Comments also may be submitted electronically at the following E-mail address: rule-comments@sec.gov. Comment letters should refer to File No. S7–8–98; this file number should be included on the subject line if E-mail is used. All comments received will be available for public inspection and copying at the Commission's Public Reference Room, 450 Fifth Street, N.W., Washington, D.C. 20549. Electronically submitted comment letters will be posted on the Commission's Internet web site (http://www.sec.gov).

**FOR FURTHER INFORMATION CONTACT:** Jerry W. Carpenter, Assistant Director, 202/942–4187; Thomas C. Etter, Jr., Special Counsel, 202/942–0178; or Jeffrey S. Mooney, Special Counsel, 202/942–4174, Division of Market Regulation, Securities and Exchange Commission, 450 Fifth Street, N.W., Mail Stop 10–1, Washington, D.C. 20549.

**SUPPLEMENTARY INFORMATION:** On March 5, 1998, the Commission proposed temporary Rule 17Ad-18 under the Securities Exchange Act of 1934. Rule 17Ad-18 would require all non-bank registered transfer agents to file with the Commission at least one report regarding its Year 2000 readiness. The initial report would be due no later than 45 days after the Commission adopts this rule. The follow-up reports, which would be due on August 31, 1998, and on August 31, 1999, would include an attestation by an independent public accountant that would give the independent public accountant's opinion whether there is a reasonable basis for the transfer agent's assertions in the reports. Additionally, the release contains a Commission advisory notice on its transfer agent record retention and recordkeeping requirements relating to the Year 2000.

The Commission has recently received requests from interested persons to extend the comment period for this release. The Commission believes that extending the comment period is appropriate in order to give the public additional time to comment on the matters the release addresses. Therefore, the comment period is extended until April 27, 1998.

By the Commission.

Dated: April 14, 1998.

**Margaret H. McFarland,**

*Deputy Secretary.*

[FR Doc. 98–10336 Filed 4–17–98; 8:45 am]

BILLING CODE 8010–01–P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

## 21 CFR Part 610

**[Docket No. 97N–0449]**

**RIN 0910–AB51**

## Revisions to the General Safety Requirements for Biological Products; Companion Document to Direct Final Rule

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

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the biologics regulations by adding cellular therapy products to the list of products exempted from the general safety test (GST) and by adding an administrative procedure for obtaining exemptions from the GST requirements. This proposed rule is a companion document to the direct final rule published elsewhere in this issue of the **Federal Register**. FDA is taking this action because the GST may not be relevant or necessary for many types of biological products, including cellular therapy products, currently in various stages of development.

**DATES:** Comments must be received on July 6, 1998. Submit written comments on the information collection provisions by June 19, 1998.

**ADDRESSES:** Submit written comments on the proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Dano B. Murphy, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

**SUPPLEMENTARY INFORMATION:**

### I. Background

This proposed rule is a companion to the direct final rule published in the final rules section of this issue of the **Federal Register**. This companion proposed rule will provide the procedural framework to finalize the rule in the event the direct final rule receives any significant adverse comment and is withdrawn. The comment period for this companion proposed rule runs concurrently with the comment period for the direct final rule. Any comments received under this companion proposed rule will also be considered as comments regarding the direct final rule. FDA is publishing the direct final rule because the rule contains noncontroversial changes, and FDA anticipates that it will receive no significant adverse comment.

A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether a significant adverse comment is sufficient to terminate a direct final rulemaking, FDA will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. For example, a comment requesting inclusion of additional product classes in the exceptions paragraph of the GST (§ 610.11(g)) will not be considered a significant adverse comment because it is outside the scope of this rule. A comment recommending a rule change in addition to the rule would not be considered a significant adverse comment, unless the comment states why the rule would be ineffective without additional change. In addition, if a significant adverse comment applies to part of a rule and that part can be severed form the remainder of the rule, FDA may adopt as final those parts of the rule that are not subject of a significant adverse comment.

A detailed rationale for the rule is set forth in the preamble to the direct final rule and in section I of this document. If no significant adverse comment is received in response to the direct final rule, no further action will be taken related to this proposed rule. Instead, FDA will publish a confirmation document within 30 days after the comment period ends confirming that the direct final rule will go into effect on September 2, 1998. Additional information about FDA's direct final rulemaking procedures is set forth in a guidance published in the **Federal Register** of November 21, 1997 (62 FR 62466).

If FDA receives any significant adverse comment regarding this rule, FDA will publish a document withdrawing the direct final rule within 30 days after the comment period ends. FDA then will proceed to respond to all of the comments received regarding this rule and, if appropriate, the rule will be finalized under this proposed rule using usual notice-and-comment procedures.

