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**Tuesday
October 5, 1982**

**REGISTRATION
REQUIREMENTS
FOR
BIOLOGICAL
PRODUCTS**

Part III

**Department of
Health and Human
Services**

Food and Drug Administration

**Licensing; Reclassification Procedures To
Determine That Licensed Biological
Products Are Safe, Effective, and Not
Misbranded Under Prescribed,
Recommended or Suggested Conditions
of Use**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 601

[Docket No. 80N-0523]

Licensing; Reclassification Procedures To Determine That Licensed Biological Products Are Safe, Effective, and Not Misbranded Under Prescribed, Recommended or Suggested Conditions of Use

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising regulations on review and classification of biological products. It is issuing new regulations for reclassifying Category IIIA biological products (recommended for continued licensing, manufacturing, and marketing pending further study). It is further amending the regulations to permit interim marketing pending completion of clinical studies of certain reclassified biological products found to be safe and presumptively effective for which there is a compelling medical need and for which there is no suitable alternative therapeutic, prophylactic, or diagnostic agent.

DATE: Effective November 6, 1982.

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SUPPLEMENTARY INFORMATION

I. Background

In the *Federal Register* of January 16, 1981 (46 FR 4634), FDA proposed to revise the classification procedures for biological products prescribed in § 601.25 (21 CFR 601.25). Under existing classification procedures, each biological product licensed before July, 1972, has been reviewed by one of six qualified advisory review panels. The review determines whether the licenses for the biological products meet contemporary standards of safety, purity, and potency (the statutory standard for licensing biological products under section 351 of the Public Health Service Act (42 U.S.C. 262)). The review also determines whether the biological products are effective for their

labeled uses and therefore not misbranded within the meaning of section 502(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(a)). Each of the six advisory review panels submitted its final report to FDA. FDA responses to each report are summarized in the January 16, 1981 proposal.

Each advisory review panel report classifies products into one of the three following categories:

1. Category I: Biological products determined by the panel to be safe, effective, and not misbranded. See § 601.25(e)(1).

2. Category II: Biological products determined by the panel to be unsafe, ineffective, or misbranded. See § 601.25(e)(2).

3. Category III: Biological products determined by the panel not to fall within either Category I or II because the available data are insufficient for classification and further testing is therefore required. See § 601.25(e)(3). These products fall into two subcategories:

a. Category IIIA: Biological products recommended for continued licensing, manufacturing, and marketing while questions raised on the products are being resolved by further study. This recommendation is based on an assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time.

b. Category IIIB: Biological products that a panel recommends should not be marketed and should not be licensed for general use while further studies are undertaken.

In February 1980, the Public Citizen Health Research Group (HRG), a private organization, filed a petition requesting that FDA remove from the market all biological products which have not been shown to be effective. Specifically, HRG requested that the Category IIIA designation be eliminated and that those products found by a panel to have inadequate evidence of effectiveness be removed from the market. Although disagreeing with HRG's contention that such an action was mandated by law, FDA proposed new procedural regulations to eliminate the Category IIIA designation. Copies of the petition, the agency's response, and other related correspondence are on file with FDA's Dockets Management Branch, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

The revised procedural regulations provide for the reexamination by an advisory review panel (or committee) of the available data for each Category IIIA product. These advisory review

panels will either be newly established, or the agency may recharter one or more of the advisory review panels involved in the original biologics efficacy review. Each panel would recommend, based on the available evidence, whether each product should be considered safe, effective, and not misbranded (Category I) and therefore eligible for continued licensing and marketing, or unsafe, ineffective, or misbranded (Category II). Those Category IIIA products found to meet standards of safety and effectiveness consistent with state-of-the-art methodology for those products would be placed in Category I and would remain on the market. In addition, those Category II products designated as safe and presumptively effective and for which there is a compelling medical need with no suitable alternative therapeutic, prophylactic, or diagnostic agent also would be permitted to remain on the market pending completion of further studies.

Interested persons were given until March 17, 1981, to file written comments. At the written request of two interested persons, FDA announced in the *Federal Register* of March 17, 1981 the extension of the comment period until May 18, 1981 (46 FR 17063). Subsequently, eight additional requests to extend the original comment period were received. Approximately 10,000 letters of comment were received, including letters from private citizens, members of Congress, physicians, health organizations, and affected manufacturers, nearly all of which were opposed to the proposed rules. Most of the letters were expressions of concern that under the new procedures the availability of certain biological products, particularly allergenic extracts, would be jeopardized. The letters rarely commented on the specific text of the proposed regulations. Indeed, many of the letters were apparently written with the misunderstanding that the proposed rules would result in the removal of allergenic extracts from the market. The specific comments received and FDA's response are discussed below. The agency also believes that a discussion is warranted of the overall concepts of the procedural regulations and the reasons that FDA is proceeding to final rulemaking.

II. Overview of the Final Regulations

FDA recognizes that the reclassification procedures could be perceived to result in the removal of a number of biological products from the marketplace. The reclassification procedures were open to this

interpretation because the scientific criteria for reclassifying Category IIIA products were not specified in the proposed rules. These scientific criteria will be considered and recommended to the agency by the advisory review panels as part of the reclassification process. Accordingly, FDA cannot predict the specific criteria that will be established as an acceptable standard of effectiveness for each particular class of products. However, it is incorrect to assume that all Category IIIA products will be reclassified into Category II as unsafe, ineffective, or misbranded and removed from the marketplace.

The scientific criteria established and used by the previous advisory review panels for determining the regulatory category (I, II, IIIA, or IIIB) for each product may not be appropriate for reclassifying Category IIIA products. Because of the availability of Category IIIA, previous advisory review panels could reasonably recommend standards of effectiveness which would necessitate scientific methodology not previously used within the affected industry for that group of products. Previous advisory panels were at liberty, through the assignment of Category IIIA, of stimulating further research on the products under review which would ultimately resolve any doubts concerning the effectiveness of the product, while not immediately jeopardizing the availability of the product. (See, for example, the discussion of the recommendations of the Panel on Review of Allergenic Extracts in response to comment 1 below.)

The advisory review panels that will review Category IIIA products under the revised procedures will not have this prerogative. Except in limited circumstances, a product must be found safe, effective, and not misbranded on the basis of currently available data to justify its continued marketing. Advisory review panels involved in the reclassification process will be obligated to recommend standards of effectiveness consistent with the available technology and readily obtainable through the use of clinical and laboratory methodology that has already been recognized by the general scientific community as practical and applicable to the products under review. Consequently, no products will be removed from the market because of the imposition of standards of effectiveness which the biological products industry is, as yet, unable to meet because of the lack of suitable technology. It is not the agency's objective that the revised procedures precipitate the removal of

any particular class of biological products from the market or that a significant number of biological products commonly used and widely accepted as a part of the medical armamentarium become suddenly unavailable to medical practitioners.

