

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 98N-0237]

RIN 0910-AC05

**New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide substantial evidence of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible. In these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and any additional supporting data.

**DATES:** This rule is effective *[insert date 30 days after date of publication in the Federal Register]*.

**FOR FURTHER INFORMATION CONTACT:**

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DMB  
Display Date 5-30-02  
Publication Date 5-31-02  
Certifier D. Hawkins

NFR 1

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## **SUPPLEMENTARY INFORMATION:**

### **I. Introduction**

In the **Federal Register** of October 5, 1999 (64 FR 53960), we (FDA) proposed to amend our new drug and biological product regulations to identify the information needed to provide substantial evidence of the effectiveness of certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. We are finalizing that proposed rule by adding subpart I to part 314 (21 CFR part 314) and subpart H to part 601 (21 CFR part 601).

This final rule provides for approval of certain new drug and biological products based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible prior to approval. Under this rule, in these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions can be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (§ 314.126). In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. Under this rule, FDA can rely on the evidence from animal studies to provide substantial evidence of the effectiveness of these products when:

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 demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents

a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in 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 pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

All studies subject to this rule must be conducted in accordance with preexisting requirements under the good laboratory practices (21 CFR part 58) regulations and the Animal Welfare Act (7 U.S.C. 2131 *et. seq.*).

Safety evaluation of products is not addressed in this rule. Products evaluated for effectiveness under subpart I of part 314 and subpart H of part 601 will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products. The agency believes that the safety of most of these products can be studied in human volunteers similar to the people who would be exposed to the product. FDA recognizes that some safety data, such as data on possible adverse interactions between the toxic substance itself and the new product, may not be available. This is not expected to keep the agency from making an adequate safety evaluation. FDA's procedures and standards for evaluating the safety of new drug and biological products are sufficiently flexible to provide for the safety evaluation of products evaluated for efficacy under subpart I of part 314 and subpart H of part 601.

This rule will not apply if product approval can be based on standards described elsewhere in our regulations (for example, accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity).<sup>1</sup>

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<sup>1</sup> An example of a drug approval based on human surrogate markers is our August 30, 2000, approval of an efficacy supplement for ciprofloxacin. Ciprofloxacin HCl was approved for postexposure management of inhalational

## II. Comments on the Proposed Rule and Our Response

We received comments on the proposed rule from two pharmaceutical companies and one physician affiliated with a university. We also received comments from the National Institutes of Health (NIH). The NIH comments were based on a prepublication draft of the proposed rule, but the comments were received too late to be addressed in the proposed rule. The NIH comments have been placed in the docket for this rule and are addressed in this document.

In addition to the changes we have made in response to comments, we have changed the titles of subpart I of part 314 and subpart H (formerly subpart G) of part 601 to better describe the scope of the subparts. Subpart I of part 314 is now entitled “Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible” and subpart H of part 601 is now entitled “Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible.” Proposed subpart G has been redesignated as subpart H in the final rule because subpart G has since been designated for regulations on postmarketing studies. Proposed §§ 601.60 through 601.65 have been renumbered §§ 601.90 through 601.95 in subpart H.

We have also changed, on our own initiative, the requirements proposed in §§ 314.610(c) and 601.61(c) (§§ 314.610(b)(3) and 601.91(b)(3) in this final rule). We have deleted the requirement that self-administered drug products approved under this rule be in unit-of-use packaging with attached patient labeling. In addition, we have eliminated the distinction between self-administered products and products administered by health professionals.

