DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 314

[Docket No. 88N-0359]

Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses

AGENCY: Food and Drug Administration.

ACTION: Interim rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is issuing interim regulatory procedures designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness. These procedures are intended to facilitate the development, evaluation, and marketing of such products, especially where no satisfactory alternative therapies exist. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures apply to products intended to treat acquired immunodeficiency syndrome (AIDS), some cancers, and other life-threatening or severely-debilitating illnesses. FDA is issuing these procedures as an interim rule with opportunity for public comment.

DATES: Interim rule effective October 21, 1988; comments by December 20, 1988.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305) Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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SUPPLEMENTARY INFORMATION: Expediting the availability of promising new therapies has been a major priority of FDA over the past several years. In the **Federal Register** of May 22, 1987 (52 FR 19466), FDA issued new regulations designed to increase the availability to desperately ill patients of promising investigational new drug (IND) and biological products before general marketing begins. This rulemaking initiative, known as the treatment IND program, was endorsed by the President's Task Force on Regulatory Relief, chaired by Vice President George Bush. The final rule has received broad support from the medical and patient communities. The significance and utility of the treatment IND program has also been recognized and endorsed by the President's Commission on the Human Immunodeficiency Virus (HIV) Epidemic.

The treatment IND regulations became effective on June 22, 1987. Since that time, seven promising experimental therapies have been made available to patients stricken with AIDS, cancer, Parkinson's disease, and other serious conditions. In February 1988, the American Medical Association and FDA cosponsored a major national conference intended to educate physicians and health care organizations about the treatment IND program. FDA has also publicized specific treatment IND approval actions in both medical and lay journals (Refs. 1 through 8).

The treatment IND program is part of FDA's comprehensive efforts to facilitate the development and availability of significant new therapies. For example, through its implementation of the Orphan Drug Act, enacted in 1983, FDA has given special emphasis to potential new therapies for rare diseases or conditions. Since 1983, FDA has granted orphan drug designation to over 200 products, many of which are for life-threatening illnesses. (Orphan drug designation provides the commercial sponsor with certain economic incentives to encourage drug development, including tax credits for the cost of clinical development and exclusive marketing rights for the designated indication upon marketing approval.) FDA has approved for marketing 27 such orphan products, including therapies to treat such life-threatening illnesses as leukemia and AIDS.

FDA has also instituted a number of management improvements designed to expedite the evaluation of AIDS-related products in particular. These include establishment of a top "1-AA" priority for the review of all AIDS products, and the creation of two new divisions—one for drugs and one for biologicals—to give special focus to the review of such products. FDA's actions have led to the approval in record time of the first drug, zidovudine (formerly called AZT), to treat the AIDS virus, as well as approval for human testing of the first potential AIDS vaccines.

Building on these achievements, on August 3, 1988, Vice President Bush, in his capacity as chairman of the Presidential Task Force on Regulatory Relief, requested FDA to develop procedures for expediting the marketing of new therapies intended to treat AIDS and other life-threatening illnesses. This charge recognized the urgency felt by desperately ill patients and their families. The charge was directed to FDA as the Federal agency that regulates the transfer of the fruits of biomedical research to the marketplace.

The procedures contained in this notice respond to the Vice President's charge. In developing these procedures, FDA met informally with representatives of AIDS interest groups as well as with representatives of consumer, health professional, academic, orphan drug, and industry organizations. FDA also met informally with leadership of the National Institutes of Health.

As described further below, FDA is issuing these new procedures as an interim rule, effective immediately, with an opportunity for public comment. Highlights of the interim rule are summarized below, followed by a section-by-section description of the new procedures.

I. Highlights of the Regulations

New procedures are being codified as part of FDA's IND regulations, by adding a new Subpart E consisting of §§ 312.80 through 312.88, and by adding a conforming amendment to FDA's new drug application (NDA) regulations, new paragraph (c) of § 314.25. The purpose of these new procedures (§ 312.80) is to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapies exist. The procedures themselves focus on the entire drug development and evaluation process—from early preclinical and clinical testing, through FDA evaluation of controlled clinical trials and marketing applications, to postmarketing surveillance—in order to treat the entire process as a coherent whole and thereby significantly increase its overall efficiency.

The scope of the new procedures (§ 312.81) will apply to new drugs, antibiotics, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating illnesses. Within the context of these procedures, the term "life-threatening" is defined to include diseases where the likelihood of death is high unless the course of the disease is interrupted (e.g., AIDS and cancer), as well as diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival (e.g., increased survival in persons who have had a stroke or heart attack). The term "severely-debilitating" refers to diseases or conditions that cause major irreversible morbidity (e.g., blindness or neurological degeneration).

