA approval of Phase II controlled clinical protocols; (g) assessment of the effect of a parallel track on controlled clinical trial enrollments; (h) a proposal for monitoring the progress of the controlled trials; and (i) evidence of efforts to assure that both patients and physicians will have information sufficient to assess risks and benefits of participation in the parallel track.[93]

Each protocol for expanded availability must include criteria for patient eligibility.[94] Expanded availability is limited to persons having HIV-related illnesses for which there is no effective or tolerable standard treatment,[95] and who cannot participate in the controlled clinical trials for any of several prescribed reasons.[96] If quantities of investigational drugs are inadequate to meet parallel track demand, protocols are expected to specify "patient priority categories" for the assessment of treatment preferences.[97] While the PHS Policy does not require sponsors to obtain FDA approval to charge parallel track recipients for treatment, sponsors must "specify the extent of economic support

89. 57 Fed. Reg. 13,258 (1992).

90. *Id.*

91. 57 Fed. Reg. 13,257 (1992). Applications are referred to the AIDS Research Advisory Committee ("ARAC"), which makes a recommendation to the Director of the National Institute of Allergy and Infectious Diseases ("NIAID"). The Director of NIAID then makes a recommendation, through the Director of the National Institutes of Health ("NIH"), to the Commissioner of the FDA. Sponsors can also opt to submit parallel track proposals directly to the FDA, without ARAC review. *Id.*

92. *Id.*

93. *Id.*

94. *Id.*

95. *Id.*

96. 57 Fed. Reg. 13,257 (1992). Acceptable reasons for inability to participate in controlled clinical trials are "(a) The patient does not meet the entry criteria for the controlled clinical trials, or (b) The patient is too ill to participate, or (c) Participation in controlled clinical trials is likely to cause undue hardship (e.g. travel time) as defined by the protocol, or (d) The controlled clinical trials are fully enrolled." *Id.*

97. 57 Fed. Reg. 13,258 (1992).

they would be willing to provide to pursue the expanded access of the investigational agent through the parallel track."[98]

In December 1992, the FDA issued yet another set of regulatory amendments ("1992 Amendments") intended to expedite approval of new drugs and biological products for the treatment of serious or life-threatening diseases.[99] Under the 1992 Amendments, full FDA approval for marketing can be granted based on a showing of "meaningful therapeutic benefit compared to existing treatment"[100] through the application of "surrogate markers."[101] Surrogate markers are indices of health that may indirectly suggest a drug's effectiveness by virtue of a valid and reliable correlation to clinical benefits.[102] For example, surrogate markers among those who test positive for HIV include the number of particular immune cells or the amount of particular viral antigens present in the blood.[103] For example, blood concentrations of CD4 immune cells are considered by some scientists to be reliable indicia of health among the HIV infected.[104] Two new AIDS drugs, DDI and DDC, were approved under the 1992 Amendments using CD4 counts as surrogate markers.[105]

Sponsors of drugs that are granted accelerated approval based on surrogate markers are required to conduct post-marketing clinical studies "necessary to ascertain the actual clinical benefit of the drug on such endpoints as survival,

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98. *Id.*

99. 21 C.F.R. pt. 314, §§ 601.40-601.45 (1993), *see also* 57 Fed. Reg. 58,942 (1992).

100. 57 Fed. Reg. 58,942 (1992).

101. *Id.* ("Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a diseased person, can be used safely only if distribution or use is modified or restricted.") *Id.* The final regulatory language adopted states, "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." 21 C.F.R. § 314.510 (1993).

102. The FDA defines a surrogate marker as "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy." 57 Fed. Reg. 13,235 (1992).

103. Elizabeth Schaefer, *AIDS Politics Change Rules*, NATURE, Jan. 17, 1991, at 187.

104. For a discussion of recent criticism of the validity of using CD4 counts as surrogate markers of health among persons with HIV, see Marsha F. Goldsmith, *HIV/AIDS Early Treatment Controversy Dues New Advice But Questions Remain*, 270 JAMA 295, (1993). *See also* Jean-Pierre Aboulker & Ann Marie Swart, *Preliminary Analysis of the Concord Trial*, 341 LANCET 889, (1993) ("Concorde has not shown any significant benefit from the immediate use of zidovudine compared with deferred therapy in symptom-free individuals in terms of survival or disease progression, irrespective of their initial CD4 count. The discrepancy between this result and the significant effect of immediate zidovudine on CD4 counts casts doubt on the value of using changes over time in CD4 counts as a predictive measure for effects of antiviral therapy on disease progression and survival.").

105. *Weighing the Benefits*, MacNeil/Lehrer NewsHour, Sept. 6, 1993, *available in* LEXIS, Nexis Library, MACLEH file.

disease complications, or longer-term symptoms."[106] The 1992 Amendments provide as well for withdrawal of approval under a number of conditions, including failure to engage in required post-marketing clinical studies and failure of post-marketing clinical studies to verify clinical benefit.[107] If a drug's safety can only be assured by restricted use or distribution, the FDA can restrict distribution "to certain facilities or physicians with special training or experience."[108] In addition, the FDA can condition distribution "on the performance of specified medical procedures."[109] Conditions of and restrictions on distribution are intended to function as protective procedures "under which beneficial but highly toxic drugs can be approved for marketing."[110] The FDA anticipates that the exercise of these distribution restrictions will be rare.[111]

These FDA changes directly and expressly seek to accelerate the availability of some AIDS treatments under limited conditions. Likewise, Congress has enacted legislation intended to expedite lab-to-market time frames indirectly. In 1992, Congress passed the Prescription Drug User Fee Act ("User Fee Act"), authorizing the FDA to collect reviewing fees from drug sponsors.[112] The User Fee Act permits the FDA to assess three kinds of fees: human drug application and supplement fees;[113] prescription drug establishment fees;[114] and

106. 57 Fed. Reg. 13236 (1992).

107. *Id.* Withdrawal of accelerated approval is authorized under the 1992 Amendments if "(1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use." 21 C.F.R. § 314.530 (1993).

108. 21 C.F.R. § 314.520 (1993); 21 C.F.R. § 601.42 (1993).

109. 21 C.F.R. § 314.520 (1993); 21 C.F.R. § 601.42 (1993).

110. 57 Fed. Reg. 13,234 (1992).

111. 57 Fed. Reg. 58,942-43 (1992).

112. Pub. L. No. 102-571, 106 Stat. 4491 (1992). The legislation authorizes fee waiver or reduction under stipulated conditions: when "(1) such waiver or reduction is necessary to protect the public health, (2) the assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances, [and] (3) the fees to be paid by such person will exceed the anticipated present and future costs incurred by the Secretary in conducting the process for the review of human drug application for such person." §763(d), 106 Stat. at 4496.

The legislation also authorizes a "small business exception" under which employers of fewer than 500 pay only one-half of the human drug application fee. §736 (b)(2), 106 Stat. 4495-96,

Critics suggest that the incremental cost of drug development attributable to FDA reviewing fees may discourage or prohibit research and development projects among all pharmaceutical firms. See Danni Sabota, Biotech Firms Brace for New FDA User Fees, HOUSTON BUS. J., Oct. 19, 1992, §1, at 1 (observing that user fees may create an insurmountable financial impediment to start-up and young biotechnology and biomedical firms that do not yet have a product on the market). They argue that this detrimental impact will be greatest upon smaller firms, which are least capable of bearing an additional financial burden, and which are vital and essential contributors to the development of new drugs. This burden on small manufacturers will be significant since the "small business exception" covers just one of the three kinds of fees established under the User Fee Act, and in that case, provides only for a reduction, rather than elimination, of the fee.

113. § 736(a)(1), 106 Stat. at 4494, One half of this fee is paid when the new drug application is filed. The fees are scheduled to increase annually between 1993 and 1997. For drug applications "for

prescription drug product fees.[115] The revenues generated by the fees will be used to hire more examiners,[116] thereby expediting the review process for all drugs.[117]

Although FDA reforms of the 1980s and 1990s expanded access to prescription drugs, the availability of less traditional treatments, such as herbs and supplements not classified as drugs, may soon become more limited. In early 1993, the FDA proposed stricter controls on over-the-counter nutritional supplements ("1993 Proposals"), under which many alternative treatments would be regulated like prescription drugs and subjected to testing and approval procedures.[118] The FDA contends that greater control over alternative treatments is necessary to ensure public safety, citing reports of "serious illnesses associated with certain herbal and other botanical supplements."[119] Some of the concern regarding treatment with vitamins, amino acids, and herbs arises from the proliferation of underground "buyers' clubs," formed in recent years to gain access to treatments for HIV illness that are unavailable in the United States.[120] While the FDA has adopted a lenient policy towards AIDS treatment buyers' clubs since the late 1980s,[121] casualties purportedly associated with products such as Compound Q, brought into the United States from China, have rekindled concerns that the FDA may have abdicated too much authority in the face of pressure from activist groups.[122]

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which clinical data. . . with respect to safety and effectiveness are required," fees increase gradually from $100,000 in 1993 to $233,000 in 1997. § 736(a)(1)(A)(i), 106 Stat. at 4494; § 736(b)(1), 106 Stat. at 4495. For drug applications "for which clinical data with respect to safety or effectiveness are not required" fees increase gradually from $50,000 in 1993 to $116,000 in 1997. § 736(a)(1)(A)(ii), 106 Stat. at 4494; § 736(b)(1), 106 Stat. at 4495.

114. § 736(a)(2), 106 Stat. at 4494-95, codified at 21 U.S.C.S. 379h (1993). This fee is assessed to owners of prescription drug establishments (i.e., the Use Fee Act's terminology designating manufacturers of prescription drugs) annually, and is scheduled to rise each year from 1993 ($60,000 per establishment) through 1997 ($138,000 per establishment). § 736 (b)(1), 106 Stat. at 4495.

115. §736(a)(3), 106 Stat. at 4495, This fee is a recurring annual fee imposed upon each approved prescription drug product. The fee is scheduled to increase annually between 1993 ($6,000 per product) and 1997 ($14,000 per product.) § 736(b)(1), 106 Stat. at 4495.

116. The Act will result in the hiring of six hundred new FDA employees, who will expedite drug approval processes. *Committee Passes Pharmaceutical Measure Designed to Improve Approval Processes*, DAILY REP. FOR EXECUTIVES, Sept. 21, 1992, at 183.

117. *See* David M. Halbfinger, *Drug Companies See Benefit in the User Fees They Will Pay*, PHILADELPHIA BUS. J., Nov. 30, 1992, § 1, at 1 (citing executives within the pharmaceutical industry who believe that the expedited review made possible by assessment of user fees will ultimately redound to both public and business interests).

118. 58 Fed. Reg. 33,690 (1993).

119. *Id.* at 33,690.

120. Mike McKee, *Notes from Underground: Buyers' Clubs Feel Heat*, RECORDER, July 29, 1993, at 11.

121. FDA Commissioner Frank Young authorized a policy in the late 1980s, under which AIDS patients have been permitted to bring AIDS treatments sold abroad into the United States, provided they are for personal use only. Joshua Hammer, *The AIDS Underground: Herbs, Hormones, and Smuggling Runs Overseas*, NEWSWEEK, Aug. 7, 1989, at 50.

122. *Id.*

The 1993 Proposals have been criticized by both conservative politicians and AIDS activists. Senate Bill 784, which would derail FDA efforts to control nutritional supplements by increasing NIH advisory and evaluative authority,[123] has received support from such unlikely allies as Republican Senator Orrin Hatch and San Francisco ACT UP.[124] Hatch casts his objections in the language of market autonomy.[125] AIDS activists couch their concerns in terms of HIV+/PWA access to promising treatments, suggesting that regulation that constrains legal access will force patients to resort to bootleg variants, the price of which will rise because the products cannot pass safely through legal distribution channels.[126] They also cite anecdotal information that suggests that many recipients of alternative treatments have become long-term AIDS survivors.[127] Proponents of holistic medicine are also opposed to the FDA proposal, suggesting that it reflects a bias in the traditional medical and pharmaceutical industries in favor of drugs over preventive and nutritional holistic alternatives that ostensibly help the body to heal itself.[128]

Taken together, the recent modifications of drug testing and approval examined in this section constitute a substantial change brought about by Congress and the FDA to meet the needs of increasingly vocal public constituencies. Reform has resulted in some change for the better and some change for the worse; some modifications go too far and some not far enough. To comprehend the particular strengths and weaknesses of drug approval reforms, it is necessary to examine and evaluate various broad policy approaches to drug testing and control.