FDA acknowledges, however, that the reclassification process may result in certain additional biological products being placed in Category II and their licenses subject to revocation procedures. The advisory panels and FDA will consider the potential public health impact of removing each Category II biological product from the market. As provided in § 601.26 (c)(2) and (d), FDA will permit the continued marketing, pending completion of additional testing, of those Category II biologic products for which there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent available in sufficient quantities to meet current medical needs. In addition, for those products for which interim marketing could not be permitted, each manufacturer would be offered an opportunity for hearing on a proposal to revoke the product's license. Through these proceedings, a manufacturer would have the opportunity to demonstrate that its product meets the appropriate scientific standards and should continue to be marketed.

The public Health Service Act (PHS Act) requires that biological products be shown to be safe, pure, and potent. FDA's obligation is to ensure that manufacturers of biological products establish that their products continue to meet these standards. The agency considers the reclassification process to be the fairest and most expedient means of fulfilling this obligation. Accordingly, through this final rulemaking, FDA is adopting the revised procedures for the reclassification of Category IIIA biological products.

III. Comments on the Proposal

Over 10,000 comments were filed in response to the January 16, 1981 proposal. A summary of the points raised in the comments and FDA's responses follow.

A. Impact on Specific Products

1. The majority of the comments expressed concern that under the proposed procedures allergenic extracts would no longer be available for treating allergy patients. Many of these comments related the experiences of the commenters, or the commenters' relatives, acquaintances, or patients, as allergy sufferers. The comments recounted the perceived success of using

allergenic extracts to alleviate the sometimes severely debilitating symptoms of allergy. Many comments observed that no alternative means of therapy for the treatment of allergies is as safe and effective as use of allergenic extracts under a physician's supervision. Some comments feared that with the removal from the market of licensed allergenic extracts, physicians may be forced to use locally made extracts of a lesser quality and that an illegal market for these products may ensue. Other comments contended that the removal of allergenic extracts from the market would deny physicians and the general public the personal freedom of choice to select an allergy therapy they thought appropriate. Accordingly, the comments recommended that the existing regulations on allergenic extracts be retained and opposed the proposed rule change which could result in allergenic extracts being unavailable to doctors for treating allergy patients.

FDA believes that the comments' concern that allergenic extracts will no longer be available is unjustified. There is no reason to expect that most of the important licensed allergenic extracts will be removed from the market once the reclassification process is completed. The effectiveness of all Category IIIA allergenic extracts will be determined as part of the reclassification process. All interested persons will have the opportunity to comment during the course of that process. Thus, comments concerning the effectiveness of allergenics are premature.

The Panel on Review of Allergenic Extracts (the Panel) has submitted its final report to FDA. Although the Panel recommended that four generic extracts be placed in Category I as fully safe and effective, all specific licensed products of these generic varieties were recommended for Category IIIA. For over 1,300 of the 1,600 generic varieties of extracts reviewed, the Panel recommended that they be placed in Category IIIA for therapeutic use. For the majority of Category IIIA products, a coordinated program of controlled clinical studies was recommended. Furthermore, the Panel found some preliminary laboratory work, e.g., development of potency assays and reference standards, were prerequisite to the successful conduct of the recommended studies.

FDA is aware that many allergenic extracts may not be amenable to controlled clinical trials. In collaboration with licensed manufacturers of allergenic extracts, independent of the review process, FDA

is developing means of establishing more precise standards and potency procedures for allergenic extracts. The successful completion of the studies recommended by the Panel would represent a significant scientific advancement in the clinical and laboratory testing of allergenic extracts. FDA would not consider it reasonable to base revocation proceedings upon the fact that licensed manufacturers and the scientific community have been unable, up to this time, to develop the scientific methodology necessary to conduct the testing recommended by the Panel. Rather, it will be the obligation of the Panel conducting the reclassification review to reexamine the scope of evidence currently available regarding the effectiveness of allergenic extracts and determine what the current practices are for the responsible assessment of the effectiveness of allergenic extracts. Furthermore, the Panel must determine whether these contemporary standards are readily applicable to each type of product under review. Products that do not meet the applicable contemporary standards will be subject to revocation proceedings. FDA believes that although certain biological products may become unavailable, this process will ensure that available allergenic products are safe, pure, and potent as required by the Public Health Service Act.

FDA remains committed to meeting its obligation of ensuring that drug products are safe and effective as required by applicable law. To further this purpose, FDA will require the updating of evidence concerning the effectiveness of allergenic extracts as suitable technology is developed.

2. Several comments said FDA should support development of potency tests and standards for allergenic extracts, rather than to take action to remove them from the market.

As described above, in collaboration with licensed manufacturers of allergenic extracts, FDA is developing methods to establish more precise standards and potency procedures for allergenic extracts. This program has included workshops for interested persons in order to demonstrate methods and equipment used in performing tests and obtaining results (see 45 FR 76251). In the Federal Register of July 31, 1981 (46 FR 39129), the agency issued a final rule which codified a more precise and reliable potency test for measuring the antigen E potency of allergenic extracts prepared from short ragweed pollen. The agency is also developing procedures for measuring the potency of allergenic extracts, including

isoelectric focusing and the radioallergosorbent test (RAST). As these methods become fully developed, FDA will consider requiring their appropriate use to substantiate the potency and effectiveness of allergenic extracts.

The development of additional tests and standards for allergenic extracts does not, however, eliminate the requirement that manufacturers establish that allergenic products meet current standards of safety, purity, and potency.

3. One comment recommended a specific method of immunological testing for demonstrating the potency of allergenic extracts. The comment recommended that extracts shown potent by the specified method be placed in Category I until other methods to substantiate effectiveness are developed.

A decision on what evidence of potency and effectiveness should be available to justify a Category I designation for allergenic extracts or other biological products will be made during the reclassification process based upon the recommendations of the appropriate advisory review panel and the comments of the interested public. The advisory review process provides opportunity for public participation, and all scientific opinions will be considered.

4. Eight comments requested that allergenic extracts be removed from the market because they are ineffective, unsafe, or both. For seven of the comments, the recommendation was based on personal experiences of having allergic symptoms which were not alleviated by the use of allergenic extracts. No data were submitted to support these comments.

The effectiveness of all allergenic extracts will be determined as part of the reclassification process. All interested persons will have the opportunity to comment during the course of that process. Thus, comments concerning the effectiveness of allergenics are premature. While therapy with allergenic extracts may not always be effective, the personal experience of these commenters is not reliable evidence of the lack of effectiveness of allergenic extracts and would not be considered in determining the effectiveness of those products. See § 601.25(d)(2). The advisory review panels involved in the reclassification process will consider all available reliable evidence in determining the effectiveness of allergenic extracts.

