30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, applicants must submit to the agency for consideration during the approval process copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication upon marketing approval.

Subsequent to marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

David A. Kessler,

Commissioner of Food and Drugs.

Dated: April 9, 1992.

Louis W. Sullivan,

Secretary for Health and Human Services.

[FR Doc. 92-8622 Filed 4-14-92; 8:45 am]

BILLING CODE 4160-01-M

federal register

Wednesday
April 15, 1992

Part V

Department of Health and Human Services

Food and Drug Administration
Public Health Service

21 CFR Part 312
Investigational New Drug, Antibiotic, and Biological Product Applications; Clinical Hold and Termination; Final Rule

Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Disease; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 89N-0510]

RIN 0905-AD19

Investigational New Drug, Antibiotic, and Biological Product Applications; Clinical Hold and Termination

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final regulation that provides additional grounds for placing an investigation on "clinical hold" and for terminating an investigational new drug application (IND). Under this rule, FDA may require sponsors to cease distributing an experimental drug in an open, nonconcurrently controlled investigation if any of several specified conditions exist. This final rule is part of the Public Health Service's (PHS's) efforts to make promising drugs widely available to people with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV)-related disease who lack satisfactory alternative therapies, while simultaneously ensuring that the adequate and well-controlled clinical trials essential to establishing a new drug's safety and effectiveness are expeditiously conducted.

EFFECTIVE DATE: June 15, 1992.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of May 21, 1990 (55 FR 20856), PHS published a proposed policy to make promising new drugs more widely available to people with AIDS and other HIV-related diseases through nonconcurrently controlled studies. These studies would be conducted in parallel with controlled clinical trails; thus, the policy became known as the "parallel track" policy. Published elsewhere in this issue of the **Federal Register** is a notice issued by PHS announcing a final policy.

The parallel track policy has the potential to provide investigational new drugs to large numbers of patients with HIV-related diseases at an early stage during drug development. To help ensure that patients are adequately protected and that safety and effectiveness information concerning experimental drugs can be developed, in the **Federal Register** of May 21, 1990 (55 FR 20802), FDA published a proposed rule that would amend its IND regulations. The amendments would permit FDA to place on clinical hold or to terminate studies that are not designed to be adequate and well-controlled, including nonconcurrently controlled studies. The current regulation gives FDA the authority to place a Phase 1, Phase 2, or Phase 3 study on clinical hold or terminate the study under specified grounds, such as exposure of subjects to unreasonable and significant risks, unqualified clinical investigators, and insufficient information in the IND to assess the risk to subjects. (See 21 CFR 312.42(b)(1) and (b)(2) and 312.44(b).) FDA published the proposed rule to add additional grounds for placing nonconcurrently controlled studies on clinical hold and terminating them.

II. Highlights of the Final Rule

This document finalizes the provisions that were contained in the proposed rule. In general, a nonconcurrently controlled study may be placed on clinical hold or terminated if certain conditions apply.

The amended regulation (21 CFR 312.42(b)) states that a study may be placed on hold for reasons specified in the current regulations. For a nonconcurrently controlled study in Phase 1, these conditions include the presence of an unreasonable and significant risk to the subjects, unqualified investigators, misleading or erroneous investigators' brochures, and insufficient information to assess risk. For Phase 2 and Phase 3 studies, a clinical hold may be imposed if any of the reasons for halting a Phase 1 study apply or if the study's plan or protocol is clearly deficient in its design. Under the amended regulation these grounds for clinical hold are applicable to nonconcurrently controlled studies, regardless of the "phase" designation.

In addition, under the revised regulation, a nonconcurrently controlled study may be placed on clinical hold if any of the following reasons apply:

(1) There is reasonable evidence that the nonconcurrently controlled study is impeding enrollment in, or interfering with, an adequate and well-controlled study of the same or another investigational drug;

(2) Insufficient quantities of the drug exist to conduct the adequate and well-controlled studies and the nonconcurrently controlled study;

(3) An adequate and well-controlled study strongly suggests that the drug is not effective;

(4) Another drug under investigation or approved for the same indication has shown a better potential benefit/risk balance;

(5) The drug is approved for the same indication in the same patient population;

(6) The drug's sponsor is not actively pursuing marketing approval with due diligence; or

(7) The Commissioner determines that conducting or continuing the nonconcurrently controlled study would not be in the public interest.

FDA ordinarily intends that clinical holds under (2), (3) and (5) listed above would apply only to additional enrollment in nonconcurrently controlled trials, rather than eliminating continued access to individuals already receiving the investigational drug.

FDA is finalizing these additional grounds for placing on hold or terminating a study that is not designed to be adequate and well-controlled. In response to comments seeking clarification of the relationship between parallel track or expanded access studies and treatment IND's, this rule also makes a minor clarification to §§ 312.34 and 312.35 (21 CFR 312.34 and 312.35) to make clearer that approval for a protocol must be obtained under §§ 312.34 and 312.35 if the criteria for §§ 312.34 and 312.35 are satisfied.

The amended regulation also provides that a study may be terminated if the sponsor fails to delay or suspend a study that has been placed on hold for any of the reasons specified in the amended regulation (21 CFR 312.44).

III. Comments on the Proposed Rule

FDA received six comments on the proposed rule. Most sought clarification on specific provisions or suggested minor changes to the proposed rule. Most of the comments focused on how this rule would affect parallel track studies. FDA notes that the responses to comments that address parallel track studies also apply to other nonconcurrently controlled studies.

1. Two comments asked FDA to clarify what constitutes "reasonable evidence" under proposed § 312.42(b)(4)(ii). The proposed rule would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found there is reasonable evidence the investigation that is not designed to be

adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug.

The preamble to the proposed rule gave examples of the types of evidence FDA would examine to determine whether the conduct or completion of an adequate and well-controlled trial has been impeded. The preamble stated that FDA would examine whether enrollment in the adequate and well-controlled trial was proceeding at the expected rate and whether an adequate number of subjects were completing the trial (55 FR 20802 at 20803). An unexpectedly slow enrollment rate or an unusually high drop-out rate that is not attributable to adverse drug experiences generally would be considered as reasonable evidence that the nonconcurrently controlled study is interfering with the conduct or completion of the adequate and well-controlled study. There may be other reasonable evidence of interference, such as affirmative statements from patients or physicians that potential participants in controlled trials are choosing not to enroll in the controlled trials, but rather are choosing to gain access to the uncontrolled trials. The facts concerning each study would be examined to determine whether a clinical hold was warranted.

2. One comment suggested deleting the phrase "or another investigational drug" at the end of proposed § 312.42(b)(4)(ii). The comment claimed that imposing a clinical hold due to the effect on another drug being studied for the same use in the same population could act as a penalty against the firm conducting the nonconcurrently controlled study.

The Federal Food, Drug, and Cosmetic Act (the act) requires sponsors to demonstrate that a new drug is both safe and effective before it can be marketed (21 U.S.C. 355(a) and (b)). This must be done through the use of adequate and well-controlled clinical trials (21 U.S.C. 355(d)). Interference with controlled clinical trials impedes the accumulation of information that is crucial to the development of new therapies. The PHS policy statement on the parallel track mechanism recognizes this fact, and the policy states that "it would be critical that the sponsor work with participating physicians to assure that reasonable efforts are made to encourage persons to enter controlled clinical trials for which they are eligible" (55 FR 20856 at 20859).

To the extent a nonconcurrently controlled study impedes or interferes with the development of important safety and efficacy data in clinical studies, it is important that FDA have the authority to impose a clinical hold on such a study. This provision is not meant to penalize sponsors of nonconcurrently controlled studies. Rather, this provision is to help ensure that the primary objective of identifying the safety and effectiveness of drugs is met. Nonconcurrently controlled studies may interfere with adequate and well-controlled studies not only of the same drug but also of other drugs being studied for the same indication. FDA, therefore, disagrees with the comment.

3. One comment suggested that FDA develop a mechanism for "recognizing the efficacy of the agent using other methods than continuation of the planned prospective controlled clinical trial." The comment argued that the rule "would coerce participation in a controlled clinical trial and force some patients into control groups and deny them access to breakthrough therapy."

The comment seems to assume that the effectiveness of experimental drugs can be determined most rapidly through mechanisms other than controlled trials. FDA disagrees with this implicit assumption. Evidence demonstrating effectiveness can be developed most expeditiously through adequate and well-controlled studies. As discussed more fully in comment 2 above, interference with the controlled trials impedes approval of new drugs. Rather than denying patients access to "breakthrough therapy," controlled trials constitute the most expeditious way of determining that a new and more effective, or "breakthrough," therapy exists.

FDA's desire to prevent impediments to the drug development process is not intended to "coerce" patients into entering controlled clinical trials. Eligible patients are free to choose whether or not to participate in clinical trials. The agency's informed consent requirements are designed to permit patients to decide whether or not to enroll in studies based on adequate information about possible risks and benefits. Drugs being studied in clinical trials are by their very nature "investigational" and not yet proven to be safe and effective for the use under study. Study participants assigned to control groups, who often receive therapy of proven effectiveness, make a necessary contribution to the determination of whether the experimental therapy is in any way useful.

4. Two comments addressed proposed § 312.42(b)(4)(iii). The proposed rule would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found that insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled. One comment asked who would determine whether drug supplies were insufficient to conduct the controlled clinical trial and the nonconcurrently controlled study. The second comment argued that sufficient quantities of the drug should be prepared and assigned to the nonconcurrently controlled study before that study is begun or else the rule would coerce patients into the controlled trial.