II. Options for Drug Access Policy: Paternalism, Open Access, and Contractarianism

The history of pharmaceutical regulation in the United States, and of the regulation of AIDS-related pharmaceuticals in particular, reflects a tension among three models of drug access. Paternalism, or regulation that seeks to protect the public against risk from unproven drugs, has been the driving force behind the traditional model of drug regulation historically embodied in FDA policy. In recent years, this philosophy has been subjected to growing criticism,

123. S. 784 103 Cong., 1st Sess. (1993).

124. Mike McKee, *Odd Alliance Fights FDA Plan: ACT UP and Orrin Hatch Want to Prevent Agency from Regulating Alternative Treatments*, RECORDER, July 29, 1993, at 1.

125. "In our free market society, consumers should be able to purchase dietary supplements, and companies should be able to sell those products so long as the labeling and advertising are truthful, non-misleading and there exists a reasonable scientific basis for product claims." *Id.*

126. *Id.*

127. *Id.*

128. *See id.* (quoting holistic health educator Carola Burroughs) ("[FDA is] narrowly focused on what drug can kill what germ . . . . They don't have a sense of the body having an innate healing sense of its own.").

specifically in regard to its application to the approval of AIDS treatments. AIDS advocates and other critics have argued that regulatory paternalism is harmful to HIV+/PWAs. They propose that the FDA should adopt an "open-access" model that would provide all HIV+/PWAs with unfettered access to all drug treatments, proven or unproven. This Part outlines the philosophies underlying these models and discusses their basic shortcomings. Ultimately, the analysis suggests that neither of these models resolves the moral and logistical problems of treatment access in the context of the AIDS epidemic. Instead, from both ethical and policy perspectives, a third approach—a contractarian model—is best.

The FDA has traditionally taken a paternalistic approach to the control of drug access, focusing almost exclusively on protecting patients from exposure to dangerous or ineffective forms of treatment. The FDA occupies a role in *loco parentis*, setting boundaries within which physicians, patients, and producers of pharmaceuticals can engage in market transactions.[129] Patients can only receive medications that have been granted government approval. Doctors must limit their treatment of patients to this same group of approved drugs, which can be prescribed only for approved purposes. And drug companies are permitted to sell drugs, through the intermediary of physician prescription, only when those drugs have received FDA approval. The professional and commercial relations that exist among doctor, patient, and drug producer are thereby constrained by the paternal decisions of the FDA.

The recent changes in drug regulation discussed in the preceding Part have reduced or eliminated impediments to speedy drug access, evincing some movement away from the paternalistic model. Nonetheless, drug regulation in the United States remains essentially paternalistic, even in regard to drugs for the treatment of life-threatening and deadly diseases. Critics of the treatment IND provision, parallel track, and other recent modifications continue to support the traditional model, wherein access to drugs is strictly controlled both prior to and after the meticulous testing processes that characterized the pre-AIDS

129. For discussion of the specific legislative and regulatory provisions that embody this approach, *see supra* part I.A.

FDA.[130] These critics have questioned the FDA's approval of specific drugs,[131] and the expedited procedures that have led to those approvals.[132]

Regulatory paternalists also invoke the specter of fraud associated with open access. Deregulation of stringent drug access laws may open markets to charlatans able to prey on the desperation of some patients. One observer notes that "[c]ancer health frauds of the '60s and '70s have turned into the AIDS health frauds of the '80s and '90s," suggesting that a multi-billion dollar industry has arisen in the sale of ineffective treatments.[133] While fraudulent schemes can be prohibited and monitored and the perpetrators prosecuted without limiting the access of the AIDS community to experimental drugs, more schemes are likely to slip through the cracks under a policy of open markets.[134]

In contrast to the paternalistic approach, the open-access model is built on a vision of unconstrained patient autonomy and self-determination.[135] Open-

130. A representative of Public Citizen, a consumer advocacy group, has criticized the recent changes. *FDA Radically Reorients Drug Approval Route*, 240 CHEMICAL MARKETING REP., No. 21, Nov. 18, 1991, at 3, 31 (quoting Dr. Sidney Wolfe, Director, Public Citizen's Health Research Group) ("[recent FDA modifications are] likely to result in serious injuries and deaths to patients.")

131. Recent research findings that cast doubt on the treatment value of many common applications of AZT have led some physicians to question the expedited procedures under which AZT was originally approved. *Weighing the Benefits*, MacNeil/Lehrer Newshour, Sept. 6, 1993), *available in* LEXIS, Nexis Library, MACLEH file (quoting Dr. Deborah Cotton of the Harvard School of Public Health) ("To have drugs come out without being really solidly proven to work meant that we'd be taking on a lot of drugs with different kinds of side effects and not enough knowledge about how they worked, or how best to put them together, so that we'd end up in a situation with a lot of choice, which is what we have now, but without any way of really making decisions about which one is best.")

132. A *New York Times* article notes that the U.S. procedures for approving AIDS treatments have become less stringent than British procedures, under which the FDA-approved treatment DDI has been rejected. Lawrence K. Altman, *AIDS Study Casts Doubt on Value of Hastened Drug Approval in U.S.*, N.Y. TIMES, Apr. 6, 1993, at C3.

Moreover, recent evidence suggests that the use of CD4 counts as proxy indicators of clinical effectiveness of AIDS treatments may be flawed. *See* Goldsmith, *supra* note 104. DDI was approved under the 1992 accelerated procedures using CD4 counts as surrogate markers. Regulatory paternalists have new fodder to support their argument that accelerated approval procedures may result in sloppy short-cuts and increased error, ultimately increasing the number of dangerous and ineffective treatments approved for marketing. Critics of the recent FDA amendments are likely to contend that the erosion of regulatory paternalism, largely in response to political pressure by AIDS activists, has gone too far, too fast. Adverse consequences of AIDS treatments dispensed as treatment INDs without sufficient evidence of clinical efficacy will inevitably fuel still more criticism of movements away from paternalism. The controversy is just beginning.

133. Mike McKee, *In AIDS Fight, Scams and Hope Compete*, LEGAL TIMES, Jan. 6, 1992, at 2 (quoting Mark Madsen, Director of Physician Education at the California Medical Association).

134. Free markets may create breeding grounds for fraud. However, given the centrality of the free market in the American capitalist economy, it is necessary to find less intrusive means of controlling fraud than the inhibition of otherwise desirable transactional freedoms. For example, enhanced enforcement of anti-fraud legislation can address unfortunate cases of deception or exploitation without hampering increased access to legitimately promising drugs.

135. These interests are also vital to the contractarian model, and will be discussed in greater detail in the subsection that follows.

access approaches to AIDS drug treatment[136] emphasize the purported right of patients to receive their choice of medication,[137] either in tandem with physician recommendation or, alternatively, in the absence of physician approval. The exigency of AIDS is offered as the foundation for this extraordinary right to complete and unfettered access to drugs. If desperate situations justify desperate measures, then the prognosis of a disease as pernicious as AIDS may justify extreme deference to the patient's autonomy, and the recognition of the broadest possible range of individual rights.

Open-access arguments are further strengthened by the claim that the stringent drug review processes of the 1962 Amendments fail to achieve the ultimate goal of the paternalistic model: the pursuit of public health and safety. To the extent that paternalism fails to meet this objective, it is an unjustifiable incursion upon individual freedom and autonomy. Arguably, the paternalistic model does indeed fail in its pursuit, as net public benefit from protection against unproven drugs is outweighed by the net public cost of the timely denial of effective treatments.[138]

Although the open-access philosophy is tempting, it is fraught with both philosophical and practical difficulties. The open-access model arguably conflicts with the right of autonomy held by patent holders and patent seekers. A regulatory obligation to provide extra-experimental treatment also creates an incremental burden for those trying to develop new drugs commercially. Any

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136. The question of open access is complex and can be addressed at a number of important levels. This Article addresses the issue of legal access: to what extent are consumers permitted to purchase or receive the pharmaceutical products they choose, within the framework of a voluntary transaction between patient and manufacturer? Implicit in this conception of access is a fundamental acceptance of capitalist markets and their ability to distribute goods in a manner generally considered acceptable within a democratic society.

The traditionally high prices of AIDS drugs create financial barriers. As a result, real (as opposed to legal) access to AIDS drugs may be impaired by inability to pay. For a discussion of some of the issues associated with the just distribution of AIDS treatments from the perspective of real access, see Steven R. Salbu, *AIDS and Drug Pricing: In Search of a Policy*, 71 WASH. U. L.Q. 691, 714-19 (1993).

Constraints upon ability to pay are compounded by insurance-related access issues. As AIDS cases tend to be concentrated among socially marginalized groups, many patients lack medical insurance necessary to pay for expensive treatments. Moreover, access is limited even among the insured, because private health insurance plans usually exclude coverage of experimental treatments. Mark Scherzer, *Private Insurance*, in AIDS LAW TODAY: A NEW GUIDE FOR THE PUBLIC 404, 422 (Scott Burris, et al., eds.) (1993).

Another conception of access, one that challenges the basic effectiveness of our capitalist market in its present form, recognizes that AIDS is becoming a disease that disproportionately afflicts disadvantaged groups such as women, racial and ethnic minorities and intravenous drug users.

137. Some commentators suggest that this right falls within the fundamental constitutional right to privacy, such that it can be abrogated only by showing of a compelling state interest. *See, e.g.*, People v. Privitera, 591 P.2d 919, 931 (Cal. 1979), *cert. denied*, 444 U.S. 949 (Chief Judge Bird, dissenting).

Others have suggested that the right may be subsumed under the Fifth Amendment guarantee that persons not be "deprived of life, liberty, or property without due process of law." Bret L. Lansdale, *Essay, A Procedural Due Process Attack on FDA Regulations: Getting New Drugs to People with AIDS*, 18 HASTINGS CONST. L.Q. 417, 421 (1991) (quoting the Fifth Amendment of the Federal Constitution).

138. Mark A. Kassel, Note, *Getting There With the Best: The Need to Shorten the Prescription Drug Approval Process*, 27 VAL. U. L. REV. 95, 99-102 (1992) (citing U.S. mortality and morbidity costs associated with delays in access to drugs available years earlier in other world markets).

such burden will tend to discourage experimentation by drug manufacturers. Furthermore, some drug companies lack the resources necessary to produce sufficient quantities of each experimental drug to provide both experimental and extra-experimental treatment.[139]

Ultimately, while the interests of patient autonomy are certainly compelling, autonomy in a free market system does not grant the individual a right to anything he or she desires. Rather, autonomy in capitalist markets must incorporate a respect for the autonomy of others, so that freedom is embodied in the right to enter consensual transactions without undue government constraint. This view of autonomy leads us to a contractarian model as the best means of balancing the individual freedom and dignity of HIV+/PWAs with both the interests of manufacturers and the social and economic benefits of the free market.

III. A Contractarian Model for the Development of Ethical, Humane, and Effective Access to HIV+/AIDS Drug Treatments

Freedom of contract is the best mechanism for reducing regulatory coercion that impinges upon individual autonomy while preserving private industry's right to self-determination. A contractarian model of drug regulation[140] begins with the assumption that HIV+/PWAs are capable of autonomous decisions about their own treatment. Under the model, drug companies would be authorized to sell experimental AIDS treatments to HIV+/PWAs with no restriction other than the requirement of physician prescription. Physician prescription would be the only permitted interference in otherwise entirely voluntary contractual arrangements. As a condition of any transaction in a treatment unapproved by the FDA, HIV+/PWAs could be required[141] to sign an informed, voluntary waiver of liability covering prescribing physicians, manufacturer-suppliers, or both. Such waivers would be judicially enforceable under express legislative or regulatory provision.[142]

139. Pharmaceutical companies sometimes must invest considerable time and money before they achieve sufficient plant capacity to manufacture enough drugs to meet total demand. *See, e.g.*, Marilyn Chase, *Biotech Breakout: Demand for MS Drug May Help Chiron Corp. Emerge From the Pack: Lottery Will Say Who Gets Product, One of Several That Hold Much Promise, Surprise Payoff from Cetus*, WALL ST. J., Sept. 1, 1993, at A1, A9 (discussing Chiron's logistical inability to manufacture enough of promising new MS drug to meet total demand during first several years of production).

140. In general, contract-based regulatory models are sometimes referred to under the label of "contractarianism," according to which regulatory roles are supplanted by an increased reliance upon individual exchange decisions. For a discussion of contractarian alternatives to regulation, *see generally* Symposium, *Contractual Freedom in Corporate Law*, 89 COLUM. L. REV. 1395, 1395-1774 (1989).

141. This requirement would not be imposed by law or regulation; rather, in a free and open marketplace, both physicians and manufacturer-suppliers should be free to require informed waiver as a condition of their voluntary participation in the transaction.

142. Meaningful assurance that waivers will be respected and recognized is necessary, because consensual arrangements for the assumption of risk by waiver are often held unenforceable under modern

AIDS drug sales would be substantially deregulated under the proposed system, and the range of private contracting decisions[143] between manufacturers and consumers would be expanded considerably.