5. The agency received several comments from concerned citizens who

had relatives, or were themselves, undergoing therapy with allergenic extracts asking whether the proposal to reclassify allergenic extracts was based on a finding that the products were harmful and might endanger a patient's health.

FDA is unaware of any data that would call into question the safety of those allergenic extracts currently in Category IIIA. The Panel on Review of Allergenic Extracts found allergenic extracts to be safe when used in accordance with generally accepted principles of immunotherapy, and the agency agrees with this finding.

6. Approximately 100 comments, many in form-letter format, recommended that Staphage Lysate (SPL), bacteriophage lysate of *Staphylococcus aureus* indicated in certain *S. aureus* infections, continue to be available to physicians. Several comments stated that therapy with SPL had alleviated a variety of serious conditions, against which other forms of therapy had failed. Two of these comments noted that, because of the small number of patients for whom SPL therapy is successfully undertaken, it will be difficult to select an appropriate population for demonstrating the product's effectiveness through controlled clinical studies, even though the product is effective and irreplaceable for treating certain patients.

Staphage Lysate was reviewed by the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" which recommended that the product be placed in Category IIIB. As announced in the final rule of January 5, 1979 (44 FR 1544), additional data were subsequently received from the manufacturer, Delmont Laboratories, adequate to reclassify SPL into Category IIIA.

SPL will be reclassified with all other Category IIIA products. The standard of effectiveness of SPL will be consistent with the current state-of-the-art for biologics testing. Thus, the difficulty of selecting the appropriate population for demonstrating SPL's effectiveness will be taken into account in reclassifying it.

Although the agency will not delay the reclassification process to accommodate the belated submission of additional data, the agency and the appropriate advisory review Panels, if still in session, will at any time review additional data concerning any product subject to reclassification. Data submitted before the publication of the applicable reclassification final rule will be reviewed to determine the data's

effect upon the product's final classification. After final classification, additional data may be submitted to support a change in regulatory status, e.g., relicensure or continued licensure, of the product. Accordingly, a manufacturer will have continued opportunity to demonstrate the effectiveness of its product, while the expedient completion of the reclassification process is assured.

7. One comment recommended that the reclassification procedures be expanded to include the re-review of Category IIIB products—biologics for which available data are insufficient to determine their safety and effectiveness and should not continue in interstate commerce while further studies are undertaken. As bases for the recommendation, the comment noted that under the proposed reclassification procedures biological products would be reviewed under revised standards of effectiveness and Category IIIB products might be upgraded to Category I under these new standards. Furthermore, the comment noted that Category IIIB products could be permitted to remain on the market pending completion of further studies if a compelling medical need is shown and there is no suitable alternative therapeutic, prophylactic, or diagnostic agent.

FDA does not accept this comment. For all biological products placed in Category III, the panel found insufficient evidence to substantiate fully the product's effectiveness. To differentiate between Category IIIA and IIIB products, each advisory review panel assessed the potential benefits and potential risks likely to result from the interim use of the product while questions concerning the product were being resolved by further study. The Category IIIB designation represents a finding that the potential risks of marketing a product outweigh the potential benefits, and therefore these products should not be marketed pending the completion of additional studies. In the interest of the public health, the agency would not accept revised standards of effectiveness that would allow the continued marketing of a product for which the potential risks, including the risk that the product is not effective, outweigh the potential benefits.

Of course, even if Category IIIB products are not reviewed as part of the reclassification process, interested persons may at any time submit to the agency additional evidence regarding the product. The additional evidence will be assessed by FDA to determine whether a reclassification of the

regulatory status of the product may be warranted. If the additional evidence demonstrates that the product meets standards comparable to those applicable to similar products placed in Category IIIA, the agency will submit the available evidence on the product to the appropriate advisory group for review and reclassification.

In addition, following the adoption of a panel's Category IIIB recommendation, each manufacturer of a Category IIIB product is offered an opportunity for hearing on a proposal to revoke the product's license. At that time the manufacturer and other interested persons may submit additional evidence to show that there is a substantial issue of fact affecting the agency's basis for the proposed license revocation. Through these proceedings, a manufacturer has the opportunity to demonstrate that its product meets the appropriate contemporary scientific standards and should continue to be marketed.

8. Several comments expressed concern that the proposed rule could possibly result in allergenic extracts for veterinary use being removed from the market.

Allergenic extracts in interstate commerce for veterinary use are regulated by the United States Department of Agriculture and not by the FDA. Accordingly, the proposed rule should not affect allergenic extracts for veterinary use.

B. Legal, Economic, and Policy Questions

9. Several comments argued that the existing biological efficacy review process is lawful and that there is no legal justification for proposing to change this process. Several comments argued that the reclassification process would serve no useful purpose and would be time-consuming, expensive, and unduly burdensome. One of these comments included a 22-page memorandum supporting the legality of the existing review process.

FDA agrees that the existing biologics efficacy review process is permitted by applicable law. A detailed discussion of the agency's legal authority is contained in the preamble to the January 16, 1981 proposed rule (46 FR 4636). The agency believes it may nevertheless lawfully change and improve the procedure. Moreover, in view of the work already completed by the advisory review panels involved in the existing efficacy review, the reclassification procedures should not be unduly time-consuming, expensive, or burdensome.

10. Numerous comments said the current review procedures are adequate

and a change is unnecessary. One of these comments noted that allergenic products present unique scientific problems which were taken into account in establishing the current review process so that patients would not be deprived of useful medical products. This comment said that under the current review process, effectiveness of allergenic products can be shown without interfering with the availability of important forms of therapy. Another comment said the risks and benefits of Category IIIA products had already been examined by the previous advisory review panels and the panels had concluded that the benefits outweigh the risks. Finally, one comment contended that the agency had not explained why it is necessary to revise current procedures.

The agency rejects these comments. The agency believes that the revised procedures will more clearly define the scientific and regulatory status of products formerly designated as Category IIIA. Those which are safe and effective (Category I) by currently available standards will be identified. If further testing is necessary, and the products are allowed to remain on the market in Category II, the procedures will assure that they are safe and that there is a medical consensus about their value. Although the six previous advisory review panels did consider the risks and benefits of all Category IIIA products, there was no request for them to determine whether the products were medically necessary, nor were the products compared with alternative forms of therapy. The agency believes that these determinations are useful in ensuring that only beneficial products remain on the market.