If a sponsor does not believe that it can produce sufficient quantities of the drug for the controlled studies as well as the nonconcurrently controlled study, it would not be appropriate for the sponsor to submit a protocol for the nonconcurrently controlled study. As discussed in the proposed parallel track policy statement (55 FR 20858), FDA generally will interact with sponsors in the development of a study protocol. This interaction should permit FDA to determine to some extent whether sufficient quantities of a drug exist or can be produced.

FDA disagrees with the second comment's assertion that sufficient quantities of a drug should be prepared and assigned to the parallel track or other nonconcurrently controlled study before it is begun. The sponsor's financial and manufacturing resources may not permit production of all of the product needed before the trials begin. Reasonable estimates of the amounts of drug needed for completion of the studies can be made, with allowance for changes as the studies progress. At the same time, a production schedule can be established to meet the estimated needs. Requiring production of the estimated quantities of drug before the studies can begin could delay completion of the studies considerably with no substantial benefit.

Allowing the studies to begin before the estimated quantities of drug are manufactured would not coerce patients into the controlled trials. In general, under the parallel track policy, patients are not eligible for enrollment in the nonconcurrently controlled trials unless they are ineligible or otherwise cannot participate in the controlled trials. If a patient enrolls in a parallel track study that is subsequently discontinued because of insufficient quantities of

drug, the patient would not, thereby, be forced into participation in the controlled trials.

5. One comment concerned proposed § 312.42(b)(4)(iv). The proposed rule would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found that the drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness. The comment recommended requiring "two or more adequate and well-controlled investigations" because, the comment explained, a single study is inadequate to tell whether a drug truly works. The comment stated that the provision would be satisfactory if FDA accepted one adequate and well-controlled study "to approve the drug in these situations."

As discussed in the parallel track policy statement, one reason for allowing expanded access to drugs during the early stages of investigation is that the available data show the drug to be promising. However, earlier availability of experimental drugs on a wide scale also exposes larger numbers of patients to greater uncertainties.

If data from one well-controlled study strongly suggest that the experimental drug lacks effectiveness, exposing larger numbers of patients to the uncertainties may no longer be justified. It does not follow that, because two adequate and well-controlled studies are required to approve a drug for marketing, therefore, two adequate and well-controlled studies should be required to place a nonconcurrently controlled study on hold. One adequate and well-controlled study may raise serious enough questions about the drug's risk/benefit potential to warrant discontinuing the nonconcurrently controlled study.

6. Proposed § 312.42(b)(4)(v) would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found that another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance. One comment suggested that, under proposed § 312.42 (b)(4)(iv) and (b)(4)(v), any information on effectiveness be provided to institutional review boards (IRB's), investigators, and subjects. The comment suggested a "decentralized" approach to the options concerning continuation of studies.

The current IND regulations require sponsors to keep each investigator informed of "new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use" (21 CFR 312.55(b)). A sponsor is also required to notify investigators and IRB's if it determines that an investigational drug presents an "unreasonable and significant risk to subjects" (21 CFR 312.56(d)). IRB's may then require that information be given to subjects if, in the IRB's judgment, "the information would meaningfully add to the protection of the rights and welfare of subjects" (21 CFR 56.109(b)). Furthermore, the informed consent regulations state that, where appropriate, subjects shall receive a "statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation * * *." (21 CFR 50.25(b)(5).)

FDA agrees with the comment's concern that information be shared with IRB's, investigators, and subjects; FDA notes that the existing requirements accomplish that goal. FDA also believes, however, that it may be appropriate for the agency to place on clinical hold a nonconcurrently controlled study, which may include subjects in many locations throughout the country. Section 312.42(b)(4)(iv) and (b)(4)(v) allows FDA to review risk/benefit analyses and to place studies on clinical hold without requiring individual IRB's, investigators, or subjects to review the information and make separate determinations before the study can be halted.

7. FDA received three comments on drug benefit/risk determinations under proposed § 312.42(b)(4)(v). The comments questioned whether a benefit/risk could be determined for investigational drugs at an early stage of drug development. One comment suggested deleting the provision entirely, while a second comment asked what type of evidence would be sufficient to show that "unreasonable and significant risks" existed. Another comment challenged FDA's authority to impose a clinical hold under such circumstances, claimed that the rule would "prioritize" pharmaceutical development, and declared that FDA cannot control or terminate investigational studies based on the perceived merits of another drug product.

The preamble to the proposed rule recognized that benefit/risk determinations may be difficult to make at an early stage of drug development (55 FR 20802 at 20803 and 20804). The preamble stated that "such [benefit/risk] judgments based on as much information as is available are appropriate in determining whether expanded access should be continued," and that evidence of "relative toxicity or effectiveness" would be examined. Id. (emphasis added). FDA agrees with the comments that benefit/risk determinations may be difficult for investigational new drugs. FDA does not, however, agree that this difficulty justifies deleting the provision. If is not possible to describe the precise risks that may be viewed as unacceptable in light of the perceived benefits in a general regulation. The circumstances of each experimental drug must be considered in judging whether a study should be allowed to continue.

FDA believes that it has clear statutory authority to promulgate these clinical hold regulations. Section 505(i) of the act (21 U.S.C. 355(i)) specifically authorizes the promulgation of regulations governing the investigational use of new drugs. Such regulations may establish "conditions relating to the protection of the public health." New § 312.42(b)(4)(v) is intended to protect the public health by providing explicit clinical hold authorization when the continued use of a drug in an uncontrolled trial is not warranted because of the potential benefit/risk balance.

As for the comment that placing a study on clinical hold based on an unfavorable benefit/risk assessment is akin to denying approval of a new drug solely because the drug is not as effective as an already approved drug, the agency does not agree that these are analogous circumstances. There is an analogy, however, between benefit/risk determinations in the new drug application context and in the IND context. The agency may deny approval of a new drug product based upon an unfavorable benefit/risk assessment; similarly, the agency may place an uncontrolled trial of an investigational drug on clinical hold based upon such an unfavorable assessment. Uncontrolled trials can mean that large numbers of patients are exposed to investigational new drugs at early stages of drug development. Although such trials can provide useful information on the safety of the drug, uncontrolled trials cannot in themselves generate sufficient information on the drug's safety and effectiveness to make a determination on whether the drug should be approved. Exposing participants in uncontrolled trials to an investigational drug when the risk/benefit assessment indicates that such exposure is unwarranted would be contrary to the interests of the public health. Nothing in the statute prohibits

the agency from protecting the public health against unwarranted investigational uses in this manner.

FDA also does not believe that clinical holds based upon unfavorable benefit/risk assessments impermissibly "prioritize" pharmaceutical development. In accordance with sponsors' support, appropriate studies of all investigational drugs with acceptable benefit/risk balances may continue as rapidly as possible. That is, putting a protocol for an uncontrolled trial on clinical hold does not mean that ongoing controlled trials are also put on hold. The controlled trials, which would provide the primary basis for an ultimate determination on the drug's approvability, would continue unless indepenedent reasons existed to discontinue the controlled trials.

8. Two comments objected to proposed § 312.42(b)(4)(vi). The proposed rule would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found that the drug has received marketing approval for the same indication in the same patient population. One comment stated that the provision was unnecessary because a parallel track study will not affect a drug's availability and could generate safety data. The second comment argued that the provision would limit access to drug products because subjects would be obliged to purchase the approved drug to continue treatment. The comment suggested giving subjects the option to continue their participation in the parallel track study so sponsors would be compelled to "price their approved drug in a manner which will recruit patients from parallel track investigations."

As discussed in the preamble to the proposed rule (55 FR 20802 at 20804), if a competing version of the same drug itself has received marketing approval for use in the same population for the same indication, there is no longer adequate justification for expanded availability. Under these circumstances, another product will have been demonstrated to be safe and effective and approved for distribution.

FDA does not believe that it would be appropriate to use its authority over investigational products to try to force manufacturers to modify prices of approved drugs. Issues of drug affordability are more appropriately dealt with under other statutes implemented by other agencies.

9. One comment asked FDA to define "due diligence" under proposed § 312.42(b)(4)(vii). The proposed rule would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if FDA found that the sponsor is not actively pursuing marketing approval of the investigational drug with "due diligence."

"Due diligence," for purposes of this regulation, denotes a good faith effort to pursue drug development and marketing approval in a timely manner. The term "due diligence" was discussed in the preamble to the treatment IND final rule (52 FR 19466 at 19470 and 19471, May 22, 1987). Similar considerations would apply in the context of nonconcurrently controlled studies under § 312.42(b)(4)(vii).

10. Proposed § 312.42(b)(4)(viii), would permit FDA to place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if the Commissioner determined that it would not be in the public interest for the study to be conducted. One comment objected to this provision because it would give the Commissioner "carte blanche extermination rights." The comment suggested revising the rule to provide examples of instances where the public interest would justify a clinical hold.

As stated in the preamble to the proposed rule, the provision giving the Commissioner the authority to impose a clinical hold, if it would be in the public interest, is designed to be flexible (55 FR 20802 at 20804). Experience with other regulations has shown that it is extremely difficult to illustrate comprehensively how a regulation would be employed. Even short lists of examples are often misconstrued as being exhaustive. This difficulty is especially true here because the public interest in imposing a clinical hold can stem from a number of sources, such as questions concerning a drug's manufacture, storage, and distribution or inspections involving the manufacturer, physician, clinical investigator, or IRB.