A key component of the procedures is early consultation between FDA and drug sponsors (§ 312.82) to seek agreement on the design of necessary preclinical and clinical studies needed to gain marketing approval. Such consultation is intended to improve the efficiency of the process by preventing false starts and wasted effort that could otherwise result from studies that are flawed in design. Most important, at the end of early (phase 1) clinical testing, FDA and the sponsor will seek to reach agreement on the proper design of phase 2 controlled clinical trials, with the goal that such research will be adequate to provide sufficient data on the product's safety and effectiveness to support a decision on its approvability for marketing. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members.

If the preliminary analysis of test results appears promising, FDA may ask the sponsor (§ 312.83) to submit a treatment protocol to be reviewed under the treatment IND regulations. Such a treatment protocol, if submitted and granted, would serve as a bridge between the completion of early stages of clinical trials and final marketing approval.

Once phase 2 testing and analysis is completed by the sponsor and a marketing application is submitted, FDA will evaluate the data utilizing a medical risk-benefit analysis (§ 312.84). As part of this evaluation, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy. In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under this rule, FDA will usually seek the advice of outside expert scientific consultants or advisory committees.

As a conforming amendment, a new paragraph (c) is being added to § 314.125 of FDA's NDA regulations. This paragraph is designed to make clear that FDA's evaluation of marketing applications for drugs to treat life-threatening and severely-debilitating diseases will incorporate the criteria being added to § 312.84. These criteria include the adoption of a medical risk-benefit analysis when assessing the safety and effectiveness of these drugs.

Finally, when approval or licensing of a product is being granted, FDA may seek agreement from the sponsor (§ 312.85) to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, and use of the drug over a longer period of time.

These procedures are modeled after the highly successful development, evaluation, and approval of zidovudine, the first drug approved to treat the AIDS virus. Close consultation between FDA, the sponsor, and the National Institutes of Health resulted in efficient preclinical animal testing (2 to 4 weeks in duration), focused phase 1 clinical testing, and a well-designed and conducted multi-center phase 2 clinical trial that provided dramatic evidence of increased survival in patients with advanced cases of AIDS. Given such evidence, FDA approved a treatment protocol in 5 days, and marketing approval in 107 days. Concurrent with approval, the sponsor agreed to conduct phase 4 research studying the effects of zidovudine in patients at an earlier stage of the disease. In total, the drug development and evaluation process, which takes an average of 8 years from initial human testing under an IND to final marketing approval, took only 2 years for zidovudine. Although the total development time will vary with different drugs, FDA believes that the approach contained in these new procedures has great potential for increasing significantly the efficiency of the drug development and evaluation process for the drugs affected.

Moreover, to the extent that the Commissioner determines that clinical trials to treat life-threatening or severely-debilitating diseases are already underway and are consistent with the requirements of these rules, upon his own initiative and in cooperation with the drug sponsor, he may recommend that a marketing application be submitted under the new procedures.

In conjunction with these procedures, FDA may, in certain circumstances, undertake focused regulatory research (§ 312.86) addressing critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. The FDA Commissioner and other agency officials will also actively monitor (§ 312.87) the progress of the conduct and evaluation of clinical trials for products covered by these procedures, and will be involved in facilitating their appropriate progress.

The final provision of these procedures (§ 312.88) references applicable safeguards inherent in existing FDA regulations to ensure patient safety during clinical testing and the safety of products following marketing approval. These safeguards include FDA requirements regarding informed consent and institutional review boards. These safeguards further include the review of animal studies prior to initial human testing, and the monitoring of adverse drug experiences during the IND, marketing application, and postmarketing phases.

FDA believes that this program, taken as a whole, establishes a new and innovative approach to stimulating the development of particularly important drugs, while at the same time building on past practices that have proven to be successful.

II. Effective Date and Opportunity for Public Comment

For the reasons described below, FDA is issuing these procedures as an interim rule, with an opportunity for public comment. Because of the urgency associated with life-threatening illnesses, the agency intends to begin implementation of these procedures immediately, but will consider modifications to them based on issues raised during the comment period and experience gained under the interim rule.

The program established in this interim rule is intended to bring about a significant improvement in the efficiency of the development, evaluation, and marketing of new therapies for life-threatening and severely-debilitating illnesses, while preserving appropriate quarantees for safety and effectiveness. Although the program is important, it

builds upon managerial and regulatory options available under existing practices and procedures. The opportunity for early consultation with sponsors on the design of clinical trials, for example, is permissible under the existing investigational new drug review provisions of FDA's regulations. Because the new program represents a fundamental commitment to expediting the development of innovative products, it is appropriate to identify and describe the components of that program and to codify them for ready reference by affected persons. Moreover, the amendment to Part 314, requiring consideration of risk-benefit criteria in decisions to approve or disapprove these drugs, is consistent with the flexibility granted to the Agency under the statute in determining whether substantial evidence of safety and effectiveness has been demonstrated.

