

The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?

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I. INTRODUCTION

In June 1987, the Food and Drug Administration (FDA) formally implemented the first in a series of four initiatives to ease and expand access to certain drugs for the treatment of serious and life-threatening conditions. These initiatives were intended primarily to target drugs that would fill existing therapeutic gaps, including not only the obvious circumstances in which no therapies are available for given conditions, but also those in which patients are unresponsive or otherwise inadequately treated with available drugs.

These programs constituted the emergence of an important historical phase in drug development in the United States, one in which disease severity became a formal determinant in the drug development and approval process. It was a period dominated by the initial confrontation with the Acquired Immune Deficiency Syndrome (AIDS) virus. Although versions of at least one of the four programs existed prior to 1987, each of these initiatives represent a response by the U.S. drug regulatory system to the AIDS epidemic. It has also been suggested by some commentators that the treatment investigational new drug (IND) rule, the first of the four programs, signaled the beginning of a revolution in the drug development process, one in which the boundaries between research and medical practice would become blurred permanently.¹

The initiatives operate at two levels. The treatment IND² and parallel track³ programs, generally referred to as early access mechanisms, provide options for the distribution of certain investigational drugs outside of, but concurrent with, traditional clinical trial protocols. A treatment IND also may be used to bridge the period between submission and FDA approval of a marketing application. Conversely, both the expedited development (Subpart E⁴) and the accelerated approval⁵ mechanisms are intended

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¹ See, e.g., William D. Appler, *The FDA's Treatment IND Rule — A Glimpse in the Future of Drug Regulation in the U.S.*, 43 FOOD DRUG COSM. L.J. 649 (1988). See generally Elliott Schuchardt, *Distinguishing Between Research and Medical Practice During Operation Desert Storm*, 49 FOOD & DRUG L.J. 271 (1994).

² Treatment Use of an Investigational New Drug, 21 C.F.R. § 312.34 (1995). See also Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19,466 (May 22, 1987).

³ Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and Other HIV-Related Diseases, 57 Fed. Reg. 13,250 (Apr. 15, 1992).

⁴ Drugs Intended to Treat Life-Threatening and Severely Debilitating Illness, 21 C.F.R. § 312.80. See also Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41,516 (Oct. 21, 1988).

⁵ Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, 21 C.F.R. § 314.500;

to move drugs to market more quickly by compressing clinical development and FDA review times. All four initiatives involve varying degrees of departure from traditional standards of drug development and/or approval by invoking a more sensitive and uncertain balancing of risks and benefits.

This study is timely, notwithstanding the range in the implementation periods of more than seven and a half years for treatment INDs to just over two years for the accelerated approval regulations. Moreover, a comprehensive review of these four initiatives is useful because of their overlapping and interrelated features: the categories of drugs and diseases targeted by each program are similar; a number of drugs have been exposed to a combination of early access and fast-track approval; the Subpart E regulations expressly call for consideration of a treatment IND protocol when early phase II data analyses appear promising; and parallel track protocols and accelerated approval have been linked in the development of several AIDS therapies, a linkage that some commentators argue should be required to ensure a sufficient pool of safety data when a drug is a candidate for review under the accelerated approval regulations.⁶

This article reviews the regulatory structure of each program and documents their implementation through December 31, 1994. Part III assesses the treatment IND regulations and the parallel track policy, while Part IV focuses on the Subpart E and accelerated approval regulations. Descriptive data are presented on the drugs involved in each initiative together with analyses of relevant clinical development and FDA review times. In conclusion, the article addresses issues generated by the data, identifies areas for further study, and questions whether the programs or their specific components could be applied more broadly.

II. DATA SOURCES AND ANALYSES

The identity of drugs involved in each initiative, and pertinent data on the development history of those drugs, were obtained from public sources and an annual survey of the pharmaceutical industry conducted by the Tufts Center for the Study of Drug Development. The descriptive data include therapeutic ratings,⁷ therapeutic class (based on the approved indication or on the designated early access indication for those drugs not yet approved for marketing), orphan drug designation, Group C status, and the identity of new chemical entities (NCEs) approved during the period 1987-1993 but not involved in any of the four initiatives. The data were confirmed and augmented by the FDA in response to inquiries under the Freedom of Information Act.

Analyses involved the following calculations for each drug: clinical phase (IND filing to new drug application/product license application (NDA/PLA) submission); FDA review phase (NDA/PLA filing to FDA approval); and total regulatory phase

Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, *id.* § 601.40. *See also* New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).

⁶ David A. Kessler, Comm'r of Food and Drugs, FDA, Lecture at the Institute of Medicine's 25th Anniversary, Seattle, Wash. (Nov. 7, 1994).

⁷ The therapeutic rating system used by the FDA's Center for Drug Evaluation and Research (CDER) for internal processing purposes categorizes drugs according to chemical composition and therapeutic potential. Between 1976 and 1992, drugs were rated as follows: A (important therapeutic gain); B (modest therapeutic gain); and C (little or no therapeutic gain). An AA category was added in 1986 to identify drugs for AIDS and HIV-related conditions. In January 1992, this system was abandoned. In its place, a two-category system was adopted: P (priority) and S (standard). Therapeutic ratings are preceded by a 1 for new chemical entities (NCEs) and a 3 for new formulations.

(IND submission to FDA approval). For drugs that received treatment IND or parallel track designation, the early access period was calculated (date of designation to NDA/PLA approval). Mean and median times were calculated for the clinical, FDA review, and total regulatory phases, as well as for the early access periods.