Furthermore, the rule does not give the Commissioner arbitrary authority to terminate a noncurrently controlled study. The clinical hold regulation states that FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and resolve matters with the sponsor before issuing a clinical hold order (21 CFR 312.42(c)). If a sponsor disagrees with the reasons cited for a clinical hold, the sponsor may request reconsideration in accordance with the dispute resolution provisions at 21 CFR 312.48. (See 21 CFR 312.42(f).) These and other procedural regulations in 21 CFR part 312 provide for notice to sponsors of deficiencies or problems and give sponsors an opportunity to correct those problems or to respond to the notice.

11. FDA also received several comments on the parallel track policy. Some comments, such as those suggesting that the parallel track policy consider a subject's economic status or provide financial incentives to sponsors, are outside the scope of this regulation and FDA's authority. Other comments asked how the policy would affect other FDA requirements. One comment asked FDA to "streamline" paperwork requirements for investigators.

FDA declines to accept the comment to the extent it asks for the elimination of recordkeeping and reporting requirements. As noted in the final policy on parallel track, the system for data collection should be specified in the parallel track protocol and should be efficient and not unnecessarily burdensome. The recordkeeping and reporting requirements for investigators under 21 CFR part 312 help FDA determine that investigational new drugs are properly distributed and administered and that adverse effects are promptly reported. Such information is particularly important for investigational new drugs that are used during early stages of drug development.

12. One comment asked whether FDA would apply the treatment IND requirements at Phase 2 and parallel track requirements at Phase 1.

Neither the treatment IND nor the parallel track policy mechanism is restricted to drugs in a particular phase. Normally, however, evidence to support treatment IND's for drugs intended for use in a serious disease has been available during Phase 3 or after all clinical trials have been completed. In a number of appropriate circumstances, such evidence was available during Phase 2. For drugs intended for use in an immediately life-threatening disease, a treatment IND is possible before Phase 3, but ordinarily not before Phase 2 (21 CFR 312.34(a)). Under the parallel track mechanism, it is expected that most drug products will be in Phase 2 or Phase 3. (See 55 FR 20802.)

13. One comment asked whether a drug in the parallel track protocol qualified for expedited review. The comment stated that a drug's eligibility for the parallel track mechanism should be a priori evidence for receiving expedited review.

Expedited review is available for new drug, antibiotic, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely debilitating diseases. The expedited review

regulations define "life-threatening" diseases or conditions to be those where the "likelihood of death is high unless the course of the disease is interrupted" or those having "potentially fatal outcomes, where the end point of clinical trial analysis is survival" (21 CFR 312.81(a)(1) and (a)(2)). The regulation defines "severely debilitating" diseases as "diseases or conditions that cause major irreversible morbidity" (21 CFR 312.81(b)). Under these definitions, drugs in the parallel track mechanism would qualify for expedited review if the therapy is being studied in clinical trials designed to investigate whether the therapy increases survival or decreases irreversible morbidity.

14. One comment noted that the rule does not give sponsors any authority to restrict, modify, or suspend a parallel track study.

The clinical hold regulation only refers to FDA's ability to impose a clinical hold. Companies are free to decide whether they wish to participate in a parallel track study, and, as with adequate and well-controlled studies, can restrict, modify, or even terminate a parallel track study in accordance with 21 CFR part 312.

15. Several comments expressed confusion over the relationship between the parallel track studies covered by this rule and treatment IND studies, and whether the two types of studies overlapped. One comment stated its belief that parallel track protocols would be granted under the provisions of the treatment IND regulations. Other comments stated that it was unclear how the parallel track proposal differed from the treatment IND program, and urged FDA to clarify the distinction between parallel track protocols and treatment IND protocols.

FDA believes that it is appropriate to clarify that parallel track protocols will be granted under the criteria specified in the parallel track policy statement, not under the provisions of the treatment IND regulations, and that the two programs are not intended to overlap. In general, FDA may grant a request for a treatment protocol for a drug if the drug is for a serious or immediately life-threatening disease, and FDA finds that the criteria in § 312.34 are met. The parallel track policy statement applies at this time to nonconcurrently controlled safety studies of only drugs for HIV-related disease. FDA may permit a parallel track protocol to begin if it satisfies the criteria in the parallel track policy statement. If a drug for HIV-related disease meets the criteria for a treatment IND, then FDA will permit use under a treatment protocol; a parallel track protocol for the same drug for precisely the same indication in the same patient population would not be permitted to go forward because the treatment IND criteria would have been met. However, if the criteria for a treatment IND are not satisfied, but the criteria for a parallel track protocol have been met, then the parallel track protocol may go forward. To clarify further the regulatory distinction between parallel track and treatment IND protocols, FDA has amended §§ 312.34 and 312.35 to clarify that the approval for any protocol that meets the treatment IND criteria must occur under the provisions of §§ 312.34 and 312.35.

The concerns raised in discussion about the proposed parallel track policy statement provided the primary impetus for the proposed changes in the clinical hold and termination regulations. However, the same or similar concerns exist for nonconcurrently controlled studies that are not part of the parallel track mechanism. Consequently, the regulation providing additional grounds for clinical hold and termination was proposed to apply to "any study that is not designed to be adequate and well-controlled" (proposed § 312.42(b)(4)). Such studies would include not only parallel track studies, but also treatment IND protocols and other uncontrolled studies, even if the disease being studied is not HIV-related or is not serious or life-threatening. To make it clearer that the provisions of proposed § 312.42(b)(4) would apply to all uncontrolled studies, including treatment IND studies, the agency is adding new § 312.42(3)(iii) to specifically cross-reference § 312.42(b)(4) in the provision on clinical holds for treatment IND studies.

IV. Economic Impact

The agency has examined the economic impact of this rule and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). This rule amends the regulations governing investigational new drugs to provide additional grounds for placing an investigation on clinical hold and for terminating an IND.

These amendments are applicable where FDA permits promising investigational new drugs to be more widely available in nonconcurrently controlled trials during the same period that adequate and well-controlled studies on the same drugs for the same indication are being conducted. The rule provides necessary safeguards in connection with nonconcurrently controlled studies. This rule does not impose additional requirements on sponsors, nor does it require the expenditure of significant resources.

Accordingly, FDA concludes that the rule is not a major rule as defined in Executive Order 12291. Further, FDA certifies that the rule does not have a significant impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1980

This final rule does not contain new collection of information requirements. Section 312.44, which is amended by the rule, contains collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 and approved under OMB control number 0910–0014.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 312 is amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

2. Section 312.34 is amended in paragraph (a) by adding a new sentence at the end of the paragraph to read as follows:

§ 312.34 Treatment use of an investigational new drug.

(a) * * * If a protocol for an investigational drug meets the criteria of this section, the protocol is to be

submitted as a treatment protocol under the provisions of this section.

* * * * *

3. Section 312.35 is amended in paragraph (a) by revising the first sentence and by adding a new sentence after it, to read as follows:

§ 312.35 Submissions for treatment use.

(a) * * * Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall submit to FDA a treatment protocol under § 312.34 if the sponsor believes the criteria of § 312.34 are satisfied. If a protocol is not submitted under § 312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under § 312.34.

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4. Section 312.42 is amended by adding new paragraphs (b)(3)(iii) and (b)(4) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(3) * * *

(iii) FDA may place a proposed or ongoing treatment IND or treatment protocol on clinical hold if it finds that any of the conditions in paragraph (b)(4)(i) through (b)(4)(viii) of this section apply.

(4) *Clinical hold of any study that is not designed to be adequate and well-controlled.* FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

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5. Section 312.44 is amended by adding new paragraph (b)(1)(xi) and by revising paragraph (b)(2)(i) to read as follows:

§ 312.44 Termination.

* * * * *

(b) * * *

(1) * * *

(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under § 312.42(b)(4).

(2) * * *

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or

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Dated: April 8, 1992.

David A. Kessler,

Commissioner, Food and Drug Administration.

[FR Doc. 92-8623 Filed 4-14-92; 8:45 am]

BILLING CODE 4160-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Disease

AGENCY: Public Health Service, HHS.

ACTION: Notice Final Policy Statement.

SUMMARY: The Public Health Service (PHS) is announcing a final policy to make promising investigational drugs for AIDS and other HIV-related diseases more widely available under "parallel track" protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. The "parallel track" initiative establishes an administrative system designed to expand the availability of promising investigational agents and to make these agents more widely available to people with AIDS and other HIV-related diseases who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

FOR FURTHER INFORMATION CONTACT: Donald Pohl, Office of AIDS Coordination (HF-12), Food and Drug Administration/PHS 5600 Fishers Lane, Rockville, MD 20857, 301-443-0104.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 21, 1990 (55 FR 20856), the PHS published a proposed policy for the expanded availability of investigational new drugs through parallel track for people with HIV infection and AIDS. 1,210 comments were received; of these, 200 were unique while the other 1,010 were form letters.

As with the proposed policy, the final policy was developed by a PHS workgroup composed of representatives from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Office of the General Counsel, and the National AIDS Program Office (NAPO), with significant input from community advocates, community physicians, clinical researchers, and industry representatives.

I. Comments

A. Expansion to Other Life-Threatening Diseases

Many comments supported the expansion of the parallel track mechanism to other life-threatening diseases. A number of comments stated that the policy as it applies to AIDS and other HIV-related disease should be evaluated before applying the policy to other diseases, while some comments supported immediate expansion to other diseases. Comments from individuals as well as manufacturers and professional associations expressed the view that the parallel track policy for AIDS and other HIV-related disease should serve as a pilot project to work out specific appropriate administrative procedures. Some individuals stated that a policy similar to parallel track for other life-threatening diseases should be developed only after consultation with advocates for patients with those other diseases.

A variety of regulatory mechanisms exists to make promising investigational agents more widely available for serious and life-threatening diseases.