To the extent that the elements of the program announced today are regarded as new rules, they are within the exception to the Administrative Procedure Act notice-and-comment requirement for general statements of policy and rules of agency organization, procedure, and practice (5 U.S.C. 553(b)(A)). Moreover, if the new program is regarded as substantive rulemaking, the Commissioner hereby finds good cause for not providing notice and an opportunity to comment prior to its effectiveness. The importance of developing new therapies for life-threatening diseases has been highlighted in recent years by the AIDS crisis. In addition, the sustained search by drug researchers for treatments for many other diseases, including Alzheimer's disease and cancer, merits immediate attention. FDA believes that, as promising new therapies for these diseases are identified, they must be developed by sponsors and evaluated by the agency as expeditiously as possible. It would therefore be contrary to the public interest to delay the implementation of this program pending the time necessary to engage in the APA's notice-and-comment procedures, and such delay would also be unnecessary because the program derives from existing regulations that have already been the subject of notice and an opportunity for comment (5 U.S.C. 553(b)(B); 21 CFR 10.40(e)).

FDA believes, however, that it should invite and consider public comment on its practices and procedures for reviewing investigational new drug, new drug approval, and biologics license applications, including those described in this notice.

III. Contents of the Program

A. Purpose

The drug development process is generally thought of, in simplified terms, as consisting of three phases of human testing to determine if a drug is safe and effective: Phase 1 with 10 to 50 patients to study how the drug is tolerated, metabolized, and excreted; phase 2 with 50 to 200 patients in which the safety and efficacy of the drug are first evaluated in controlled trials; and phase 3 with 200 to 1,000 or more patients to confirm and expand upon the safety and efficacy data obtained from the first two phases. (For purposes of this discussion, the word "drug" is meant to include new drugs, antibiotic drugs, and biological products.)

A recent study of new drug development has documented the percentage of drugs whose development is discontinued after each of these phases. Of the 174 new chemical entities that entered phase 1 testing under U.S. IND's between 1976 and 1978, 70 percent successfully completed phase 1 and moved on to phase 2, while 33 percent successfully completed phase 2 and moved on to phase 3. At this point the dropout rate slowed considerably, as 27 percent successfully completed phase 3 and were submitted to FDA in the form of a marketing application, and 20 percent actually received marketing approval from the agency (Ref. 9).

The three phases describe the usual process of drug development, but they are not statutory requirements. The basis for marketing approval is the adequacy of the data available; progression through the particular phases is simply the usual means the sponsor uses to collect the data needed for approval. The statute itself focuses on the standard of evidence needed for approval, as derived from adequate and well-controlled clinical investigations, with no mention of phases 1, 2, and 3. FDA believes that if sufficient attention is paid to the quality and amount of data obtained in phase 2, it should be possible to identify early those drugs that represent safe and effective treatments for life-threatening and severely-debilitating diseases—and to develop the evidence needed for their marketing—in the course of carrying out the first controlled trials.

This program is based on that premise. For drugs intended to treat life-threatening and severely debilitating illnesses, it should be possible to reduce the total premarket drug development time by designing and conducting phase 2 controlled trails that are capable of providing necessary data on the drug's safety and effectiveness. FDA would analyze data from such studies utilizing medical risk-benefit considerations appropriate for drugs intended to treat life-threatening or severely-debilitating illnesses. The treatment IND, as appropriate, could continue to serve as a bridge between phase 2 trials and the point of marketing approval. Drug sponsors might also conduct postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. The FDA Commissioner and other agency officials would actively monitor the process to ensure that such products are developed by the sponsor and analyzed by the agency as expeditiously as possible.

Section 312.80 of the rule summarizes the program's purpose: to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated in FDA's new drug application regulations (§ 314.105(c)), while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. In promulgating this interim rule, FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. The procedures contained in this rule reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures outlined in this notice should be interpreted consistent with this statement of purpose.

B. Scope

Section 312.81 of the rule outlines the scope of this rule. The rule applies to new drug, antibiotic, and biological products being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

A "life-threatening" disease is defined as one in which the likelihood of death is high unless the course of the disease is interrupted (e.g., progression from asymptomatic HIV infection to

symptomatic HIV infection, or further progression to a later stage of AIDS; metastatic cancer; amyotrophic lateral sclerosis). This use of the term "life-threatening" plainly includes any disease whose progression is likely to lead to death, especially in a short period of time (e.g., 6 months to 1 year). This section also applies to any condition in which a study is to be carried out to determine whether the treatment has a beneficial effect on survival (e.g., increased survival after a stroke or heart attack).