The contractarian model satisfies to a significant extent three essential policy objectives that pull in different directions. These policy objectives, discussed individually in the sections that follow, are (A) the protection of the rights and interests of the individual (in this instance, of the HIV+/PWA); (B) the preservation of corporate autonomy; and (C) the promotion of the state's interest in public health.

A. *Protection of the Rights and Interests of the Individual*

The interests of HIV+/PWAs should inform government regulation of the development and distribution of AIDS drugs. Given the urgency of the HIV+/PWA's needs, society must resist efforts to sacrifice their interests as individuals, even in the face of efforts to benefit society as a whole. A policy that seeks to protect the rights of individuals, in this case HIV+/PWAs, should be based on a recognition of personal privacy, autonomy, dignity, and respect, and must meet the essential moral requirement that persons be treated as ends rather than means.

A right to privacy exists regarding the choice of medical treatment.[144] This right is not absolute, but rather is circumscribed by the state's countervailing interest in protecting the public welfare. Courts have adopted various approaches in balancing the right of individual autonomy against the interest of the state. Some courts have emphasized individual interests over state interests in cases of life-threatening diseases or conditions. Accordingly, the Supreme Court of New Jersey has held that "the State's interest . . . weakens and the individual's right to privacy grows as the degree of bodily invasion increases and the prognosis dims."[145] However, the Supreme Court held in

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contract doctrine. For discussion of this phenomenon, *see* PETER W. HUBER, LIABILITY: THE LEGAL REVOLUTION AND ITS CONSEQUENCES (1988); WALTER K. OLSON, THE LITIGATION EXPLOSION: WHAT HAPPENED WHEN AMERICA UNLEASHED THE LAWSUIT (1991).

Courts must respect patients' assumptions of super-normal risks if the market is to accord patients reasonable rights to self-determination. Without the assurance that they will be exonerated from product liability, manufacturers would be foolhardy to dispense unapproved drugs in deference to some abstract ideal of patient autonomy. In other words, the contractual system will work only if the courts respect all consensual, risk-shifting arrangements by which patients assume the full burdens of their decisions.

143. The arguments herein presume a libertarian consent model of contractual exchange, according to which legitimacy of obligation is a function of (a) entitlement to transfer and (b) intent to transfer. For explanation of the consent model of contract, see Randy E. Barnett, *Squaring Undisclosed Agency Law with Contract Theory*, 75 CALIF. L. REV. 1969, 1978-79 (1987).

144. For discussion of patient autonomy rights in the choice of treatment generally, see Judith F. Daar, *A Clash at the Bedside: Patient Autonomy v. A Physician's Professional Conscience*, 44 HASTINGS L.J. 1241 (1993).

145. Matter of Quinlan, 355 A.2d 647, 664 (N.J. 1976).

Rutherford v. United States that the state's interests can trump those of even terminally ill cancer patients. In *Rutherford*, the Court held that terminally ill patients do not have a right to purchase the unapproved drug laetrile, even in light of trial evidence suggesting that the drug is nontoxic and even effective.[146] Justice Marshall's opinion focused on the FDA's intent in the process of policy implementation, observing that "the FDA has never made an exception for drugs used by the terminally ill." Furthermore, Marshall supported the FDA's statutory authority: "To accept the proposition that the safety and efficacy standards of the [law] have no relevance for terminal patients is to deny the Commissioner's authority over all drugs, however toxic or ineffectual, for such individuals."[147] While the opinion did not expressly address the privacy interests of the plaintiffs, Marshall's confirmation of the broad authority of the FDA to monitor all drugs suggests by implication that such interests are either limited, or else insufficiently compelling to erode FDA control.[148]

Other decisions that bear on this issue suggest that fundamental privacy rights do not provide terminally ill patients with a constitutional right of autonomous choice of treatment. While the Supreme Court in *Whelan v. Roe* defined privacy in terms of "the interest in independence in making certain kinds of important decisions,"[149] it also noted that the realm of this interest has been limited to "matters relating to marriage, procreation, contraception, family relationships, and child rearing and education."[150] In *People v. Privitera*,[151] the Supreme Court of California cited *Whelan* to suggest that patients' access to laetrile or other medical treatments does not fall within the sphere of privacy,[152] and can therefore be impeded by state interests under a rational basis standard. Thus, while the Court in *Rutherford* failed to address the privacy question expressly, it is unlikely that HIV+/PWA access to unapproved drug treatment would be considered constitutionally protected.[153] Nevertheless, Congress and

146. United States v. Rutherford, 442 U.S. 544, 548 (1979).

147. *Id.* at 557-58.

148. For commentary on *Rutherford*, *see* David L. Leitner, *Laetrile and the Law: An Analysis of Rutherford v. United States*, 5 OKLA. CITY U. L. REV. 11 (1980); Comment, *Laetrile: Supreme Court Upholds FDA "New Drug" Classification; Still No Constitutional Right of Access to Unapproved Drugs*, 3 DET. C.L. REV. 871 (1980).

149. 429 U.S. 589, 599-600 (1977).

150. *Id.* at 600, n.26 (quoting Paul v. Davis, 424 U.S. 693, 713 (1976)).

151. 591 P.2d 919 (Cal. 1979).

152. Classification of child rearing and education as more fundamentally private concerns than the decision of a terminally ill patient regarding his or her treatment seems highly arbitrary.

Chief Justice Bird apparently concurs with this sentiment, as she states in dissent in *Privitera*: "[C]hoice of [cancer] treatment [is] one of the more important decisions a person may ever make, touching immediately on his or her being. For this reason, I believe the right of privacy, under both the state and federal Constitutions, prevents the state from interfering with a person's choice of treatment on the sole grounds that the person has chosen a treatment that the state considers 'ineffective.'" *Id.* at 927.

153. *Id.* at 922. The purpose here is not to suggest that *Rutherford* should be overturned, or that the holding in *Rutherford* should be limited to the sale of laetrile and not extended to AIDS drug access, although such arguments can persuasively be made. *See, e.g.*, Scott H. Power, Comment, *The Right of*

the FDA should voluntarily concede authority over those drug treatments available to HIV+/PWAs in deference to their individual autonomy interests. The entire class of HIV+/PWAs can rationally be exempted from FDA regulations by virtue of the universally severe and terminal nature of AIDS.[154]

Regulatory deference to individual privacy and autonomy is appropriate not only because the stakes and risks are reduced in the instance of untreatable, terminal diseases, but also because, in the case of AIDS, as in the case of any life-threatening disease, the gap between insiders and outsiders cannot be navigated by empathy.[155] This "empathic failure" is perhaps the most compelling justification for Congress and the FDA to defer to the judgment of individual HIV+/PWAs and abdicate their authority in this area. Empathic failure refers to the inability of legislators and regulators to understand the needs of a group they seek to protect. This inability can stem from the uniqueness of the group and from a lack of metaphors or analogies that can mediate the difference between insider and outsider perspectives. In the case of HIV and AIDS,[156] legislators and regulators as a group[157] cannot expect to understand what ultimately must be an extremely subjective experience, one that falls outside the realm of the universal human condition. Having HIV or AIDS is a special situation, and lawmakers as a body should admit that they

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Privacy in Choosing Medical Treatment: Should Terminally Ill Persons Have Access to Drugs Not Yet Approved By the Food and Drug Administration?, 20 J. MARSHALL L. REV. 693 (1987) (supporting a constitutional right of terminally ill patients to receive treatments that have not received FDA approval); Jon S. Batterman, Note, *Brother Can You Spare a Drug: Should the Experimental Drug Distribution Standards be Modified in Response the Needs of Persons with AIDS?*, 19 HOFSTRA L. REV. 191, 204-05 (1990) (suggesting that cancer and AIDS can be distinguished by virtue of greater scarcity of therapies available to treat latter).

154. The discussion of autonomy interests includes the right of PWAs to make potentially bad decisions under the present conditions, which include (a) severity and fatality of the disease, (b) lack of an effective treatment or cure, (c) lack of information, and (d) high levels of risk associated with either a decision to enter any treatment or a decision to refrain from receiving any treatment.

Under these precise conditions, respect for individual liberty includes the right to make risky decisions, even when those decisions may not have been the best ones given hindsight. (*But see* Marsha N. Cohen, *Getting New Drugs to People With AIDS: A Public Policy Response to Lansdale*, 18 HASTINGS CONST. L.Q. 471, 472 (1991) (suggesting that "deprivation of life and liberty of PWA is predicated on the assumption that the therapies delayed by the FDA are in fact 'helpful'.") As for individual liberties, the deprivation is complete regardless of whether the therapy is ultimately helpful or harmful. When the future benefit of the therapy is questionable, optimization of liberty includes the ability to assume risks, irrespective of whether that assumption eventually leads to benefit or detriment.

155. Ironically, one person who unsuccessfully sought access to an unapproved drug to treat his father's life-threatening disease says that he received an FDA form letter beginning with the words, "We deeply empathize." *See* Lochhead, *supra* note 15. In regard to AIDS, empathy supports a policy of relatively greater access. PWAs are rarely observed rallying for stronger regulatory control over experimental drugs.

156. The argument here is being applied to the specific instances of HIV and AIDS, but can logically be extended to other conditions that meet the definitional requirements of empathic failure.

157. This argument assumes that, as a decision-making group, legislators will be comprised of a ratio of HIV+ to HIV- members in a relatively proportionate relationship to the HIV+ to HIV- ratio of the population at large. Accordingly, the number of decision-making HIV+ individuals who are aware of their HIV status, and therefore potentially empathic, will be small.

cannot cross the boundaries that define that situation, however imaginative or sympathetic those lawmakers may be.

Paternalistic protection in the face of empathic failure demands an enormous leap of understanding. Ultimately, the leap is impossible. The exercise of governmental authority therefore manifests a kind of arrogance, to wit: "While there is an essential difference between us, one that I cannot fathom, one that had become an essential compelling reality of your life, I will nonetheless supplant your judgment with my own."[158] Regardless of what the Constitution does or does not guarantee, regardless of whether the law holds legislators accountable for respecting the privacy and autonomy of HIV+/PWAs, Congress and the FDA should hold themselves accountable to the highest standards of respect for the individuals they are meant to serve. In this light, attempts to substitute administrative judgment for the personal assessments of responsible citizens under conditions of empathic failure form an intolerable derogation of human dignity.[159]

Respect of individuals also requires that we treat persons as ends rather than means.[160] A paternalistic regulatory scheme violates this tenet. It forces HIV+/PWAs to undertake a risk they might not choose to assume under conditions of greater autonomy—the risk of receiving placebo treatment within a control group. From the perspective of an HIV+/PWA as patient rather than as subject, experimental participation infringes on personal control over treatment options. While individuals should be allowed to choose to be part of a randomized study, the government should not effectively force them to do so in order to obtain access to drugs. The loss of control experienced by the subject of medical experimentation takes two forms: the risk of receiving placebo treatment, and the risk of receiving a drug treatment other than that which the patient would choose if permitted to do so without constraint.

The risk of receiving placebo treatment is a byproduct of experimental control. Under the simplest form of research design, equal numbers of subjects are randomly assigned to one of two groups: the treatment group and the

158. The empathic failure argument is not mitigated by the possible presence of HIV+/PWAs within the decision-making ranks of the FDA, because the Agency acts as an institutional and organizational entity whose members are predominantly non-HIV+/PWAs. For this reason, the FDA is essentially an agency that falls outside the shared circle of the AIDS community. As stakeholders, their professional claims cannot logically compare with the claims of PWAs. Because these two communities, the FDA and PWAs, are separated by an intellectually and emotionally unbridgeable gulf, any FDA imposition of authority without a compelling necessity is an act of arrogance in violation of the freedom, autonomy, and privacy of the members of the AIDS community.

159. The 1987 and 1988 Amendments were initial and substantial concessions of authority by the FDA, in deference to patient autonomy under the very peculiar conditions of AIDS in the late 1980s. The alterations recommended in this Article are logical extensions of these concessions, and all are justifiable under the same privacy and autonomy considerations discussed herein.

160. *See generally* IMMANUEL KANT, GROUNDWORK OF THE METAPHYSICS OF MORALS (H.J. Paton trans., Harper & Row 1964) (1762).

control group.[161] The treatment group receives the drug being tested, while the control group receives a placebo.[162] Subjects are therefore as likely to be placed in control groups as they are to receive the drug being tested. Within the constraints of this process, HIV+/PWA access to innovative drug treatments is arbitrary and precarious, and shrouded in the scientific secrecy of blind and random assignment.