These specific processes (such as the NIH AIDS Research Advisory Committee (ARAC) and the specific National Human Subjects Panel described below) are not applicable to other life-threatening diseases. This parallel track policy describes processes specifically for AIDS and other HIV-related diseases. However, PHS invites patient groups, physicians and sponsors interested in developing a similar process for other life-threatening diseases to work with PHS on issues concerning expanding the parallel track mechanism for other life-threatening diseases.

Currently, other mechnisms exist for making investigational drugs available prior to approval to persons with life-threatening diseases for which there is no satisfactory alternative therapy. Under the treatment IND procedures, eligible patients can have access to investigational drugs intended to treat serious or life-threatening diseases that meet established criteria. For cancer patients in particular, FDA and the National Cancer Institute (NCI) have described a special category of drugs, "Group C" drugs, which may be provided to eligible patients through protocols outside the controlled clinical trials prior to approval. In many instances it appears these mechanisms adequately address demand for early access.

PHS intends to evaluate the parallel track experiences specifically to determine whether worthwhile benefits are provided in addition to those available under mechanisms such as the treatment IND or Group C approaches. The evaluation would also include a consideration of whether parallel track has had detrimental effects on individuals or on the ability to determine the safety and effectiveness of promising therapies.

Even though a combination of safeguards has been built into this policy (including careful product selection, informed consent, patient and physician education, a national human subjects protections review panel, community involvement, and oversight), allowing increased availability of drugs prior to definitive evidence of either safety or efficacy carries potential risks for the participants.

B. NIH AIDS Research Advisory Committee (ARAC)

1. Role of the ARAC in Review of Drugs for Parallel Track

Some comments endorsed the proposed role of the AIDS Research Advisory Committee (ARAC) in reviewing sponsors' requests and in making recommendations regarding parallel track protocols. Other comments requested further clarification of the ARAC's role in the parallel track process. Two comments stated that sponsors should not have the option of bypassing ARAC review.

As outlined in the policy, IND sponsors will submit parallel track proposals to FDA as amendments to existing INDs. The sponsor may be the manufacturer of the drug or another organization conducting drug trials. Unless the sponsor objects, FDA will refer the parallel track proposal to the ARAC for consideration. Requests for ARAC review will be processed and scheduled by National Institute for Allergy and Infectious Diseases (NIAID) Committee staff. After review of the proposal, the ARAC will make a recommendation to the Director, NIAID. The Director of NIAID will then forward a recommendation through the Director of NIH to the FDA Commissioner.

In this process, the ARAC serves as an expert advisory panel composed of persons with HIV-related disease, physicians, non-government scientists, and representatives of activist organizations. In addition to reviewing and making recommendations on parallel track proposals generated by IND sponsors, the ARAC may make recommendations, based upon available evidence, concerning termination of parallel track protocols. While the ARAC plays a vital role in the review of parallel track protocols, the policy will still allow sponsors to request that their protocols not be reviewed by the ARAC.

2. Non-Sponsor Requests for ARAC Consideration

A number of comments stated that in addition to sponsors, any interested person should be able to petition the

ARAC to consider the appropriateness of parallel track protocols for specific drug products.

An entity which is authorized to distribute the drug, which has access to all data necessary to support an IND, and which is willing and able to carry out the responsibilities of the sponsor of an investigational new drug application is necessary for the initiation of a parallel track protocol. As discussed in the proposed policy statement, deliberations about whether or not a specific drug is appropriate for parallel track study can best be accomplished through the review of a detailed parallel track protocol in conjunction with the controlled clinical trials protocols for that same drug.

Information needed to evaluate the benefits and risks of a drug is ordinarily information that is proprietary to the drug manufacturer. Unless the sponsor of an investigational drug indicates a willingness to provide the necessary information and to conduct a parallel track study, the ARAC would be frustrated in its attempt to review a drug for appropriateness for parallel track availability.

The NIH, as part of its research mandate, has a public responsibility to ensure that research showing high promise is pursued and supported. Therefore, the NIH can be requested to take on the obligation of developing a drug lacking private sector sponsorship, and in that role also assume any responsibilities for implementing a parallel track program. The decision to assume these obligations would, of course, be guided by the available resources and competing needs for those resources. The ARAC, which has programmatic advisory responsibilities for NIAID, might be consulted in such decisions.

There may be extraordinary circumstances in which a non-sponsor has sufficient information about the drug and its potential usefulness for the intended patient population and condition to be treated, and about the clinical trials to permit meaningful review of a parallel track proposal. In such circumstances, the non-sponsor could request NIAID to refer the matter to the ARAC for review and recommendation. If NIAID determined that a meaningful review and recommendation could be accomplished, it could refer the matter for ARAC consideration. Because PHS expects that such circumstances would be rare, the policy statement has not been amended to refer specifically to such requests by non-sponsors.

3. ARAC's Role in Defining "Standard Treatment"

A number of comments stated that the ARAC should have the authority to define "standard treatment" as applied to the eligibility criteria for each parallel track protocol. The ARAC may make recommendations with respect to any aspect of a proposed parallel track protocol, including the section dealing with eligibility criteria. The ARAC may review the description of standard treatment, as well as the descriptions of when it will be considered that standard treatment "cannot be tolerated" or is "no longer effective".

As with the other aspects of approval for parallel track protocols, FDA has the authority to make the final determination on the acceptability of the eligibility criteria in the protocol. In making determinations regarding parallel track protocols, FDA will consider the ARAC's recommendations on each issue. Further discussion of "standard treatment" appears below, at F. "Eligibility Criteria." Even when a sponsor elects not to have ARAC review, FDA may elect to consult ARAC on the appropriateness of the description of standard therapy.

4. ARAC as the Interim National Human Subjects Protections Review Panel (National Human Subjects Panel)

Several comments raised concerns about the proposal to have an ad hoc subcommittee of the ARAC function as an interim national human subjects protections review panel. PHS has determined that it would be more appropriate to have the AIDS Program Advisory Committee (APAC) at NIH serve as this interim panel. The comments regarding this interim group and other institutional review board (IRB) issues are described more fully below under M. "Human Subjects Protections."

C. Review Criteria

Some comments criticized the proposed parallel track review criteria and process as overly complex and likely to delay access to experimental treatments. One comment stated that the ambiguity of the criteria makes it difficult to assess the potential impact of the policy on drug availability. The proposed policy statement listed eight categories of information that the FDA and the ARAC would ordinarily consider in reviewing a proposal to make an investigational drug available through a parallel track protocol. In general, PHS believes that this is the minimum information needed to enable the decision makers to assess potential risks and benefits to the recipients of the drug in parallel track studies and the potential effect on the controlled trials.

Unless the information specified for review is available, PHS does not believe that it would have sufficient information to justify exposing large numbers of subjects to the investigational drug through parallel track protocols. By enumerating the kinds of information to be provided, PHS believes that a sponsor can more readily prepare an acceptable parallel track proposal, which the FDA and the ARAC can review without delays to request additional needed information. If adequate, the expanded access studies can be permitted to go forward expeditiously.

The policy statement describes in general terms the kinds of information needed to support a parallel track proposal; it allows flexibility and room for appropriate adaptation to the unique circumstances of particular drugs or patient populations. Involving the FDA, the NIH, and the ARAC in the review process is intended to provide a variety of expert opinions on the merits of a parallel track proposal. PHS believes that the procedures provide a reasonable approach to dealing with the complexities of expanded access and should not result in any undue delay in drug availability.

D. Impact of Parallel Track on Clinical Trials

Some comments suggested that parallel track studies should be delayed for a period of time to allow for Phase 2 controlled trial accrual. One comment stated that the controlled trial enrollment should be completed before a drug is made available through parallel track. Others expressed the view that individuals enrolled in expanded access trials were ineligible for controlled trials, and the low accrual rates in controlled trials were due instead to overly restrictive enrollment criteria.

The proposed policy statement indicated that Phase 2 controlled clinical trial protocols are to be approved by the FDA and patient enrollment initiated prior to or simultaneously with release of drugs for expanded availability under the parallel track protocol. As discussed in the proposed policy statement, PHS recognizes that well controlled clinical trials are crucial to establishing the safety and effectiveness of new treatments. It is therefore extremely important that the parallel track studies not delay or compromise the controlled trials to support product approval.

The combination of specific enrollment criteria and the timing of beginning enrollment in the controlled trials and the parallel track studies should adequately prevent the parallel track studies from having a detrimental effect on the controlled trials. As some of the comments pointed out, patients are not eligible for parallel track protocols unless they cannot participate in the controlled trials. Once the controlled clinical trials have been approved, the eligibility criteria for those trials are clear. If the eligibility criteria for the parallel track protocol are honored, the start of accrual in the parallel track protocols should not interfere with accrual in the controlled trials. PHS recognizes, however, that if physicians enroll patients in the parallel track protocol who are in fact eligible for a controlled trial, accrual in the controlled trials may be adversely affected. PHS will consider methods of monitoring parallel track enrollment to determine whether eligibility criteria are being followed.

PHS believes that it is important that patient enrollment in the controlled trials be initiated prior to or simultaneously with release of drug for expanded availability under a parallel track protocol. PHS does not believe that it is necessary to require that the enrollment in the controlled trials be completed before beginning accrual in the parallel track protocols. Accrual in large studies can take many months or longer before complete enrollment; in the absence of extraordinary circumstances, such a delay in beginning studies with different eligibility criteria would not be appropriate. In some situations it may be appropriate for accrual in the controlled trial to have already begun before initiating the expanded access trials. Such determinations should be made based upon the circumstances of the particular drug patient population.