The term "severely-debilitating" is defined as a disease or condition that leads to major irreversible morbidity (e.g., severe functional deficits in multiple sclerosis, Alzheimer's disease or progressive ankylosing spondylitis; prevention of blindness due to cytomegalovirus infection in AIDS patients).

With respect to "severely-debilitating" illnesses, the procedures contained in this rule are applicable to those instances where the studies proposed will examine the treatment's capacity to prevent or reverse what would otherwise be irreversible damage, such as putting ankylosing spondylitis into remission and stopping joint damage and deformity, or preventing blindness. It is in such studies that excellence in study design and an early answer to key questions on safety and effectiveness are especially critical. The agency notes that there are many other studies that examine symptomatic relief (e.g., pain of ankylosing spondylitis) rather than irreversible morbidity. While products being studied for symptomatic relief of a severe disease would likely qualify for treatment IND consideration under § 312.34(b)(2), they would not be covered by the procedures contained in this interim rule.

In all of the cases covered by these new procedures, when the end points of clinical study relate to survival or prevention of major disability, they are of such great importance that it is imperative that the first controlled clinical trials be designed and conducted as well as possible. If this is not done, preliminary reports of success from poorly designed studies might make it difficult ever to carry out the proper trials. FDA believes it is clearly in the public interest to assure in such situations, to the extent possible, that the first clinical trials be designed so that the true merit of the drug or biologic can be evaluated as promptly as possible. FDA will also expedite the designation of eligible orphan products to provide additional incentive for their development.

The agency recognizes that the scope of these procedures is subject to interpretation, and the examples given above are illustrative only. FDA intends to be flexible in its implementation of this program and, subject to available resources, provide early advice when it is sought. The agency encourages sponsors to consult with FDA on the program's applicability to particular products.

C. Elements of the Program

1. Early consultation. A key component to be addressed is early consultation, which is covered in § 312.82 of the rule. In 1987, FDA codified the practice that, upon request of a drug's sponsor, FDA medical staff will hold a conference with the sponsor at the end of phase 2 testing. (See § 312.47(b)(1).) The goal of this conference is to reach agreement on a plan of phase 3 testing that will provide the needed remaining evidence of the drug's safety and efficacy to gain marketing approval. If, however, the evidence obtained from well-planned and well-executed phase 2 research is sufficient under the statute for marketing approval, there may be no need for additional phase 3 premarket testing, and the drug can become available much more rapidly than usual.

This is most likely to occur for drugs to treat life-threatening illnesses where the relatively small amount of data available at this stage may nevertheless be sufficient for approval. For example, phase 2 research was sufficient for approval of zidovudine the only drug approved thus far to treat the AIDS virus. Zidovudine was developed and approved in record time, largely because further premarketing (phase 3) studies were not needed to support safety and effectiveness following completion of a highly successful well-controlled multicenter phase 2 study that demonstrated dramatic effects on survival.

There have been other circumstances, particularly in the oncology area, where early (phase 2) results were such that additional studies were not needed to conclude that the drug was effective and that its benefits outweighed its risks. For example, the licensing of alpha interferons to treat hairy cell leukemia was based on phase 2 trials that showed partial or complete remission of the disease in 75 to 90 percent of patients.

To build upon these successes, FDA is instituting a process for conferences to be held at the end of phase 1 (rather than waiting until the end of phase 2) with the sponsors of drugs and biologics intended to treat life-threatening and severely-debilitating illnesses, especially where there are no satisfactory alternative therapies. The purpose of these conferences will be to review the product's phase 1 test results and phase 2 plans for clinical testing. If enough is known about the drug at that time, agreement would be reached on a phase 2 testing program (e.g., the design of the studies, the number of patients to be tested, the end points to be used, and the proposed mode of replication), that would be sufficient to establish the drug's safety and effectiveness. Where the data resulting from these phase 2 studies prove sufficient to allow a determination that, on the basis of risk-benefit considerations detailed further below, the drug is safe and effective, FDA will approve the drug without further preapproval studies. In this case, phase 2 thus obviates the need for further research in phase 3, if the phase 2 trials prove successful. Of course, when the results of phase 2 research do not provide evidence that fulfills the statutory criteria for approval, further preapproval studies will be necessary.