Finally, the agency is well aware that many biological products may not be readily amenable to controlled clinical trials. This issue was recognized in FDA's proposal, and some of the particular problems presented by the testing of allergenic products were discussed. See 46 FR 4637-4638. The agency does not intend to require that any biological product meet a higher standard than is feasible considering the current state-of-the-art of biologics testing. Conversely, the continued licensing of products without reasonable evidence of safety and effectiveness for the labeled indications cannot be condoned. Should future scientific advances create questions concerning the safety or effectiveness of a licensed product, adequate provision for the resolution of questions is provided under current biologics regulations, e.g., 21 CFR 601.5 through 601.9.

11. A comment argued that by eliminating the Category III classification but providing for the interim marketing of certain biologics reclassified into Category II, the agency is, de facto, creating a new Category III which presents the same procedural weaknesses that resulted in the former classification system that had been challenged in HRC's petition. The comment contended that the new reclassification system would be subject to further litigation which would result in further procedural changes and ultimately cause certain biological products to be unavailable to those who need them.

FDA disagrees with the comment. The reclassification procedures are responsive to applicable legal requirements and to the needs of the public at large. The proposed provision for interim marketing of biological products that are found to be medically necessary and for which there is no suitable alternative therapeutic, prophylactic, or diagnostic agent for the product is quite different from Category IIIA. Category IIIA has been a broad classification that permitted the continued marketing of a product even though the product might not have been a medical necessity or might have been intended to treat a condition for which there was suitable alternative therapy. Thus, Category IIIA products will not automatically meet the strict criteria the agency is establishing for the continued marketing of a product under Category II pending further testing.

12. Some comments said allergenic extracts are not drugs and therefore should not be subject to the same regulatory requirements as chemically derived drugs.

FDA rejects these comments. Any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man is a drug within the meaning of section 201(g)(1) of the act. As such, it must be effective for its labeled uses and therefore not misbranded under section 502(a) of the act, and it must be safe, pure, and potent, as required under the PHS Act.

Although all biological products are drugs within the meaning of the act, they are not subject to the new drug provisions. Biological products are licensed before marketing under section 351 of the PHS Act. The criteria for licensure under the PHS Act are that products be safe, pure, and potent. Accordingly, the agency has consistently applied scientific standards appropriate for biological products which, in the case of standards for purity and effectiveness, for example,

may not be identical to those applied to chemically derived drugs.

13. One comment argued that the reclassification procedures improperly shift the burden of proof regarding the requirement for license revocation. The comment said the burden of establishing lack of effectiveness for a previously licensed biological product should rest upon the agency.

The agency rejects this comment. When the agency proposes to revoke a license, it bears the initial burden of adducing new information, which may consist of a reevaluation of the information available when the product license was approved, that shows that the drug is not shown to be effective. See *Hess & Clark v. FDA*, 495 F. 2d 975 (D.C. Cir. 1974). To meet its burden, the agency need only raise significant doubts as to the prior showing of effectiveness. Once this threshold burden is met, the manufacturer is required to prove that the product is effective. Thus, the reclassification procedures are not improper in shifting the burden of proof to the manufacturer.

14. One manufacturer of a Category IIIA product argued that the proposed reclassification procedures are unfair because they could result in a Category IIIA product's being removed from the market before completion of testing now being conducted.

The agency disagrees with the contention that the procedures are unfair. The agency believes it is justified in removing from the market any biological product which does not meet the current efficacy standards and for which there is no compelling medical need or for which there is a suitable alternative treatment. Several manufacturers have been engaged in additional studies since 1979 to document the effectiveness of biological products placed in Category IIIA. All data and information submitted up to the time of publication of the final rule reclassifying these biological products will be considered by FDA in determining the appropriate classification (Category I or II). In addition, a manufacturer of a product ultimately placed in Category II that seeks to dispute the agency's findings will be given an opportunity for a hearing to present its views. Thus, the agency does not believe that the reclassification procedures are unfair.

15. One comment said the proposed rule was a "major rule" under Executive Order 12291 because it would have an annual effect on the economy of \$100 million or more. The comment noted that the sales of allergenic extracts are in excess of \$40 million and the fees for

medical services related to these products are several times that amount.

The agency rejects this comment. This rule is not a major rule as defined by Executive Order 12291. The rule is procedural and does not, indeed cannot, directly result in any product's removal from the marketplace. Moreover, any assumptions at this time about which, if any, products may eventually be removed from the marketplace are purely speculative. When each advisory group's recommendations for reclassification of Category IIIA products and FDA's responses are published in a proposed rule, the agency will be able to determine with greater certainty the economic impact of reclassifying biological products. At that time, each proposal will be assessed under Executive Order 12291 to determine whether it is a major rule.

C. Procedural Questions

16. Several comments urged that members of certain organizations with interests in the science of allergy medicine be appointed to the advisory review panels involved in the reclassification of Category IIIA allergenic extracts. The comments urged that the panel membership be as diverse as possible to ensure representation of all responsible medical and scientific opinions.

FDA agrees that the panel membership should represent all responsible opinion. Further, the agency believes that the panel should consist of qualified persons selected on the basis of their expertise in the subject matter with which the panel is concerned. These criteria were met in the selection of the former Panel on Review of Allergenic Extracts, which included members that are highly qualified in the field of allergy medicine, representative of responsible medical and scientific opinion, and familiar with the data presented to FDA on the safety and effectiveness of the Category IIIA allergenic extracts. The agency therefore believes that the public interest would be best served by asking the former allergenic panel to serve as the new Panel for the purpose of reclassifying those products originally recommended for Category IIIA. If not all the previous panel members are available to serve, FDA will ask for the nominations of appropriately qualified persons for membership to fill the vacancies. Any organization may nominate one or more of its members for service on the panel. However, members would be selected on the basis of their expertise, without consideration of their professional affiliations.

17. One comment recommended that a biologic product be reviewed and reclassified only after it is definitively placed in Category IIIA as a result of a final rule issued under § 601.25(g). The comment contended that the notice and comment procedures of the reclassification process do not compensate for summarily interrupting a review process in which manufacturers have been participating in good faith for a number of years.

FDA disagrees with this comment. The agency has yet to respond by proposed rulemaking to the recommendations contained in the reports of three advisory panels: the Panel on Review of Blood and Blood Derivatives, the Panel on Review of Bacterial Vaccines and Toxoids, and the Panel on Review of Allergenic Extracts. The information concerning all products recommended for Category IIIA by these panels will be forwarded to the appropriate advisory review panel for reclassification. During the reclassification process, interested persons, including the manufacturers of products being reclassified, will be offered the same opportunity for participation in the decisionmaking process as would be offered by the existing procedures under § 601.25. Specifically, interested persons may attend meetings and appear before an advisory review panel; notice will be provided through publication of the advisory review panel's report and FDA's responding proposed rule; and opportunity for comment and submission of additional information will be offered by the proposed rule; the final rule will provide notice of the agency's decision; and finally, for those products reclassified into Category II, a notice of opportunity for hearing will be published on the agency's intent to revoke the product license. FDA believes that these procedures offer adequate opportunity for the participation of all interested persons; therefore, the agency sees no benefit derived from delaying the reclassification procedures while duplicative procedures are undertaken to classify products as Category IIIA through final rulemaking.