Requests to add other products to the named exceptions will be considered separately by FDA. If FDA agrees that other products should be excepted from the GST, it will propose those exceptions under other independent rulemaking actions. Any parties interested in commenting on this document should do so at this time. This action is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiative, and is intended to reduce the burden of unnecessary regulations on biological products without diminishing the protection of the public health.

Under § 610.11 (21 CFR 610.11), a test for general safety shall be performed on biological products intended for administration to humans. A GST is one of several tests in part 610, General Biological Product Standards (21 CFR part 610), that are intended to help ensure the safety, purity, and potency of biological products administered to humans. The test is used to detect extraneous toxic contaminants that may be present in a particular biological product. As outlined in § 610.11, an amount of the final container product is injected into the peritoneum of guinea pigs and mice. The GST is satisfactory when the criteria in § 610.11(d) are met, i.e., injected animals survive the test period, they do not exhibit an unexpected or non-specific response that may indicate a difference in quality of the product, and they weigh no less at the end of the test period than they did at the time of injection. Section 610.11(g) identifies the biological products for which the GST is not required.

The requirement for a GST was originally intended as a means by which harmful extraneous toxins could be detected that published in a document in the **Federal Register** of March 15, 1976 (41 FR 10888). The source of such toxins may be bacterial toxins that persist even after the bacteria producing the toxins had been removed by filtration or killed by sterilization, or formulation errors that result in harmful levels of certain substances, e.g., preservatives. The test continues to serve as a safety net to detect harmful contaminants that may enter or be introduced into the final container through undetected failures in the manufacture of biological products.

In the last 15 years, technological advances have increased the ability of manufacturers to control and analyze the manufacture of many biotechnology derived biological products. After more than a decade of experience with these products, FDA found that it could evaluate many aspects of a biological product's safety, purity, or potency with tests other than those prescribed in part 610. In response to these developments, FDA published in the **Federal Register** of May 14, 1996 (61 FR 24227), a final rule exempting certain biotechnology and synthetic biological products from, among other things, specified regulations applicable to biological products, including the GST (§ 601.2).

Recent scientific advances have dramatically increased the diversity of biological products regulated under section 351 of the Public Health Service Act (the PHS Act). In particular, cellular-based therapies intended for the diagnosis, cure, mitigation, treatment, or prevention of disease in man have been the subject of much biomedical research and are used with increasing frequency. Typically, cellular therapies use autologous or allogeneic cells, often lymphocyte subpopulations, but other cell types may be used, obtained from a donor and manipulated ex vivo to varying degrees before use in the recipient patient. The ex vivo manipulation may consist of, for example, growing a small number of cells to increase their number (cellular expansion), selective enrichment of a specific cell subpopulation, or the addition of specific cell factors or genetic sequences. A common characteristic of cellular therapies is the need for a relatively short turn-around time between first obtaining the cells and their final infusion as a cellular therapy product into the patient. In many cases, cells used in the final cellular therapeutic are obtained only hours before they must be used and turn-around times of several days or less are presently typical. A test, such as the GST, that requires 7 days to complete is not compatible with such products and such a requirement would make it impossible to use many of these products. Furthermore, because the procedures and materials used to produce cellular therapy products are stringently controlled and monitored, the likelihood of an extraneous toxic component contaminating a final product is greatly reduced.

In the **Federal Register** of June 3, 1994 (59 FR 28821 and 28822), FDA announced that the Center for Biologics Evaluation and Research (CBER) would review certain biologics regulations to identify regulations that are outdated, burdensome, inefficient, duplicative, or otherwise unsuitable or unnecessary. FDA included § 610.11 in the review. On January 26, 1995, FDA held a public meeting to discuss the retrospective review of regulations applicable to biological products and to provide a forum for the public to voice its comments regarding the retrospective review. At the meeting, only one comment addressed whether § 610.11 should be retained unchanged, modified, or deleted. The comment acknowledged the utility of the GST for products that have a high degree of intrinsic variability. However, despite its recognized value in some specific cases, the comment questioned the rationale for requiring the GST for all biological products intended for administration to humans. The comment noted that the amount of final container product administered to animals for the GST may not have any correlation with the human dose, that some biological products possess extensive documented histories of no GST failure, and that each run of the test requires the use of at least four animals. The comment suggested that FDA revise § 610.11 to grant exemptions from the GST when the test is unnecessary to evaluate the safety of a specific product.