Whether a product is self-administered or administered by a health professional, it is important to inform patient recipients that a product approved under this rule has not been studied for efficacy

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anthrax. The approval was based, in part, on human studies demonstrating that ciprofloxacin achieved serum concentrations reaching or exceeding levels associated with improved survival of animals exposed to aerosolized *Bacillus anthracis* spores. The results from these studies were combined with the knowledge of effectiveness in humans of ciprofloxacin for other bacterial infections, including pneumonia. The validity of the human surrogate marker was supported by animal studies.

in humans because of ethical or feasibility reasons.<sup>2</sup> It is also important that patient recipients receive information about indications, dosage and administration, contraindications, reasonably foreseeable risks, adverse reactions, anticipated benefits, and drug interactions. This rule requires that all of this information be provided to patient recipients of products approved under subpart I of part 314 and subpart H of part 601.

We believe, however, that the proposed unit-of-use packaging and attached patient-labeling requirement could have had the unintended effect of hampering the distribution and dispensing of these products in the event of an emergency. The added bulk of unit-of-use packaging could have made stockpiling and transporting more difficult in many cases. The proposed requirement might also have hampered the speedy distribution of products for additional indications previously approved outside of this rule.

Applicants may meet the requirements of new §§ 314.610(b)(3) and 601.91(b)(3) in a variety of ways, as long as sponsors make provisions to get the information to patients. For example, the sponsor could provide reproducible master copies of labeling information or presentations for patient recipients that would be appropriate in the event of an emergency.

We have also changed proposed §§ 314.610(c) and 601.61(c) (§§ 314.610(b) and 601.91(b) in this final rule) to require that the patient labeling explain that, for ethical or feasibility reasons, the product's approval was based on efficacy studies conducted only in animals. This explanation will better inform patient recipients about the nature and ethical basis of the product approval under this rule and how that approval differs from approval of products based on standard human efficacy studies.

Finally, we have added to §§ 314.610(b)(1) and 601.91(b)(1) (proposed §§ 314.610(a) and 601.61(a)) a requirement that applicants include a plan or approach to fulfilling postmarketing study commitments as part of their application. We recognize that such studies normally will not be

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<sup>2</sup>In some cases, however, such as with anti-infective drug products, it would usually be expected that human data on safety and effectiveness for other indications may be available.

conducted unless an emergency arises that requires the product's use. Furthermore, when the product is used in an emergency, it may not be feasible for sponsors to conduct postmarketing studies in a timely manner, nor is it our intention to require sponsors to send investigators into areas of exposure. We do, however, believe that applicants can plan a postmarketing study approach, in consultation with the agency, as part of an overall response to an event.

The requirement to submit a plan for postmarketing studies is consistent with the requirements for sponsors under the accelerated approval process provided for in subpart H of part 314.

The procedures in subpart H and in this rule are similar because, to assess efficacy, both allow use of an endpoint that is not a clinical endpoint showing a benefit. Instead the rules under subpart H allow for reliance on a clinical surrogate endpoint and this rule allows for the use of animal data as an endpoint.

Postmarketing studies are critical in both of these situations to verify and describe the clinical benefit of the drug or biological product. The postmarketing studies may provide us with data that directly verify that the product provides the desired benefit in humans, such as increased survival or prevention of major morbidity.

(Comment 1) One comment suggested that we define "lethal" and "permanently disabling." The comment expressed concern that without such definitions, subpart I of part 314 and subpart H of part 601 will be misapplied in situations where clinical testing can and should be carried out.

The definitions of "lethal" and "permanently disabling" would seem to be well understood. Although we share the concern that too expansive an interpretation of "lethal" or "permanently disabling" could lead to attempts to apply this rule when human studies are, in fact, feasible, we are also concerned that too restrictive a definition of "lethal" or "permanently disabling" could lead to failure to apply subpart I of part 314 and subpart H of part 601 in situations where they should be applied to protect the public health. We believe that, as a general matter, we must rely on the good sense and responsibility of those health professionals who will be seeking to apply

subpart I of part 314 and subpart H of part 601 in the future, and on responsible review of specific cases by FDA. Nevertheless, we can provide guidance for applying subpart I of part 314 and subpart H of part 601 by clarifying that a “lethal substance” is one that is likely to kill at least some of the humans who have been exposed to the substance and a “permanently disabling substance” is one that is likely to cause a permanent physical or mental impairment that substantially limits one or more of the major life activities in at least some of the humans who have been exposed to the substance.