18. One comment suggested that FDA eliminate the requirement for publication of a proposed order containing FDA's initial conclusions concerning the report of each advisory review panel. See § 601.26(d). The comment said the proposed order is unnecessary because advisory review panel reports have been released to the public, and FDA could therefore ask for

public comment on the reports while FDA is evaluating the reports.

FDA does not agree with this suggestion. The agency believes that the substitute procedure proposed by this comment would not give the public an opportunity to comment on the agency's reaction to the panel report. The opportunity to comment is particularly important where the agency disagrees with the recommendation of a panel. Without a proposed order, the public could assume, perhaps incorrectly, that FDA agrees with the recommendations in the panel report and thus miss an opportunity to comment.

FDA believes that public participation is an important aspect of all agency rulemaking proceedings, especially where, as here, the public has demonstrated a very strong interest in the subject of the proceeding. Accordingly, there is no justification for eliminating the public's opportunity to comment on the agency's proposed order issued under § 601.26(d).

19. One comment addressed § 601.25(d)(2), which provides guidance for assessing evidence of effectiveness under the existing biologics efficacy review and, by reference, for the reclassification process. The regulation states that controlled clinical studies may be waived for other forms of evidence if controlled clinical studies are found not to be reasonably applicable or not essential to substantiating the effectiveness of a biological product. The comment argued that this statement inappropriately implies that controlled clinical studies are favored over other types of evidence and should be required unless unusual circumstances justify a special exemption for a particular product. The comment recommended that the waiver concept be eliminated as inappropriate and misleading and that the regulations be amended to state that forms of evidence other than "substantial evidence" are equally acceptable to document a product's effectiveness and to justify a Category I designation.

FDA does not accept this comment. The agency does indeed consider controlled clinical studies to be the preferred form of evidence for documenting a product's effectiveness. As stated elsewhere in this document, the agency recognizes that such studies may not, as yet, be readily applicable to many types of biological products and therefore should not be required. However, the agency believes that controlled clinical studies should be performed in circumstances where clinical studies have been firmly established as feasible for establishing

the effectiveness of a biological product. Accordingly, the agency is retaining the requirement that controlled clinical studies be used to establish the effectiveness of a biological product, unless shown to be inapplicable or not essential for the product under review.

D. Interim Marketing Pending Completion of Additional Testing

20. One comment on § 601.26(c)(2) and (d) recommended the deletion of the provisions to allow the continued marketing of certain Category II biological products pending the completion of additional studies. The comment argued that there is an inherent risk associated with any potent drug, including a biological product, and that this risk should overrule any justification for allowing the continued marketing of a biological product of dubious effectiveness. Other comments argued that the standard for determining whether the continued marketing of a product pending testing should be permitted is too narrow and would result in forcing products off the market. One of these other comments said the only requirements should be that there be strong evidence that the biologic is safe, presumptive evidence that it is effective, and widespread medical acceptance of its use.

FDA rejects these comments. The interim marketing provision in § 601.26(c)(2) and (d) is neither too broad nor too narrow. Although there is an inherent risk associated with any drug, the advisory review panels involved in the existing biologics efficacy review process have already determined that the potential benefits of continued marketing of all Category IIIA products on an interim basis outweigh any potential risks associated with the use of these products. Moreover, the reclassification regulations require that there be evidence, indicating presumptively, the effectiveness of a Category II product before interim marketing pending completion of additional studies may be permitted. Accordingly, the public will not be subjected to any undue risks as a result of the interim marketing provisions of the reclassification regulations.

As to those comments arguing that the interim marketing provision is too narrow, the agency believes that there is no justification for the interim marketing of a product requiring further efficacy testing if there is no compelling medical need for the product or if there is a suitable alternative product. Accordingly, the agency believes that the additional criteria contained in the proposed rule are not too narrow.

21. One comment suggested that additional requirements be added to part of the interim marketing provision that requires the agency to determine "the likelihood that, based upon existing data, the effectiveness of the product eventually can be established by further testing" under § 601.26(c)(2). The comment suggested that for a product to be marketed pending further testing, FDA should require that there be some evidence, albeit inconclusive, that the drug had some benefits. The comment further suggested that in reclassifying such a product, the advisory review panel and FDA should describe the data relied upon, set forth the panel's and FDA's evaluation of the data, and explain why this testing shows that the drug has a benefit.

Although the requirements suggested by this comment are implicit in the propose regulation, FDA has amended the final rule to make clear that evidence of the product's effectiveness must be available, either specific to that product or generic to that class of products, to permit the continued marketing of the product pending further testing. Such evidence need not conclusively demonstrate the product's effectiveness, but should be adequate to show that the product is presumptively effective and, therefore, of benefit. The regulation further requires that this evidence be described and evaluated by the advisory review panels and FDA, and that there be an explanation why the evidence shows that the product will provide a benefit. The agency could not reasonably determine that the effectiveness of a product can eventually be established without some evidence which suggests that the product is of benefit.

22. One comment suggested that FDA consider a product's risks when determining whether to allow the product to be marketed pending further testing.

FDA agrees with this comment and has amended § 601.25(c)(2) and (d) to specify that the risks of a biological product should be considered when determining whether to permit a product to be marketed pending further testing.

23. One comment on § 601.26(c)(2) and (d) argued that a Category II designation of "unsafe, ineffective, or misbranded" is inappropriate for those biological products for which continued marketing is recommended pending further testing. The comment noted that under § 601.26(c)(2), a product for which a compelling medical need has been identified may not be recommended for continued marketing unless the panel determines that "based upon existing data, the effectiveness of the product

can eventually be established by further testing and new test development." The comment found this determination to be incompatible with a designation of "unsafe, ineffective, or misbranded." The comment expressed the concern that a Category II designation could lead to widespread misunderstanding that patients are receiving a product affirmatively shown to be ineffective or unsafe. Accordingly, the comment recommended that such products conditionally be placed in Category I, or in a new "Category I (Conditional)." The comment recommended that only products determined by the panel to be safe be placed in this category, to eliminate any doubts concerning safety.