Regardless of when accrual in the controlled trial begins, if there is evidence that the parallel track study is interfering with the successful enrollment in, and completion of, the controlled trials, FDA may terminate the parallel track study. (See discussion below at 0. "Terminating Protocols.") In addition, PHS is prepared to appropriately revise this policy if a more systematic interference of controlled trials becomes obvious.

E. Protocol Development

A number of comments asked for assurance that there would be input from people with AIDS, the FDA, the ARAC, community physicians, the primary care physicians in the design of parallel track protocols. One comment requested that specific criteria for the design of protocols be required.

As discussed in the proposed policy statement, FDA regulations set forth the general elements required to be contained in protocols for studies of investigational drugs (21 CFR 312.23(a)(6)). The sponsor would develop the protocol, which is then reviewed by others, including the ARAC, under parallel track procedures. Representation of people with HIV disease and community and primary care physicians on the ARAC provides one opportunity for input of theses groups in the development of the protocol design. The FDA will review the design of the protocol as part of determining the acceptability of the sponsor's parallel track submission . Sponsors of parallel track studies who desire waiver of local IRB review under 21 CFR parts 56 and 45. CFR part 46 may include such requests in their submissions.

F. Eligibility Criteria

1. Patient's Inability To Take Standard Treatment

Several comments stated that the non-response to Zidovudine (ZDV/AZT) or Dideoxyinosine (ddI) as well as intolerance should establish eligibility of a patient for a parallel track study. Similarly, a number of comments stated that a drug available under a treatment IND should not be considered "standard treatment" for purposes of the parallel track eligibility criteria. Conversely, another comment stated that a patient should be intolerant of AZT or geographically distant from clinical trials to qualify for parallel track.

A basic premise regarding drugs under consideration for parallel track protocols is that there is not yet sufficient evidence of the drug's safety and effectiveness to support approving the drug for marketing.

Because of the increased uncertainties as to a product's safety and effectiveness when drugs are made available at such an early stage of the development of safety and effectiveness information, it is appropriate that enrollment in parallel track studies be limited to those patients who cannot take therapies already shown to have acceptable benefit/risk ratios. Approved products have been found to have acceptable benefit/risk ratios for labeled indications based upon adequate and well-controlled studies as well as other available information. PHS believes that in most circumstances it will be clear that the available information supports the conclusion that only patients who cannot take or do not respond to either an approved drug or one available under a treatment IND, for the same clinical condition for which the parallel track investigational drug is being studied, should be eligible for the parallel track protocol.

Nevertheless, PHS also believes that those preparing and reviewing the proposed protocol should have flexibility in determining what constitutes standard treatment for the particular condition and patient population identified in the proposed parallel track study, in order to take into account unique circumstances. To allow the determination to be made on a case-by-case basis, PHS has removed from the policy statement the parenthetical phrase defining standard therapy as "a drug approved for marketing or available under a treatment IND for the same clinical condition for which the investigational drug is being studied." PHS expects that in many circumstances standard treatment would include both approved drugs and drugs available under a treatment IND. With regard to the eligibility of those patients who do not respond to standard therapy or drugs available under treatment IND, this determination will also be made on a protocol specific basis. For many protocols, the criterion of "the patient cannot take standard treatment because it is . . . no longer effective" will most likely include circumstances under which the drug was never effective.

2. Patient's Health Status

A number of comments expressed concern that people who are HIV-positive and asymptomatic should have access to experimental therapies before they become clinically ill.

The proposed policy statement included as a criterion of patient eligibility that the patient have clinically significant HIV-related illness or be at imminent health risk due to HIV-related immunodeficiency. HIV-positive individuals who are not manifesting clinical symptoms may still be at imminent risk because of their immune status. Such individuals may be eligible for appropriate parallel track protocols.

Each parallel track protocol will identify the intended patient population, as well as the condition being studied. The parallel track policy permits submission and acceptance of appropriate protocols for studies of asymptomatic individuals at imminent health risk due to HIV-related immunodeficiency.

3. Access to Parallel Track Studies for Underserved Populations

A number of comments expressed concern that parallel track studies be accessible to underserved populations, especially women and minorities. Others also raised questions about the eligibility of those who cannot afford standard therapy to participate in parallel track studies.

The eligibility criteria for a parallel track protocol should not arbitrarily exclude specific patient populations without adequate scientific justification. The question of access to parallel track studies for all eligible patients who wish to participate can be addressed to some extent through educational programs. The educational program, which is to be addressed in each protocol, includes education of physicians, patients, IRBs, community-based health institutions, community and migrant health centers, the general public, and affected communities. Educational initiatives in community health centers and drug treatment centers, as well as in such programs as the AIDS Clinical Trails Groups (ACTG) and the Community Program for Clinical Research on AIDS (CPCRA), should facilitate enrollment from all eligible groups.

Involvement of community physicians and community-based programs should help to provide access to parallel track studies for traditionally underserved populations. The system for collecting and reporting data should be efficient and not unnecessarily burdensome to encourage community physician participation (see "Patient Data" section).

PHS believes that economic status is not an appropriate criterion for enrollment in clinical trials and that economic issues should be addressed through other means. However, PHS recognizes that economic problems impede access to therapy for low-income patients. There are public health care programs, not within the purview of PHS, established to make approved drugs available to those patients who need the drugs but cannot afford to pay for them. A further discussion of cost issues related to parallel track studies appears below at L. "Economic Concerns."

G. Geographic Concerns

Most of those who commented on geographic concerns stated that a benefit of parallel track would be to make therapies available outside of urban centers. One comment stated that the geographic dispersion of patients in parallel track protocols might compromise the value of the data collected. Another comment stated that expanded access should be restricted to a limited number of patient subsets—including those denied access to clinical trials due to geographic location.

Parallel track studies are intended to provide access to promising investigational drugs for patients who cannot participate in the controlled trials while generating data on the safety and effectiveness of the drug. The proposed policy statement included undue hardship among the reasons for inability to participate in the controlled trials and defined undue hardship as including excessive travel time to the study site.

PHS recognizes that the geographical dispersion of the clinical investigators can create some difficulties in collecting the data from parallel track trials. However, all participating physicians will be required to report data as specified in the protocol, and the sponsor will be responsible for gathering and organizing the data. Appropriate design and conduct of the data collection process should minimize the problems created by geographical dispersion. Additional concerns about data collection are discussed below at I. "Patient Data."

Although PHS agrees that parallel track studies should be available for those who cannot participate in controlled trials because of geographical distance, PHS does not believe that parallel track studies should be restricted by geographic location. For example, patients who live near the location of a controlled trial site may be ineligible to participate in the controlled trials for other reasons. They may not meet the entry criteria, they may be too sick, or the controlled trials may be fully enrolled. PHS believes that these patients should not be excluded from parallel track studies solely because of geographic proximity to the study site of the controlled trials.

H. Physician Criteria

Some comments addressed the qualifications for physicians who participate in parallel track studies. Of these comments, some stated that participating "physicians" should include physician groups, clinics, and community-based health care facilities because many patients have no primary physician. Other comments raised questions about the training of physicians, specific minimum qualifications, and incentives for physicians to participate.

As discussed in the proposed policy statement, physicians administering investigational drugs under parallel track protocols become clinical investigators subject to all the obligations and responsibilities of investigators. The protocol should specify the minimum qualifications for participating physicians and the process by which a physician may be accepted by the sponsor as a clinical investigator under the expanded availability protocol.

Physician groups, clinics, and other community-based facilities are eligible if they meet the specified qualifications. The data collection and reporting procedures, as well as the education and training programs, for participating physicians should be designed to ensure an adequate and appropriate study without creating unnecessary burdens or disincentives for the physicians. The opportunity to provide a treatment option for patients who cannot participate in the controlled trials or take standard therapy should be a significant incentive for physicians to participate in parallel track studies.

I. Patient Data

The comments identified a number of concerns regarding data collection, including the need for well-defined data collection requirements and a cost efficient, time efficient, uncomplicated data collection system. Some comments urged permitting community research groups to collect data on effectiveness as well as safety. Other comments raised concerns about the confounding of results due to patient noncompliance with protocols and difficulty analyzing data without control group study designs. Some comments requested that FDA consider data generated in parallel track studies in granting marketing approval. In addition, questions were raised about who will pay for the cost of data collection, who will analyze the data, and what incentives exist for physicians to submit data.

PHS agrees that well-defined data collection requirements should be specified in the parallel track protocol. The system for collecting and reporting data should be efficient and not unnecessarily burdensome for the participating physicians. All participating physicians will be required to report safety data.

PHS agrees that parallel track protocols may appropriately provide for community research groups or other specified investigators to collect data on effectiveness as well as safety. The nature and extent of effectiveness data collection may vary in different clinical settings.

The sponsor will analyze the parallel track data and report the results to FDA under the IND. Ongoing review of available data will be provided by a

Data and Safety Monitoring Board or its equivalent established by the sponsor. In general, the sponsor will be responsible for the costs of the parallel track protocol. Economic considerations are discussed more fully below at L. "Economic Concerns."

PHS also agrees that the interpretation of data from uncontrolled studies can be difficult. As with all clinical trials, it is important that participating patients comply with the protocols to produce reliable and interpretable data. Data from the parallel track studies can be included in any submission for marketing approval made by the sponsor. Such data may provide corroborating information; however, data from adequate and well-controlled studies demonstrating effectiveness and from all reasonably applicable studies demonstrating safety are required, by law, for marketing approval.