Because the end-of-phase 1 conference server the same function (except earlier in the process) as an end-of-phase 2 conference would otherwise serve, FDA will apply the same procedures to both meetings, as codified in § 312.47(b)(1). This includes provision for documenting the agreements reached at the meeting. In order to provide the broadest possible expertise available, FDA may invite to the meeting one or more of its advisory committee members or other scientific consultants. The sponsor may, of course, also bring scientific consultants to the meeting.

With respect to study design, the agency recognizes that there has been some confusion about the role of placebo-controlled studies in patients with a life-threatening disease. FDA believes that a requirement for placebo-controlled studies is *not* appropriate in those situations where there is known to be an effective therapy, for the stage of disease or condition under investigation, that can improve survival or prevent irreversible morbidity. For example, in the case of symptomatic AIDS or advanced AIDS-related complex (ARC), where zidovudine is known to improve survival, it would not be appropriate to compare a new drug with placebo. Rather, the new drug should be compared with zidovudine. It would also be possible to compare the new drug plus zidovudine with zidovudine alone, but in neither case would it be necessary to deny patients therapy with zidovudine which is known to improve survival. In contrast, where no therapy has been shown to be effective, it is scientifically and ethically appropriate

to randomize patients to test drug and placebo. This was done with zidovudine and, by providing early and clear evidence of benefit in terms of improved survival, enabled FDA to confer the rapid approval that made the drug widely available to AIDS patients.

The Institute of Medicine, in its recent report entitled, "Confronting AIDS: Update 1988," emphasized the importance of controlled clinical trials as the "fastest, most efficient way to determine what treatments work" (Executive Summary at page 19; Report at page 139) (Ref. 10). As the report continues, "Conducting well-designed trials from the beginning will benefit more patients, sooner, than any other approach. Poorly designed trials, or administering drugs without controls and 'observing' the course of the disease, risk being inconclusive or drawing incorrect conclusions." (Report at page 139) (Ref. 10). FDA fully supports the early initiation of well-designed phase 2 controlled clinical trials as the most efficient mechanism of evaluating treatments for the desperately ill.

When planning phase 2 studies, it will be particularly important to make optimal use of pharmacokinetic/pharmacodynamic studies carried out in phase 1. Such phase 1 data are particularly useful in selecting the best dose(s) and dosing intervals for phase 2 testing. Therefore, FDA input should be helpful in the design of phase 1 studies also.

FDA can also make the drug development process more efficient by interacting with the drug sponsor, even before phase 1 testing begins, to help identify the animal studies necessary to assess the toxicity of the new drug and assure that clinical studies can be initiated with reasonable assurance of safety. In consulting with sponsors on animal studies, FDA takes into account the seriousness of the disease to be treated and the nature of the clinical studies planned. In this way, FDA involvement can facilitate the initiation of trials in human patients as early as the safety studies in animals permit, thereby reducing potential barriers to innovation at this early but important stage of new pharmaceutical development.

For example, using this process, some new AIDS drugs have been able to enter clinical testing after animal studies that were 4 weeks long or less in duration, and the preclinical animal studies completed before initial human use of zidovudine were 2 to 4 weeks long. By working closely with the sponsor, FDA can suggest the minimum amount of preclinical testing needed to go forward without compromising the safety of clinical study paricipants. Unnecessary animal studies can be avoided, animal lives can be spared, and the sponsor can move the drug into clinical testing in the shortest possible time. Moreover, early FDA involvement can also shorten the time it takes the agency to review and IND submission and lessen the likelihood of FDA placing the application on clinical hold.

2. Treatment IND's. Section 312.83 of the rule outlines the role of the treatment IND in the context of this overall program. As codified in §§ 312.34 and 312.35, treatment IND's are intended to permit the wider use of promising experimental drugs for serious and immediately life-threatening illnesses in patients who lack satisfactory alternative therapy. Within the drug development process, treatment IND's can provide a bridge between the completion and initial analysis of promising phase 2 studies and the point of marketing approval. Thus, when early evidence from phase 2 indicates that a drug for a life-threatening or severely-debilitating illness is promising, FDA will actively work with the sponsor to evaluate the appropriateness of a treatment protocol. This approach was used during the development of zidovudine, and allowed wide availability of the drug to over 4,000 patients while the marketing application was being assembled by the sponsor and reviewed by FDA. In addition, FDA will continue to work actively to educate physicians and drug sponsors on how to utilize the treatment IND process most effectively.

3. Risk-benefit analysis. Section 312.84(a) of the rule provides that FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

While the statute uses the terms safety and effectiveness, rather than risks and benefits, the decision on whether to approve a drug inherently represents a medical risk-benefit judgment. The agency recognizes that safety and effectiveness are not absolute (i.e., not all drugs are free of risk or have unequivocal benefits), but must be assessed in light of what condition the drug treats. This is particularly true in the case of drugs to treat life-threatening diseases, where drugs that are quite toxic may nevertheless be considered safe under the circumstances.