Under more complex experimental designs, patients may be randomly and blindly assigned, typically in equal numbers, to a control group or to one of several different treatment groups.[163] For example, an experiment designed to test drugs A, B, and C in comparison to each other and to placebo treatment would provide for the random assignment of subjects into four groups of equal size, receiving drug A, drug B, drug C, or a placebo. In these experiments, the subject's risk of receiving placebo treatment is compounded by another risk—the risk of receiving an undesired treatment. A well-informed patient may assess drug B as desirable and drugs A and C as undesirable, based on preclinical information available in scientific and medical literature. Moreover, a patient may evaluate some unapproved treatments as more appropriate based on his or her symptoms. This is particularly likely to occur in the case of AIDS, a disease that manifests itself in a variety of ways among different people.

Unless the FDA provides a treatment option that is not buried in regulatory qualifications, and that is comparable to the clinical experimentation option, HIV+/PWAs suffer significant incursions into individual dignity and respect. The failure to provide more universal, nonpaternalistic HIV+/PWA treatment options is a failure to recognize the individual freedom and responsibility that are fundamental to human dignity. The approval system in its present form eliminates the individual's option to learn all there is to know about treatments, and to choose that treatment which seems most promising or appropriate. By forcing patients into the maze of uncertainty created by random assignment and experimental control, the regulatory system disempowers the individual from dominion over one of the most fundamental of personal decisions. The process is dehumanizing and degrading. As one commentator observes in regard to the FDA, "They play God with us."[164]

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161. For a more detailed explanation of classical research control, *see infra* part III.C.2.

162. The assignment of subjects into two groups is intended to acount for the "placebo" effect common to any and all forms of treatment, whereby changes in medical condition result from the patient's expectation of improvement. Randomizing subjects into the two groups should eliminate bias that might otherwise result from self-selection.

163. Typically, one control group can provide comparative non-treatment data for all treatment groups.

164. *See* Lochhead, *supra* note 15 (quoting George Rehnquist, President, Families for Alzheimer's Rights Association).

A paternalistic system of drug regulation also treats individuals as means by condoning the use of experimental drugs by individuals who agree to act as research subjects, while denying access to the same drugs for medically supervised treatment purposes when individuals limit their status to the role of patient. From the standpoint of means-ends analysis, for what purposes is the state willing to allow the possible sacrifice of human health or human lives? Under a traditional paternalistic scheme such as the 1962 Amendments,[165] the answer is that sacrifices for the advancement of science are far more acceptable than sacrifices for individual treatment.[166] In other words, a paternalistic system legitimizes risk of life to advance science, but not to promote individual control over treatment. FDA regulations that effectively protect the availability of experimental subjects more comprehensively than they protect the availability of risky treatments at patient behest are indicative of such paternalistic priorities. They suggest that the agency has traditionally considered human sacrifice as a means towards scientific knowledge to be more compelling than human sacrifice in deference to individual treatment preferences. Given that the risks associated with unapproved drug use are identical in the cases of clinical trials and nonexperimental treatment, FDA receptiveness to the former and aversion to the latter suggest that terminally ill patients have been worth more as guinea pigs than as autonomous individuals. This observation does not suggest that the need for experimental subjects is an inadequate rationale for permitting the consensual participation of HIV+/PWAs in what is often risky research. Rather, it suggests that if we are willing to condone and encourage freely chosen and individually assumed risk-taking to achieve the advancement of science, we should also be ready to permit patients to make comparable free and responsible choices in regard to their own treatment.

Contractarian access to AIDS drugs would increase patient autonomy significantly by limiting government interference to situations in which countervailing interests demand recognition. Regulation may be necessary for the protection of (a) the public at large; (b) non-patient stakeholders, such as private pharmaceutical companies; and (c) patients themselves. Contractarianism enhances the opportunities for patient self-determination by deregulating access in a manner that preserves justifiable interests of both the public at large and of non-patient stakeholders. It shifts responsibility for protecting the interests of patients from the shoulders of a paternalistic government onto those of the patients themselves. To the extent that patients can be accorded self-governance at little or no cost to the state interest in public health or the interests of private stakeholders, the patient's interests in privacy, autonomy, dignity and respect should prevail.

165. *See supra* text accompanying notes 41-43.

166. For discussion of the hurdles for administering treatment INDs, *see supra* text accompanying notes 56-62.

B. *The Preservation of Corporate Autonomy*

Open access to experimental AIDS drugs, under which the autonomy interests of the patient confer an absolute right to purchase the treatment of choice, must be balanced against corporate autonomy interests in determining which drugs to investigate, manufacture, and market, and under what conditions. In a free and open market, the consumer's ability to purchase any product is limited by a manufacturer's willingness to sell that product. The contractarian model proposed in this part recognizes the legitimacy of both consumer autonomy and manufacturer autonomy, such that access to AIDS drugs must be achieved by voluntary and uncoerced agreement by both parties to the transaction.[167]

Proponents of unbridled consumer autonomy may suggest that the stakes of HIV+/PWAs should outweigh the interests of pharmaceutical companies, based upon the obvious exigency of fatal illness and the superiority of claims based on life over those based on profits. These arguments might be persuasive, except that a mandate requiring companies to provide experimental drugs to all HIV+/PWAs would ultimately be dysfunctional to patients.

Specifically, requiring corporations to provide access to experimental drugs to all HIV+/PWAs would probably delay some important experimentation. A laboratory will often be able to design a reasonable, scientifically sound experiment far more quickly than it is able to set up the manufacturing capability to provide an experimental drug to all patients who want it. Because reliable statistical data are ordinarily generated using samples rather than entire populations, experimentation can proceed without the logistical, operational, and financial planning that supports mass production. If a company were required to provide extra-experimental access in order to engage in experimentation, the burden of establishing production facilities and distribution channels would likely delay much experimentation. In the end, the overall pace

167. Contract is the most powerful tool created by Anglo-American law for the preservation of the transactional autonomy of parties to any exchange. Voluntary consensual arrangements are also self-adjusting and self-monitoring, providing natural protections of the interests of all stakeholders. Because the uncoerced consent of both the supplier and the purchaser are necessary to the negotiation of an enforceable contract, each party is afforded the greatest possible bargaining scope, restricted only by the interests of the other transactor. The free market supports deals considered acceptable by all consenting private parties, and the public interest is protected as a by-product.

Private pharmaceutical companies must protect their own ability to engage in ongoing research projects. Companies may refuse to make negotiation concessions likely to impede the feasibility and profitability of longer-range projects. They must balance the provision of immediate benefits to patients with the ability to engage in ongoing AIDS research. AIDS patients become the advocates of immediate treatment, and pharmaceutical companies act as advocates of long-range strategic planning, including the maintenance of promising new research activity. As AIDS patients are accorded autonomy consistent with the autonomy of other parties to private transactions, the public receives the benefit of both ongoing AIDS treatment and ongoing AIDS experimentation.

of AIDS research would be retarded by regulatory fiat requiring companies to provide open access to experimental AIDS drugs.

Moreover, burdensome requirements forcing corporations to provide access to experimental drugs to all HIV+/PWAs might discourage private companies from engaging in any AIDS drug experimentation at all. The same dynamic that can impede AIDS drug experimentation can also completely derail it. Companies will not investigate potential AIDS drugs if mandated extra-experimental distribution becomes prohibitively costly. An open-access policy may thus destroy the viability of some research projects. For example, companies that lack the plant capacity to manufacture a drug in sufficient quantities to meet demand cannot sustain open-access marketing. Likewise, companies unwilling or unable to absorb the costs associated with mandatory marketing of experimental AIDS drugs are likely to pursue alternative projects that are unfettered by a mandatory marketing policy, and therefore more strategically or financially desirable. Ultimately, the danger of compelling pharmaceutical companies to sell experimental drugs to extra-experimental patients is not limited to experimental delay, but may result in an overall chilling effect upon private AIDS drug experimentation.

C. *Promotion of the State Interest in Public Health*

A patient's privacy rights are bounded by the state's interest in protecting the public welfare broadly, and the public health specifically.[168] Nonetheless, the state's legitimate stake in protecting individual persons is and should be diminished when the individual is terminally ill and there are no effective, FDA-approved treatments.

Although the state's ability to interfere with private action is circumscribed by these conditions, it is not eliminated. Even if the welfare of individual HIV+/PWAs were removed entirely from the realm of state authority, public health would remain a concern of the state. Because AIDS is an infectious disease, privacy interests of HIV+/PWAs can never completely supplant the state's interest in regulatory oversight.

The state has a legitimate interest in protecting the public by curtailing the spread of AIDS. This interest is attenuated, however, in its application to patient choice of AIDS treatments. The logical connection between treatment options and the state interest in reducing the incidence of infection depends upon a correlation between specific treatment options and eliminating the virus from individuals, and thereby reducing the number of new opportunities for infection. Since there are presently no effective treatments or cures for AIDS, and specifically none that destroy the virus and the possibility of subsequent

168. *See supra* part III.A.

transmission, an individual's decisions regarding treatment will not be more threatening to the public health than FDA doctrine.[169] Because the government has little practical expertise in AIDS and HIV treatment on which to based claims of superior knowledge or experience, its position for asserting paternalistic control is substantially weakened. The argument that the individual must be forced to take a proven, effective drug rather than an experimental drug of choice in order to protect self and others is ineffectual when no such effective drug exists.

Still, given the presence of other government interests, such as the need to control insurance costs that are spread across the population, it is reasonable to incorporate a very limited form of restriction on the actions of both the company and the consumer. This restrictive force should be the prescribing physician, who can serve as an intermediary between the company and the consumer.

While the state interest in the health of individuals is easily outweighed by the interest of individual autonomy in a free society, the state role in eradicating AIDS cannot be so readily dismissed. A preference ordering that ranks individual rights higher than social expediency suggests that respect for individuals should override the public utility derived from treating individuals as research subjects.[170] This ordering suggests that the scientific and medical communities should consider HIV+/PWAs primarily as patients to receive treatment, and as research subjects only to the extent that the latter role is consistent with the former. A regulatory system that optimizes individual patient autonomy, particularly in regard to debilitating and fatal diseases, is morally justifiable because it acknowledges this essential priority ordering, valuing basic respect for individual rights over the interest of scientific advancement.

Moreover, the interests of scientific and medical advancement need not be sacrificed by deregulating the consensual exchange of unapproved AIDS treatments. There are methodologies that advance the state's interest in ongoing, effective AIDS research and development while still preserving individual rights to negotiate treatment with providers and suppliers. Open medical treatment under the contractarian model is compatible with rapid applied scientific progress.

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169. In other words, the state can presently offer no HIV+/AIDS treatments that in any way reduce infectivity of HIV. Were the state able to offer such treatments, it would have a rational argument that the public's interest in mitigating future incidence of infection might override some autonomy interests. Without access to a set of approved treatments that effectively reduce infectivity, the state cannot argue persuasively that control over individual treatment is rationally related to control over future infection rates.

170. *See supra* part III. A.

1. *Enhancing Clinical Trials*

Opening the channels of experimental drug distribution is likely to provide valuable information that will ultimately expedite and enhance the quality of AIDS drug research. When the distribution of untested drugs is hastened and expanded, the drugs will be consumed more quickly, and by greater numbers of PWAs, than under the present system.[171] The body of informal information will therefore develop more quickly, and the quality of that information will be enhanced by the increased number of patients providing feedback on the use of experimental drugs.

More specifically, large numbers of users of untested drugs will make informal observations regarding the apparent effects of the drugs. Suppose that ten friends share similar manifestations of AIDS. Within a month of using Drug X, they observe that all symptoms of each of the ten friends enter remission. They have no traditionally sound scientific basis for concluding that Drug X is effective. However, it is not irrational to find the observation encouraging and to report the results to the AIDS and scientific communities as well as to the public at large. After receiving this report and similar reports from other groups of patients, Company A, the patent holder of Drug X and twenty other theoretically promising drugs, may decide to focus experimentation on Drug X.

Although informal observations do not provide an adequate basis for data analysis, they can be potent sources of both research priority strategies and scientific hypotheses. By opening access to untested drugs in a manner that speeds distribution and expands the pool of potential recipients, there will be a dramatic increase in the amount of information available to HIV+/PWAs, their physicians, and medical and scientific investigators, who can then interpret the scientifically uncontrolled data in useful ways.