J. Monitoring

A number of comments stated that monitoring the parallel track studies for both safety and effectiveness was desirable, but may not be possible. These comments urged that monitoring for safety information should be given a higher priority. Some comments also argued that appropriate training and adequate informed consent procedures should help to provide quality control for the studies.

As previously stated, all participating physicians will be required to provide safety data from their patients enrolled in parallel track protocols. Each protocol will provide a specific monitoring system, which will include the establishment of a Data and Safety Monitoring Board (DSMB) or its equivalent. The DSMB, or its equivalent, will monitor the studies and gather information from all studies in which the investigational drug is being tested. As the information accumulates, it will be used to update the informed consent document or to take other appropriate action, including terminating the study.

PHS also intends that the ARAC and others periodically review the parallel track program as a whole to help assess its benefits and potential or possible detrimental effects.

K. Education and Information

Some comments called for more specific language in the policy statement outlining what is required of parallel track proposal sponsors in developing an education program. The comments agreed that the success of parallel track will depend on the education of physicians and other caregivers on management of HIV disease, parallel track drugs, conduct of trials, and data collection, as well as on the education of the public and people with HIV-related disease concerning available treatment options.

PHS agrees that the education program accompanying a parallel track study is extremely important. Because of the varieties of potential investigational drugs, patient populations, caregivers, and conditions to be treated, it is not feasible to try to specify the details of an education program applicable to every protocol. In general, each program should be designed to adequately educate patients, physicians and other caregivers, IRBs, affected communities, and the general public. It is extremely important that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the parallel track drug, as well as, the risks and benefits of other treatment options.

The sponsor will be required to specify in the parallel track protocol the particular educational program for the investigational drug to be administered under the protocol. FDA will review the description of the educational program as part of the determination of acceptability of the protocol as a whole. Ordinarily, the ARAC will also review and make recommendations concerning this portion of the protocol, as well as others.

Other institutions, including the Health Resources and Service Administration (HRSA), FDA, NIH, manufacturers, and professional organizations will collaborate in disseminating information and providing general training and education concerning HIV-related disease and the parallel track policy.

L. Economic Concerns

Many comments addressed the issue of access to health care, and the affordability of therapies for underserved populations. Some comments stated that the success of parallel track will depend on providing therapies to the uninsured and the underinsured. Other comments stated that there should be third-party reimbursement for parallel track studies.

Several comments expressed concern about the costs to drug manufacturers participating in parallel track. The concerns raised included the costs of increased production of the drug for parallel track use without the guarantee of approval, as well as insurance and other potential product liability costs. Questions were raised about eligibility for cost recovery under parallel track protocols. One comment asked that eligibility of a drug for parallel track be sufficient for the drug to receive review under FDA's expedited review procedures.

Although not within its purview, PHS recognizes the importance of the reimbursement issues concerning experimental therapies and reaffirms its commitment to help facilitate consideration of these issues.

PHS also recognizes that there can be significant costs to manufacturers in sponsoring or participating in parallel track studies. However, PHS has no control over manufacturers' costs, such as insurance costs, or potential product liability exposure. IND sponsors are ordinarily not permitted to charge for investigational drugs. However, under 21 CFR 312.7, sponsors may request approval from FDA for charging based upon an explanation of why charging is necessary to undertake or continue the study. As with other clinical trials, sponsors of parallel track studies may make requests under this provision. Even if such approval is obtained, under no circumstances may a sponsor commercialize a product by charging more than needed for cost recovery.

A drug cannot be approved for marketing without evidence from adequate and well-controlled studies demonstrating effectiveness and all reasonably applicable studies demonstrating safety, acceptance of a parallel track protocol does not represent any guarantee that the drug will ultimately be approved for marketing. However, FDA's expedited review procedures, described in subpart E of 21 CFR part 312, are applicable to new drug, antibiotic, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely debilitating diseases. Parallel track therapies, like other therapies being studied for the treatment of HIV-related diseases, will be eligible for FDA's expedited review procedures, if the therapy is being studied in clinical trials designed to investigate whether the therapy increases survival or decreases irreversible morbidity. The FDA gives AIDS-related drugs the highest priority review and encourages IND sponsors to consult with the agency as early as possible in the drug development process.

M. Human Subjects Protections

1. Need for Local IRB Review

Some comments suggested that local IRB review of parallel track protocols should not be waived under 21 CFR part 56 or 45 CFR part 46. Some comments supported the concept of giving the local

IRB jurisdiction over trials in their area, while a national human subjects protections review panel (national human subjects panel) would establish guidelines and protocols and have general oversight responsibilities for parallel track. Others argued that a national panel would simply duplicate the work of the local board, resulting in delay of initiation of studies, confusion over authority, and additional costs. The benefits of local IRB review were cited as the following:

(1) Having established relationships with local investigators and physicians;

(2) Having knowledge of state and local laws and requirements;

(3) Having access to local knowledge and expertise; and

(4) Being able to satisfy the requirement of many institutions that local IRBs review all research involving human subjects conducted by their physicians, faculty members, and other investigators.

As noted in the proposed policy statement, even if the requirement for local IRB review is waived, local IRBs would continue to have the option of reviewing expanded availability protocols. PHS recognizes the benefits of local IRB review, and reaffirms its position that such review is ordinarily most appropriate. However, as noted in the policy discussing the HHS regulations, in the context of parallel track protocols, loal IRB review and a written assurance of compliance is generally not practical for many reasons:

(1) Local review could slow the dissemination of drugs under parallel track policies and procedures;

(2) Local review could be made without sufficient information on which to base a recommendation;

(3) Local review could result in considerable delays if physicians are required to form their own IRBs; and

(4) Local review might place IRBs in a situation in which it is difficult to monitor activities of physicians for whom they are not otherwise responsible.

Consequently, PHS continues to believe that a national human subjects panel can provide sufficient protection for patients in parallel track studies and that waiver of local review is generally appropriate.

The national human subjects panel should be composed of broad-based membership, including appropriate geographic, racial, ethnic, and gender representation. PHS does not believe that the national panel review would cause any additional delay, confusion, or cost. If a local IRB decides to review a protocol, the expert review, analysis, and guidance of the national human subjects panel would be helpful to the local panel in its review, which could be conducted more efficiently and expeditiously.

2. The Identity of the Interim National Panel

Some comments expressed concern that the ARAC should not function as the interim national human subjects panel. The comments argued that ARAC's main role in evaluating and making recommendations regarding therapies for parallel track conflicted with the role of an IRB; that ARAC members were selected for their scientific and medical expertise, and that IRB membership should be more broad based; and the ARAC would be overburdened with the additional responsibility.

PHS agrees with the comments that it would be more appropriate for the ARAC not to serve the additional function of the interim national human subjects panel. PHS has determined that the AIDS Program Advisory Committee (APAC), an advisory committee to NIH, should function as the focus of the national human subjects panel until a permanent body is established. The APAC has broad-based membership and familiarity with clinical research and, with respect to parallel track, will perform the function of human subjects protections review.

N. Informed Consent

A few comments stated that reaching traditionally underserved communities would require extensive informed consent, outreach, and on-going education. One comment expressed concern that the absence of standard therapy would cloud the judgment of individuals opting for parallel track. Another stated that even those individuals who can take standard therapy should be permitted to choose experimental treatment if fully informed of the risks. One comment also stated that the informed consent procedure for parallel track need only be altered slightly from the procedure currently used for controlled trials and treatment INDs. One group commented that a mechanism should be developed to enhance physician awareness of the importance of the informed consent process.

PHS emphasizes that adequate and appropriate informed consent procedures are fundamentally important to parallel track protocols. The informed consent document and the process for updating the document as information about the drug becomes available are intended to ensure that all subjects can understand the potential risks and benefits of the investigational drug and of other treatment options. The informed consent process should be presented in appropriate language to enable the individual patient to make an informed decision. It is crucial that participating physicians fully appreciate the importance of obtaining adequate informed consent. PHS agrees that the procedures currently used for controlled trials and treatment INDs can provide valuable guidance for developing informed consent procedures in the parallel track context. PHS does not agree that informed consent can completely substitute for the eligibility criteria set forth in the policy statement, which provide additional protection for individuals against uncertainties from drugs still in the early stages of development.

O. Terminating Protocols

A few comments on the policy statement discussed the criteria for terminating or curtailing a parallel track protocol. One comment agreed with the general concept, but suggested clarification of the criteria. Another comment expressed concern about terminating a protocol if it is determined that another product demonstrates a better potential balance of risks and benefits. That comment also questioned FDA's legal authority to terminate a drug study based on relative risks and benefits.

PHS continues to believe that it is important that parallel track protocols be terminated or curtailed if the circumstances set forth in the policy statement develop. The general criteria for termination are intended to protect individual subjects as well as to enable the contolled clinical trials essential to establish the safety and effectiveness of new drugs to be carried out.

A proposed regulation detailing the FDA's authority to terminate studies was published in the same issue of the Federal Register as the proposed policy statement (55 FR 20802). Comments relating to the substance of the criteria for termination and the FDA's legal authority are addressed in the preamble to the final regulation, published elsewhere in this issue of the Federal Register.

II. Final Statement of Policy

PHS is prepared to work with patient groups, physicans and sponsors on issues concerning the development of comparable mechanisms for other life-threatening diseases when there is significant support to do so. The final statement of PHS policy on expanded

availability of investigational new drugs through a parallel track mechanism for people with AIDS and HIV-related diseases follows:

Introduction

Through this notice, the Public Health Service is announcing a final policy under the Food, Drug and Cosmetic Act (the Act). The purpose of this policy is to permit promising investigational agents to be made available to people with AIDS and HIV-related diseases who are not able to take standard therapy, or for whom standard therapy is no longer effective, and who are not able to participate in ongoing controlled clinical trials. Through this policy, promising new drugs would be made available through studies without concurrent control groups to monitor drug safety that are conducted in parallel with the principal controlled clinical investigations (hence the name "parallel track").