In carrying out the statutory mandate, FDA will consider the seriousness of the disease being treated in balancing risks and benefits. For example, as a class, oncologic drugs are highly toxic, but this is acceptable when they are used to treat illnesses for which they represent the only available method of treatment and when they can have a favorable influence on survival or on intractable symptoms. Moreover, dramatic responses (i.e., great benefit), especially on significant end points like survival or progression to an inevitably fatal stage of illness, make it easier to conclude that the benefits of treatment outweigh its risks, even if not all important questions about the drug are answered. Clearly, for a life-threatening illness, a relatively high level of known risk and some uncertainty about potential risk from the drug can be acceptable in exchange for the improved survival provided by effective drug treatment for a condition that, left untreated, would result in death. Similarly, for the same life-threatening illnesses, evidence of effectiveness must be weighed against risks of the drug and the knowledge that death would result in the absence of treatment.

Section 312.84(b) of the rule provides that the agency will usually seek the advice of outside expert consultants or advisory committees in reaching its conclusions. That section also provides that FDA will notify the members of the relevant standing advisory committee of the filing of a marketing application covered by this rule, and its availability for review.

In seeking to utilize phase 2 data for final decisionmaking, FDA would be trying to increase the likelihood that a safe and effective drug, especially one that affects mortality or major irreversible morbidity, would be shown safe and effective in the shortest possible time by assuring that the initial studies are adequate to do this—i.e., to provide evidence, even though derived from a limited data base, that would be sufficient to reach a benefit-risk judgment. FDA's goal is to be able to reach a scientifically defensible decision based on the results of well-designed phase 2 controlled clinical trials. If, on the basis of phase 2 testing, a therapy is found to effectively treat a life-threatening disease for which no other therapy exists, it would not be appropriate to continue premarketing research into phase 3. However, poorly

designed phase 2 studies serve to retard the drug development process.

If FDA concludes that the data presented are not sufficient for marketing approval, § 312.84(b) of the rule provides that FDA will issue a letter to the sponsor describing the deficiencies in that application, including why the results of the research design agreed to under § 312.82 of this rule, or in subsequent meetings, did not provide sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

To increase the likelihood that phase 2 testing can provide sufficient results, sponsors could need to plan phase 2 studies that are somewhat larger and more extensive than is currently the norm, including a mode for replication of key findings. Moreover, to avoid missing an effect by using too little drug, or to avoid studying a dose that proves toxic, it may be necessary to study several doses in the first formal trials, an approach that may require a larger study but can plainly save time, thereby enabling physicians to treat patients with life-threatening illnesses more rapidly. However, it should be appreciated that is a drug has only minor or inconsistent therapeutic benefits, its positive effects may be missed in this stage of clinical testing, even if the drug ultimately proves to be beneficial following more extensive phase 3 trials.

The issue of replication requires careful consideration. The requirement in the statute for adequate and well-controlled "clinical investigations" (21 U.S.C. 355(d) (emphasis added)) has long been interpreted to mean that the effectiveness of a drug should be supported by more than one well-controlled clinical trial and carried out by independent investigators. This interpretation is also consistent with the general scientific demand for replicability to ensure reliability of study results. Therefore, as a general requirement, the clinical trials submitted in a marketing application—including trials on products covered by this rule—must include studies by more than one independent investigator, each of whom has studied a number of patients adequate to generate statistically reliable results.

When applying the statutory requirement of "adequate and well-controlled investigations" to a drug for a life-threatening or severely-debilitating disease, FDA will consider the quality of the data submitted, including the assurance of the data's consistency, reliability, and reproducibility. There have been a few unusual instances in which a particularly persuasive multi-center study has been accepted in support of a claim of increased survival because the study was, due to its design and dramatic and reliable results, considered highly persuasive; therefore, replication was not required for ethical reasons. One such example was the approval of zidovudine to treat AIDS patients (discussed earlier in this preamble). A second example involved the approval of timolol for reduction of post-infarction mortality, where a major effect on mortality was demonstrated in a large multi-center study. The timolol study was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance associated with the critical finding.

In both these instances, the sufficiency of a multi-center study for marketing approval was based on the research being well-designed and well-conducted, and a dramatic increase in survival of the patients using the drug. Under these circumstances, FDA believed it would be unethical to repeat the trial. FDA would consider applying the same principle to other such cases in which the outcome of a multi-center study demonstrated a consistently dramatic increase in survival among independently evaluable study sites and where repetition of the study would be unethical. However, the agency cautions that persuasively dramatic results are rare and that two entirely independent studies will generally be required. Sponsors should therefore plan in advance a strategy for replication of key findings through a second well-controlled study. Such replication need not delay approval where a sponsor carries out all necessary clinical studies concurrently.