Open, extra-experimental, consensual exchanges of unapproved drugs will not impair a corporation's ability to engage in experimentation. Specifically, the availability of treatment INDs is unlikely to impede commercial investigators looking for subjects. Not all reasonable patients will prefer treatment INDs to clinical INDs. Doomsayers who predict that treatment INDs will eliminate the pool of subjects who agree to participate in clinical trials

171. This phenomenon is already occurring, albeit outside the law. The development of an AIDS underground has included the organization of drug smuggling rings engaged in the illegal dispersion of drugs from Mexico and other countries to United States PWAs. The underground responds to medical journal reports of promising but untested treatments by sending members to countries like Mexico, where drug access is less rigorously restricted. Anecdotal information resulting from this process is incorporated into ongoing scientific and medical research in an interactive process, as patients, physicians, and researchers engage in a dialogue that is responsive to promising but nonscientifically documented trends. *See generally* PETER S. ARNO & KARYN L. FEIDEN, AGAINST THE ODDS: THE SAFETY OF AIDS DRUG DEVELOPMENT, POLITICS AND PROFITS 60-70 (1992) (discussing of the AIDS Underground).

ignore or underestimate the diversity of preference functions within the population. Specifically, they ignore two important sources of variance that may have substantial effects on shaping individual choice: variance in risk assessment and variance in financial resources.[172]

Variance in risk assessment refers to the differences among rational decisions that are derived from decentralized, individual calculations of comparative risks. Different people allocate different risks to the alternatives of treatment and nontreatment. This can be demonstrated intuitively by simply observing the varying receptiveness of individuals to the use of pharmaceutical medications. Some seek drug treatments for the slightest ailment, while others avoid drugs well beyond the point at which such avoidance is probably advisable. The chance of receiving a placebo by virtue of falling randomly in a control group rather than an experimental treatment group will not be valued consistently among decentralized decision-makers choosing between clinical INDs and treatment INDs.

Of course, if variance in individual preference were simply divided between drug users and drug avoiders, there would still be a problem finding experimental subjects when both clinical and treatment IND options are available. Drug users would prefer treatment INDs, and drug avoiders would choose neither. Neither group would desire clinical INDs. Fortunately, decision-making differences among individuals are complex, incorporating an array of factors that allow for a rich variety of decisional combinations.[173] When we add another layer of human variance to the drug-user/drug-avoider taxonomy, we begin to locate possible pools of voluntary experimental subjects. Consider, for example, differences in valuation of faith and altruism. Since a patient cannot know whether the use of an untested drug will be helpful or detrimental, an element of hope or faith invariably enters the decision-making process. The tendency to place one's trust in hope or faith will of course vary among individuals. For example, some may believe that the vicissitudes of AIDS may best be trusted in the hands of external forces. In others, hope and faith may combine with a strong sense of altruism. A patient may logically choose a clinical IND over a treatment IND, reasoning that while both are risky, at least the former will provide information that may be helpful to humanity in the search for effective AIDS treatments.[174] Given the high level of uncertainty

172. The effect of variance in financial resources upon consumer choices is so firmly implanted in neoclassical economic theory as to be axiomatic. The influence of risk propensity and risk averseness is an important factor in modern decision theory. *See* KENNETH R. MACCRIMMON & DONALD A. WEHRUNG, TAKING RISKS: THE MANAGEMENT OF UNCERTAINTY 277-95 (1986).

173. Numerous factors enter into decisions made by individuals who each have unique utility preference functions. Because of the principle that different people value different things, humans given choice will generally make a variety of decisions.

174. *See* Cheryl Clark, *Private Groups Helping Test AIDS Drugs: U.S. Efforts Too Slow, Activists Contend*, SAN DIEGO UNION-TRIB., July 11, 1993, at B1 (quoting a patient who has chosen to participate in an experiment in which he may be receiving either a treatment or a placebo: "If I don't benefit from

surrounding either option, some HIV+/PWAs will prefer to enter experimentation that has the potential to increase our understanding of HIV and AIDS.

Variance in financial resources, like variance in individual risk assessment, also serves to ensure that clinical INDs will not be undermined by treatment INDs. Corporations can and will employ a range of incentives to make clinical INDs attractive. Under the changes of FDA rules proposed in this Article, companies would be granted increased latitude in determining whether to exact reasonable fees for any INDs, either treatment or clinical.[175] In the unlikely event that a company is unable to generate adequate interest in clinical trials by virtue of preference variance within the large pool of HIV+/PWAs, it can use incentives to generate sufficient interest. A company might charge recipients of treatment INDs but not participants in clinical IND testing,[176] or decide not to market an IND for treatment purposes prior to FDA approval.[177]

Even if a substantial majority of patients prefer treatment INDs to clinical INDs, the sheer numbers of HIV+/PWAs ensure that any reasonable research project need not be aborted for lack of subjects. The lamentably rapid spread of AIDS mitigates concerns regarding availability of experimental participants. Recent CDC figures indicate that 242,000 Americans were diagnosed with AIDS by September 1992,[178] and that this number will increase to one-half million by 1995.[179]

2. *Other Approaches to Data Collection*

In evaluating the effect of treatment INDs on research, we must also reassess the arguments for reliance on classic methods of experimentation. Rapid medical advances can be achieved both through traditional, controlled scientific experimentation and through less traditional or pre-experimental observation. The scientific method is crucial to the systematic development of

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this, somebody else might.")

175. *See infra* text accompanying notes 206-212.

176. This strategy is subject to criticism for both the direct exploitation of the poor, and the indirect exploitation of racial minorities who are over-represented among the poor. Yet the criticism is no more compelling here than it is when lodged against our health care system in general. Under our current system, the wealthy have the resources to purchase products or options that the poor may be unable to afford. Nonetheless, because such undesirable class stratification will result from this incentive strategy, companies able to generate desired experimental participation without resorting to the indirectly coercive forces of financial exigency may prefer not to adopt a policy of charging only for treatment INDs.

177. A fundamental tenet of the proposed amendments bears reiteration: transactions in INDs are consensual under the changes, and can only occur when both the sponsor decides to market and a consumer decides to purchase. This means that companies, while not required to delay marketing until final FDA approval, could decide that such delay is nonetheless necessary to generate sufficient numbers of experimental subjects.

178. *See AIDS Deaths Mount More Slowly, supra* note 7.

179. Amanda Husted, *CDC: 330,000 Americans Will Die From AIDS by 1995*, ATL. CONST., Jan. 15, 1993, at D3.

knowledge, and is admittedly the most thorough and rigorous vehicle by which our understanding of nature may be improved. Nonetheless, while alternative approaches may not give the quality of information we have come to expect from traditional experimentation, they have the potential to generate useful information regarding the value of proposed treatments while maintaining respect for patient/subject autonomy. These alternative methods can provide the scientific community with suggestive information regarding the nature of HIV/AIDS and its responsiveness to various interventions while granting HIV+/PWAs more treatment options. Alternative methods should not replace classically designed studies. These options should be seen as supplementary, offering additional options to HIV+/PWAs, and allowing us to treat patients as ends in themselves rather than as means employed in the quest for scientific knowledge.

Biomedical research has traditionally been based on randomized, double-blind, placebo-controlled experiments. As noted above, to provide useful comparative information, subjects are randomly assigned either to a group that receives the experimental treatment or to a control group that receives a placebo. Randomization helps isolate the relationship between treatments and observed effects. When subjects are randomly assigned to groups and attended identically in all respects other than the experimental treatment, statistically significant differences observed between groups can be inferred to result from treatment. Randomization controls for any systematic group variance that could confound the study.[180] For example, randomization eliminates biases that might result from self-selection based on individual treatment preference.[181]

In a "double-blind" trial, neither investigators nor subjects know who has been assigned to specific treatment and control groups. Because subjects are not informed of their group assignments, researchers can ensure that data are uninfluenced by subject expectations. For example, patients asked whether they have had night sweats may be more likely to answer "yes" if they think that

180. Additionally, use of large samples reduces the likelihood of coincidental between-group disparities.

181. When patients choose whether to take a treatment, they may base their decision on some secondary characteristic that is extraneous to the effect of the treatment being examined. Differences in observable results may logically be a function of either treatment differences or of secondary characteristic differences.

For example, suppose that without random assignment, patients with Kaposi's sarcoma will tend to take Drug A, and those with pneumocystis will tend to take Drug B, on the basis of previously untested scientific hypotheses concerning likely effectiveness. Observations that a non-randomized group of Drug A users are less likely to develop retinitis than a non-randomized group of Drug B users can be interpreted in several ways. It is possible that Drug A inhibits retinitis; it is also possible that those with Kaposi's sarcoma—the secondary characteristic—are less likely to develop retinitis than those with pneumocystis. When patients choose their own treatments, an infinite number of self-selection biases, both obvious and invisible, can potentially exist. Those who examine differences cannot confidently attribute causality to the one dimension they have chosen to examine without controlling for all other possible differences between groups.

they are receiving a placebo rather than a drug treatment. Investigators are also kept ignorant of particular group assignments to prevent either intentional or inadvertent skewing of interpretations, especially interpretations that favor hypotheses that the investigator is hoping to prove.

For these reasons, double-blind, randomized control studies are optimal in their ability to reduce "noise," or the presence of extraneous signals that can be misinterpreted as effect. Because experimental controls are the best way to demonstrate a direct and clear causal link between treatment and effect, the clinical trials required for traditional FDA approval of new drugs are undoubtedly the most scientifically sound means of establishing safety and effectiveness.

Alternative means of control can be evaluated in terms of the quantity and quality of comparative information that they provide. From the standpoint of the quality of comparative information, placebo control of treatment groups is the most useful means of control,[182] followed in declining order by two non-placebo control methods: control of a treatment group by comparing it to a previously tested alternative treatment,[183] and control of a treatment group by comparing it to a previously untested alternative treatment.[184] Alternatives to the ideal of placebo control, while imperfect, can nonetheless be a source of medical and scientific knowledge. Moreover, they allow us to protect the autonomy and dignity of HIV+/PWA subjects.

Testing of INDs using non-placebo controls can be achieved by comparing the post-treatment health status of subjects who have been randomly assigned to various treatment groups that receive different dosages of the drug being tested.[185] A similar measure of control that permits reasonable inference can also be derived by comparing groups of patient-subjects receiving different drug treatments. Finally, longitudinal observational studies permit reasonable comparisons of outcomes in individual patient-subjects over time, without the use of placebo control.[186] Accordingly, the FDA has suggested that placebo

182. Placebo control of treatments permits inferences regarding the effects of treatment versus nontreatment, unconfounded by any between-group differentiation that may result from attitudinal, physiological, or behavioral variance that may be related to knowledge regarding one's treatment status.

183. The control here is limited by the lack of a placebo baseline from which to make clean comparisons between treatment and non-treatment. The control that does exist allows comparisons between a treatment that has been studied, and about which information is known, and the experimental treatment. This comparison can provide useful information as to the value of the proposed treatment relative to the value of the tested treatment.

184. This alternative is similar to the previous one, except that the utility of neither treatment being examined has been firmly established through use of placebo-controls. The information provided is limited to a relative ordering of two largely unknown entities.

185. *See infra* text accompanying notes 193-94.

186. Sheldon Greenfield, *The State of Outcome Research: Are We on Target?*, 320 N. ENG. J. MED. 1142 (1989).

control is inappropriate for the testing of treatments for life-threatening diseases when an effective therapy exists that can function as a non-placebo control.[187]

Assigning patients with life-threatening diseases to placebo groups is not only a denial of basic human dignity; it may also be an inadvertent source of bad science. In order to ensure that they receive some form of treatment, some HIV+/PWAs enrolled in placebo-controlled trials have taken their pills to independent laboratories to have them chemically analyzed.[188] Forthright participation as research subjects may depend on the patient's belief that the study serves not only the interests of science, but also the interests of the patient.[189] Patients who initially agree to participate in clinical trials may feel pressure to participate in more than one trial to obtain pills that test as nonplacebos, thereby deceiving researchers and invalidating trial results.[190] Furthermore, some attrition that confounds the value of research findings in randomized trials can result from a patient's disillusionment upon discovering that he or she is receiving a placebo. Patients may also drop out of trials or fail to comply with medication instructions if they simply come to suspect, perhaps because they see little improvement in their health, that they are receiving a placebo.

Investigators examining the effects of aerosolized pentamidine on the incidence of pneumocystis carinii pneumonia ("PCP") during the late 1980s encountered additional pragmatic limitations that foreclosed the possibility of placebo-controlled experimentation. Intravenous pentamidine was available for prescription, and patients could easily dissolve the product in water and use a nebulizer to manufacture an aerosol form at home. As a result, a gray market developed for the highly touted aerosolized pentamidine, leading researchers to conclude that the recruitment of subjects for a placebo-controlled experiment might be difficult.[191]

Given these practical considerations, researchers studying aerosolized pentamidine designed their research project in the form of "dose response trials." This method compares dependent variable responses (here, episodes of PCP and their severity) to different levels of treatment dosage.[192] This technique

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187. 21 CFR § 314.126(b)(2)(iv) (1993).