III. EARLY ACCESS PROGRAMS

A. Treatment IND Regulations: 21 C.F.R. Section 312.34

The practice of releasing investigational drugs for treatment purposes predated the 1987 treatment IND regulations.⁸ The FDA has a long history of informally approving treatment protocols or compassionate use INDs for individual patients with life-threatening conditions who are ineligible for ongoing clinical trials and unresponsive to existing therapies.⁹ FDA regulations also provide for an emergency IND procedure under which the agency may authorize the shipment of a drug for a specified use in advance of IND submission.¹⁰ For example, cancer drugs have been distributed prior to approval through the Group C program, which was established in 1976 under the joint auspices of the FDA and the National Cancer Institute.¹¹ The 1987 treatment IND regulations represented an expansion and codification of these existing procedures.¹²

The intent of the treatment IND initiative reflects a treatment-research duality: to make “promising investigational new drugs” available to patients for treatment purposes¹³ and to obtain additional data on the drug’s safety and effectiveness. The program applies only to drugs intended for the treatment of “immediately life-threatening” and “serious” diseases for which no satisfactory therapy is available. Also, the sponsor must exercise due diligence in the pursuit of marketing approval, and either the drug must be under investigation in a controlled clinical trial or all clinical trials must have been completed.

Although sponsors may charge a fee for drugs distributed through either of the two early access programs, they are given considerably greater latitude under the treatment IND regulations. Assuming adequate clinical trial enrollment and the absence of any commercialization, sponsors may bill patients on a cost-recovery basis for a drug distributed under a treatment IND. The amount charged may not exceed the manufacturing, research and development, and distribution costs. A complete summary of the program’s operational structure and safeguards, as well as the obligations of treatment IND sponsors, is found in Table I (below).

The length of time a drug is available under a treatment IND (the early access period, which extends from the date of treatment IND designation to the date of FDA

⁸ The original proposal for the treatment IND program was published in June 1983. In that same year, the FDA estimated that 30% of the 1100 INDs submitted were for treatment use. 48 Fed. Reg. 26,720 (1983); see also Appler, *supra* note 1.

⁹ Frank E. Young, John S. Norris, Joseph A. Levitt, & Stuart L. Nightingale, *The FDA’s New Procedures for the Use of Investigation Drugs for Treatment*, 259 JAMA 2267 (1988).

¹⁰ 21 C.F.R. § 312.36.

¹¹ Letter from Marion Finkel, Assoc. Dir. for New Drug Eval., FDA, to Dr. Carl Leventhal, Dep. Dir., Bureau of Drugs, and Dr. John Jennings, Assoc. Comm’r for Med. Affrs. (Aug. 3, 1977).

¹² Sheila R. Shulman & Drusilla S. Raiford, *FDA Regulations Provide Broader Access to Unapproved Drugs*, 30 J. CLINICAL PHARMACOLOGY 585 (1990).

¹³ The regulations exhibit some flexibility on the timing of the drug’s distribution. For serious diseases, a drug generally may be released during phase III clinical trials; for immediately life-threatening diseases, distribution may occur at an earlier stage, but “ordinarily not earlier than phase II.” 21 C.F.R. § 312.34(a).

marketing approval) is significant for several reasons. It is during this period that the sponsor must absorb all or a portion of the cost of making the drug more broadly available. It also represents the time during which the drug is available to physicians and patients prior to marketing approval, providing early market exposure for the product and, in many instances, the opportunity to accrue a positive response within the patient community. In the case of already-marketed drugs, the early access period provides an opportunity for limited promotion of the unapproved use. Advertisements directed to physicians and relevant patient populations about the treatment IND distribution for the specific investigational use are permitted.

1. Treatment IND Implementation: June 22, 1987 — December 31, 1994

The FDA designated thirty-three treatment INDs involving thirty-two drugs in the first 7.5 year period following the effective date of the regulations.¹⁴ More than half (56%) of the designations were made during the first 2.5 years of the program. The annual rate of designations has declined from a peak of nine in 1989 to only two in both 1993 and 1994.¹⁵ As of December 31, 1994, twenty-eight treatment INDs had received FDA marketing approval, leaving only five active designations.

The designated drugs are set forth in Table II. Descriptive information about each drug is provided, including the treatment IND indication, the clinical phase in which the designation was granted, and the date of FDA marketing approval for the twenty-eight drugs subsequently approved within the study period.

The FDA assigned a therapeutic rating of AA, A, or P to twenty-one (88%) of the twenty-four drugs approved by the Center for Drug Evaluation and Research (CDER).¹⁶ With one exception,¹⁷ the drugs were in phase II or phase III clinical trials, or phase III had been completed, at the time of designation. Although the scope of the regulations expressly extends to promising new drugs, two designations involved new formulations¹⁸ and four involved new indications for approved drugs.¹⁹ A charge was imposed for nine (27%) of the treatment INDs distributed during the study period, including eight that had orphan designation and three that involved already-approved drugs (see Table II).

The treatment IND indications cover a variety of disease categories; cancer (n=11) and AIDS or HIV-related indications (n=10) account for almost two-thirds of the designations. The remainder of the drugs target conditions such as Parkinson's disease, Alzheimer's disease, neonatal respiratory distress syndrome, obsessive compulsive disorder, and multiple sclerosis. Twenty-four (73%) of the treatment INDs also have been designated as orphan drugs. Eleven subsequently have been approved for marketing under the Subpart E procedures and two have been approved under the accelerated approval regulations.

¹⁴ One drug, Oxandrin (oxandrolone), received two treatment IND designations, each for a different indication.

¹⁵ In a sharp reversal, reflecting a possible resurgence of interest in treatment INDs, the FDA announced nine designations in 1995.

¹⁶ Supplemental approvals and biologics approved by the Center for Biologics Evaluation and Research (CBER) do not receive a therapeutic rating.

¹⁷ Videx (didanosine), a drug used for the treatment of AIDS, received a treatment IND designation while still in phase I clinical trials.

¹⁸ Nebupent (aerosolized pentamidine) and Liorsal (baclofen intrathecal).