This policy, developed by the Public Health Service with significant input from community advocates, industry representatives, the research community, and other interested members of the public, represents a further step in expanding availability of promising investigational drugs under the Act to those persons with AIDS and HIV-related diseases who are without satisfactory alternative therapy and who cannot participate in the controlled clinical trials. Because some investigational drugs for these conditions may be more widely available at a very early point in the drug development process, this procedure recognizes the need for participating physicians and their patients to consider what is and is not known about the risks and benefits of a variety of potential therapeutic agents when making clinical decisions.

Patients and physicians must recognize that products available under this procedure will be in the very early stages of product development and will only be made available to provide potential therapeutic options to those people with serious and life-threatening HIV-related disease who have no satisfactory alternative therapy. It must be clearly understood that the earlier availability of experimental treatments on a wide scale exposes larger number of patients to greater uncertainty and the risk of unforeseen and serious reactions.

There are many issues and problems related to providing potential therapies to individuals with HIV-related diseases. Although certain problems have been addressed in this document, others, in particular some that are not within the purview of the Public Health Service still require attention, but will not be discussed in this publication. For example, this policy does not deal with aspects of the health care system that can affect the availability and affordability of parallel track mechanisms to underserved groups. It also does not address the role of third-party payers in covering the costs of medical services associated with the use of parallel track drugs, nor does the policy address the liability of manufacturers sponsoring a parallel track drug. While the Public Health Service recognizes the importance of these issues, and will attempt to facilitate a broader consideration of them, they are beyond the scope of this policy.

In the development of this policy, it was recognized that well conducted clinical trials are crucial to the development of new treatments. While the goal of making promising investigational agents more widely available to persons with HIV infection and no therapeutic alternatives is an important one, controlled clinical trials that yield definitive information on the safety and effectiveness of investigational new drugs must continue. This policy includes sufficient safeguards and oversight to ensure that it neither delays nor compromises the controlled clinical trials.

Background

Normally, the development of a new experimental therapy proceeds through a systematic series of clinical trials that yield data growing from an initial understanding of appropriate dosing, side effects, and initial hints of efficacy, to a substantial body of definitive evidence of safety and effectiveness sufficient to support product marketing. This often lengthy approach is based upon well substantiated and widely accepted scientific and ethical principles and a mandate from society that protection of individuals from undue risks of experimental therapy is essential.

Although the AIDS epidemic has heightened interest in expanded access to investigational drugs, the issue is not new. Persons with life-threatening diseases for which no satisfactory alternative therapy is available have at times requested an investigational new drug prior to the drug's approval by the Food and Drug Administration (FDA). The issue has been dealt with by FDA in the past in both formal and informal ways. In the 1970's a number of large protocols were developed in which physicians, generally at academic referral centers, had access to investigational drugs for persons with serious or life threatening conditions who were without satisfactory alternative therapy. The drugs in these protocols were usually under active development in controlled trials and some of these protocols involved large numbers of patients. A similar mechanism was developed to provide investigational drugs to persons with cancer.

The FDA and National Cancer Institute (NCI) have described a special category of investigational drugs, "Group C" drugs, which may be provided by oncologists to appropriately chosen patients through protocols outside the controlled clinical trials prior to the drug's approval.

In 1987, FDA incorporated into a final regulation the treatment investigational new drug application (Treatment IND). Under a Treatment IND protocol, eligible patients have access to investigational drugs intended to treat serious or life-threatening diseases. A Treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks, but before marketing approval has been granted. Treatment IND status has been granted for 18 investigational new drugs, 6 of these for AIDS-related conditions.

Under this policy, expanded availability protocols might be approved for promising investigational drugs when the evidence for effectiveness is less than that generally required for a Treatment IND. The expanded availability protocol may include one or more studies without concurrent control groups and may be accompanied by a Treatment IND protocol. All drugs distributed under the parallel track mechanism will be under a study protocol. Data, particularly pertaining to side effects and safety will be collected under these studies. However, most of the data essential for market approval will come from the controlled clinical trials.

As is the case for all investigational uses of drugs, FDA has authority for approving and monitoring the study protocols that are developed under this expanded availability policy. A regulation detailing the FDA's authority to terminate nonconcurrently controlled studies is published elsewhere in this issue of the **Federal Register.**

Selection of Investigational Therapeutic Agents for Expanded Availability Through Parallel Track

FDA encourages potential parallel track sponsors (as defined at 21 CFR 312.3(b)) to seek advice and information

from FDA and other scientists outside the agency as early, and as frequently as possible, during the pre-application process.

The FDA authority for the final decisions regarding which investigational agents will be placed in a program for expanded availability. Applications for experimental therapies to be considered for expanded access (parallel track) are to be submitted to FDA as amendments to existing INDs.

(1) FDA will refer all parallel track proposals to the AIDS Research Advisory Committee (ARAC), a committee chartered by the National Institute of Allergy and Infectious Diseases (NIAID) unless the sponsor indicates otherwise. This committee, composed of outside scientists and physicians experienced with AIDS, persons with HIV-related diseases, and others, will review the available data and make a recommendation to the Director of NIAID. After review, the Director of the NIAID will forward a recommendation, through the Director of the NIH, to the Commissioner of the FDA. In all cases, requests to be presented to the ARAC will be screened and scheduled by NIAID Committee Management Staff.

(2) If the sponsor prefers, the formal parallel track proposal can be submitted to the FDA for review without being forwarded to the ARAC.

Review Criteria

Ordinarly in reviewing a proposal to make an investigational drug available through a parallel track proposal, the ARAC Committee and FDA will consider whether there is:

1. Sufficient information showing:

a. Promising evidence of efficacy based on an assessment of all laboratory and clinical data;

b. Evidence that the investigational drug is reasonably safe, taking into consideration the intended use of the drug and the patient population for which this drug is intended; and

c. Sufficient data to recommend an appropriate starting dose.

2. Preliminary pharmacokinetic and dose-response data and, ideally, data about interactions with other drugs commonly used in the intended patient population.

3. Evidence of a lack of satisfactory alternative therapy for defined patient populations. In general, the investigational drug should meet a serious unfulfilled health need such that the potential benefits justify the considerable risks of very early expansion of use.

4. A description of the patient population to receive the drug under expanded access. Patient priority categories based on clinical condition should be determined if the drug may not be available in sufficient quantities to supply all of those who satisfy the basic eligibility criteria.

5. Assurance that the manufacturer is willing and able to produce sufficient amounts of the drug product for both the controlled clinical trials and the proposed expanded availability study.

6. A statement of the status of the controlled clinical trial protocols. Phase 2 controlled clinical trial protocols are to be approved by the FDA and patient enrollment initiated prior to or simultaneously with release of drugs for expanded availability under the parallel track protocol.

7. An assessment of the impact that the parallel track study may have on patient enrollment for the controlled clinical trials and a proposed plan for monitoring progress of the controlled trials.

8. Information describing the informational, educational and informed consent efforts that will be undertaken to ensure that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the investigational agent being studied in the parallel track process.

In general, deliberations about the advisability of expanded availability for a specific drug can be accomplished best during the review of a relatively detailed protocol for expanded availability in conjunction with the review of the protocols for the controlled clinical trials. While a detailed protocol is not required during the initial discussion stage, an outline of the proposed parallel track study should be provided.

Review and approval of a formal IND protocol is to be carried out by FDA, which may elect to involve one or more advisory committees in the review process. The FDA, through its existing regulations and procedures, may also discuss proposed protocols with appropriate consultants to the Agency.

A decision not to allow expanded availability of an investigational drug would not imply a judgement about a drug's ultimate safety or efficacy nor preclude additional controlled trials.

Protocol Development and Approval

The protocol for distribution and monitoring of an investigational drug under parallel track (expanded access protocol) is to be developed by the manufacturer or other sponsor. The FDA has regulatory authority for approval of the protocol and, in most cases, will interact with the sponsor during its development.

Elements to be contained in the expanded access protocol are to be the same as those for other protocols of investigational agents in clinical trials (21 CFR 312.23 part (a)(6)). Normally, a protocol submission for a parallel track study would include information about: The administration of the protocol; the sponsor's responsibilities under the protocol; patient selection criteria; phasing in of expanded use; physician selection for participation; dosage level and frequency; data reporting requirements and data collection forms; data monitoring procedures by the sponsor; physician and patient educational materials; patient consent documents; and criteria for terminating the protocol.

Eligibility Criteria for Patients To Receive Investigational New Drugs Through Parallel Track

Criteria for patient eligibility are to be included in each protocol for expanded availability. General principles for determining patient eligibility are described below. They are intended to provide flexibility as the specific criteria may vary for different agents and different clinical situations.

The determinants of patient eligibility include all of the following:

1. The patient has clinically significant HIV-related illness or is at imminent health risk due to HIV-related immunodeficiency.

2. The patient cannot participate in the controlled clinical trails because:

(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.

3. The patient cannot take standard treatment because it is contraindicated, cannot be tolerated, or is no longer effective. (The terms "cannot be tolerated" and "no longer effective" should be defined in each protocol. Generally these definitions will include a description of the standard therapy including dosages and the minimum duration of treatment to assess clinical utility, the range and severity of adverse reactions that constitute intolerance, and the clinical conditions or laboratory markers that constitute evidence that the therapy is no longer effective). If the basis for enrollment in the parallel track study is that standard treatment is no longer effective, the patient's physician

or physician group would be required under the protocol to certify that the patient is failing clinically despite reasonable efforts to optimize therapy with the standard treatment.