FDA agrees that it is inappropriate to designate as "unsafe, ineffective, or misbranded" products to which these terms do not apply; however, it is even more inappropriate to designate such products as "safe and effective". In considering an appropriate designation for products placed in Category IIIA under the original review process, the agency notes that all of these products were found to be safe for their indicated uses. Also, under § 601.26(c)(2), as amended in the final rule, there must be evidence showing presumptively that a product is of benefit before FDA may permit continued marketing pending further testing. Accordingly, FDA is amending § 601.26(c)(2) and (d) to provide the designation of "safe and presumptively effective" for those products that the panel recommends should remain on the market pending further testing. For regulatory purposes, such products will be in Category II, and FDA will initiate a proceeding to revoke their product licenses if adequate additional studies are not undertaken.

24. One comment recommended that the agency make more specific the requirement that the panels and the agency take into account the seriousness of the disease or condition to be treated by a Category IIIA product in determining whether to allow a product to remain on the market pending further testing. The comment said that only products intended to treat a disease or condition that can be fatal, would require hospitalization, or would be so seriously incapacitating as to prevent patients from engaging in normal activities should be allowed to be marketed pending further testing.

The agency rejects this comment. The agency agrees that FDA and the panels should give careful consideration to the seriousness of the disease intended to be treated before permitting the interim marketing of a Category IIIA product that is reclassified into Category II. However, the agency does not believe it

necessary to set in the regulations a rigid standard for assessing the severity of the target disease. The agency believes that there may be a compelling medical need for some biological products that are intended to treat a disease or condition that is not life-threatening. The standard recommended by this comment could arbitrarily exclude important biological products intended to treat diseases that seriously affect a patient's health.

The agency notes that paragraph XIV of the court order in *American Public Health Assn. v. Veneman*, 349 F. Supp. 1311 (D.D.C. 1972), was not limited to drugs indicated for life-threatening or seriously incapacitating conditions. The order required FDA to expedite the removal from the market of drugs reviewed under the Drug Efficacy Study Implementation and found lacking substantial evidence of effectiveness. Paragraph XIV of the order permitted the continued marketing of "medically necessary" drugs pending the completion of clinical trials. The court did not impose a requirement that paragraph XIV drugs be limited to drugs intended to treat diseases of a defined severity, and the agency sees no reason to impose such a limitation on biological products. Accordingly, the agency does not agree that the interim marketing provision of the reclassification regulations should be limited to drugs intended for treating life-threatening or seriously incapacitating diseases.

25. One comment suggested that the reclassification regulations require the agency to describe what alternative treatment or drugs were considered in determining whether a biological product should be permitted to be marketed pending further testing and why such treatment or drugs are not suitable.

The agency agrees with this comment, and the regulation has been amended in § 601.26(c)(2) to reflect the change. The agency notes, however, that the availability of suitable alternatives may be made on a generic basis for a class of products rather than on a product-by-product basis. This is important because for some biological product categories there are thousands of similar individual products, and it would be burdensome and unnecessary to perform the same analysis for each individual product.

26. Several comments argued that the requirement that there are no suitable alternative therapeutic, diagnostic, or prophylactic agents for a biological product permitted to be marketed pending further testing was too restrictive, was not required in the

Veneman case cited above, and has no logical or scientific basis.

One of these comments argued that several DTP (diphtheria, tetanus, and pertussis) vaccines now in Category IIIA could not be marketed under the proposed procedures because there are some Category I DTP vaccines on the market. The comment argued that the removal from the market of the Category IIIA DTP vaccines would create a shortage of these vaccines. Another comment argued that the existence of a suitable alternative diagnostic or therapeutic agent is a highly subjective judgment that should be made by physicians.

FDA agrees that the "suitable alternative" criterion was not required by the court in *Veneman*; however, the agency has decided to include this criterion because the agency believes that there is no scientific or other justification for the marketing of a product that has not been adequately tested when there are suitable alternative remedies. The agency recognizes that this determination is a medical judgment. The term "suitable" will therefore be interpreted to ensure that medically necessary biological products are available to the public. For example, two biological products may be indicated to treat the same disease, but have different side effects. This difference might make one of these medications unsuitable for a particular patient and thus not a "suitable alternative" under § 601.26 (c)(2), (d), and (e).

The agency agrees that if a shortage of the suitable alternative product exists, such as the Category I DTP vaccine discussed in the comment, it is appropriate, indeed medically necessary, to permit the interim marketing of a Category II product that meets the other requirements for continued marketing pending testing. The agency has therefore amended § 601.26 (c)(2), (d), and (e) to require the agency, before permitting the interim marketing of a Category II product, to find that there is no suitable alternative therapeutic, prophylactic, or diagnostic agent for the product that is available in sufficient quantities to meet current medical needs.

E. Additional Testing and Labeling During Interim Marketing

27. One comment on § 601.26(f)(1) stated that it is scientifically impossible and not cost-effective to require within 30 days of publication of the final order the submission of protocols for, and the undertaking of, further studies that would be appropriate to resolve the

questions raised about allergenic extracts.

FDA disagrees with the contention that 30 days is inadequate time to initiate the requisite studies; however, to assure that the affected manufacturers have ample time for receiving and reviewing the final rule mandating the studies and to prepare a written statement in reply, FDA is extending the time to 60 days.

FDA believes that manufacturers will have sufficient time to submit protocols and begin testing within 60 days of publication of the final order. The necessary tests will be described in the proposed rule. Upon request, FDA will review draft protocols for additional studies at any time during the reclassification process. Because manufacturers will receive adequate notice and guidance from FDA, the agency believes that any requisite additional studies may readily be initiated, under an appropriate protocol, within 60 days of publication of the final order. As provided in § 601.26(f)(1), FDA may extend this 60-day period, if necessary to accommodate any reasonable delays.

The intent of § 601.26(f)(1) is to assure that the manufacturer is taking positive steps toward demonstrating the effectiveness of its product. A simple statement that the manufacturer intends to undertake studies would not be adequate. FDA recognizes that considerable preliminary administrative and scientific work may be necessary prior to initiating a clinical study. Accordingly, the statement submitted to FDA should indicate that the necessary preliminary actions are underway and should outline the subsequent actions that the manufacturer intends to take to resolve the questions raised about the product.

Any additional studies that may be required under § 601.26(f)(1) will be based upon already established scientific principles and will be readily applicable to the affected products. To make clear that manufacturers will not be required to conduct tests that are not scientifically feasible, the agency has deleted the phrase "and new test development" from the following sentence in § 601.26(c)(2): "The [panel] report shall also recommend with as much specificity as possible the type of further testing and new test development required * * *"

28. One comment suggested that there should be additional safeguards to ensure that manufacturers marketing biological products pending further testing do not extend the testing period without adequate justification. The

comment recommended that a definite time limit be established for all such testing and that licenses be revoked if the specified time period is not complied with.