¹⁹ Eprex (erythropoietin); Retrovir (zidovudine); and Oxandrin (oxandrolone) (two new indications).

On average, the early access period for the twenty-eight treatment INDs subsequently approved for marketing was 1.5 years, with a wide range from 4.3 months to 5.8 years. The four treatment INDs involving new indications or new formulations of already-approved drugs had early access periods at the short end of the range (mean 1.1 years).

The more extensive FDA involvement with treatment IND drugs prior to NDA submission raises the question of whether any advantage accrues in terms of the speed with which they reach the market. Figure I presents a comparison of the mean clinical and FDA review phase lengths for the twenty treatment IND NCEs approved between 1987 and 1993 (new formulations and supplementals excluded) with twenty-one nontreatment IND NCEs having a similar FDA therapeutic rating distribution (AA, A, P) approved during the same period. Data on the twelve treatment INDs approved under the Subpart E and the accelerated approval regulations also are provided.

The mean clinical phases for the treatment IND NCEs and for the nontreatment IND comparison group were similar (7.7 years versus 7.5 years). However, when the twelve treatment INDs approved under the Subpart E or the accelerated approval regulations (six of which were for AIDS or HIV-related conditions) were removed from the sample, the mean clinical phase for the remaining drugs increased to 10.3 years, almost three years longer than the nontreatment IND comparison group.

Analysis of the respective FDA review phase lengths revealed somewhat different results. The twenty approved treatment INDs had a mean FDA review phase of 1.2 years compared to 2.3 years for the nontreatment IND group (see Figure 1). This difference in approval times was maintained even when the fast-track approvals among the treatment INDs were removed from the sample (1.5 years versus 2.3 years).²⁰

Overall, the average total regulatory phase for original treatment IND approvals was more than one year shorter than that for the nontreatment IND NCEs (8.8 years versus 9.9 years) (see Figure 1).²¹ The apparent advantage for the treatment INDs, however, disappeared when the drugs approved under either the Subpart E or the accelerated approval regulations were removed from the sample. The eight nonfast-track treatment INDs had a mean total regulatory phase almost two years longer than the nontreatment INDs.

Four of the six treatment INDs involving new indications or new formulations for already-approved drugs received FDA approval during the study period. The treatment IND indication for three of the four drugs was AIDS or an AIDS-related condition. The mean FDA review phase for these four applications was just over one year. In comparison, for the period 1989 to 1993, the mean FDA review phase was three years for all supplemental indications approved by the FDA's antiviral division (n=10), and 2.2 years for the anti-infective (n=19) and metabolic/endocrine (n=7) divisions.²²

²⁰ Differences in the distribution of FDA reviewing divisions between the treatment IND and nontreatment IND samples could contribute to the differences in FDA review times. For example, the oncologic/pulmonary division reviewed 45% of the drugs in the treatment IND sample, while the antiviral division reviewed 27% of them. In contrast, each of these divisions reviewed only 12% of the NCEs in the comparison group. Database of FDA-approved NCEs maintained by the Tufts Center for the Study of Drug Development.

²¹ When the treatment IND biologics are removed from the sample, the average total regulatory phase lengthens by approximately seven months, primarily due to the longer clinical phase.

²² Joseph A. DiMasi, Jeffrey S. Brown & Louis Lasagna, *An Analysis of Regulatory Review Times of Supplemental Indications for Already-Approved Drugs: 1989 to 1993*, 30 DRUG INFO. J. (to be published in May 1996).

2. *Comments on Treatment IND Implementation*

After an apparently enthusiastic initial response to the treatment IND regulations, the annual rate of designations has tapered off. There are several possible explanations for this trend.

The treatment IND regulations were implemented during the tenure of FDA Commissioner Frank Young. The agency's recruitment of treatment IND sponsors may have become less intense following Commissioner Young's departure in December 1989. Furthermore, the perception exists that the industry has never fully supported the treatment IND concept.²³ With the benefit of some experience, sponsors may have become even more wary of the potential problems and uncertainties of IND implementation, including the cost of making the drugs available, third party payors' contractual exclusion of reimbursement for experimental therapies, and, in some cases, for the care associated with their administration.²⁴

During the study period, almost three-quarters of the treatment INDs were distributed free of charge. The burden of assuming either the full or partial costs could serve as a disincentive, particularly for smaller pharmaceutical and biotechnology firms. The financial commitment required for a treatment IND may be difficult to determine at the outset because the costs will vary with the length of the early access period and the number of patients ultimately receiving the drug. While the twenty-eight treatment INDs subsequently approved for marketing during the study period had a mean early access period of 1.5 years, the early access period for 25% of them ranged from 1.7 to 5.8 years. An unforeseeable delay in FDA marketing approval could markedly increase costs. Moreover, once the drug has been made available for treatment purposes outside of clinical trials, a sponsor might find it difficult to discontinue the treatment IND in the absence of a compelling safety problem or an early termination of clinical trials.

In addition to these financial implications, the following issues may have resulted in sponsor skepticism concerning the treatment IND process: limitations on the use of the data submitted in marketing applications; communication difficulties with large numbers of community-based physicians; expanded liability exposure; and the ability of patients to opt out of clinical trials once a treatment IND drug is available more broadly, potentially jeopardizing the value of the trials.

Notwithstanding the above concerns, there are documented benefits to undertaking a treatment IND.²⁵ The current study provides a more precise measure of some of these benefits. The period of market exposure prior to FDA marketing approval (eighteen months, on average) not only helps to meet the therapeutic needs of seriously ill patients, it also may establish a market niche for a treatment IND drug among prescribers and patients.

²³ *The Treatment IND: Is It Dead?*, U.S. REG. REP., Apr. 1991, at 4-5; *U.S. Treatment IND/Expedited Approvals — How Do They Work?*, 1364 SCRIP, Nov. 25, 1988, at 18.

