referred to as the Petitioners).[4] The Petitioners assert that a complainant's right to some form of prompt or immediate Commission remedy is essential in a complaint procedure responsive to the needs of the restructured gas and electric power industries. The Petitioners submit that some form of Commission remedial action as soon as possible after the filing of a formal complaint must be available. The Petitioners contend that to suggest that such remedies might be within the Commission's authority to grant while removing from the Commission's new and comprehensive complaint regulations any reference to such remedies, creates ambiguity about whether the Commission truly intends to make early remedial action a component of its revised complaint procedure. The Petitioners argue that where, as here, the Commission is adopting a comprehensive new complaint procedure, it should include therein some codification of each element of its new complaint policy.

The Commission finds it unnecessary to modify the regulations as requested because they already encompass the kind of relief sought. In the Commission's view, there is a difference between preliminary and interim relief on the one hand, and what the Petitioners refer to as ''immediate'' or ''early'' Commission action on complaints on the other hand. References to preliminary and interim relief, as well as the use of the *Virginia Jobbers* standards, led many parties to believe that the Commission would be granting relief akin to temporary restraining orders or preliminary injunctions, and that such relief would be based on standards other than those contained in the applicable statutes. Order No. 602–A eliminated such references to make clear that the Commission would not and could not exercise any authority beyond its statutory authority.

The elimination of the references to preliminary and interim relief does not mean that the Commission lacks the authority to address complaints quickly. The Petitioners have recognized that the Commission may issue an interim order, which resolves some issues while leaving others to be determined at a later time, that is based on findings made pursuant to the standards contained in NGA section 5 or FPA section 206. Moreover, as recognized in Order No. 602–A, the Commission could also take such interim actions as granting a stay, granting an extension of time, issuing stop work orders or others orders contemplated by certificate or hydroelectric license conditions, or issuing show cause orders. Other actions, such as issuing show cause or declaratory orders, while not final action, also convey a message to the parties that in the Commission's view a complainant has presented a solid case for the relief sought that will be granted in the absence of convincing evidence to the contrary.

The Commission recognizes that timely redress of a complaint is essential in today's constantly evolving energy markets. In Order No. 602, the Commission introduced the Fast Track procedures precisely for this reason. Because the Commission realizes that time is of the essence in many complaint proceedings, it committed to issuing merits order on Fast Track complaints within 20 days after the answer is filed.[5] The Commission also stated that if the development of a factual record was necessary to the resolution of a complaint, hearing procedures could be compressed into a few days.

The Petitioners request for rehearing essentially deals with the timing of Commission action, hence their use of the words ''prompt,'' ''immediate'' and ''early.'' In the Commission's view, the Petitioners'' concerns can be adequately addressed under the regulations adopted because any complaint in which time is of the essence can be filed under the Fast Track procedure in § 385.206(h). A party filing such a complaint can show that the standard complaint resolution process may not provide timely relief as quickly as circumstances may demand and that expedited resolution under the Fast Track is thus appropriate. In resolving the merits of a complaint, whether under the Fast Track or standard procedures, the Commission must apply the standards contained in the statutes it administers. The Commission thus can reach a final resolution under its governing statutes through standard procedures or using expedited processing.

The modifications contained in Order No. 602–A were not meant to suggest that complaints could only be resolved through a lengthy administrative hearing. As § 385.206(h)(1) states, ''Fast Track procedures may include expedited action on the pleadings by the Commission, expedited hearing before an ALJ, or expedited action on requests for stay, extension of time, or other relief by the Commission or an ALJ.'' The revised complaint regulations do not prevent a potential complainant from requesting ''immediate'' action on the merits of its claims, but rather, are specifically designed to address particular situations that demand the immediate resolution requested by the Petitioners. The Petitioners' concerns thus already have been taken into account and incorporated into the regulations to provide for the prompt and immediate resolution they seek.

List of Subjects in 18 CFR Part 385

Administrative practice and procedure, Electric power, Penalties, Pipelines, Reporting and recordkeeping requirements.

In consideration of the foregoing, the Commission denies rehearing.

By the Commission.

David P. Boergers,

Secretary.

[FR Doc. 99–25797 Filed 10–4–99; 8:45 am]

BILLING CODE 6717–01–P

[4] The Undersigned Parties consist of the Pipeline Customer Coalition, American Public Power Association, Transmission Access Policy Study Group, National Rural Electric Cooperative Association, Pennsylvania Office of Consumer Advocate, and Transmission Dependent Utility Systems.

[5] See, for example, North American Energy Conservation, Inc. v. CNG Transmission Corporation, 88 FERC ¶ 61255 (1999), where the answer to the complaint was filed on September 3, 1999, and the order on the merits of the complaint was issued September 17, 1999.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

RIN 0910–AA89

[Docket No. 98N–0237]

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its new drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This proposal would apply when the traditional efficacy studies in humans are not feasible and cannot be ethically

conducted under FDA's regulations for adequate and well-controlled studies in humans. The agency is proposing this action because it recognizes the need for adequate medical responses to protect or treat individuals exposed to these lethal or permanently disabling toxic substances.

DATES: Submit written comments by December 20, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St., NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Bonnie M. Lee, Division of Compliance Policy, Office of Enforcement, Office of Regulatory Affairs (HFC–230), Food and Drug Administration, Rockville, MD 20852, 301–827–0415.