(Comment 2) One comment stated that the rule does not explicitly cover infectious substances and pointed out that not all infectious substances produce toxins. The comment suggested replacing “toxic” with “toxic and/or infectious” in proposed §§ 314.600 and 601.60 (§ 601.90 in this final rule).

The rule is certainly intended to cover products for treatment of infections. At some level, an infectious agent that is lethal or permanently disabling is toxic to its host, even if that agent is not itself a “toxin” or a producer of “toxins” within a strict definition of the word. Because we do not use “toxin” in the rule, and “toxic” is accurate, we do not believe we need to replace “toxic” with “toxic and/or infectious” to indicate that products for the treatment of infections may be approved under this rule.

(Comment 3) One comment noted that the proposed rule did not discuss criteria that should be applied in determining if “an important medical need is not adequately met by currently available therapies.” The comment suggested that we state that we will use the criteria given in our guidance for industry entitled “Fast Track Drug Development Programs—Designation, Development, and Application Review” (September 1998).

We have decided to eliminate the requirement that “products would be expected to provide meaningful therapeutic benefits to patients over existing treatments,” as well as the limitation that the toxic agent be “without a proven treatment” (proposed §§ 314.600 and 601.60). Recent events involving the multiple exposures to anthrax in our population, and deaths resulting from those

infections, have indicated a need for a wide range of therapeutic options that, in some instances, might be inappropriately limited by requiring new products to have a therapeutic benefit over existing treatments, or to be used only in the absence of a proven treatment. Availability of a variety of drug and biological products is important because, for example, patient recipients may be allergic to one product and require another, may be intolerant of a product because of side effects, or may respond more favorably to one product than another. We also believe that a wider variety of therapeutic choices will limit potential problems with availability, accessibility, and distribution of products. We have modified the final rule to address these concerns and help ensure the availability of more than one therapeutic option.

(Comment 4) One comment requested that antivenin and antitoxin products of animal origin be considered for inclusion specifically on the list of new drugs and biological products to which the rule applies.

There is no list of products that may be approved based on evidence of effectiveness from efficacy studies in animals. The rule provides criteria to determine if evidence of effectiveness from efficacy studies in animals may support approval of a product. If an antivenin or antitoxin product of animal origin meets the criteria specified in the rule, it may be approved on the basis of evidence of effectiveness from efficacy studies in animals.

(Comment 5) One comment requested that we revise proposed §§ 314.610 and 601.61 (§ 601.91 in this final rule) to state that substantiation in multiple animal species is required only where appropriate. The comment stated we should not limit ourselves to approvals only when there is substantiation in “multiple” animal species. The comment contended that where independent studies in a single species meet the general principles of independent substantiation as described in the guidance for industry entitled “Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products” (May 1998), those studies are sufficient to substantiate effectiveness as a matter of science and a requirement of substantiation in multiple species would result in an unnecessary delay of agency approval. According to the comment, these concerns are particularly

important where viruses have a narrow host range and conducting efficacy trials in more than one animal species in such cases either is not feasible or provides only limited additional information that is relevant to the full-blown disease in humans. The comment suggested that the requirement of substantiation in multiple species in a given case should depend on the known host range and the availability of animal model systems.

We share some of the concerns expressed in the comment, but we believe the proposed remedy goes too far. Approval of the use of a drug lacking human evidence of effectiveness represents a significant departure from ordinary practice. There are countless examples of treatments with favorable effects in animals that did not prove effective in humans. Although this rule does, for good reason, allow reliance on animal studies when human studies cannot be conducted, in general we expect that the evidence, to be persuasive, should be developed in more than one animal species unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. We recognize that conducting studies in more than one species can result in added expense, but we believe this is warranted because of the additional assurance they would provide.