²⁴ David W. Barry, *A Perspective on Compassionate Parallel Category C Treatment Track IND Procedures*, 45 FOOD DRUG COSM. L.J. 347 (1990). See also NATIONAL CANCER INST., FINAL REPORT OF THE NATIONAL COMMITTEE TO REVIEW CURRENT PROCEDURES FOR APPROVAL OF NEW DRUGS FOR CANCER AND AIDS (Aug. 15, 1990).

²⁵ In part, the resurgence in treatment IND designations in the post-study period (1995) may be due to an increasing willingness by third-party payors to cover treatment INDs. For example, both private payors and some state Medicaid programs have agreed to pay for Serono Laboratories' Serostin for the treatment of AIDS wasting. Jim Shrine, *Serono Files NDA for Serostin to Treat AIDS Wasting*, BIOWORLD TODAY, Sept. 21, 1995, at 1.

²⁵ NATIONAL CANCER INST., *supra* note 24.

Although there is no indication in the regulations that the treatment IND initiative was intended to reduce the time required to move a drug to market, the treatment INDs approved during the study period benefited from shorter FDA review times. This was most apparent for the twelve treatment INDs approved under the Subpart E or accelerated approval regulations, but it also was evident, albeit to a lesser extent, for the remaining treatment INDs. The shorter FDA review time may be a consequence of the agency's early involvement with the drug and with clinical trial data prior to formal NDA/PLA submission. Furthermore, the additional safety data obtained during the early access distribution strengthens an NDA/PLA submission and contributes to a faster review.²⁶

The four already-approved drugs with treatment IND designation for either a new formulation or a new indication had a mean FDA review phase of only 12.8 months. Because average review times for supplemental approvals are generally as long as, or longer than, the associated original approval,²⁷ sponsors may want to consider a treatment IND designation as a means to speed the approval process for new indications that fall within the scope of the regulations.

B. *The Parallel Track Policy*

The parallel track initiative, outlined in a Public Health Service policy statement on April 15, 1992, established an administrative mechanism to expand the availability of "promising investigational therapies" beyond the parameters of the treatment IND regulations.²⁸ Access to an investigational drug may be authorized as early as the end of phase I, provided that phase II controlled clinical trials have been approved by the FDA and patient enrollment for those trials has been initiated. The program is intended primarily for patients who are unable to participate, for medical or geographic reasons, in ongoing clinical trials. Of the four initiatives reviewed in this report, parallel track is the only one that is designed exclusively for patients with AIDS and HIV-related conditions.

The policy requires that all participating physicians file safety reports. Data from parallel track studies may be used in marketing applications to corroborate clinical trial data. Their usefulness in supporting such applications is limited. Parallel track distributions are not controlled trials and involve numerous community-based physicians. As a result, the emphasis is on safety rather than efficacy data.

To balance the increased risk associated with earlier distribution, the parallel track policy imposes additional levels of oversight. The AIDS Research Advisory Committee (ARAC) at the National Institutes of Health serves an advisory function to the FDA by reviewing and making recommendations on specific parallel track proposals. The policy also calls for the creation of a National Human Subjects Protection Review Panel to ensure that protocols adhere to legal and ethical guidelines.

Although charging for drugs distributed under parallel track protocols is not pro-

²⁶ D. Feigal, Constructing a Framework for Surrogate Endpoint Selection, Address at Am. Acad. of Arts & Sci. meeting, "FDA Accelerated Approval: Dealing with Uncertainty," Cambridge, Mass. (Sept. 23, 1994); Kessler, *supra* note 6.

²⁷ Joseph A. DiMasi et al., *supra* note 22.

²⁸ 57 Fed. Reg. at 13,250. Open label protocols may have been the precursor to parallel track in both design and structure. This mechanism is still used. For example, Glaxo Wellcome's experimental drug lamivudine (3TC) for the treatment of AIDS was distributed to some 35,000 patients under an open label protocol. F-D-C REP. ("The Pink Sheet"), Nov. 27, 1995, at 6.

hibited, the practice is governed by the more restrictive clinical trial rule that requires prior written authorization from the FDA.²⁹ The sponsor must establish why the trial or distribution cannot proceed in the absence of the charge, and why the sponsor should not absorb the expense as a normal cost of doing business. As with treatment INDs, the charge is limited to cost-recovery. Other features of the parallel track policy are detailed in Table I.

1. *Parallel Track Implementation: April 15, 1992 — December 31, 1994*

Only one drug has been distributed under an official parallel track protocol since publication of the final policy statement in April 1992. The FDA approved the parallel track designation for Zerit (stavudine) for the treatment of AIDS on October 5, 1992. The drug was distributed to over 13,000 patients at no charge during a twenty-one month early access period.³⁰ The Antiviral Drug Advisory Committee recommended approval of Zerit on May 20, 1994, and the FDA granted marketing approval under the accelerated approval regulations on June 24, 1994. The total regulatory phase (IND submission to NDA approval) was 5.5 years.

Prior to the publication of the final parallel track policy statement, two other drugs for the treatment of AIDS, Videx (didanosine/ddI) and Hivid (zalcitabine/ddC) were distributed under expanded access protocols, establishing the model for the parallel track program. Beginning in October 1989, Bristol-Myers Squibb distributed Videx to approximately 26,000 patients at no charge for a two-year period preceding FDA marketing approval.³¹ The NDA for Videx was based on phase I studies with 170 adults and ninety-eight pediatric patients.³² However, safety data on approximately 8000 patients generated during the early access distribution were used to augment the clinical trial data. Hoffmann-La Roche undertook a similar distribution of Hivid to over 6,000 patients during a sixteen-month expanded access program that began in June 1990.³³

2. *Comments on Parallel Track Implementation*

The concerns associated with treatment INDs are heightened in the context of a parallel track protocol when release is authorized as early as the end of phase one. The level of risk assumed by patients and sponsors is greater, and FDA authorization to charge for the drug is unlikely. Moreover, the large numbers of patients involved in parallel track distributions make these undertakings costly and require sponsors to have an abundant supply of their drug available early in the development phase. This supply factor was an issue temporarily for one of the protease inhibitors under development for the treatment of AIDS.³⁴

²⁹ 21 C.F.R. § 312.7(d)(1).