The agency does not agree with this comment. The agency believes that the reclassification regulations are adequate for prompt, timely, additional testing. Manufacturers are required to submit, within 60 days after publication of the final order, a written statement that studies adequate and appropriate to resolve the questions raised about the product have been undertaken. If no such commitment is made, or if the commitment is inadequate, the agency must revoke the license. Manufacturers are also required to submit a progress report twice a year until completion of the studies. If the progress report is not submitted, or is inadequate, or if the studies are not being pursued promptly and diligently, or if interim results indicate that the product is not a medical necessity, the agency is required to initiate a proceeding to revoke the license. The agency believes that these safeguards are adequate to ensure that testing is completed promptly.

29. One comment recommended that patients taking biological products that are being marketed pending testing sign a consent form stating that FDA has yet to determine that the drug is effective.

The agency rejects this comment. The agency believes that the label statement required by § 601.26(f)(4) (set forth in the next numbered paragraph) is adequate to inform consumers about the status of FDA's review of the product's effectiveness. The suggested procedure is not only unnecessary, but burdensome.

It should be noted that § 601.26(f)(5) requires that informed consent be obtained from all participants in any additional studies required for biological products being marketed pending further testing.

30. One comment suggested that the word "fully" should be deleted from the following labeling statement required by § 601.26(f)(4): "The Food and Drug Administration has directed that further investigation be conducted before this product is determined to be fully effective for labeled indication(s)." The comment said the word "fully" implied that the product had been found to be partially effective.

The agency agrees that the word "fully" should be deleted from this statement, but has further amended the statement to read as follows: "The Food and Drug Administration has directed that further investigation be conducted

before this product is conclusively determined to be effective for labeled indication(s)." The agency has added the word "conclusively" to this statement because it accurately implies that there has been an initial determination of presumptive effectiveness of the product.

31. One comment addressed § 601.26(f)(4), which requires a disclosure statement for those biological products remaining on the market while undergoing further study. The comment noted that allergenic extracts are normally marketed in such small vials or in such mixtures as to make it impossible to disclose prominently the fact that further testing is necessary to determine whether the product is effective. The comment also noted that, as research on allergenic extracts continues, many allergenic mixtures will contain both some allergens to which the disclosure statement applies and other allergens that have been shown to be safe and effective. The comment therefore recommended a more general disclosure that would inform consumers that the product may contain one or more allergenic extracts that require further testing before it can be determined that they are safe and effective.

FDA does not accept this comment at this time. The agency notes that the text of § 601.26(f)(4) was codified under § 601.25(h)(4) on January 3, 1979 (44 FR 1544) and is not a new requirement. Further, § 601.26(f) sets forth general procedures for additional studies and labeling requirements for all classes of biological products requiring such additional studies. In the rulemaking to be initiated by publication of the recommendations for allergenic extracts as a proposal, FDA will consider any comments submitted concerning labeling requirements for extract mixtures containing components that have been recommended for classification into different categories.

32. The agency is amending § 601.26(f)(4) by revising the labeling box statement to accommodate the identification in the labeling of advisory groups which do not have the terms "Panel on Review of * * *" as part of their name.

F. Miscellaneous

33. At the time of the January 16, 1981 proposed rule, FDA planned to publish soon afterward the proposed orders based on the reports of the Panels on Review of Blood and Blood Derivatives and on Review of Bacterial Vaccines and Toxoids. These proposed orders have yet to be published. To avoid unnecessary delay in the reclassification

process, the agency has decided to publish this final rule on reclassification procedures before publishing the proposed rules based on the reports of these two panels. The products recommended for Category IIIA in the final reports of these panels will be reviewed and reclassified under the procedures made final here.

As announced in the preamble to the January 16, 1981 proposed rule, the products recommended for Category IIIA in the final report of the Panel Review of Allergenic extracts will be reviewed and reclassified under the procedure made final here. As announced in the **Federal Register** of April 21, 1981 (46 FR 22808), a copy of the final report is on public display and may be reviewed at the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. A copy of the final report may be obtained (\$46.50 for a paper copy and \$4.00 for microfiche)¹ from the National Technical Information Service (NTIS), U.S. Department of Commerce, Springfield, VA 22161 (703-487-4650). All correspondence to NTIS should include references to the NTIS Accession Number PB 81-18215.

As a reference, the agency is listing the products recommended for Category IIIA by the Panel on Review of Blood and Blood Derivatives and the Panel on Review of Bacterial Vaccines and Toxoids. (Note: For those products followed by the word "revoked" the product license has been revoked at the request of the manufacturer, and further regulatory proceedings will be unnecessary.)

a. *The following products were recommended for Category IIIA by the Panel on Review of Blood and Blood Derivatives:*

Whole Blood (Human) Heparinized;
Factor IX Complex (Human) (Proplex),
for use in congenital and acquired
deficiencies of factors II, VII, and X,
Travenol Laboratories, Inc., Hyland
Therapeutics Division, License No.
140;

Fibrinolytic (Human) (Thrombolysin),
Merck Sharp & Dohme, Division of
Merck & Co., Inc., License No. 2;
Fibrinolytic and Desoxyribonuclease,
Combined (Bovine), and Fibrinolytic
and Desoxyribonuclease, Combined
(Bovine), with Chloramphenicol (Elastin
powder for solution, Elastin ointment
and Elastin-Chloromycetin ointment),
Parke-Davis, Division of Warner-
Lambert Co., License No. 1.

¹ Note.—Prices subject to change; additional charges for rush handling or personal pickup.

b. *The following products were recommended for Category IIIA for all labeled indications by the Panel on Review of Bacterial Vaccines and Toxoids:*

Pertussis Immune Globulin (Human),
Cutter Laboratories, Inc., License No.
8;

Streptokinase—Streptodornase
(Varidase, Jelly) (revoked), Lederle
Laboratories, Division American
Cyanamid Company, License No. 17;
Pertussis Immune Globulin (Human),
Travenol Laboratories, Inc., Hyland
Therapeutics Division, License No.
140.

c. *The following products were recommended for Category I when used for booster immunization and for Category IIIA when used for primary immunization, by the Panel on Review of Bacterial Vaccines and Toxoids:*

Diphtheria and Tetanus Toxoids
Adsorbed (revoked), Diphtheria and
Tetanus Toxoids and Pertussis
Vaccine Adsorbed (with potassium
alum) (revoked), Tetanus Toxoid
(revoked), Tetanus Toxoid Adsorbed
(revoked), Dow Chemical Company,
License No. 110;