Furthermore, reliance on our guidance entitled “Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products” is misplaced. That guidance was drafted to provide advice on the quantity of data from clinical studies needed to support a finding of effectiveness and, specifically, on when the agency ought to rely on a single human study. The guidance addressed cases in which the issue is the credibility of the data itself, not the relevance of the data to humans. In this rule, the issue is the ability of results from animal studies to predict the human response, and not the credibility of the animal finding itself (although, of course, the animal studies should be replicated or substantiated in each species as needed to ensure credible results). The need for multiple species in certain cases is to enhance the likelihood that the data are pertinent to humans.

We do recognize, however, that the multiple species requirement could be inappropriate or unnecessary in certain situations. For example, there may be only one species capable of reacting with a response predictive for humans. This would occur where there is only one nonhuman host for the targeted microorganism. There may also be other situations in which studies in a particular species are specifically well recognized as predictors of effectiveness in humans. Thus, circumstances in which the agency will rely on evidence from studies in one animal species to provide substantial evidence of the effectiveness of these products in humans would generally be limited to situations where the study model is sufficiently well-recognized so as to render studies in multiple species unnecessary. In addition, other human data for the product could provide support for such approvals.

Accordingly, we have changed proposed §§ 314.610 and 601.61 (§ 601.91(c) in this final rule) to require that approval be based on studies in more than one animal species unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. The agency believes that demonstrating effectiveness in studies conducted in a single animal species using a well-characterized animal model will most often be done for anti-infective drug products. The pathophysiological mechanisms of infectious diseases are usually very well understood, and animal models for many infectious diseases have been studied for years and are very well characterized.

(Comment 6) One comment suggested we remove the requirement that there be a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. The comment stated it is hard to say when we understand something reasonably well and that, if we decide to retain the requirement, we should state at what level (e.g., cellular, molecular) the mechanism must be understood.

A disease's or toxin's mechanism of action does not need to be understood before a safe and effective treatment or preventative can be devised. Quinine and Jenner's smallpox vaccine were both developed before the acceptance of the germ theory of disease. Neither is there a general

requirement that an applicant who is relying on human testing to establish effectiveness demonstrate the mechanism of action of the drug or biological product that is the subject of the marketing application. It is generally sufficient to demonstrate that a product is safe and effective. It is generally not required that an applicant demonstrate how or why the product is safe and effective.

It is true that a pathophysiologic understanding of a disease and treatment is not required when human studies are used to support approval. In the case of human drug or biological products approved on the basis of evidence of effectiveness from studies in animals, however, we are requiring an understanding of the mechanism of the toxic substance or infectious organism and its prevention or reduction by the product. This understanding helps provide assurance that the efficacy data from studies in animals can be applied to humans. We have not specified exactly what degree of pathophysiologic understanding is needed, and that will be a matter of judgment. The level of understanding could range from a complete understanding of how a toxic substance works at the cellular level in both human and animal cells together with a clear understanding of what the antidote does at the molecular level to a less complete understanding. The level of required understanding of the mechanism of action of the toxic substance or infectious organism and the product may vary from toxic substance to toxic substance or infectious organism to infectious organism and could even vary from one product to another intended to treat the same condition.

(Comment 7) One comment suggested that an institutional review board (IRB) or other ethical scientific review body determine if it would be unethical to conduct studies in humans. The comment also said we do not mention who would make the determination that it would be unethical to conduct studies in humans.

The final determination that it is unethical to conduct studies in humans will be made by the reviewing officials in FDA. We anticipate that in most cases the determination as to whether it would be unethical to conduct studies in humans will not be difficult. In those cases that are difficult, the views of one or more IRBs, individual ethicists and clinicians, and FDA advisory

committees could be sought by a sponsor or FDA. A case where such a consultation could be useful is one in which a putatively subtoxic dose would be used in humans to establish at least a mechanism for protection, if not actual protection.

(Comment 8) One comment noted that we said in the proposed rule:

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 (64 FR 53960 at 53964 and 53965).