SUPPLEMENTARY INFORMATION:

I. Introduction

FDA is proposing to amend its new drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because they would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers without a proven treatment and field trials (assessment of use of the product after accidental or hostile exposure to the substance) are not feasible. The agency is proposing that, in these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions could be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (21 CFR 314.126). Under the proposed rule, FDA could rely on the evidence from animal studies where: (1) There is a reasonably well understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product; (2) the effect is independently substantiated in multiple animal species, including species expected to react with a response predictive for humans; (3) the animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and (4) the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans, and it is therefore reasonable to expect the effect of the product in animals to be a reliable indicator of its efficacy in humans. It is also expected that the data or information on the kinetics and pharmacodynamics of the drug or biological product will be sufficiently well understood in both animals and humans or there will be some other relevant data or information in animals and humans to allow selection of an effective dose in humans.

Safety evaluation is not discussed in this proposal because the agency believes that, with one limitation, the safety of these products can be studied in human volunteers similar to the people who would be exposed to the product. The limitation is the inability to examine possible adverse interactions between the toxic substance and the new product. Safety and efficacy of a product are ordinarily studied together in the patient population at risk or with the condition to be treated. An interaction of the pharmacologic effects of the two should emerge in the animal studies of efficacy but certain kinds of effects are not easily detected in animals (e.g., effects on memory or cognitive function). Possible interactions between the product and underlying disease or another substance to which the user might be concomitantly exposed can be evaluated by studying safety in a population similar to the ultimate user population and under conditions approximating those in which the drug will be used. In section VII of this document, the agency seeks comments on the safety evaluation of these products.

This proposal will not apply if product approval can be based on standards described elsewhere in FDA's regulations (e.g., accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity).

II. Background

In the **Federal Register** of July 31, 1997 (62 FR 40996), FDA published a document entitled ''Request for Comments'' (hereinafter referred to as the July 1997 request for comments) related to the use of drugs and biological products in military and other emergency settings to treat or prevent toxicity of chemical or biological substances. The July 1997 request for comments included specific questions in the three following subject areas.

First, the agency asked whether its rule permitting waiver of informed consent in very limited circumstances involving military exigencies should be revoked or amended, and if so, how. In the **Federal Register** of December 21, 1990 (55 FR 52814), FDA issued an interim rule (''Informed Consent for Human Drugs and Biologics; Determination that Informed Consent is Not Feasible'') allowing the Commissioner of Food and Drugs (the Commissioner) to make the determination, in response to product specific requests from the Department of Defense (DOD), that obtaining informed consent from military personnel for the use of an investigational drug or biological product is not feasible in certain battlefield or combat-related situations.

Second, because information on a product's efficacy in reducing or preventing toxicity of chemical or biological substances is important, the agency also asked when, if ever, it is ethical to expose volunteers to toxic chemical and biological substances to test the efficacy of products that may be used to provide potential protection against those substances.

Third, because these products are critically important, even if they cannot be ethically tested in humans to demonstrate efficacy, the agency asked what evidence of efficacy, other than that from human trials, would be appropriate to demonstrate the safety and efficacy of products that may provide protection against toxic chemical and biological substances (62 FR 40996).

Elsewhere in this **Federal Register**, consistent with the Defense Authorization Act of 1998, FDA has published an interim final rule revoking the 1990 interim final rule and establishing new criteria and standards for the President of the United States to apply in making a determination that informed consent is not feasible or is contrary to the best interests of the individual recipients. That document addresses the first issue. This notice addresses the second and third issues.

A. When Is It Ethical to Expose Volunteers to Toxic Chemical and Biological Substances to Test the Efficacy of Products That May Be Used to Provide Potential Protection Against Those Substances?

In response to the July 1997 request for comments, FDA received nine comments on this question.

Two comments stated that it is never ethical to expose volunteers to toxic chemicals or biological substances to test the efficacy of products that may be used to provide potential protection against those substances.

Another comment, which appeared to conclude that human trials could perhaps be carried out in some cases, stressed that a ''volunteer'', by definition, must be fully aware of any harm that he or she may incur as a result of participation in such a study. All information regarding exposures must be relayed to the volunteer, and the volunteer should confirm that he or she accepts those risks. If data from animal testing are supplied, the volunteer must also be fully aware that the data may not be relevant to how a human may respond. This comment concluded that ''[a]nimal testing, an abhorrent practice, often puts human health in peril via misleading data.'' The comment also suggested that the developers of these drugs, if they are confident that they are both safe and effective, should offer themselves for final testing of safety and efficacy. This comment also stated that it seemed more ethical to attempt antidote experiments on ''victims of such poisonings in regions where such abhorrent 'weapons' are used to create morbidities'' rather than deliberately exposing any healthy individuals to such poisons for the purpose of testing antidotes, and concluded the comment with the suggestion that in vitro or computer-model testing would be preferable to human antidote testing unless one could ensure fully informed consent from a nonvulnerable population.

A fourth comment stated that it is not ethical to conduct clinical testing with toxic chemical or biological substances unless there is certainty that their effects are fully reversible. Because it is not scientifically possible to prove that substances are completely safe and their effects fully reversible, such studies are not possible.