Finally, § 312.84(d) of the rule provides that marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in 21 CFR Part 314 or Part 600, as well as those in this interim rule. FDA has also added a conforming amendment to § 314.125 of the new drug application regulations, noting that for drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88, the criteria contained in paragraphs (b)(3), (4), and (5) of § 314.125 shall be applied according to the considerations contained in § 312.84.

While FDA can contribute to the design of the controlled clinical trials, and actively urge that such trials be pursued, the agency has no direct control over the pace at which trials are initiated and completed. Success of drug development depends on the willingness of the sponsor and clinical investigators to devote the necessary time and resources to complete the studies expeditiously.

4. Phase 4 studies. Section 312.85 of the rule describes the role of phase 4 studies in this program. If FDA approval is gained on the basis of limited, but sufficient, clinical trials, it will usually be important to conduct postmarketing (phase 4) clinical studies that will extend the knowledge about the drug's safety and efficacy and allow physicians to optimize its use. For example, in the case of zidovudine, early appearance of a dramatic improvement in survival of the treated patients was taken as clear evidence that, for the relatively advanced HIV-infected patients treated, the benefits clearly outweighed the risks. Although significant side effects of zidovudine were found, the clinically demonstrated benefit of prolonged survival clearly outweighed those risks.

This does not mean that all important questions were answered at the time of approval of zidovudine and that research into its use could end. It was critical to examine—after marketing—its use in earlier stages of the disease, where its toxicity might outweigh its benefit (i.e., in earlier stages of the disease, survival is much greater without treatment so that there is less improvement possible, but toxicity might be just as severe). It was also important to explore dosing regimens that might be less toxic and equally effective. In addition, as with any drug, it is important to consider whether there are long-term adverse effects that might "take away" the early gain. As with zidovudine, FDA has generally been able to obtain a voluntary agreement with drug sponsors about the need to do such followup studies and the nature of their design, because sponsors also recognize important gaps in the data base and believe they need to be filled. Section 312.85 of the rule codifies this practice.

5. Focused FDA regulatory research. The responsibility for conducting the preclinical and clinical testing needed to gain marketing approval clearly rests with the drug's sponsor. This rule does not alter that responsibility. Recognizing the lack of available therapy for certain life-threatening and severely-debilitating illnesses, § 312.86 of the rule provides that in certain circumstances FDA may, in its discretion, undertake research on critical rate-limiting aspects of the preclinical, chemical/manufacturing,

and clinical phases of drug development and evaluation. For example, FDA often needs specific information upon which critical regulatory decisions are made—e.g., manufacturing standards and assays for vaccine or biotechnology products. Recent examples include FDA potency testing of vaccines and development of assay methods for drug bioavailability. FDA is prepared to intensify this practice on a limited basis as a means of meeting a public health need in facilitating the development of therapies to treat life-threatening illnesses, rather than merely waiting passively.

6. Active monitoring of conduct and evaluation of clinical trials. Section 312.87 of the rule provides that the Commissioner and other agency officials will actively monitor the progress of the conduct and evaluation of clinical trials and be involved in stimulating their appropriate progress. Recognizing that people with life-threatening diseases face a catastrophic condition that requires special attention, it is imperative that the conduct of clinical trials and FDA's evaluation of them proceed as expeditiously as possible. FDA actions would include, for example, contacting the sponsor directly when clinical trials are not proceeding on schedule. FDA may also convene special meetings of its advisory committees, as necessary, rather than waiting for the next scheduled periodic meeting.

Finally, FDA, in conjunction with other Public Health Service agencies, will utilize, to the extent possible, clearinghouse mechanisms for informing physicians and patients of investigational therapies for life-threatening illnesses. Existing mechanisms of this type will be augmented, as appropriate.

7. Safeguards for patient safety. If successfully implemented, this program will expedite the availability and approval of new therapies for life-threatening and severely-debilitating illnesses while assuring that the products are shown safe and effective under the law. Section 312.88 of the rule references safeguards inherent in FDA regulations that ensure the safety of clinical testing and the safety of products following marketing approval. These include the requirements for informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23); IND safety reports during the conduct of clinical trials and treatment IND protocols (§ 312.32); safety update reports during the review of marketing applications (§ 314.50); and adverse drug reaction reports after products are approved for marketing (§ 314.80).