The comment asked us to consider requiring consultation with an advisory committee either before conducting the animal studies or before approval of the product, or both.

We want to reiterate our statement in the proposed rule that we intend usually to consult with an advisory committee during the approval process. Indeed, we may consult with an advisory committee more than once on a single product if circumstances warrant it. Consultation with an advisory committee could occur early in the development process; to discuss whether the concept of using certain animal data to support efficacy is reasonable.

Even though consultation with an advisory committee is generally desirable, it is not always practical. For example, products reviewed under this rule may be part of the response to a public health emergency; therefore, there may not be time to convene an advisory committee. Accordingly, we believe that it would be inappropriate to absolutely require consultation with an advisory committee.

(Comment 9) One comment questioned whether patient labeling is adequate to inform patients that a product has been approved on the basis of animal efficacy data, particularly in situations where military personnel are ordered to take a product approved under this rule. The comment did not suggest an alternative to the provisions of the rule.

Sections 314.610(b)(3) and 609.91(b)(3) provide that for products or specific indications approved under this rule, applicants must prepare, as part of their proposed labeling, labeling to

be provided to patients or potential patients. The patient labeling, written in language that can be easily understood by the general public, must explain that, for ethical or feasibility reasons, the product's approval was based on efficacy studies conducted in animals alone. The labeling must give the 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. If possible, the patient labeling must be available with the product to be provided to patients or potential patients prior to administration or dispensing of the product for the use approved under this rule. We intend that in interpreting §§ 314.610(b)(3) and 601.91(b)(3), the word "possible" be given its ordinary and literal meaning. Situations in which it would be inconvenient or require some effort to make the labeling available for patients should not be equated with situations in which it would be impossible to do so.

These provisions, coupled with communications within a health care provider-patient relationship should, as a general matter in both civilian and military contexts, adequately ensure that patients are informed that the product they are taking has been approved based on animal efficacy data.

(Comment 10) One comment suggested that labeling a drug or biological product approved on the basis of evidence of effectiveness from studies in animals as "FDA approved" is misleading, because patients would assume that the product had been approved based on human studies. The comment suggested that we treat the product as an investigational new drug, but waive certain requirements generally applied to investigational new drugs, if those requirements would provide obstacles to the product's use in an emergency.

We agree that the labeling would be misleading if information were not included to explain to patients or potential patients that the effectiveness of the product was demonstrated in animals not humans, and that this reliance on animal efficacy data was based on ethical and feasibility concerns. Therefore, under sections 502(a) and 701(a) of the Federal Food, Drug, and Cosmetic

Act (the act) (21 U.S.C. 352(a) and 372(a)) (and consistent with the legal authority cited in the preamble to the proposed rule (64 FR 53960 at 53964)), we have revised the language in §§ 314.610(b)(3) and 601.91(b)(3) to require that this information be included in the patient labeling.

Where the evidence of effectiveness comes from studies in animals, regulating new drug or biological products as investigational drugs presents several difficulties. These difficulties have led us to this rulemaking. The proposed rule describes our concerns with relying solely on the investigational new drug regulations (64 FR 53960 at 53963) for such approvals. There may be cases, however, when an application does not meet the criteria of this rule, and approval of the product is not feasible. Should an emergency situation arise under such circumstances, it is conceivable that the product could be used under the investigational new drug regulations.

(Comment 11) Another comment suggested that, unless “lay persons” may use the product, we prohibit advertising of drug or biological products approved on the basis of evidence of effectiveness from studies in animals. The comment further recommended stringent controls on the advertising of products that could be used by “lay persons.”

Such a sweeping prohibition would likely give rise to constitutional issues regarding the regulation of commercial speech. In addition, the suggestion presents serious public health concerns. A prohibition on advertising could limit health care providers’ and public health and emergency preparedness officials’ awareness of the products approved under this rule. Limiting awareness of these products, which are intended to reduce or prevent life-threatening or disabling toxicity, does not seem desirable or appropriate.