Two comments did not appear to think such testing was impossible, but they pointed to significant difficulties. The comments noted that testing the efficacy of any product is never ethical unless the subjects truly volunteer with full informed consent. The comments suggested that one way to ensure voluntariness and informed consent would be to require that DOD and the Veterans Administration (VA) recruit only non-DOD and non-VA volunteers who are not otherwise ''beholden'' to these agencies for their employment or pensions. The comments note that given the risks, it would be highly unlikely that anyone would volunteer, and, therefore, efficacy testing may not be possible.

An additional comment, also apparently reflecting the view that studies might be possible, stated that volunteers should receive experimental products only after being counseled by medical, legal, and religious personnel, and only after being offered a nongovernment ''second opinion.'' The comment stated that all issues of facts should be written, witnessed, and notarized, and each volunteer's family must have access to what, when, and where the individual was exposed to the experimental product.

DOD strongly opposed testing of such products in humans and also stated that testing of sublethal doses of the toxic substances would be uninformative. DOD stated:

> The products under development are to be used to protect service members against lethal exposure to chemical and biological warfare agents. It is never ethical to expose volunteers to such lethal amounts of these agents in order to test the potential effectiveness of pretreatment, treatment or prophylactic products.
>
> Dose or concentration ranging studies are normally required for new or new-indication studies of drugs or biologics. Because response to treatment of sublethal doses of chemical or biological agents (weapons) could not be extrapolated to predict response to higher doses, a lethal dose would be necessary to test the effectiveness of the protective drug or biologic. If lethal doses were given to volunteers, a 100% effective rescue agent would need to be available, in case the protective agent failed and potentially fatal toxicity had to be reversed. Antidotes to probable threat agents do not currently exist.

A public interest group recommended that FDA address the complex issues raised by these questions in a separate proceeding and a separate public forum, noting that the ethical issues raised by these questions are not limited to the evaluation of products for use in the military context, but also arise with respect to products designed to protect individuals who may be exposed to toxic substances in the workplace or in other situations (e.g., exposure to pesticides or industrial toxins).

The agency has reviewed the comments and finds them in accord with its longstanding analysis. Therefore, FDA again concludes that it would be unethical to expose volunteers to potentially lethal or permanently disabling doses of toxic biological, chemical, radiological, or nuclear substances to test the efficacy of products that may be used to provide protection against those substances. Based on this conclusion and in recognition of the need to take all possible steps to protect individuals exposed to such agents, the agency has written this proposal. Section VII of this document discusses specific issues that deserve further consideration. The agency believes that the comments it has received thus far are sufficient for it to proceed with this proposal and that an additional public forum is not necessary before this proposal is issued for comment.

B. What Evidence Would Be Needed to Demonstrate Safety and Efficacy of Products That May Be Used to Provide Protection Against Toxic Chemical and Biological Substances That Cannot Be Ethically Tested in Humans?

FDA received nine comments in response to this question in the July 1997 request for comments. Most of the comments did not address the specific kinds of information that would be needed for approval.

One comment expressed support for the idea of approving such ''emergency'' drugs based on animal studies. Another comment stated that:

> * * * [e]ffectiveness studies in animals and human phase I studies (pharmacokinetic/antibody response) should have resulted in plausible evidence that a protective product will have a reasonable risk/benefit ratio in a combat situation or during an attack on civilians. The phase one studies should include the generation of data in children and take into account anticipated combination(s) with other products and immunization schedules.

A third comment recommended that FDA scientific advisory committees be used to advise, on a case-by-case basis, on data (e.g., nonclinical or surrogate markers of efficacy) required to demonstrate efficacy. Additionally, postmarketing clinical efficacy data could be obtained from, for example, incidents involving accidental exposures by at risk workers or operating forces, and this data could also contribute to the body of ''substantial evidence'' needed to demonstrate efficacy. This comment emphasized that, as with other FDA regulated products, data related to the safety and efficacy of medical products that DOD may want to give to its personnel should be considered on a case-by-case basis, taking into account

the intended indication and levels of medical supervision for product use.

Two comments stressed that while it may not be ethical to test efficacy of these products in humans, this does not preclude testing to demonstrate their safety. (The agency notes that this proposal does not address trials required to demonstrate safety; the safety of these products will be studied under existing rules in human volunteers.) These comments stressed the importance of establishing a product's safety in the specific population ''at issue'' and at the proposed dosage levels. Further, when synergistic exposures or stresses are likely, these should be incorporated into the safety testing as much as possible. For pyridostigmine bromide, in particular, these comments stressed that its safety should be studied under high heat conditions and in combination with insecticides and pesticides, including DEET, Permethrin, Malathion and/or Dursban.

The DOD's comment on this question addressed only the issue of relying on a human surrogate marker (already possible under current regulations at subpart H of part 314 (21 CFR part 314) and subpart E of part 601 (21 CFR part 601) (the Accelerated Approval regulations)) and did not consider the case where there is no human surrogate marker that is at least reasonably likely to predict clinical efficacy in humans. DOD added, however, that:

> In addition, other information should be obtained in order to better understand and perhaps predict the reactions of the drug or vaccine when given to a large group of DoD personnel. These might include metabolic and disposition pathways in both the animal model and in humans and population studies in humans to understand clinical covariates to predict response ranges in very large groups.