³⁰ *Bristol-Myers Squibb Zerit for AIDS Available to Wholesalers July 8 Following Accelerated Approval June 25; Stavudine AWP is \$186.72 for 30-Day Supply*, F-D-C REP. ("The Pink Sheet"), July 4, 1994, at 11-12.

³¹ Kessler, *supra* note 6.

³² Stephen K. Carter, *Cancer and AIDS Clinical Trials — Balancing Research and Patient Care*, Address at the Seventh Annual Sterling Visiting Professorship in Pharmacology, Tufts Univ., Dep't of Pharmacology & Experimental Therapeutics, Boston, Mass. (Jan. 11, 1995).

³³ *Roche "Large Simple Trial" for ddC/AZT Could Involve Thousands*, F-D-C REP. ("The Pink Sheet"), Feb. 24, 1992, at T&G 7.

³⁴ Steve Usdin, *The Rational Alternative for AIDS*, BIOCENTURY PART II, Feb. 27, 1995, at B1. Hoffmann-

These factors plus the fact that the pool of potential parallel track candidates is limited by the program's current restriction to drugs for AIDS and AIDS-related conditions, may partially explain the marginal utilization of the program during its two-year history. It certainly cannot be explained by the lack of investigational drugs for AIDS. The pool of drugs in development for AIDS and related conditions has been increasing annually since 1987. In 1992, the year that the parallel track policy was finalized, there were ninety-one drugs in development for AIDS and AIDS-related conditions, approximately 50% of which were in phase I or phase II clinical trials.³⁵ In 1993, the number of drugs in development had risen to 103. Even allowing for overlap between the years and phases, and assuming the possibility of more than one trial per drug, it is fair to conclude that either sponsors have refrained from participating in the program or that drugs in development have not been sufficiently promising to qualify for a parallel track protocol.

Although the initiative was not intended to provide research data, both the FDA and the participating sponsors have acknowledged that for the three drugs either formally (Zerit) or informally (Videx and Hivid) distributed under a parallel track protocol, a volume of safety data was generated that ultimately facilitated approval under the accelerated approval regulations.³⁶

IV. EXPEDITED AND ACCELERATED REVIEW REGULATIONS

A. Subpart E Procedures: 21 C.F.R. Section 312.80

As with the treatment IND initiative, the FDA's Subpart E regulations represent a codification of a number of established agency procedures. The scope of the Subpart E regulations, however, extends well beyond early access. Subpart E was designed as a means for moving drugs for life-threatening and seriously-debilitating illnesses through the development and review phases and into the marketplace with greater speed and efficiency. To facilitate this goal, the regulations advocate the broadest flexibility in the application of traditional statutory standards.

The regulations formally adopt the model established during the development and approval of AZT (zidovudine), the first drug authorized for the treatment of AIDS.³⁷ Under this model, the drug development process is viewed as a "coherent whole;" interventions at one stage are designed to lead to efficiencies in the next.³⁸ Collaboration between the sponsor and the FDA from the early preclinical phase through postmarketing surveillance is a key factor in this model. Other features of the Subpart E initiative include ongoing clinical trial monitoring and evaluation by the FDA, active consideration by the agency of treatment IND designation at the end of phase II, and the elimination of phase III clinical trials.

La Roche released its protease inhibitor (saquinavir) through an early access program late in 1995. *Roche to Launch Protease Inhibitor Expanded Access Program in Third Quarter 1995; Abbott Lower-Dose Agent May Have Advantage in Production Scale-Up Race*, F-D-C REP. ("The Pink Sheet"), Feb. 27, 1995, at 3-4.

³⁵ PHARMACEUTICAL MANUFACTURERS ASS'N, IN DEVELOPMENT: AIDS MEDICINES, DRUGS AND VACCINES (1993).

³⁶ Kessler, *supra* note 6; Carter, *supra* note 32.

³⁷ Kenneth I. Kaitin, *Case Studies of Expedited Review: AZT and L-Dopa*, 19 L. MED. & HEALTH CARE 242 (1991).

³⁸ 53 Fed. Reg. at 41,516.

The process under Subpart E may begin as early as the pre-IND meeting to reach agreement on the design of animal studies and phase I clinical trials. The sponsor may request an end-of-phase I conference for the specific purpose of coordinating the conduct and design of an expanded, multicenter phase II study. The goal of this expanded phase II study is to generate sufficient data to allow NDA/PLA submission at the end of phase II. At the time of approval, the FDA may request phase IV (post-approval) studies.

The compression of the clinical phase is linked to a shift in the FDA approval standard. The Subpart E regulations adopt a "medical risk-benefit analysis" which expressly requires the introduction of two additional factors to the FDA evaluation process: the severity of the disease to be treated and the absence of satisfactory therapeutic alternatives. The regulations assume a willingness on the part of desperately ill patients to accept more unknowns and thus a higher level of risk.

1. Subpart E Implementation: October 21, 1988 — December 31, 1994

Twenty-eight³⁹ Subpart E approvals were reported by CDER⁴⁰ during the approximately six-year period following promulgation of the regulations (see Table III). Six of these approvals were new formulations of already-approved drugs.