Diphtheria and Tetanus Toxoids
(revoked), Diphtheria and Tetanus
Toxoids Adsorbed (revoked), Tetanus
and Diphtheria Toxoids Adsorbed
(For Adult Use) (revoked), Tetanus
Toxoid (revoked), Tetanus Toxoid
Adsorbed (revoked), Eli Lilly and
Company, License No. 56;

Tetanus Toxoid, Istituto Sieroterapico
Vaccinogeno Toscano Sclavo, License
No. 238;

Diphtheria and Tetanus Toxoids
Adsorbed, Diphtheria and Tetanus
Toxoids and Pertussis Vaccine
Adsorbed, Tetanus and Diphtheria
Toxoids Adsorbed (For Adult Use),
Tetanus Toxoid, Tetanus Toxoid
Adsorbed, Lederle Laboratories,
Division American Cyanamid
Company, License No. 17;

Tetanus Toxoid Adsorbed, Merck Sharp
& Dohme, Division of Merck & Co.,
Inc., License No. 2;

Diphtheria and Tetanus Toxoids and
Pertussis Vaccine, Tetanus and
Diphtheria Toxoids Adsorbed (For
Adult Use), Tetanus Toxoid, Tetanus
Toxoid Adsorbed, Merrell-National
Laboratories, Division of Richardson-
Merrell, Inc., License No. 101 (see
below);

Diphtheria and Tetanus Toxoids
Adsorbed, Tetanus Toxoid Adsorbed,
Michigan Department of Public
Health, License No. 99;

Diphtheria and Tetanus Toxoids
(revoked), Diphtheria and Tetanus

Toxoids Adsorbed (revoked), Diphtheria and Tetanus Toxoids and Pertussis Vaccine (revoked), Tetanus Toxoid (revoked), Tetanus Toxoid Adsorbed (revoked), Parke-Davis, Division of Warner-Lambert Company, License No. 1;

Tetanus Toxoid Adsorbed, Swiss Serum and Vaccine Institute Berne, License No. 21;

Diphtheria and Tetanus Toxoids Adsorbed (revoked), Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (revoked), Diphtheria Toxoid (revoked), Tetanus and Diphtheria Toxoid Adsorbed (For Adult Use) (revoked), Tetanus Toxoid (revoked), Texas Department of Health Resources, License No. 121;

Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Wyeth Laboratories, Inc., License No. 3.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Tetanus Toxoid Adsorbed to Connaught Laboratories, Inc. Connaught was issued License No. 711 on January 3, 1978.

34. The agency has decided to retain §§ 601.25(e)(3) and (f)(3) in the biologics regulations which define Categories IIIA and IIIB and provide for the interim marketing of Category IIIA products, pending the completion of additional studies. The agency is appending a footnote to these paragraphs noting that the provisions permitting the interim marketing of certain biological products (Category IIIA products) no longer apply and are superseded by the reclassification procedures in § 601.26. The agency had originally proposed to delete these paragraphs from the regulations. By retaining these paragraphs and noting that certain provisions are no longer operative, the definitions and criteria for Categories IIIA and IIIB are preserved. In general, the agency believes that retention of these paragraphs is necessary to preserve the continuity and clarity of the procedures described under § 601.25.

35. The agency is amending the regulations by inserting requirements concerning the institutional review of clinical investigations involving human subjects. These requirements were added to § 601.25 by a final rule in the

Federal Register of January 27, 1981 (46 FR 8942) and effective on July 27, 1981. In this final rule, they are being moved from § 601.25 to § 601.26 by revising paragraph (f)(1) and adding a new paragraph (i).

36. FDA is hereby requesting interested persons to submit, for review and evaluation by the appropriate advisory review panel, published and unpublished data and information pertinent to the reclassification of Category IIIA products. Data already submitted in support of an amendment to a product license will be considered in reclassifying the product and need not be resubmitted. Data and information submitted under this notice, and falling within the confidentiality provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) will be handled as confidential. Data and information not falling within the confidentiality provisions of one or more of the above statutes will be made publicly available 30 days after publication of the proposed order to reclassify the Category IIIA biological products under review, issued under § 601.26.

The agency has examined the economic impact of this rule and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, this rule provides procedures for the review and reclassification of certain biological products previously placed in Category IIIA. This rule places no additional restrictions, requirements, or other economic burdens upon manufacturers of biological products, physicians, or consumers. Any future actions proposed in accordance with these procedural regulations will be assessed separately under Executive Order 12291 and the Regulatory Flexibility Act to determine the economic impact of the proposed action. Therefore, the agency concludes that the final rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

List of Subjects in 21 CFR Part 601

Biologics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 701, 52 Stat. 1040-1042 as amended, 1050-1051 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the

Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended) (5 U.S.C. 553, 702, 703, 704) and 21 CFR 5.11 as amended (see 47 FR 16010; April 14, 1982), Part 601 is amended as follows:

PART 601—LICENSING

1. In § 601.25, by adding a footnote to paragraphs (e)(3) and (f)(3) and by deleting paragraph (h) and designating it "reserved" and by deleting paragraph (1), as follows:

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

- * * * * *
- (e) * * *
- (3) * * * 2
- (f) * * *
- (3) * * * 2
- (h) [Reserved]
- * * * * *

2. By adding new § 601.26 to Subpart C. to read as follows:

§ 601.26 Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

This regulation establishes procedures for the reclassification of all biological products that have been classified into Category IIIA. A Category IIIA biological product is one for which an advisory review panel has recommended under § 601.25(e)(3), the Commissioner of Food and Drugs (Commissioner) has proposed under § 601.25(f)(3), or the Commissioner has finally decided under § 601.25(g) that available data are insufficient to determine whether the product license should be revoked or affirmed and which may be marketed pending the completion of further testing. All of these Category IIIA products will either be reclassified into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded) in accordance with the procedures set forth below.

(a) *Advisory review panels.* The Commissioner will appoint advisory review panels and use existing advisory review panels to (1) evaluate the safety and effectiveness of all Category IIIA biological products; (2) review the

² *Note*—As of November 8, 1982, the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under § 601.26 of this chapter. The superseded text is included for the convenience of the user only.

consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at the Commissioner's discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

(h) [Reserved]

(i) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981, shall include statements regarding each

clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent under Part 50 of this chapter. Such a study is also subject to the requirements for institutional review under Part 56 of this chapter, unless exempt under § 56.104 or § 56.105.

Effective date. This regulation becomes effective November 6, 1982.

(Secs. 201, 502, 701, 52 Stat. 1040-1042 as amended, 1050-1051 as amended, 1055-1056

as amended (21 U.S.C. 321, 352, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); secs. 4, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 702, 703, 704)

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: September 3, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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