We believe that the advertising provisions in §§ 314.640 and 601.94 of this rule provide adequate protection against false or misleading advertising, and no additional requirements are needed. As discussed in the preamble to the proposed rule (64 FR 53960 at 53964), we proposed the requirements pertaining to promotional materials in order to provide for the safe and effective use of these products. These requirements, along with others, are similar to those in the accelerated

approval regulations in subpart H of part 314 and in subpart E of part 601. In issuing the accelerated approval regulations, we stated that the special circumstances under which those products would be approved and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justified review of promotional materials before and after approval (57 FR 58942 at 58949). Similarly, the special circumstances of all product approvals under subpart I of part 314 and subpart H of part 601 and the possibility that promotional materials could adversely affect the even more sensitive risk/benefit balance justifies advance review of promotional materials.

We intend to review all such promotional materials under these new regulations promptly, and to notify the applicant of any identified problems as soon as possible (see also 57 FR 58942 at 58950). Also as with the accelerated approval regulations' requirements for promotional materials (§§ 314.560 and 601.46), FDA may terminate the requirements for advance submission of promotional materials under these new regulations at §§ 314.650 and 601.95 if the agency determines, on its own initiative or in response to a petition submitted by the sponsor, that the requirements are no longer necessary for safe and effective use of the product. When we remove the requirement for advance submission of promotional materials, we will continue to offer a prompt review of all voluntarily submitted promotional materials.

(Comment 12) We received some comments addressing questions posed in section VII, "Discussion," of the proposed rule. In this final rule, we have addressed comments that dealt with the rule itself. Comments that dealt with questions related to the application of this rule, rather than the requirements, will be addressed if and when we draft a guidance on this subject.

### **III. Legal Authority**

We did not receive any comments discussing our legal authority to approve new drugs and biological products based on evidence of effectiveness from studies in animals. We have concluded, for the reasons set out in section V of the proposed rule, "Legal Authority," (64 FR 53960 at 53964), that we have the legal authority to approve new drugs and biological products based on evidence of effectiveness from studies in animals.

(Comment 13) We received a comment asserting that under the court's holding in *American Pharmaceutical Association v. Weinberger*, 377 F.Supp. 824 (D.C.D.C. 1974) *aff'd sub nom. American Pharmaceutical Association v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1976) (*per curiam*), we do not have the legal authority to impose the distribution controls proposed in §§ 314.610(b) and 601.61(b) (§§ 314.610(b)(2) and 601.91(b)(2) in this final rule). The comment asked that, if we disagree with their characterization of the law, distribution controls not be applied just because a product was approved under the provisions of this rule. The comment also asked that we give examples of situations where we would impose distribution restrictions.

For a full discussion of FDA's authority to impose distribution restrictions to ensure the safe use of drug products, see the agency's proposed and final rules amending part 314 by adding subpart H on accelerated approval of new drugs for serious or life-threatening illnesses (proposed rule at 57 FR 13234, April 15, 1992; final rule at 57 FR 59842, December 11, 1992). Those rules relied on sections 501, 502, 503, 505, and 701 of the act (21 U.S.C. 351, 352, 353, 355, and 372) as authority for FDA to issue regulations to help ensure the safety and effectiveness of new drugs.

We agree with the comment that distribution controls should not be placed on a product solely because it is approved under the provisions of this rule. New §§ 314.610(b)(2) and 601.91(b)(2) authorize distribution controls—they do not require them.

We do not believe it would be useful to give examples of situations where distribution controls may be necessary to ensure safe use of the product. Products approved under this rule could be indicated for widely differing conditions, and those products could be used in unique circumstances presenting many distinct safety concerns. It would not be practical to try to devise a list of representative examples of situations where distribution controls would be appropriate.