The Public Citizen Litigation Group without further elaboration rejected as illegal the idea that animal data or other nonhuman data could serve as a basis for approval of an antidote and stated that both the ethical standards for informed consent as well as the standards for establishing safety and efficacy should apply equally to products used in military and civilian populations.

III. Introduction to the Rule

FDA has determined that the requirement for human studies to demonstrate efficacy has the effect of preventing the development and availability of approved drug and biological products to reduce or prevent serious or life-threatening toxicity resulting from exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances.[1] In reaching this conclusion, FDA considered two possible kinds of human efficacy studies: (1) Clinical studies in which the toxic substance is given to volunteers and harm is prevented because the product proves to be fully efficacious, and (2) field studies in which toxicity following an accidental or hostile exposure is reduced or prevented by the product. In many cases involving these products, however, the first kind of study cannot ethically be performed; and, as to the second, there may be no opportunity to conduct them, or such field studies may not provide adequate information.

Although such products may be used, and potentially used widely, under the investigational provisions of the Federal Food, Drug, and Cosmetic Act (the act), which, among other things, require informed consent, this is a suboptimal solution for many reasons. In truly emergent circumstances, where the population needing treatment cannot be identified in advance and may be large, obtaining informed consent may be impossible. Allowing a waiver of the informed consent requirement as ''not feasible'' in circumstances where the product is to be given to competent individuals has proved to be extremely controversial. (See, elsewhere in this issue of the **Federal Register**, FDA's interim final regulations for waiver of informed consent in certain situations related to military combat.) Thus, the agency is presented with two choices for this class of products: (1) Make no adjustments to its current regulations, which would likely severely restrict the ability to use such products; or (2) identify an alternative basis for establishing efficacy for such products, and if safety and efficacy are established, grant marketing approval for the product with appropriate restrictions and requirements, including patient-directed labeling describing the basis of the product approval to help assure the safest possible use. FDA believes that approval should not be withheld for a product that is intended to, and is being widely used to, reduce or prevent the lethal or permanently disabling toxic effects of chemical, biological, radiological, or nuclear substances, that has been fully studied for safety in humans, and that has been determined to be effective based on the best human and animal evidence that can be obtained ethically. Accordingly, FDA is proposing regulations that would describe how efficacy for these products can be demonstrated.

FDA is proposing to amend part 314 by adding subpart I, consisting of §§ 314.600 through 314.650, and to amend part 601 by adding subpart G, consisting of §§ 601.60 through 601.65.

IV. Scope

This proposal would apply to new drug and biological products to be used in the reduction or prevention of serious or life-threatening consequences resulting from exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances, where: (1) The products would be expected to provide meaningful therapeutic benefits to patients over existing treatment; (2) the conduct of human challenge/protection efficacy trials would be unethical because it would be necessary to administer a potentially lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance to human volunteers without a proven effective treatment; and (3) field trials[2] are not feasible. This proposal would not apply to products that could be approved under standards described elsewhere in the regulations (part 314 or part 601), e.g., products for which traditional human efficacy studies could be conducted ethically or for which there is an acceptable human surrogate endpoint or for which accelerated approval would apply. As in past efforts to expedite access to new drugs by accelerating approval (subpart H of part 314 and subpart E of part 601) or facilitating access to investigational agents and speeding development and review of these products (21 CFR 312.34 *Treatment use of an investigational new drug*), FDA proposes to apply these procedures where an important medical need is not adequately met by currently available therapies. If such a need does not exist, the agency believes that the usual procedures provide for the most appropriate and thorough approach to ensuring efficacy of drugs prior to marketing. This proposal is consistent

[1] The agency has expanded the scope of this proposal to include not only biological and chemical substances, but also radiological and nuclear substances in order to include all types of substances that could be lethal or permanently disabling.

[2] As used in this document, ''field trials'' are well-controlled studies that can sometimes be conducted when the toxic substance is naturally occurring and there are individuals who are at risk for exposure to the toxic substance. For example, the anthrax vaccine was approved based on a successful well-controlled field trial in mill workers at high risk for anthrax exposure. In other cases, it is possible that accidental or hostile exposures to toxic substances could be treated and the effects observed. However, the ability to conduct such studies cannot usually be anticipated and their historically controlled nature makes them difficult to interpret.

with the recent changes in the act on fast track products made in the Food and Drug Administration Modernization Act of 1997. Consistent with these changes, FDA is committed to facilitating the development and expediting the review of drugs for serious and life-threatening conditions that address unmet needs (section 506 of the act (21 U.S.C. 356)).

Sponsors are encouraged to meet with FDA early in the drug development process to determine the nature of the regulatory review that FDA will apply.

V. Legal Authority

In developing this rule, FDA considered the question of whether it has the authority to approve a product without determinative efficacy studies in humans when it would be unethical to conduct such studies. FDA also considered, assuming it has such authority, what data, other than determinative efficacy studies in humans, could constitute sufficient evidence of efficacy to support product approval. These questions have arisen recently because of concerns raised regarding the nation's ability to adequately respond to threats of chemical, biological, radiological, and nuclear agents that could be used to cause serious harm to humans. FDA has not previously addressed this issue in any of its regulations. As described in the next paragraphs, FDA has the authority to issue regulations describing the type of evidence that may be the basis of an efficacy determination for drugs and biological products that are therapies for toxic agents in situations where it would be unethical to conduct a clinical investigation in humans to demonstrate efficacy.