Almost two-thirds (61%) of the twenty-eight approvals involved drugs for the treatment of cancer (n=7) and AIDS or other HIV-related conditions (n=10). Seventy-seven percent were rated by the FDA as AA, A, or P;⁴¹ more than one-third (36%) were distributed prior to approval under a treatment IND protocol; and 54% (thirteen original NCEs and two new formulations) had received an orphan drug designation.

The sample examined in this report offers only a limited view of how effective the Subpart E initiative may be in achieving its goal. A central feature of the regulatory scheme is FDA/sponsor collaboration from an early stage in the development process, but only three of the twenty-eight approvals in the study period had an IND submission date after the effective date of the regulations, October 21, 1988. The remainder were designated as Subpart E approvals retroactively; in two instances, the designation followed NDA submission. Therefore, the time during which these drugs could have benefited from the Subpart E regulatory procedures varied considerably. Although the procedures were available informally to the FDA prior to the 1988 regulations, the extent to which they were used is unclear. The following analyses should be considered in that context.

Excluding two outliers⁴² and the six new formulations, the mean clinical phase for

³⁹ In FDA reports, the agency has categorized Videx (ddI) and Hivid (ddC) as "expedited" or Subpart E approvals. The development experience with these drugs, however, created the prototype for the accelerated approval regulations. They are therefore included among the accelerated approvals reviewed later in this report.

⁴⁰ In response to a request for a list of Subpart E approvals, CBER indicated that no separate record is maintained for biologics approved for severely-debilitating or life-threatening illnesses. Letter from Marlene G. Swider, Pub. Affrs. Specialist, CBER, to Jeffrey Brown, Res. Ass't, Tufts Ctr. for the Study of Drug Dev., Tufts Univ. (Sept. 30, 1994).

⁴¹ See *supra* note 7.

⁴² The NDA for Nimotop (nimodipine), the first drug designated as a Subpart E approval, was submitted approximately six years prior to the implementation of the Subpart E regulations, and was approved two months following implementation. Similarly, the NDA for Eulexin (flutamide) was first submitted to the FDA in September 1980; the NDA was amended in October 1988 to add the indication that was approved under Subpart E approximately four months later.

the twenty Subpart E drugs approved through December 31, 1994 was 6.2 years, with a wide range of 2.2 to 15.3 years. On average, the FDA review phase was 1.3 years, and the total regulatory phase was 7.5 years. For the thirteen original NCEs with both Subpart E status and orphan designation, the mean FDA review phase was 1.2 years. For the six Subpart E approvals involving new formulations of already-approved drugs, the mean FDA review phase was 11.5 months.

Figure II provides a comparison of the phase times for Subpart E approvals with the phase times for similarly rated non-Subpart E NCEs approved during the same period (1988 — 1993). On average, the total regulatory phase for Subpart E drugs was 3.3 years less than that for the non-Subpart E comparison group. Although a difference was observed in both the clinical and the FDA review phases, the greater disparity was evident in the clinical phase, which was 2.7 years shorter for the Subpart E approvals; the mean FDA review phase was only 6.3 months shorter.⁴³

The speed with which the six Subpart E drugs for AIDS or HIV-related conditions moved through the system contributed to the apparent success of the Subpart E regulatory scheme. If these six drugs are removed from the sample, the average total regulatory phase for the fourteen remaining Subpart E drugs jumps by one year, primarily due to a longer clinical phase. The Subpart E sample minus the six AIDS-related drugs, however, still had an average total regulatory phase that was more than two years shorter than that of the comparison NCE group.

A more striking difference in phase lengths was observed for the small subset of three drugs⁴⁴ for which INDs were filed after the effective date of the regulations. On average, these drugs had a clinical phase of 2.5 years and an FDA review phase of 9.2 months, resulting in a total regulatory phase of 3.3 years. When the subset is expanded to include the four Subpart E drugs with INDs submitted after December 31, 1986,⁴⁵ the phase lengths increase somewhat; the average total regulatory phase of 4.5 years, however, remains short by traditional standards.

2. Comments on Subpart E Implementation

The results of the above analyses suggest that the Subpart E procedures hold promise for a substantial decrease in clinical development times and a lesser, although not insignificant, decrease in FDA review times.

The Subpart E sample's comparatively short average total development time of 7.5 years was achieved principally through the compression of the clinical phase and, to a lesser extent, an abbreviated FDA review phase. The benefits of a short review period were even more pronounced for the three drugs with INDs filed after the formal implementation of the regulations.

These results suggest that the Subpart E pathway should be among the options explored in the initial stages of product development. This may be of particular relevance for orphan drugs because the nature of most orphan indications makes these drugs likely candidates for Subpart E approval. The hallmark of the procedure is early

⁴³ If the three Subpart E biologics are removed from the sample, the clinical phase lengthens by 4.5 months, and the FDA review phase remains the same.

⁴⁴ The three Subpart E approvals with INDs filed after the implementation of the Subpart E program were: atovaquone (Mepron), tacrolimus (Prograf), and imiglucerase (Cerezyme) (see Table III).

⁴⁵ This date was selected with reference to the development of AZT. Although AZT was not approved until March 19, 1987, the framework for the development of that drug, and thus the framework for the Subpart E regulations, already had been established.

and intensive FDA/sponsor collaboration. The agency's investment in the development process appears to decrease the drug's time to market. In view of the benefits associated with the Subpart E procedures, the question arises as to whether the scope of the Subpart E regulations should be expanded to include other categories of drugs and indications.