#### **IV. 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.

#### **V. Federalism**

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

#### **VI. Analysis of Impacts**

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)) and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). 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). Unless the agency certifies that the rule is not expected to have 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 economic impact of a rule on small entities. Section 202 of the Unfunded Mandates Reform Act (Public Law 104–4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditure by State,

local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

The agency has determined that the rule is consistent with the principles set forth in the Executive order and in these statutes. FDA finds that this rule will not have an effect on the economy that exceeds \$100 million in any one year (adjusted for inflation). The current inflation-adjusted statutory threshold is about \$110 million. Therefore, no further analysis is required under the Unfunded Mandates Reform Act. Because this rule does not impose any new costs on small entities, FDA certifies that this rule will not result in a significant economic impact on a substantial number of small entities. Thus, the agency need not prepare a Regulatory Flexibility Analysis. The agency reached the same conclusions in its proposed rule. FDA has not received any new information or comments that would alter its previous determinations.

## **VII. The Paperwork Reduction Act of 1995**

This final 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). The title, description, and respondent description of the information collection provisions are shown below 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.

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

*Description:* FDA is amending its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide substantial evidence of effectiveness 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 the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials

are not feasible prior to approval. In these circumstances, when it may be impossible to demonstrate effectiveness through adequate and well-controlled studies in humans, FDA is providing that certain new drug and biological products intended 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 taking 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<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.610(b)(2) and 314.630 601.91(b)(2) and 601.93	1	1	1	5	5
314.610(b) and 314.640 601.91(b) and 601.94	1	1	1	240	240
<b>Total</b>					<b>245</b>

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL DISCLOSURE/RECORDKEEPING BURDEN<sup>1</sup>

21 CFR Section	No. of Record-keepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
314.610(b)(2) and 314.630 601.91(b)(2) and 601.93	1	1	1	1	1
314.610(b) 601.91(b)	1	1	1	1	1
<b>Total</b>					<b>2</b>

<sup>1</sup> 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 parts 310 and 600 (21 CFR parts 310 and 600), and 314. 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 AER; 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.

The information collection provisions in this final rule have been approved under OMB control number 0910-0423. This approval expires December 31, 2002. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

### **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, 21 CFR parts 314 and 601 are amended as follows:

**PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW 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, 355a, 356, 356a, 356b, 356c, 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 When Human Efficacy Studies Are Not Ethical or Feasible**

Sec.

314.600 Scope.

314.610 Approval based on evidence of effectiveness 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 When Human Efficacy Studies Are Not Ethical or Feasible****§ 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. 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; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy

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 the products to which it does apply.

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

(a) 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 studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, 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.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies*. The applicant must conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such

studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure 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 ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product, such as:

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

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

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For drug products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must 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. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the drug product for the use approved under this subpart, if possible.

#### **§ 314.620 Withdrawal procedures.**

(a) *Reasons to withdraw approval.* 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 ensure 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 functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

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

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

(2) The presiding officer, the advisory committee members, 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 requirements 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 must 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 must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

#### **§ 314.650 Termination of requirements.**

If FDA determines after approval under this subpart that the requirements established in §§ 314.610(b)(2), 314.620, and 314.630 are no longer necessary for the safe and effective use of a drug product, FDA 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 ensured 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, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

4. Subpart H, consisting of §§ 601.90 through 601.95, is added to read as follows:

### **Subpart H—Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible**

Sec.

601.90 Scope.

601.91 Approval based on evidence of effectiveness from studies in animals.

601.92 Withdrawal procedures.

601.93 Postmarketing safety reporting.

601.94 Promotional materials.

601.95 Termination of requirements.

## **Subpart H—Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible**

### **§ 601.90 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. 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; and field trials to study the product's efficacy after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy 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 the products to which it does apply.

### **§ 601.91 Approval based on evidence of effectiveness from studies in animals.**

(a) FDA may grant marketing approval for a biological product for which safety has been established and for which the requirements of § 601.90 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, 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.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies*. The applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure 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 ensure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:

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

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

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must 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. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible.