FDA approves new drugs under the authority of the act and biologics under section 351 of the Public Health Service Act. The act authorizes the Secretary of Health and Human Services (the Secretary) to issue an order refusing to approve a new drug application if the Secretary finds that ''there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof * * *'' (section 505(d) of the act (21 U.S.C. 355(d).) The term substantial evidence is defined as: * * * evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.
Id.

In interpreting the term ''substantial evidence,'' FDA has viewed the phrase ''adequate and well-controlled investigations, including clinical investigations'' as meaning that efficacy determinations must include studies of efficacy in humans. The agency's regulations did not contemplate situations in which efficacy studies cannot be ethically conducted in humans, and FDA believes that it would be inconsistent with the statute's public health objectives to conclude that FDA cannot use some other basis for considering the efficacy of such products. The legislative history does not address this issue. Concluding that such products cannot ever be approved because human efficacy trials cannot be conducted is contrary to the public interest and inconsistent with the act's purpose of public health protection. Courts have recognized that remedial statutes such as the act are to be liberally construed consistent with the act's overriding purpose to protect the public health. (*United States* v. *An Article of Drug * * * Bacto-Unidisk*, 394 U.S. 784 (1968).)

FDA has therefore tentatively concluded that, where definitive human efficacy studies cannot be ethically conducted because they would necessarily expose healthy subjects to a potentially lethal or permanently disabling substance, the statutory standard should be interpreted as permitting efficacy to be based on adequate and well-controlled investigations that are not conducted in humans. This conclusion is consistent with the recognition by Congress of the importance of ethical behavior in the study of unapproved products. For example, Congress has acknowledged the need: (1) For informed consent in clinical research (section 505(i)(2) of the act); (2) to have due regard for patients in issuing regulations for investigational use of drugs (section 505(k) of the act); and (3) for experts to act ''fairly and responsibly'' in evaluating efficacy (section 505(d) of the act). Where human efficacy trials cannot be done ethically, experts are without human studies upon which to fairly and responsibly conclude that a product is effective. In the situations described previously, the agency believes that adequate and well-controlled animal studies may provide sufficient data to warrant approval. For FDA to approve products where definitive efficacy studies cannot be conducted in humans there must be sufficient data available to meet the statutory standard. The data must be such that experts are able to fairly and responsibly conclude ''that the drug will have the effect it purports or is represented to have * * *'' in humans. Where data from adequate and well-controlled animal studies meet this standard, FDA may approve the product. Unless such data exist, FDA will not approve the product.

VI. Elements of the Proposal

For the limited types of products within the scope of this proposal, FDA would grant marketing approval for a new drug or biological product on the basis of adequate and well-controlled animal trials when it is scientifically reasonable to expect that the effect of the drug or biological product in animals is reasonably likely to predict clinical benefit in humans. Safety evaluation is not discussed in this proposed rule because the safety of these products can be studied in human volunteers. In order to provide for the safe and effective use of these products, similar restrictions, withdrawal procedures, postmarketing safety reporting requirements, and requirements pertaining to promotional materials contained in the accelerated approval regulations in subpart H of part 314 and in subpart E of part 601 are included in this proposal, with appropriate modifications. (The rationale and authorities for including these requirements remain unchanged and are described in the **Federal Register** of April 15, 1992 (57 FR 13234), proposed accelerated approval regulations.) Thus, the agency intends to require, under §§ 314.610(a) and 601.61(a), postmarketing studies if a product approved under this subpart is used in a situation that makes such studies feasible and ethical. The agency may also require, for example, under §§ 314.610(b) and 601.61(b) that: (1) The product be stored at the control and direction of competent military and civilian emergency governmental personnel; (2) the product be used at the direction of, and as ordered by, competent military and civilian emergency governmental personnel; and (3) applicants be obligated to followup on its use and report to FDA in Phase 4 reports and descriptions of adverse reactions. In addition, in order to assure public knowledge of products approved under this rule, the agency is proposing to add a new requirement pertaining to providing specific information on the product to its recipients (§§ 314.610(c) and 601.61(c)). The agency also intends in most cases to consult on applications to market such products with an advisory committee, supplemented with

appropriate expert consultants, in meetings open to the public in order to receive expert advice on whether a particular set of animal data support efficacy of a product under this rule.

Under the rule, FDA will rely on the efficacy evidence from adequate and well-controlled studies in animals only where: (1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention by the product; (2) there is independent substantiation of the effect in multiple animal species, including species expected to react with a response predictive for humans; (3) the animal study endpoint is plainly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and (4) the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans, and FDA therefore concludes that the effect of the product in animals is reasonably likely to predict clinical benefit in humans. Where it is possible to conduct human efficacy studies of products, these will continue to be required. Safety evaluation of these products in humans will be required.

To the extent possible, human experience that is potentially relevant should be obtained, such as effects on potential human surrogate markers or studies of low, sublethal doses of the toxic substance, where such doses may be defined and where the studies are sufficiently cautious in design and monitoring. If the surrogate endpoint effect is reasonably likely to predict clinical benefit, and it is possible to design postmarketing studies to confirm effectiveness (which could depend on the occurrence of an unpredictable toxic exposure), such that the drug could be approved under subpart H of part 314 and subpart E of part 601, the accelerated approval regulations, it would not be considered under this proposal.