188. Joseph Palca, *AIDS Drug Trials Enter New Age*, 246 SCIENCE, Oct. 6, 1989, at 19, 20.

189. *Id.*

190. *Id.*

191. A. Bruce Montgomery, *How the Recent Changes in Expedited Drug Approval Procedures Affect the Work of a Clinical Investigator*, 45 FOOD DRUG COSM. L.J. 339, 340 (1990). This study is an example of an alternative method of inquiry which yielded significant and useful information as well as an important AIDS treatment. Nonetheless, these investigators make the untenable judgement that the availability of gray-market treatment precluded the possibility of recruiting participants for placebo-controlled testing. As previously observed, treatment options do not necessarily eliminate the pool of patients willing to engage in experiments in which non-treatment is a random possibility. *See supra* text accompanying notes 173-180.

192. Montgomery, *supra* note 191.

permits inferences regarding both relative effectiveness and relative toxicity of various dosages. While it was initially treated with skepticism by the scientific community,[193] the technique eventually led the FDA to approve aerosolized pentamidine, the most successful PCP treatment presently available. By providing all patient-subjects with some dosage of treatment, investigators accomplish ends that simultaneously serve both patients and science. They treat patients as ends deserving the freedom to choose to receive some dosage of a promising treatment. Since, at some critical cutoff point, lower dosages will actually be more effective than higher dosages, and because these cutoff points are the unknowns to be determined in the study, patients gain no helpful information by independently analyzing pills. Furthermore, patients are receiving a professionally prepared version of the product, and therefore have no incentive to choose home-grown versions. Finally, since the use of respectful research approaches will encourage patient-subjects to comply with the instructions they are given, designs that maximize human dignity can also add an increment of scientific validity.

"Meta-analysis" is another technique that can supplement classic methods of experimentation. Meta-analysis pools the data from various existing studies for further exploration and analysis, stretching the utility of limited numbers of clinical trials.[194] The purposes of meta-analysis are "(1) to increase statistical power for primary end points and for subgroups, (2) to resolve uncertainty when reports disagree, (3) to improve estimates of effect size, and (4) to answer questions not posed at the start of individual trials."[195]

Meta-analysis is potentially a valuable source of research efficiency that may enable more respectful treatment of patients as ends rather than means, while simultaneously preserving the ability to investigate promising new drugs. Meta-analysis reduces the number of research subjects needed, by using each set of clinical trial data more thoroughly and efficiently. If the data generated in clinical trials can serve multiple functions, and can be the source of several variants of analysis, then more extra-experimental treatment options can be offered to patients without sacrificing the adequacy of the pool of subjects for scientific inquiry. Through meta-analysis, we can mitigate the concern that options like treatment INDs or parallel track trials will impoverish the quantity and quality of AIDS research.

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193. An NIH grant proposal covering this research was rejected on methodology grounds. *Id.* at 341.

194. For early discussions of this procedure, see Gene V. Glass, *Primary, Secondary, and Meta-Analysis of Research*, 5 EDUC. RESEARCHER 3 (1976); Richard J. Light & Paul V. Smith, *Accumulating Evidence: Procedures for Resolving Contradictions among Different Research Studies*, 41 HARV. EDUC. REV. 429 (1971).

195. Henry S. Sacks et al., *Meta-Analyses of Randomized Controlled Trials*, 316 N. ENG. J. MED. 450 (1987). The authors raise concerns regarding varying levels of quality and utility of meta-analyses, but suggest that the process can be of value in achieving the aforementioned ends if methodological care is exercised. *Id.* at 454.

Real world experience, like laboratory experimentation, can inform the process of drug evaluation. For several decades, scientists have been using innovative statistical and design techniques that allow various inferences of causality within the context of "field research," or research occurring outside ideal laboratory conditions. Among the most promising is path analysis, in which correlation coefficients can be interpreted deductively in order to infer causal probabilities.[196] To the extent that such techniques exist, they may enable pools of treatment IND patients to provide important scientific information. Likewise, parallel track trials may be valuable sources of reasonably high-quality data, notwithstanding the absence of classical experimental conditions and controls. The expansion of these options should expedite the collection of secondary quality statistical findings, which can then be used to assist clinical researchers in framing more useful, better informed research questions.

Under conditions of crisis such as the AIDS epidemic, quantity of data is extremely important. While we must provide opportunities for rigorous testing of the most promising treatments, receptiveness to innovative and less traditional ways of learning and understanding will open fruitful and perhaps crucial avenues of investigation. Moreover, the utility of classical experimentation may be impeded by the high levels of noise that exist in HIV and AIDS research. As more HIV+/PWAs use combinations of treatments, efforts to assign subjects to randomly selected groups in order to control for unintended agents of causality will be frustrated. This dynamic may force scientists to analyze all data using statistical tools that rectify failure in experimental control, even within the context of ostensibly controlled experimentation. As clinical and treatment data begin to share variability that must be controlled using techniques other than randomization, the superiority of experimental research designs over field studies is diminished. Both inside and outside the lab, dirty data are becoming an unavoidable reality.[197]

D. *The Utility of the Contractarian Model for Balancing Interests.*

The contractarian model balances our desire to provide HIV+/PWAs with the greatest freedom of choice in their own medical treatment and the need to ensure both public health and AIDS research progress. Contractarian access preserves the autonomy of both supplier and consumer and reduces regulatory interference by the government, thereby facilitating a maximum number of mutually advantageous transactions. Companies that are able to provide extra-experimental access to all patients will have the ordinary market incentives to

196. For a good discussion of path analysis, see THOMAS D. COOK & DONALD T. CAMPBELL, QUASI-EXPERIMENTATION: DESIGN & ANALYSIS FOR FIELD STUDIES 301-21 (1979).

197. For discussion of this phenomenon, see James J. Eigo, *Expedited Drug Approval Procedures: Perspectives from an AIDS Activist*, 45 FOOD DRUG COSM. L.J. 377, 382 (1990).

do so. Likewise, consumers will gain the freedom to enter purchasing transactions autonomously. The preservation of freedom of contract will thus increase the number of treatment options available for HIV+/PWAs. By respecting not only the patient's freedom of choice, but also the manufacturer's autonomy, an increase in drug access can be accomplished without hindering or discouraging the ongoing experimental efforts that should be considered an essential component of any sensible public policy.

A reasonable contractarian policy can and should place the condition of physician prescription on both individual and corporate transactional autonomy. The physician is a compromise intermediary between otherwise freely contracting parties. Doctors can provide some professional control over treatments that may sound appealing to the relatively unsophisticated nonprofessional, but which may be known professionally to be unsound and unreasonably dangerous.[198] Use of doctors also decentralizes the exercise of the state's public welfare interest, so that contractual decisions are not broadly monitored by one central authority, but rather are watched by thousands of professionals in consultation with their patients. This decentralization is crucial to the maintenance of any meaningful patient autonomy, as patients will be able to find physicians willing, after a waiver of liability, to authorize for the terminally ill all but the most patently dangerous treatments. While some physicians will be extremely cautious by nature, others will be willing to help patients take reasonable risks. Utilization of medical professionals as exclusive mediators between private contracting rights and government welfare interests is an effective way to ensure a reasonable balance between the two.

IV. Implementing the Contractarian Model

While the recent legislative and regulatory amendments discussed in Part II have brought the drug approval process increasingly closer to a contractarian ideal, there is room for improvement. The following recommendations are intended to bring the relevant laws and regulations closer to the contractarian model.

198. The role of the doctor here is a minimal incursion upon contractarian freedom of transaction. Because the body of medical information regarding AIDS and HIV is both voluminous and highly complex, limited governmental regulation that requires physician prescription of unapproved drugs may be necessary to compensate for unintended individual error that is likely to occur when information processing challenges surpass cognitive abilities.

Recommendation 1: *Make treatment INDs available during all phases of clinical testing.*

The 1987 Amendment has the potential to reduce the average time frame between the identification of promising drugs and their availability to patients in the form of treatment INDs. By permitting treatment IND distribution following Phase II success,[199] Congress has shaved five and one-half years off the average estimated twelve-year period from initiation of investigation to treatment access.[200] Still, a six and one-half year average delay remains before HIV+/PWAs gain access to a newly identified potential treatment. As previously noted, the early stages of drug development can span many years.

The FDA's restriction of treatment INDs to the post-Phase II period under ordinary circumstances is insupportable. Drugs approved for Phase I clinical testing have been cleared for human experimentation, suggesting that the use of these products by humans is reasonable and medically promising. Under the means-ends guidelines discussed above, the FDA should never be willing to sanction the use of people as experimental subjects, and hence as a means of gaining scientific or medical knowledge, unless it is also willing to approve commensurate treatment in recognition of patients' rights to be considered as ends unto themselves. If the FDA's rational cut-off for human testing is that point at which preclinical trials have proven promising, its cut-off for human treatment should coincide. The government's inability to distinguish reasonably between experimental and treatment approval thresholds renders the present system arbitrary and untenable.

Qualification of treatment INDs prior to Phase I testing, but after successful preclinical testing, is a better option. The FDA can reasonably prohibit the dispensing of treatment INDs prior to the execution of successful preclinical testing. There is, incontrovertibly, no useful information available at this stage. Furthermore, the chances are extremely low that drugs under preclinical testing will qualify to proceed to the clinical testing stages. Indeed, only one in five thousand drugs proceeds, from preclinical to clinical testing.[201] The possible benefits of providing treatment INDs at this stage are nearly nonexistent, while the risks are exorbitant.

Expansion of the sphere of treatment INDs is likely to yield increased efficiency as a by-product. Under the existing provisions for emergency IND approvals on an ad-hoc basis,[202] the FDA may be required to make a prohibitive number of custom-tailored, and therefore time-consuming and inefficient, decisions. The emergency IND process typically entails telephone requests,

199. *See* Rotman, *supra* note 61 and accompanying text.
200. *Id.* at 46.
201. *See* Lochhead, *supra* note 15.
202. *See* sources cited *supra* note 62.

made by physicians to the FDA, for special permission to provide an unapproved treatment to a patient who has a life-threatening disease and no alternative treatment options.[203] Given the increasing number of HIV+/PWAs who will meet these criteria, the incidence of emergency IND requests is likely to increase in the future. By expanding drug eligibility for treatment IND status to all stages of clinical trials, we would expedite the inclusion of drugs into an efficient "blanket" category that requires only one FDA decision for a large number of patients who meet the emergency IND criteria. The efficiency gains that accrue thereby would permit the FDA to focus its resources on the expedient review of other applications.

Recommendation 2: *Permit pharmaceutical companies to demand payment for both clinical[204] and treatment INDs.*

Under the 1987 Amendment, manufacturers are permitted to sell INDs only under certain conditions.[205] Companies are not ordinarily permitted to charge subjects for drugs administered as clinical INDs. Under the norms of commercial experimentation, the cost of supplying test products is ordinarily borne by the sponsor.[206] The 1987 Amendment therefore requires application for, and FDA approval of, schemes to charge subjects for clinical INDs. Approval is granted if necessary to underwrite clinical IND expenses, but not for general commercial purposes.[207] Likewise, sale of treatment INDs requires FDA approval, which will not be granted for commercial marketing purposes.[208]

Sponsoring firms should be permitted by regulatory provision to charge recipients of clinical and treatment INDs regardless of whether the fees are necessary to support related research. The rationale for permitting companies to charge for both clinical and treatment INDs is compelling, regardless of whether sales revenues are needed to underwrite clinical expenses. A misguided tendency to equate the sale of unapproved products with exploitation supports the regulatory inclination to prohibit sales of experimental drugs. Yet the sale of a relatively proven product is conceptually indistinguishable from sale of an untested product. Under norms of contractual autonomy, buyers would be enticed to purchase either product only because they believe that it has some acceptable potential to deliver desirable medical results. In the case of both

203. *See* Cooper, *supra* note 62, at 335.

204. For the purpose of this discussion, reference to the ability to charge for clinical INDs refers as well to the ability to charge for their parallel track trial counterparts.

205. *See supra* text accompanying note 66.

206. Lisa C. Will, Note, *Accelerated FDA Approval of Investigational New Drugs: Hope for Seriously Ill Patients*, 94 DICK. L. REV. 1037, 1051 (1990).

207. *Id.*

208. Approval for the sale of treatment INDs also requires adequate enrollment in ongoing clinical investigations and the active pursuit of marketing approval with due diligence. *See supra* note 66 and accompanying text.

approved and experimental drugs, the user receives a product that has been manufactured and distributed by a private company that has a right to demand compensation.

This right should supersede the current criteria for the sale of INDs, as it reflects a manufacturer's need to cover expenses and make a reasonable profit. Recognition of this right is sound public policy that will encourage research efforts. The ability to generate revenues increases the money available for the financing of clinical INDs, regardless of whether the money is technically "necessary" for ongoing research. It is wise to allow companies to develop sales revenues freely, because revenues ultimately support clinical trials of a greater variety of drugs.