#### **§ 601.92 Withdrawal procedures.**

(a) *Reasons to withdraw approval.* 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 ensure 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 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 functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

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

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

(2) The presiding officer, the advisory committee members, 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.

**§ 601.93 Postmarketing safety reporting.**

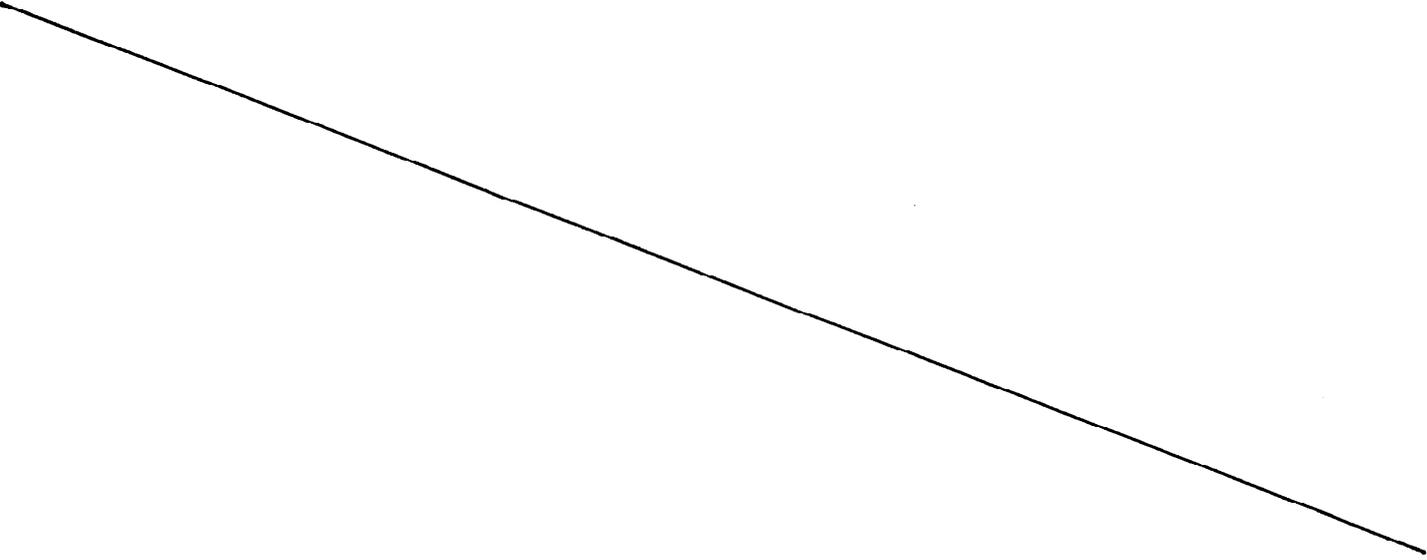
Biological products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

**§ 601.94 Promotional materials.**

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must 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 must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

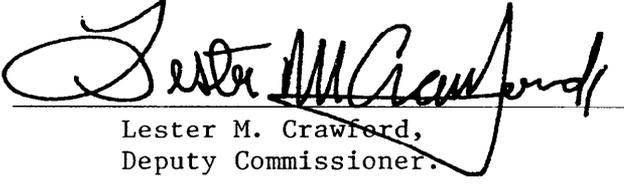
**601.95 Termination of requirements.**

If FDA determines after approval under this subpart that the requirements established in §§ 601.91(b)(2), 601.92, and 601.93 are no longer necessary for the safe and effective use of a biological product, FDA will so notify the applicant. Ordinarily, for biological products approved under § 601.91, 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 § 601.91, the restrictions would no longer apply when FDA determines



that safe use of the biological product can be ensured 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 23, 2002.

  
Lester M. Crawford,  
Deputy Commissioner.

[FR Doc. 02-????? Filed ??-??-02; 8:45 am]

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Dawn P. Hawkins