B. Accelerated Approval Regulations: 21 C.F.R. Sections 314.500 and 601.40

Of the four initiatives reviewed in this report, the accelerated approval rule (effective on January 11, 1993) represents the most significant departure from the traditional FDA standards for drug approval. Although the accelerated approval and the Subpart E regulations target drugs intended for similar patient populations,⁴⁶ the standards for approval under the two programs differ significantly. The major point of departure is that accelerated approval may be granted on the basis of the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time. There need not be a direct, validated link between the surrogate marker and clinical benefit at the time of approval. Approval may be based on a clinical endpoint other than survival or irreversible morbidity. The drug must offer a meaningful therapeutic benefit over existing treatments. Such therapeutic benefits could include a promise of greater efficacy, a more favorable safety profile, a new option for patients who are intolerant or nonresponsive to existing therapies, or a new formulation of an approved drug with obvious benefits for patient care.

Uncertainty is a prerequisite for consideration under this program. If the predictive value of the surrogate in terms of clinical outcome has been established, the drug must be evaluated under either the traditional or the Subpart E review procedures. The acceptable level of uncertainty for approval is unclear, although there is reason to believe it is considerable. In the preamble to the proposed rule, the FDA acknowledged that the surrogate marker and the disease under treatment eventually may prove to have no relationship.⁴⁷ The legitimacy of a surrogate marker is determined in the post-approval (phase IV) studies required as a condition of FDA approval.

Until recently, the FDA has avoided characterizing accelerated approval as "conditional approval," but rather has maintained that accelerated approval is "full" FDA approval. Nevertheless, some ambiguity has arisen over the status of the approval granted by the rule.⁴⁸ For example, in its approval letter for Zerit (stavudine), the agency stated that the determination on whether "to grant full approval or to continue accelerated approval" will be made following submission of data from one of the required phase IV studies.⁴⁹

⁴⁶ The two sets of regulations have minor differences in terminology. The Subpart E regulations refer to "life-threatening and severely debilitating illnesses," 21 C.F.R. § 312.80, while the accelerated approval regulations refer to "serious or immediately life-threatening illnesses" 21 C.F.R. §§ 314.500, 601.40. The preamble to the proposed rule for the accelerated approval regime indicates that drugs for the treatment of chronic diseases that may have debilitating outcomes, such as depression, rheumatoid arthritis, and diabetes, also may be candidates for accelerated approval. 57 Fed. Reg. 13,235 (Apr. 15, 1992).

⁴⁷ New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13,234 (Apr. 15, 1992).

⁴⁸ FDA Letter of Approval for Zerit (stavudine) from James Bilstad, M.D., Dir., Off. of Drug Evaluation II, CDER, FDA, to Douglas C. Kriesel, Ph.D., Bristol-Myers Squibb (June 24, 1994).

⁴⁹ *Id.* at 3.

Furthermore, in addition to requirements for phase IV studies, conditions may be attached to an accelerated approval under sections of the regulations that attempt to compensate for the lack of certainty about the drug's safety and efficacy:

- conditions of approval may restrict the distribution and use of the drug to specific health care facilities or groups of physicians, or may require that a specific test or procedure be linked to the administration of the drug;⁵⁰
- promotional materials intended for distribution within 120 days of product approval must be submitted to the FDA during NDA/PLA review; thereafter, submission is required thirty days prior to intended use;⁵¹
- a streamlined withdrawal procedure provides a rapid mechanism for the FDA to remove the drug from the market in any of the following six circumstances: (1) anticipated clinical benefit is not confirmed in post-approval studies, (2) the sponsor fails to exercise due diligence in the conduct of post-approval studies, (3) restrictions on use and distribution of the drug prove insufficient to ensure safe usage, (4) violation of the restrictions on use and distribution, (5) promotional materials prove to be false or misleading, or (6) other evidence indicates that the drug is not safe or effective under its conditions of use.⁵²

1. *Accelerated Approval Implementation: January 11, 1993 — December 31, 1994*

Table IV lists the eight approvals under the accelerated approval regulations as of December 31, 1994.⁵³ In addition to the two AIDS drugs (Videx [ddI] and Hivid [ddC]) approved prior to publication of the final rule, six approvals were granted in the two-year period following the effective date of the regulations. The approvals include three original NCEs, two biotechnology-derived drugs, and three efficacy supplements for already-approved drugs. Five of the eight approvals involve monotherapy and/or combination therapies for AIDS; the remaining three drugs are indicated for cystic fibrosis, multiple sclerosis, and mycobacterial infections.

On average, the clinical phase length for the five original approvals was 4.2 years. For all eight approvals, the mean FDA review phase was 9.1 months (8.4 months for the five original approvals and 10.3 months for the three supplementals). The individual FDA review phases for the eight approvals are shown in Table IV.

Six of the eight accelerated approvals were granted on the basis of a change in a surrogate marker. Changes in the CD4 cell count and in P24 antigen levels were relied on in the accelerated approval of the AIDS therapies. For Betaseron (interferon beta-1b), the endpoint represented a change in the number of multiple sclerosis lesion areas observable on magnetic resonance imaging.⁵⁴ Surrogate validation, in terms of establishing a correlation with slower disease progression, longer survival, or fewer opportunistic infections, is the goal of the post-approval studies.

Regardless of whether a surrogate endpoint was relied on, all approval letters issued pursuant to the regulations made the conduct of specific confirmatory studies a

⁵⁰ 21 C.F.R. §§ 314.520(a)(1), (2); 601.42(a)(1), (2).

⁵¹ *Id.* §§ 314.550, 601.45.

⁵² *Id.* §§ 314.530, 601.43.

⁵³ The FDA granted five additional approvals under the accelerated approval regulations in 1995.

⁵⁴ FDA Press Release, FDA Licenses Interferon Beta-1B for Treatment of Multiple Sclerosis (Apr. 25, 1994).

condition subsequent to approval. None of them included institutional or prescriber restrictions on the use of the drug.