Unfortunately, by restricting charges for INDs, the 1987 Amendment underestimates the role of the profit motive in encouraging new research projects. Just as sales revenues that directly support appurtenant clinical IND trials enhance the feasibility of those trials, so do sales revenues that are not directly rechanneled into the appurtenant clinical trials nonetheless enhance the desirability of those trials. Sales revenues also enhance both the feasibility and the attractiveness of subsequent trials. As long as manufacturers are permitted to sell their drugs for treatment purposes, they will have a greater incentive to produce them and to make them available for treatment use.[209] Immediate revenues thus act as an incentive to develop and continue clinical IND trials, regardless of whether that incentive is in the form of essential experimental financing or unessential, but nonetheless desirable, commercial profit. The line drawn in the 1987 Amendment is arbitrary, and purports to distinguish between revenue motives that are largely indistinguishable. From a policy perspective, inward cash flows are always an incentive to continue operations and expand into new projects, whether those cash flows are vital to progress, or simply desirable to the organization.

Related to policy decisions regarding manufacturer charges for INDs is the complex question of equitable pricing in a contractarian model of constrained regulation. In regard to both clinical and treatment IND charges, a number of dynamics are likely to interact. Drug companies, which have not been reluctant to charge exorbitant fees for patented HIV and AIDS treatments,[210] may show equally little self-restraint if given free rein to establish fees for INDs. In an open and free economy, however, the profit- maximization motive is ordinarily modulated by competitive supply sources. If consensual transactions in treatment INDs for AIDS were liberalized as this Article recommends, there would be an open market for these drugs. Likewise, the employment of parallel track trials will hasten the development and distribution of drugs. The ability

209. *See* Will, *supra* note 207, at 1052.
210. For a detailed discussion of this problem, see Salbu, *supra* note 136, at 691.

to charge exorbitant prices for treatment INDs and parallel track drugs would be checked naturally by the forces exerted by competitor products.[211] We should expect that opportunities for price gouging would decline in an open market for treatment INDs and parallel track drugs when compared to the present market for a very limited number of patented, fully approved AIDS treatments.

Ultimately, expansion of free contracting for treatment INDs and parallel track drugs, including freedom in pricing decisions, will redound to the benefit of patients. Whereas artificial pricing caps impose authoritarian protection upon consumers who may neither want nor need that protection, in a contractarian system caps also create a compelling regulatory disincentive to corporations considering whether to market experimental products as treatment INDs, or to engage in parallel track trials. Artificial pricing constraints may thereby reduce the number of options available to the consumers whose freedom of choice should be a driving force in HIV and AIDS drug access reform.

Regulators will never be able to provide, simultaneously, the cheapest possible treatment and the widest possible variety of treatment choices for patients. Any regulatory policy aimed at achieving one of these ends will fall short of the other. By relegating pricing to the free market, regulators would allow autonomous, freely transacting consumers maximum voice in this tradeoff. Consumer willingness to pay prices above those that might have been set by regulators would support the research, development, and marketing efforts needed to increase the future available pool of drugs. As that pool of treatment options expands, the growth in supply competition would exert a downward pressure on prices. In this manner, the deregulation of the market for INDs would naturally modulate prices, while encouraging the speedy development of new products.

Recommendation 3: *Render voluntary waivers strictly enforceable by express regulatory provision.*

Individual freedom and responsibility of HIV+/PWAs are optimized when drug manufacturers are encouraged to provide early access to experimental drugs, either as treatment INDs or on a parallel track.[212] Policies that reasonably

211. This addresses in good part the "imbalance in power" argument that may be raised by those demanding regulatory pricing constraints. While marketers of unique patented products under a highly restrictive FDA approval process have daunting pricing power, marketers of unpatented treatment INDs under liberalized access have far less power. When AZT became the first and only drug available for the treatment of AIDS, the manufacturer effectively controlled the only promising treatment for a deadly disease. The pricing power inherent in such a position is self-evident. As more companies are able to distribute a wide variety of drugs under the recent FDA modifications, competitive forces move closer each day to eliminating the kinds of power disparities that might otherwise provide the best rationale for artificial price restraints.

limit potential liability encourage companies to market these products, thereby contributing to AIDS patient autonomy.

One such policy is the strict and unqualified support of voluntary, informed liability waivers.[213] Respect for waivers will reduce the risk and potential cost of lawsuits, thereby encouraging companies to market treatment INDs and to engage in parallel track trials.[214] Voluntary waiver is consistent with the contractarian approach and is a particularly apt mechanism for enhancing a patient's options. Enforceability of waiver is also philosophically sound: if patients are to exercise freedom of choice in the realm of unproven drugs, they should also be held responsible for the risks inherent in the use of such products.

Clear and unambiguous regulatory support of voluntary waivers is necessary in order to limit the ability of courts to nullify waivers as unconscionable.[215] For waivers to function effectively, they must be invulnerable to attacks based in equity, and this invulnerability must be communicated clearly to manufacturers analyzing marketing risks. While the unconscionability doctrine corrects for power imbalances under ordinary circumstances, it can add little of value to the transactions that occur between pharmaceutical manufacturers and HIV+/PWAs who purchase their products. Power disparity is not an extraordinary characteristic in these transactions; rather, power disparity is the defining characteristic that justifies the transactions. The lack of any meaningful choice has been the driving force behind the FDA's concession of authority to HIV and AIDS drug consumers.[216] Under such

212. For discussion of the reasons that current tort liability practices discourage pharmaceutical companies from the development and manufacture of AIDS treatments, see Sally-Anne Danner, Note, *The Vaccine Ailment: A Cure to Encourage Litigation-Shy Pharmaceutical Companies to Manufacture an AIDS Vaccine*, 14 HAMLINE J. PUB. L. & POL'Y 67 (1993).

213. For discussion of the need to allow PWAs to assume the risk of unproven treatments, see Ben Borson et al., *Heightened Treatment Options for Terminal Cases*, RECORDER, May 5, 1993, at 10.

214. Companies have delayed the trial and marketing of new drugs because of fears regarding potential liability. For example, Abbott Laboratories, fearing litigation and product liability, requested federal government indemnity. When the government failed to respond to the request, Abbott delayed clinical trials of HIVIG, a promising AIDS treatment. Mike McKee, *Company Wants Indemnity Before It Tests AIDS Drug*, N.J.L.J., Aug. 17, 1992, at 4. Like governmental indemnification of liability, enforcement of individual waiver of liability would reduce risk and encourage companies like Abbott to pursue both clinical trials and concurrent marketing of eligible drugs.

215. Courts may declare contract clauses, including liability waivers, unenforceable for unconscionability when the voluntary nature of risk assumption becomes doubtful. Typically, this occurs when the seller has substantially greater power than the buyer, often by virtue of having control over the only available source of an important good, and the buyer is required to accept the seller's waiver provisions on a "take-it-or-leave-it" basis. For more detailed elaboration of the nature of unconscionability, see JOHN D. CALAMARI & JOSEPH M. PERILLO, CONTRACTS 397-409 (3d ed. 1987).

216. The limitations on choice for AIDS patients seeking treatment come from several sources. Obviously, the lack of highly effective treatments means that patients make choices within a highly circumscribed arena of options: they try to choose the best from a lot that is moderately successful at best. Moreover, the conditions under which experimental participation will be permitted may be heavily monitored. Apart from physiological and symptomatic qualifications, patients may also be required to agree not to receive other, potentially promising treatments, for either the same symptoms or separate

circumstances, permitting nullification of waivers for unconscionability may destroy the viability of all waivers, and thus dramatically decrease the availability of treatment INDs and parallel track trials.[217]

Critics of strict waiver enforcement policies question the very idea of "informed consent"[218] under the conditions of high uncertainty that are typical of clinical and parallel track trials of unapproved drugs. Both the "informed" and the "consent" aspects can be troublesome at the margins. Specifically, two questions are important: (1) is the patient to be considered adequately informed when accurately told that the existing information regarding risks is negligible? (2) when significant information regarding potential costs and benefits of treatment does exist, how much detail passes the threshold of adequate informing? In regard to consent, the truly voluntary nature of consent forms for AIDS treatments has been questioned, under the reasoning that high-risk or suspect subpopulations are least likely to be able to resist coercion.[219]

A number of factors may indicate a gap between a signed consent form and truly voluntary consent. The signer may not read the form, particularly when the form is highly detailed, elaborate, and legalistic in its language. Even if the signer does read the form carefully, voluntariness of consent may be compromised if the patient is especially vulnerable to overpersuasion or coercion. AIDS occurs disproportionately among several groups who may be particularly susceptible to undue influence, such as intravenous drug users, prisoners, prostitutes, and the mentally incompetent.[220]

These observations underscore the risk that signed waivers or disclaimers do not reflect an underlying free and informed waiver of future claims. For this reason, courts can and should assess the reality of informed consent. Manufacturers seeking to shift the risk of liability squarely onto the shoulders of patients should be permitted to do so, but only when the manufacturers ensure meticulously that they receive real, voluntary, informed consent. This means that signed release forms should be considered fully binding, if and only

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symptoms that are being addressed by the experimental drug. Jerome Groopman, *Breaking the Drug-Approval Log-Jam: Rx for the FDA*, NEW REPUBLIC, Feb. 13, 1989, at 17.

217. Because of power disparities between manufacturers and consumers, AIDS patients may believe they have no meaningful option but to sign liability waivers in order to receive any treatment. The lack of alternatives should not, however, be the basis for permitting court nullification of technically voluntary waivers. Nullification for unconscionability would effectively reduce the options of patients further by discouraging manufacturers from providing treatment INDs or parallel track trials. Moreover, the argument that patients have no meaningful alternative but to sign non-negotiable waivers is weakened as more drugs for the treatment of AIDS receive FDA approval, and as more competitors, armed with the ability to require waivers, compete to sell their treatment IND products.

218. For discussions of the doctrine of informed consent, see Karp v. Cooley, 493 F.2d 408 (5th Cir. 1974), Canterbury v. Spence, 464 F.2d 772, 779-89 (D.C. Cir. 1972), *cert. denied*, 409 U.S. 1064 (1972).

219. Alison J. Arnold, *Developing, Testing, and Marketing an AIDS Vaccine: Legal Concerns for Manufacturers*, 139 U. PA. L. REV. 1077, 1089-90 (1991).

220. *Id.* at 1089.

if the patient is fully capable of understanding the terms of the agreement, which have been explained clearly, unambiguously, and straightforwardly.[221]

Another problem with liability waivers concerns the amount of information that constitutes adequate informing. Recently, five deaths occurred among fifteen drug trial participants when a treatment for hepatitis B proved potentially fatal.[222] Several drug research experts examined in this case questioned whether the informed consent document "told the volunteers enough."[223] Because such concern is justifiable, enforceable waiver based on informed consent should be predicated on proof that (a) researchers fairly, accurately, and clearly explain all known risks; (b) researchers disclose the extent to which suspected, potential, but unconfirmed risks may exist; and (c) researchers state, clearly and conspicuously, that unknown risks may exist, and may reveal themselves during the course of trials or subsequent to trials.

In other words, waivers should be upheld on the condition that they provide any and all information available that is material to patients considering whether to participate in either clinical or parallel track trials or to use treatment INDs, and on condition that communication of the information is clear, accurate, and accessible. Under this principle, accurately informing patients that it is too early in the research process to have identified any risks constitutes acceptable informing. On the basis of this information, patients can determine freely the extent to which they wish to undertake unknown risks, given the range of existing options. The danger of manifestation of unknown treatment risks is a reality of drug testing, particularly in areas such as HIV and AIDS research, where the level of scientific and medical understanding is still low. Free and autonomous agents should be allowed to avail themselves of untested treatments, provided they are willing to reach consensus with drug providers regarding risk allocation. If this principle is to be at all meaningful in practice, courts must be mandated to respect all voluntary risk allocation agreements, even when patients are agreeing to assume the risk of the unknown.

Recommendation 4: *Revoke accelerated approval using surrogate markers if treatment INDs are made available during all phases of clinical testing.*

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221. In regard to highly complex, elaborate, and legalistic terminology, it is reasonable to place a burden on the provider of the waiver form to explain all material components in plain language. Because patients will likely be willing to sign relatively unreadable forms without examining them in detail, and because untutored patients may not understand the meaning of legal terminology, the plain language requirement is a reasonable one, necessary to the retention of informed consent as a meaningful tool in increasing access to unproven drugs.

222. Lawrence K. Altman, *Fatal Drug Trial Raises Questions About "Informed Consent,"* N.Y. TIMES, Oct. 5, 1993, at C3.

223. *Id.*

The FDA approval process is so entrenched in American culture that citizens and residents of the United States are likely to interpret FDA approval as confirmation of both safety and effectiveness. Calling a drug "FDA approved" evokes images of testing and experimentation so rigorous as to approach proof of safety and efficacy.