VII. Discussion

In situations where definitive human efficacy studies cannot be ethically conducted, a possible means of demonstrating efficacy could be through animal studies. FDA seeks comments on the following issues:

1. As indicated previously, the agency has never before permitted a sponsor to rely on animal studies to support a finding of ''substantial evidence'' and approval of a drug under section 505 of the act. Although the agency has attempted to propose a very narrow exception to the need for human studies in a situation where human studies seem truly impossible, the exception might be viewed by some as establishing the principle that animal studies may be relied on ''for good reason'' under the act; other ''good reasons'' might be advanced. What are the risks of the approach taken in this rule, if any, to the efficacy standard? To what extent, if any, would it diminish the efficacy standard? What impact would it have, if any, on how the agency might apply the efficacy standard to other drugs in the future?

2. If the agency proceeds to finalize this rule, are there additional limitations that should be placed on any approval based on animal data? For example, should the agency place additional advertising restrictions on these products, and describe the restrictions and the legal basis for such restrictions?

3. What would make animal data sufficiently predictive of efficacy in humans to warrant product approval based on such data? The agency has identified several elements that are important. These elements include consistency of results across species, and an effect on the same morbidity/mortality endpoint in animals that is of interest in humans together with a good understanding of the mechanisms of the effect of the toxin and the product. Information about the relative sensitivity of the species to the toxin or agent (compared to humans), and consistent dose-response and pharmacokinetic/pharmacodynamic relationships in various animal species might also make animal data more persuasive. Are there other elements that should be considered?

4. How can the correct human dose be selected? Presumably, if multiple animal species show a consistent relation of protective effect to exposure (minimum blood levels, average concentration, etc.), a response of a pharmacodynamic marker, or measure of dose (e.g., milligram (mg)/meter^2 dose, mg/kilogram dose, or cumulative dose), a similar human dose, or a human dose giving the same blood concentration or pharmacologic effect could be chosen. If species differ in their susceptibility to the toxic agent, what approaches could help identify the proper human dose of the drug? For example, would the largest dose (concentration) needed in any species be the best choice?

5. What constitutes ''independent substantiation in multiple animal species'' (i.e., consistency of results across species)? How many species represent a reasonable number and should at least one primate species be included? In what situation(s) might a primate species be unnecessary? If efficacy results across species are not consistent, would a single unprotected species (without clear explanation) undermine the entire premise on which approval would be based? If the inconsistency would not undermine the premise, what are examples of situations where one could conclude a treatment will be effective in humans even though there is an unprotected species and no clear explanation of why it is unprotected?

6. As discussed previously, safety evaluation is not discussed in this document because safety will be studied in human volunteers. If efficacy of a product were demonstrated through animal studies rather than studies in humans, are there special considerations that should apply to the safety data base? If so, what do these special considerations consist of and why should they be applied to the data base? To what extent should interactions with potential concomitant treatments and concomitant environmental exposures be studied?

7. In the July 1997 request for comments, FDA requested comments on: When is it ethical to expose volunteers to toxic chemical and biological substances to test the effectiveness of products that may be used to provide potential protection against those substances? As described earlier in this document, the agency received nine comments, most of which expressed considerable doubt regarding whether it would be ethical to expose volunteers to toxic substances to test the efficacy of these products. Although the agency has concluded in proposing this rule that it will generally not be possible ethically, in the cases described, to conduct human studies, it is also true that it is critically important for a product intended to reduce or prevent lethal consequences to be effective when used. The agency therefore is requesting further comment on this issue. It would be helpful to receive information, with examples if available, on the value of studying sublethal doses of toxins in humans and evaluating the ability of these products to protect against the sublethal effects. This would not be equivalent to testing the product against a full dose of the toxin, but it could support the fundamental similarity of responses in animals and humans to the toxin and the product.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

IX. Executive Order 12612: Federalism

Executive Order 12612 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant effect on federalism. Using the criteria and principles set forth in the order, FDA has considered the proposed rule's impact on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government. FDA concludes that this proposal is consistent with the principles set forth in Executive Order 12612.

Executive Order 12612 states that agencies formulating and implementing policies are to be guided by certain federalism principles. Section 2 of Executive Order 12612 enumerates fundamental federalism principles. Section 3 states that, in addition to these fundamental principles, executive departments and agencies shall adhere, to the extent permitted by law, to certain listed criteria when formulating and implementing policies that have federalism implications. Section 4 lists special requirements for preemption.

Section 4 of Executive Order 12612 states that an executive department or agency foreseeing the possibility of a conflict between State law and federally protected interests within its area of regulatory responsibility, is to consult with States in an effort to avoid such conflict. Section 4 also states that an executive department or agency proposing to act through rulemaking to preempt State law is to provide all affected States notice and an opportunity for appropriate participation in the proceedings. As required by the Executive Order, States have, through this notice of proposed rulemaking, an opportunity to raise the possibility of conflicts and to participate in the proceedings (section 4(d) and (e)). Consistent with Executive Order 12612, FDA requests information and comments from interested parties, including but not limited to State and local authorities, on these issues of federalism.

X. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Title II of the Unfunded Mandates Reform Act (Public Law 104–4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order and in these two statutes. The agency has determined that this rule is a ''significant regulatory action'' as defined in section 3(f)(4) of the Executive Order because it raises novel policy issues. However, the rule is not an ''economically significant'' rule as defined in section 3(f)(1) of the Executive Order, as it will not have an annual effect on the economy of $100 million or more, nor will it impose material adverse effects. With respect to the Regulatory Flexibility Act (5 U.S.C. 605(b)), this rule will permit products to be approved that could not be approved under existing regulations and very few products will need to meet the requirements of this rule. Therefore, the Commissioner certifies that the rule will not have a significant economic impact on a substantial number of small entities. Accordingly, under the Regulatory Flexibility Act, no further analysis is required. Similarly, because the rule does not impose any mandates on State, local, or tribal government, or the private sector that will result in a 1-year expenditure of $100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

XI. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given in the following paragraphs with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: New Drug and Biological Products; Animal Efficacy Studies.

Description: FDA is proposing to amend its new drug and biological product regulations to identify the evidence needed to demonstrate the efficacy of drug and biological products used to treat or prevent the toxicity of chemical, biological, radiological, or nuclear substances when definitive efficacy studies in humans cannot be ethically conducted because they would involve administering a lethal or permanently disabling toxic substance to healthy human volunteers without a proven treatment and when field trials are not feasible. In these circumstances, when it may be impossible to demonstrate efficacy through the adequate and well-controlled studies in humans, FDA is proposing that certain new drug and biological products to treat or prevent serious or life-threatening conditions could be approved for marketing based on studies in animals, without the traditional efficacy studies in humans. FDA is proposing this action because it recognizes the importance of improving medical response capabilities to the use of lethal or permanently disabling chemical, biological, radiological, and nuclear substances in order to protect individuals exposed to these substances.

Respondent Description: Businesses and other for-profit organizations, and nonprofit institutions.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.610(b)(3) and 314.630 601.61(b)(3) and 601.63	1	1	1	5	5
314.610(c) and 314.640 601.61(c) and 601.64	1	1	1	240	240
Total					245

[1] There are no capital costs or operating and maintenance costs with this collection of information.

TABLE 2.—ESTIMATED ANNUAL DISCLOSURE/RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
314.610(b)(3) and 314.630 601.61(b)(3) and 601.63	1	1	1	1	1
314.610(c) 601.61(c)	1	1	1	1	1
Total					2

[1] There are no capital costs or operating and maintenance costs with this collection of information.

FDA estimates that only one application of this nature may be submitted every 3 years; however, for calculation purposes, FDA is estimating the submission of one application annually. FDA estimates 240 hours for a manufacturer of a new drug or biological product to develop patient labeling, and to submit the appropriate information and promotional labeling to FDA. At this time, FDA cannot estimate the number of postmarketing reports for adverse drug or biological experiences associated with a newly approved drug or biological product. Therefore, FDA is using one report for purposes of this information collection. These reports are required under 21 CFR parts 310, 314, and 600. Any burdens associated with these requirements will be reported under the adverse experience reporting (AER) information collection requirements. The estimated hours for postmarketing reports range from 1 to 5 hours based on previous estimates for adverse experience reporting; however FDA is estimating 5 hours for the purpose of this information collection.

The majority of the burden for developing the patient labeling is included under the reporting requirements, therefore, minimal burden is calculated for providing the guide to patients. As discussed previously, no burden can be calculated at this time for the number of AER reports that may be submitted after approval of a new drug or biologic, therefore, the number of records that may be maintained also cannot be determined. Any burdens associated with these requirements will be reported under the AER information collection requirements. The estimated recordkeeping burden of 1 hour is based on previous estimates for the recordkeeping requirements associated with the AER system.

XII. Request for Comments

Interested persons may, on or before December 20, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314 and 601 be amended as follows:

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

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e.

2. Subpart I, consisting of §§ 314.600 through 314.650, is added to read as follows:

Subpart I—Approval of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted

Sec.
314.600 Scope.
314.610 Approval based on evidence of efficacy from studies in animals.
314.620 Withdrawal procedures.
314.630 Postmarketing safety reporting.
314.640 Promotional materials.
314.650 Termination of requirements.

Subpart I—Approval of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted

§ 314.600 Scope.

This subpart applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances, where the products would be expected to provide

meaningful therapeutic benefits to patients over existing treatments (e.g., ability to treat a condition that has no current therapy, ability to treat patients unresponsive to, or intolerant of, available therapy, or ability to improve patient response compared to available therapy). This subpart applies only to those new drug products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance without a proven treatment; and field trials to study the product's efficacy after an accidental or hostile exposure are not feasible. This subpart does not apply to products that can be approved based on standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for these products.

§ 314.610 Approval based on evidence of efficacy from studies in animals.

FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of § 314.600 are met based on adequate and well-controlled animal trials when the results of those animal studies establish that the drug product is reasonably likely to predict clinical benefit in humans. FDA will rely on the evidence from studies in animals only where: There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product; the effect is independently substantiated in multiple animal species, including species expected to react with a response predictive for humans; the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans. Approval under this subpart will be subject to three requirements:

(a) *Postmarketing studies.* The applicant shall conduct postmarketing studies to verify and describe the drug's clinical benefit when such studies are feasible and ethical. Such postmarketing studies may not be feasible until an exigency arises that necessitates use of the product. When such studies are feasible, the applicant shall conduct such studies with due diligence.