The protocol should establish patient priority categories if a sufficient quantity of the investigational drug is not likely to be available to all those who would satisfy the basic criteria for eligibility.

Because the primary objective of the IND phase of drug development is to establish the safety and efficacy of the drug through controlled clincial trails, it is critical that the sponsor work with participating physicians to assure that reasonable efforts are made to encourage persons to enter controlled clinical trails for which they are eligible. The protocol should specify a process for determining if a person for whom the investigational drug is being requested under the parallel track protocol is eligible for a controlled clinical trial of the drug, and methods for contacting clinical trial directors for possible inclusion.

The expanded availability protocol should not exclude certain patient populations based on age, sex or medical status unless there is adequate justification. Protocols should also consider and address potential problems associated with use of the drug in such special populations. The regulations for human subjects protections are discussed later in this document.

Criteria for Physician Participation in Parallel Track

As specified in FDA's IND regulations (21 CFR part 312) physicians administering investigational drugs under parallel track protocols become clinical investigators subject to all the obligations and responsibilities of investigators. The protocol will specify the minimum qualifications for participating physicians and the process by which a physician may be accepted by the sponsor as a clinical investigator under the expanded availability protocol. Physicians are required to certify that the patients meet the requirements of the protocol and that all efforts have been made to optimize standard therapy prior to enrollment in parallel track protocols. Because investigational drugs will be made available through parallel track protocols when relatively little is known about the drug, physicians must be familiar with potential adverse effects, willing to instruct patients in the early recognition of these effects and willing to monitor their patients closely. Participation by all physicians, including those serving rural, inner-city, medically indigent, and racial and ethnic minority populations should be encouraged.

Collection of Patient Data in Parallel Track Protocols

The data to be collected by the participating physicians and reported to the sponsor will be specified in each parallel track protocol. All participating physicians will be required to report safety data, while the nature and extent of efficacy data collection may vary in different clinical settings. The frequency of reporting will be specified in the protocol. Because of the early stage at which investigational drugs are to be made available under a parallel track protocol, and the relative lack of information about risk that is likely to exist, it is critical that participating physicians comply with data reporting requirements to provide important information on the risk of the drug and to assure patient safety.

The data collection forms should be designed to be easy to use and as concise as possible. Appropriate data collection and reporting by the administering physician is a prerequisite for continued drug supply.

Monitoring the Protocols

The sponsor of a parallel track protocol should monitor the study closely through a specific monitoring mechanism described in the protocol. The sponsor should establish a Data and Safety Monitoring Board (DSMB) or its equivalent with responsibility for monitoring the parallel track studies and gathering information from all protocols testing the investigational drug. The DSMB or its equivalent may recommend to FDA, the Sponsor, ARAC and other appropriate bodies that the parallel track and/or clinical trial protocols be terminated. (See Terminating Protocols).

The description and mechanism of operation of the DSMB (or other monitoring system) and its precise relationship to the sponsor and other oversight bodies will be specified in the expanded availability protocols.

The sponsor is responsible for submitting reports to the FDA as required in the IND regulations (21 CFR part 312), except where a waiver has been specially granted.

Education and Information

An extremely important accompaniment to a parallel track protocol is a program for the education of physicians, patients, IRBs, community-based health institutions, community and migrant health centers, the general public, and affected communities to ensure that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the parallel track drug as well as the risks and benefits of other treatment options. These programs, as noted in the "Review criteria" section above, should reflect the joint efforts of the PHS, the medical community, industry, academic communities and AIDs-related organizations. These education programs are in addition to the information provided through the informed consent process. Sponsors should specify how their particular education program will be carried out as well as how new information will be collected, analyzed, and publicly circulated.

Economic Considerations

Existing IND regulations permit sponsors to request the recovery of costs for certain investigational drugs in clinical studies, in the unusual circumstance in which the trial could not otherwise continue (see 21 CFR 312.7(d)(1)). FDA approval of a request to charge must be obtained.

Sponsors should specify the extent of economic support they would be willing to provide to pursue the expanded access of the investigational agent through the parallel track. They should also specify the degree of support, if any, they would provide for the administration of the drug for the conduct of necessary laboratory and clinical testing to determine product safety and the monitoring, collection, and distribution of drug-specific information through their education programs.

Human Subjects Protections

There are two sets of relevant federal regulations for the protection of human subjects which include requirements for local institutional review board (IRB) review and informed consent: the FDA regulations (21 CFR parts 50 and 56) that apply to all investigational drug studies, and HHS regulations (45 CFR part 46) which pertain to institutions that receive HHS support for research involving human subjects.

(a) HHS Regulations

Certain requirements of the current HHS regulations cannot reasonably be met for drugs released under the parallel track program. These regulations require local IRB review and approval of each protocol and written Assurance of Compliance from each organization or individual practitioner involved in the research and not affiliated with an assured institution. This is generally not practical for many reasons: (1) Local IRB

review could slow the dissemination of drugs under parallel track policies and procedures; (2) local review could be made by IRBs without sufficient information on which to base a recommendation; (3) local review could result in considerable delays if physicians are required to form their own IRBs; (4) local review might place IRBs in a situation in which it is difficult to monitor activities of physicians for whom they are not otherwise responsible. Consequently, the Secretary of HHS will consider, on a protocol-by-protocol basis, waiving the provisions of 45 CFR part 46.

Other mechanisms, in lieu of local IRB review, to provide for review of the protocol according to established ethical principles and to develop informed consent procedures appropriate to the parallel track program are described below.

(b) FDA Regulations

Prior to proceeding with a parallel track protocol, a sponsor must comply with FDA's IRB regulations. FDA regulations would allow a waiver where FDA determines that it is in the best interests of the subjects and that a national human subjects panel would provide an adequate mechanism for protecting patients. The Commissioner of Food and Drugs will consider a sponsor's request for waivers of the provisions of 21 CFR part 56 dealing with local IRB review, including § 56.107(a).

(c) National Human Subjects Protections Review Panel

While local IRBs would always have the option of reviewing expanded availability protocols, a national human subject protections review panel (national human subjects panel) with a broadly-based membership would be established. This panel will provide for patient protection, including approval of consent procedures and documentation and provide for continuing ethical oversight of each parallel track protocol. It will be particularly important for this body to review the proposed informed consent process of each protocol and review an initial "model" informed consent document, and to review the process to update the procedures and the document as knowledge about the investigational drug becomes available. The national human subjects panel will also ascertain that for each parallel track protocol the sponsor has established an appropriate procedure for data and safety monitoring.

The AIDS Program Advisory Committee (APAC) in NIH will establish an ad hoc subcommittee to carry out the duties of the national human subjects review panel until a permanent body is established. Outside consultants representing the relevant specialties and constituencies will be called on as needed to advise this body. PHS will take steps necessary to create a chartered national human subjects protections review panel with a broadly-based membership.

IRBs would continue to review drugs on the controlled clinical trial side of the "parallel track." In addition, individual institutions have the option to require that their IRBs review the expanded availability protocols when a study is conducted by the institution or its affiliated investigators.

Informed Consent

It is important that potential participants in the parallel track have as much information as is available in order to make informed decisions. The informed consent process must make clear the risks involved in taking a drug about which relatively little is known. The proposal for agents in the parallel track must describe a detailed process for informed consent, including specific information about patient and physician education. A proposed informed consent document is required to be included with the protocol. There should also be a description of how the informed consent document will be updated and how physicians and patients and the national human subjects panel will be notified of new information (e.g. toxicity, adverse reaction reports) after the initial informed consent document has been put into use.

Terminating Protocols

Because the parallel track program allows early, widespread distribution of investigational agents prior to full marketing approval, it is necessary to develop criteria to terminate or curtail a parallel track program. In general, these should include the following:

(1) Evidence that subjects are being exposed to unreasonable and significant risks,

(2) Evidence that the parallel track study is interfering with the successful enrollment in, and completion of, adequate and well-controlled studies of this or other investigational drugs,

(3) Evidence that the sponsor is not in active pursuit of marketing approval,

(4) The product has been studied in an adequately controlled clinical trial that strongly suggests lack of effectiveness,

(5) Another product approved or under investigation for the same indication in the same population demonstrates a better potential balance of risks and benefits,

(6) The drug receives marketing approval for the same indication in the same patient population,

(7) Insufficient product exists to conduct both the parallel track protocols and the controlled clinical trials,

(8) The Commissioner of Food and Drugs determines that, in the interest of the public health, the parallel track study should not be continued.

A principal purpose of the Data and Safety Monitoring Board, or its equivalent, would be to examine data to determine if the parallel track and/or clinical trials should be stopped and to make recommendations to the sponsor, FDA, ARAC, and other oversight bodies. A regulation detailing the FDA's authority to terminate these studies, as well as other uncontrolled studies, is published concurrently with this policy statement.

Periodic Review

A periodic review of the implementation and progress of expanded availability of all investigational drugs being distributed by a parallel track study will be conducted by the PHS. The objective of this periodic review would be to help ensure the continued rapid development and evaluation of therapeutic agents for treatment or prevention of HIV infection and HIV-associated diseases, as well as the safety of participants in these trials.

Dated: April 8, 1992.

James O. Mason,

Assistant Secretary for Health.

David A. Kessler,

Commissioner, Food and Drug Administration.

[FR Doc. 92-8624 Filed 4-14-92; 8:45 am]

BILLING CODE 4160-17-M