2. *Comments on Accelerated Approval Implementation*

Given that the five original drugs granted accelerated approval had a mean total regulatory phase of just under five years and a mean FDA review phase of 8.3 months, the agency clearly has satisfied its initial goal of moving selected drugs to market more quickly. Although the initiative's implementation during its first two years primarily has involved drugs for the treatment of AIDS, important new therapies for multiple sclerosis and cystic fibrosis were also approved under these regulations.

However, the FDA has announced that it is exploring ways to refine the accelerated approval rule.⁵⁵ At this point in the evolution of the program, the focus has shifted somewhat. Currently, the emphasis is less on speeding the availability of new compounds than it is on establishing therapeutic value. Concerns have been raised, primarily by AIDS patients, that the FDA has departed too radically from its traditional evidentiary standard for approval. Much of the concern centers on the use of invalidated surrogate markers as the basis for FDA approval. The most frequently used surrogate, CD4 cell counts, appears to be a weaker predictor of clinical outcome than previously anticipated.⁵⁶ AIDS groups have objected to the lack of guidelines for the selection of surrogate endpoints and to the absence of a strategy on which to base validation.⁵⁷ In January 1995, the National Task Force on AIDS Drug Development recommended to the Secretary of Health and Human Services that more attention be paid to the selection of surrogate endpoints for protease inhibitors, the next class of AIDS drugs.⁵⁸

Among other issues being explored is the use of innovative study designs to generate more meaningful information about accelerated approval candidates prior to approval. The FDA has been receptive to the use of historical controls, open label studies, telescoped trials, and, more recently, retrospective identification of study endpoints.⁵⁹ An expanded use of large simple trials also is being explored.⁶⁰ The American Foundation for AIDS Research has been a proponent of a not-so-simple model for large clinical trials designed to generate more reliable data.⁶¹

The FDA also has responded to the question of how successful the regulations are in providing an incentive for firms to invest in AIDS research.⁶² The agency's answer reflects some disappointment. The current assessment is that the regulatory criteria for accelerated approval have inadvertently encouraged firms to develop analogues or small

⁵⁵ See Kessler, *supra* note 6.

⁵⁶ *Id.*

⁵⁷ D. Link, Constructing a Framework for Surrogate Endpoint Selection, Address at Am. Acad. of Arts & Sci. meeting, "FDA Accelerated Approval: Dealing with Uncertainty," Cambridge, Mass. (Sept. 23, 1994); Gay Men's Health Crisis, Memorandum to David A. Kessler, Comm'r, FDA (Jan. 3, 1994) (recommendations on ddC approval questions).

⁵⁸ OFF. OF HIV/AIDS POL'Y, U.S. PUB. HEALTH SERV., RECOMMENDATIONS TO THE SECRETARY FROM THE NAT'L TASK FORCE ON AIDS DRUG DEVELOPMENT (JAN. 19, 1995).

⁵⁹ Steve Usdin, *DOX-SL Survives Close Call*, *BIOCENTURY EXTRA*, Feb. 15, 1995, at 1.

⁶⁰ Kessler, *supra* note 6.

⁶¹ Ellen C. Cooper, A Prospective Randomized "Master Antiretroviral Trial:" A Proposal for Improving the Quality of Information on the Clinical Usefulness of New AIDS Drugs, Address at the Drug Information Ass'n's meeting, "The Changing Regulatory Environment and Its Impact on Global Healthcare," Orlando, Fla. (June 25-29, 1995).

⁶² See Kessler, *supra* note 6.

improvements on existing therapies that benefit narrow groups of the affected population, rather than breakthrough compounds with broader implications for treatment of the disease. Given the range of important issues that have emerged in the program's brief history, it seems reasonable to anticipate some amendment to the rule or to the way in which it is interpreted.

V. CONCLUSION

The FDA, through its early access and fast-track approval programs, has expanded the boundaries of traditional drug regulation in the United States. During this process, the agency's role has shifted from that of regulator to one of collaborator in the development and review process. This shift may have significant long-term implications for the agency. Although an arms-length relationship between the agency and the industry it regulates is desirable for a number of reasons, more flexibility may be warranted. Earlier and more intensive collaboration between the FDA and industry sponsors could have payoffs in terms of more efficient and less costly drug development. The early results under the Subpart E regulations suggest that a model incorporating a sense of partnership between the key parties — starting in the preclinical phase and continuing through phases I and II — could substantially shorten the time to market. Based on these results, the FDA should consider formally extending the model to a broader group of diseases.

Some reevaluation and fine-tuning may be needed at this point on several other fronts. It may be time to revisit the issue of reimbursement for drugs subject to early access distribution. Treatment INDs, for example, have more well-established safety and efficacy profiles than the approved-investigational drugs available under the accelerated approval regulations. Under current policies, however, the latter are immediately eligible for third-party payment, while the former are not. FDA approval is the determining factor, and as a rigid requirement it seems artificial. A reimbursement model similar to that established for Group C cancer drugs would serve the FDA's objective of easing access to these important new medicines and might serve as an incentive to industry by buffering the costs of participation in an early access program.

A review of the accelerated approval regulations is underway in response to concerns raised largely by the AIDS community. Vast quantities of safety data, while offering a comfort-zone for new therapies, are insufficient to justify agency approval in the face of significant uncertainty about drug efficacy. Linked to these concerns are questions about the structure of large clinical trials and parallel track distributions.⁶³ The FDA is expected to deal with these issues in its current review.

As the FDA's initiatives have permitted access to important new compounds at increasingly earlier points in the development process, evidence on which to make informed risk/benefit determinations has become significantly less substantial. The challenges raised by this shift in the development and approval of important new drugs continue to emerge.

⁶³ M. Harrington, Summary of Proceedings, Am. Acad. of Arts & Sci. meeting, "FDA Accelerated Approval: Dealing with Uncertainty," Cambridge, Mass. (Sept. 23, 1994).