(b) *Approval with restrictions to assure safe use.* If FDA concludes that a drug product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product, such as:

(1) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(2) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(3) Distribution conditioned on specified recordkeeping requirements.

(c) *Information to be provided to patients and potential patients; unit of use packaging.* For drug products approved under this subpart, applicants shall prepare, as part of their proposed labeling, labeling to be provided to patients or potential patients. The patient labeling will explain that the drug's approval was based on efficacy studies conducted in animals alone, give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. For self-administered drug products, there shall be unit-of-use packaging and attached patient labeling containing this information. For drug products administered by health professionals, the patient labeling shall be available with the product to be provided to patients prior to administration of the drug product, if possible.

§ 314.620 Withdrawal procedures.

(a) For new drugs approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research (CDER) will give the applicant notice of an opportunity for a hearing on CDER's proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 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 function.* 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, up to three representatives of the applicant, and up to three representatives of CDER 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 of Food and Drugs' 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.

§ 314.630 Postmarketing safety reporting.

Drug products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.640 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants shall submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant shall submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.650 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 314.610(b), 314.620, and 314.630 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.610, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the drug product's clinical benefit. For drug products approved under § 314.610, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

4. Subpart G, consisting of §§ 601.60 through 601.65, is added to read as follows:

Subpart G—Approval of Biological Products for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted

Sec.

Subpart G—Approval of Biological Products for Use Against Lethal or Permanently Disabling Toxic Substances when Efficacy Studies in Humans Ethically Cannot Be Conducted

§ 601.60 Scope.

This subpart applies to certain biological products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances, where the products would be expected to provide meaningful therapeutic benefits to patients over existing treatments (e.g., ability to treat a condition that has no current therapy, ability to treat patients unresponsive to, or intolerant of, available therapy, or ability to improve patient response compared to available therapy). This subpart applies only to those biological products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance without a proven treatment; and field trials to study the product's efficacy after an accidental or hostile exposure are not feasible. This subpart does not apply to products that can be approved based on standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for these products.

§ 601.61 Approval based on evidence of efficacy from studies in animals.

FDA may grant marketing approval for a biological product for which safety has been established and for which the requirements of § 601.60 are met based on adequate and well-controlled animal trials when the results of those animal studies establish that the biological product is reasonably likely to predict clinical benefit in humans. FDA will rely on the evidence from studies in animals only where: There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product; the effect is independently substantiated in multiple animal species, including species expected to react with a response predictive for humans; the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans. Approval under this subpart will be subject to three requirements:

(a) *Postmarketing studies.* The applicant shall conduct postmarketing studies to verify and describe the biological product's clinical benefit when such studies are feasible and ethical. Such postmarketing studies may not be feasible until an exigency arises that necessitates use of the product. When such studies are feasible, the applicant shall conduct such studies with due diligence.

(b) *Approval with restrictions to assure safe use.* If FDA concludes that a biological product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:

(1) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(2) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(3) Distribution conditioned on specified recordkeeping requirements.

(c) *Information to be provided to patients and potential patients; unit of use packaging.* For biological products approved under this subpart, applicants shall prepare, as part of their proposed labeling, labeling to be provided to patients or potential patients. The patient labeling will explain that the biological product's approval was based on efficacy studies conducted in animals alone, give the biological product's indication(s), directions for use (dosage and administration), contraindications, a description of any

reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. For self-administered biological products, there shall be unit-of-use packaging and attached patient labeling containing this information. For biological products administered by health professionals, the patient labeling shall be available with the product to be provided to patients prior to administration of the biological product, if possible.

§ 601.62 Withdrawal procedures.

(a) For biological products approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research (CBER) will give the applicant notice of an opportunity for a hearing on the CBER's proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 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 function.* 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, up to three representatives of the applicant, and up to three representatives of CBER 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 of Food and Drugs' 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.

§ 601.63 Postmarketing safety reporting.

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

§ 601.64 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants shall submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant shall submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.65 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 601.61(b), 601.62, and 601.63 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.61, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the biological product's clinical benefit. For biological products approved under § 601.61, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

Dated: May 25, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99–25377 Filed 10–4–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF TRANSPORTATION

Coast Guard

33 CFR Part 20

46 CFR Part 5

[USCG–1998–3472]

RIN 2115–AF59

Rules of Practice, Procedure, and Evidence for Administrative Proceedings of the Coast Guard

AGENCY: Coast Guard, DOT.

ACTION: Reopening of comment period on interim rule.

SUMMARY: The Coast Guard is reopening the period for public comment on its interim rule, Rules of Practice, Procedure, and Evidence for Administrative Proceedings of the Coast Guard. Because of several requests for extension, the Coast Guard is reopening the period for 180 days.

DATES: Comments must reach the Coast Guard on or before April 3, 2000.

ADDRESSES: Please submit your comments and related material by any one of the following methods (but by only one, to avoid multiple listings in the public docket):

(1) By mail to the Docket Management Facility, [USCG–1998–3472], U.S. Department of Transportation, room PL–401, 400 Seventh Street SW., Washington, DC 20590–0001.

(2) By delivery to room PL–401 on the Plaza level of the Nassif Building, 400