In addition to these regulatory safeguards designed to assure patient safety, FDA's practices and procedures provide additional safeguards to assure the quality and integrity of the drug development and review process. These include conducting on-site audits of key studies and/or clinical investigators to assure authenticity of the data submitted to FDA, and inspections of manufacturing facilities before marketing approval is granted to assure that manufacturers are able to produce properly formulated compounds.

D. 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.

E. Economic Impact

FDA has considered the economic impacts of this interim rule and concludes that additional costs resulting from this rule will be negligible, and to the limited extent that they may occur, they will likely be more than off-set by the societal benefits of this rule.

The compression of the drug development process set forth in this rule for life-threatening and severely-debilitating illnesses presents a trade-off for affected sponsors. They would be relieved of conducting the customary phase 2/phase 3 clinical studies if they participate in early study design consultation with FDA, conduct a sufficiently comprehensive phase 2 study, and stand ready to conduct any necessary phase 4 studies. Considering the probable time savings of this process, it is expected that the net cost of clinical development and regulatory review for a sponsor will remain constant or possibly decrease. Even if costs were to increase slightly, the societal benefits would more than likely compensate for any added costs since a considerable patient population would be receiving the life-saving benefits of the expedited therapy over an extended period of time that would not otherwise be realized.

Accordingly, FDA concludes that this interim rule is not a major rule as defined by Executive Order 12291, which would require a regulatory flexibility analysis. Furthermore, this rule is not expected to impose substantial impacts on a significant number of small entities which would require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

F. Paperwork Reduction Act of 1980

This interim rule does not contain new collection of information requirements. Section 312.88 does refer to regulations that contain 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. Sections 312.23 and 312.32 were approved under OMB control number 0910-0014. Section 314.50 was approved under OMB control number 0910-0001. Section 314.80 was approved under OMB control number 0910-0230.

References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Young, Frank E., and Stuart L. Nightingale, "FDA's Newly Designated Treatment IND's," "Information on Treatment IND's as They Become Available to the Practitioner," *Journal of the American Medical Association*, 260:224–225, 247, 1988.

2. Young, Frank E., John A. Norris, Joseph A. Levitt, and Stuart L. Nightingale, "The FDA's New Procedures for the Use of Investigational Drugs in Treatment," *Journal of the American Medical Association*, 259:2267–2270, 1988.

3. "Drugs Hold Hope for Parkinson's Obsessive-Compulsive Patients," *FDA Consumer*, September 1988:31.

4. Young, Frank E., "Experimental Drugs for the Desperately Ill: A Progress Report," *FDA Consumer*, May 1988:2–3.

5. "Updates," *FDA Consumer*, February 1988:2–3.

6. Young, Frank E., "New Drug Development in the United States," *FDA Consumer*, November 1987:4–5.

7. "Updates," *FDA Consumer*, September 1987:5–6.

8. Young, Frank E., "Experimental Drugs for the Desperately Ill," *FDA Consumer*, June 1987:2–3.

9. Office of Planning and Evaluation Study 77, "The Outcome of Research on New Molecular Entities Commencing Clinical Research in the Years 1976–78," FDA, May 1988.

10. "Confronting AIDS: Update 1988," Institute of Medicine, 1988.

List of Subjects

21 CFR Part 312

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

21 CFR Part 314

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, Parts 312 and 314 are amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. Subparts E and F are redesignated as Subparts F and G, respectively, and new Subpart E is added consisting of §§ 312.80 through 312.88 to read as follows:

Subpart E—Drugs Intended To Treat Life-threatening and Severely-debilitating Illnesses

Sec.

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

Subpart E—Drugs Intended To Treat Life Threatening and Severely-debilitating Illnesses

§ 312.80 Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated § 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

§ 312.81 Scope.

This section applies to new drug, antibiotic, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and

(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

§ 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing. The procedures outlined in § 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

§ 312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§ 312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in § 312.42(b)(3)(ii)).

§ 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under § 312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under § 314.101 or Part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue (for a drug) a not approvable letter pursuant to § 314.120 of this chapter, or (for a biologic) a deficiencies letter consistent with the biological product licensing procedures. Such letter, in describing the

deficiencies in the application, will address why the results of the research design agreed to under § 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in Part 314 or Part 600 of this chapter, as well as those in this subpart.

§ 312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

§ 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

§ 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

§ 312.88 Safeguards for patient safety.

All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (Part 50 of this chapter) and institutional review boards (Part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

2. The authority citation for 21 CFR Part 314 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); 21 CFR 5.10, 5.11.

3. Section 314.125 is amended by adding paragraph (c) to read as follows:

§ 314.125 Refusal to approve an application.

* * * * *

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in § 312.84 of this chapter.

Otis R. Bowen,

Secretary of Health and Human Services.

Dated: October 18, 1988.

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