The purest contractarian might suggest that the FDA approval process be abandoned entirely, in deference to freedom of transaction bounded only by individual decisions based upon assessment of scientific and medical information. In the real world, FDA approval operates as a necessary certification process, whereby government officials use their time and expertise to digest vast quantities of highly technical information in order to render centralized decisions. This process is valuable, and should be preserved for the vast majority of drugs that are used by people who do not face life-threatening diseases for which there are no approved and effective treatments.

Broad, contractarian authorization of treatment INDs for patients faced with life-threatening diseases is an effective method of meeting the class's special needs. If we remove regulatory impediments from the 1987 Amendments and permit consensual transactions to treatment INDs during all phases of clinical trials, then accelerated approval of new drugs becomes redundant. Likewise, the need for accelerated review via surrogate markers, a process that may ultimately be harmful, is also largely redundant.

The danger of accelerated approval under the 1992 Amendments is a function of the relative potential fallibility of surrogate markers as indicators of safety and effectiveness, and the faith that Americans place in the FDA approval process. Conclusions based on use of surrogate markers are more susceptible to error than conclusions based on the primary effects that they ostensibly represent. As noted above, a recent study suggests that the validity of CD4 counts as a proxy for health may be less than was once believed.[224] The weight that the public places on full FDA approval for marketing is probably unjustified under the eroded standards of accelerated approval.

An unfettered treatment IND option is preferable to accelerated approval for marketing, because it achieves the same ends—getting experimental treatments with no approved alternatives to patients suffering life-threatening diseases as quickly as possible, without giving inadequately tested drugs an imprimatur that suggests to the average consumer that they have passed stringent and exacting standards. Treatment INDs can be labeled as such, clearly notifying users that they are using inadequately tested or untested experimental drugs. In contrast, users of drugs that have received accelerated marketing approval are unaware that these drugs have been approved under a reduced-threshold standard. Although regulations require post-marketing monitoring of

224. *See* Goldsmith, *supra* note 104 and accompanying text.

drugs approved in the accelerated process,[225] the consumer simply sees the drug as proven under FDA's ostensibly high standards. In effect, accelerated approval will result in the inadvertent deception of many consumers, who are purchasing experimental treatment labeled FDA-approved.

> Recommendation 5: *The FDA should carefully monitor "opportunities" for consultation with manufacturers regarding research.*

Procedures allowing drug sponsors to consult with FDA authorities during the course of experimental design and IND application compilation were adopted in 1988 in an effort to expedite drug approval processes.[226] While these provisions are intended to hasten sponsor progress by helping companies do things properly[227] the first time, they are also potential sources of both delay and scientific conservatism. Whereas unilateral experimental design can move relatively quickly, impeded only by the limitations of the laboratory itself, consultation with FDA authorities can add a layer of bureaucracy and delay to the process. What begins as an opportunity to make use of FDA's resources in planning methodology and presenting data may become a de facto requirement, as regulatory authorities may come to view collaborative efforts as superior to independent efforts. Furthermore, administrative consultation during early stages of research design may subject the process of developing innovative projects to the premature influence of bureaucratic control. It may be unwise to burden incipient creativity with the regulatory realities that every successful commercial laboratory must ultimately face.

Since these risks may outweigh the potential benefits of early FDA involvement in research design, the FDA should diligently and fairly monitor the effectiveness of an early advisory role. The FDA should solicit anonymous responses from industry laboratories as part of its evaluation of the value of the pre-approval advising option. If the program is successful, manufacturers will have incentives to report the program's effectiveness openly and candidly, as they will benefit from marginal improvements in the approval process. If, however, the program becomes overly intrusive, or otherwise impedes the progress of independent research, manufacturer comments to this effect will have credibility, given that the manifest purpose of the program is to facilitate the manufacturers' progress.

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225. 21 C.F.R. § 314.80 (1992).

226. *Id.* § 312.80.

227. "Properly" in this context may conceivably be interpreted to mean, "in a manner that will satisfy the FDA and be likely to result in FDA approval."

Recommendation 6: *Parallel track trials should be permitted during all phases of testing, and the mechanism for establishing a parallel track option should be simplified.*

Parallel track trials are associated with potential benefits and potential costs. While promising new drugs are made available more rapidly to HIV+/PWAs, possibly dangerous or ineffective drugs will also be more quickly and widely dispersed, without the strict monitoring and review controls associated with clinical trials.[228] Under a contractarian analysis, supported by a fundamental respect for individual freedom and autonomy, the parallel track program should remain an option for patients. An individual may elect to participate, assuming both the risk and the possible reward of a highly speculative treatment. Conversely, a patient may elect to pursue other options, concluding that the parallel track is too risky. Under conditions of speculation and uncertainty, choice should be maximized, as long as parallel track programs provide the clearest and most forthright explanation possible of potential risks and rewards, as well as the limitations of parallel track monitoring.

The Public Health Service's stated goal of expanded access[229] should continue to be its preeminent concern. While the scientific functions of parallel track studies are important, they must remain a secondary goal. Toward this end, some of the requirements for parallel track proposals may be inappropriate. As in the case of treatment INDs, the requirement that Phase II approval be received prior to commencement of parallel track trials[230] is arbitrary. If we are willing to use patients for clinical experimentation during Phase I, we should also be willing to allow them to receive treatment on a parallel track during Phase I.

Likewise, some parallel track application criteria suggest that availability of patients for experimentation is still seen as more important than respect for patients as autonomous individuals. These troublesome criteria include assurance of manufacturer willingness and ability to support production at adequate levels to supply both controlled clinical trials and expanded availability study, and assessment of the effect of parallel track on controlled clinical trial enrollments.[231] These provisions are also likely to be wasteful of time and effort, since companies have little incentive to support parallel track activity that might jeopardize the viability of premarketing clinical trials. Both the

228. Mary T. Griffin, *AIDS Drugs and the Pharmaceutical Industry: A Need for Reform*, 17 AM. J.L. & MED. 363, 381-82 (1991).

229. According to the Public Health Service's own summary of the PHS Policy, the purpose is "to make promising investigational drugs for AIDS and other HIV-related diseases more widely available . . . while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out." 57 Fed. Reg. 13,250.

230. *See supra* note 93 and accompanying text.

231. *Id.*

number of prospective patient-consumers and the company's ability to produce sufficient quantities of a product are basic strategic considerations that a company must take into account in assessing the viability of any market expansion. Bureaucratic imposition of these requirements is likely to be both redundant and cumbersome.

Recommendation 7: *The FDA should consider and review foreign drug summary approval recommendations.*[232]

The 1991 proposed drug approval reforms included a recommendation for expanded U.S. recognition of foreign drug approvals.[233] While the use of foreign approval information and supporting data enhances the total data base upon which FDA decisions can be made,[234] any summary acceptance of either foreign approvals or supporting data is both unnecessary and highly risky.

The reforms suggested in Recommendations 1 through 6 are intended to increase contractual access to AIDS drugs by expanding the number of reasonable alternative routes to such access. These alternative routes push the balance between access and consumer protection to its limits: they provide every reasonable opportunity for the exercise of free and responsible choice. The integrity of the underlying drug approval process, however, must be upheld. In order for that process to provide a basic level of protection against dangerous drugs, standards of approval and control over the approval process must be maintained.

Since the degree of scientific rigor required by the drug approval policies of foreign governments varies greatly, the U.S. government cannot delegate responsibility to foreign bodies without abdicating its own responsibility to monitor drug safety and effectiveness. Data from foreign administrative sources is always potentially useful and can be evaluated on an ad hoc basis. For these reasons, the FDA should remain open to considering studies conducted beyond the borders of the United States, as well as other information that can be supplied by foreign administrative bodies. The ultimate valuation and use of all such information, however, should remain within the discretion of expert

232. By "foreign drug summary approval," I refer broadly to any partial or complete conclusive application of foreign drug approval determinations to the FDA approval process. The 1991 recommendation that foreign drug approvals serve as "primary evidence" of safety probably would fall just short of summary approval if the evidence were merely persuasive, but would pass into the unacceptable realm of summary approval if the evidence were viewed as in any way conclusive.

233. *See Recommendations to Speed Drug Approvals Issued, supra* note 75, at 43,623.

234. For this reason, the FDA should be permitted to analyze data supplied in the process of foreign drug approval applications to determine the value and persuasiveness of the data. To the extent that rigorous research findings can be used to support the FDA's own findings, two important goals may be served: (i) avoiding expenditure of research and development funds on redundant research, freeing those funds for more original research; and (ii) expediting the drug approval decision process by exploiting existing high quality research and development. *Id.*

FDA staff. If such valuation were to be incorporated in automatic summary approval through reciprocity, the integrity of FDA approval and FDA standards would become intolerably compromised.

Recommendation 8: *Congress should scrutinize the User Fee Act.*

The User Fee Act authorizes the FDA to charge reviewing fees to drug sponsors in order to increase the number of reviewers and expedite the overall review process.[235] While the goal of hastening the processing of new drug applications ("NDAs") is laudable, it is also costly. Under the User Fee Act, administrative efficiency is supported directly by charges paid by those who file NDAs. In other words, the industry is required to absorb a new cost which goes directly to support a regulatory bureaucracy that is routinely criticized for being unnecessarily cumbersome and exacting.

The User Fee Act fashions a remedy for excessive FDA intrusiveness and bureaucracy by bolstering that bureaucracy with a new source of financial support. Because this new funding comes from the pockets of private firms engaged in costly research, the expense of which is ultimately passed to consumers, the Act may bear a number of negative effects. First, it may strengthen FDA power and authority over experimental drugs by reinforcing its administrative ranks via increased outside financing. In other words, by shifting operational expenses from the bureaucracy's direct budget to private firms, the User Fee Act potentially increases the entrenchment and potential complacency of that bureaucracy. Second, it will impose an additional cost of applied research on all private firms, large and small, thus creating one more disincentive to engage in new projects. Third, it may cause an increase in the price consumers are ultimately asked to pay for those drugs that they are permitted to receive, as manufacturers seek to cover their own increased costs. Thus the problem of excessive bureaucratization and governmental control will not be alleviated by taxing regulated entities in order to build, expand, and strengthen the bureaucracy. Public savings are being purchased at the potential expense of private efficiency, as another administrative cost is imposed on pharmaceutical companies.

There remain a number of pressing questions arising out of the User Fee Act. To what extent can the User Fee Act be expected to expedite the processing of NDAs? Does the fee requirement discourage private companies from engaging in AIDS research aimed at new product development? In instances where no such chilling effect on research is found, does the fee requirement hinder AIDS drug research by reducing financial resources available to support laboratory work? Under the principles of a free market,

235. *See supra* notes 112-17 and accompanying text.

regulation must be carefully scrutinized to ensure that the protections it offers outweigh the impediments it places upon private concerns. When these impediments are in fact directly purchased by those parties subjected to regulation, the rigor with which we test a regulation's validity should be redoubled.

Conclusion

The recommendations in this Article are neither overwhelmingly supportive nor overwhelmingly critical of existing legislative and FDA policies regarding access to AIDS drug treatments. Generally, the proposals suggest that both Congress and the FDA have become increasingly responsive to legitimate public demands for a system that more flexibly balances individual freedom with consumer protection. The contractarian approach leaves the basic FDA approval process intact, but provides alternative channels of access where the exigencies of AIDS demand greater responsiveness.

While this Article's conclusions address HIV and AIDS specifically, they logically apply as well to any disease that is life-threatening and for which there is no approved and relatively risk-free treatment. Those with such diseases comprise a class whose autonomy interests are great: the stakes are high; the risks are discounted. When faced with a life-threatening disease for which there is no proven effective treatment, an individual consumer may reasonably assess the potential benefit of using an experimental drug as outweighing the risks.

Purer versions of contractarianism might suggest that complete market freedom be accorded to all sellers and buyers of drugs. This unrestrained model of contractarianism is rejected for a number of important reasons. First, the FDA approval process ordinarily serves a useful function. It provides a public good by assessing a large body of potential pharmaceutical treatments in a manner that individual consumers cannot replicate. Ordinary consumers lack the time, resources, scope, incentives, and expertise to evaluate and assess the treatment virtues of new drugs under investigation. Without a body like the FDA to take on these tasks, they would remain unaddressed.

Second, the FDA protects important consumer interests. Under normal conditions, consumer desire to use unapproved products would be an extremist exercise of individual freedoms. It is not unreasonable for the government to protect people from irrational choices in complex markets, given the potentially dire consequences and the negligible potential gains under ordinary circumstances. Life threatening diseases such as HIV and AIDS, however, are extraordinary. Regulatory paternalism loses its glimmer when individual stakes are so high, and when centralized expert judgment yields so little tangible advantage over private choice. Until HIV and AIDS research provides a true best option, government regulation of options should be restrained.