FDA received several comments from the public regarding issues raised at the January 26, 1995, meeting. Two comments agreed with the suggestion made at the public meeting that § 610.11 be amended to include a provision that would allow certain products to be exempted from the GST upon approval of the Director, CBER. Another comment suggested that exemptions be permitted for appropriate biological products by the Director, CBER, after a suitable qualification period was met without any failure of the GST, such as 1 year of production or after 10 consecutive production lots pass the GST. The comment suggested that a demonstrated record of GST compliance also be supported by well-documented in-process safety controls, long-term compliance with current good manufacturing practices (CGMP) regulations (21 CFR parts 210 and 211), and the use of sophisticated analytical techniques capable of adequately characterizing the final product and validating its safety.

On March 17, 1997, FDA held a public meeting to discuss the agency's proposed approach to the regulation of human cellular and tissue-based products. The meeting was attended by FDA, members of industry, representatives from accrediting organizations, and interested members of the public. During the meeting, two attendees addressed the use of the GST with cellular therapy products. The comments regarded the 7-day incubation time of the test as an unworkable requirement for many cellular therapy products and suggested that such products be exempted from

the test, including allogeneic and autologous cell therapy products.

## II. Highlights of the Proposed Rule

FDA agrees with the comments received that cellular therapy products should be exempt from the GST requirement. FDA is proposing this rule to expand the exceptions in § 610.11(g) to include ''cellular therapy products.'' In addition, FDA is adding an administrative procedure for manufacturers of other biological products to request and obtain exemptions from the GST. Many biological products are currently manufactured, or will be manufactured in the future, under highly controlled and rigorously monitored conditions. Therefore, under the amended rule, manufacturers of biological products that employ appropriate production controls and quality assurance safeguards would be permitted to apply for an exemption from the GST requirement. Such manufacturers will be required to provide supporting documentation to the Director, CBER, as to why a product should not be subject to the GST requirement. The request shall include an explanation of why the GST is unnecessary or cannot be performed due to the mode of administration, the method of preparation, or the special nature of the product and shall describe alternate procedures, if any, to be employed. The Director, CBER, may grant an exemption if she finds that the manufacturer's submission justifies an exemption.

The value of the GST as a final assay for the presence of extraneous toxins may be diminished for certain biological products, such as vaccines containing recombinant or purified protein antigens. Recombinant protein antigens are not produced from infectious bacteria or virus and antigens derived from infectious pathogens may undergo many production steps that kill or neutralize the pathogen or inactivate toxic materials. Therefore, for these kinds of products, the risk is extremely low that viable pathogenic or toxic materials will persist through production to the final filling. The effectiveness of such steps can be validated by specific in-process tests and controls which can be used to alert manufacturers to potential problems. To further reduce the possibility that an undetected extraneous toxin could contaminate the product just before or during the final fill stage, a manufacturer may use production facilities and final fill equipment that can detect or enable the detection of any loss in the integrity of the production and fill processes. In addition, a method of production and detailed product characterization able to meet requirements similar to those set out in § 601.2(c) could be used to demonstrate the safety, purity, and potency of a biological product without the use of the GST. Each manufacturer will be responsible for identifying the product or products that are produced in such a manner that makes the GST unnecessary to ensure the safety, purity, and potency of the biological product. Manufacturers wishing to obtain an exemption to the GST for a particular product would contact the appropriate product division of CBER for specific information regarding how to apply and what information should be included in the application or supplemental application.

## III. Analysis of Impacts

### *A. Review Under Executive Order 12866 and the Regulatory Flexibility Act*

FDA has examined the impact of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 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 impact; and equity). This proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The proposed rule is a significant regulatory action as defined by the Executive Order and is subject to review under the Executive Order because it deals with a novel policy issue.

In accordance with the principles of Executive Order 12866, the result of the proposed rule will be a substantial reduction in burdens on applicants filing for approval of certain biological products.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small business entities. Because, as stated previously, the overall result of the proposed rule will be a substantial reduction of the regulatory and reporting burdens, the agency certifies that the proposed rule will not have a significant negative economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required. This proposed rule also does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act because it does not impose a mandate that results in an expenditure of $100 million or more by State, local, and tribal governments in the aggregate, or by the private sector, in any one year.

### *B. Environmental Impact*

The agency has determined under 21 CFR 25.31(j) 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.

## IV. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (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 burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

*Title:* Requests for Exemptions from the General Safety Testing Requirements for Biological Products.

*Description:* FDA is proposing to revise the requirements for general safety testing (GST) set forth in § 610.11. The test serves as a safety net to detect harmful contaminants that may enter or be introduced into the final container through undetected failures in the manufacture of biological products. The revision would add ''cellular therapy products'' to the list of products excepted from the GST, and add an administrative procedure for obtaining

exemptions from the GST requirements for other biological products. FDA is proposing the new administrative procedure because the GST may not be feasible or appropriate for some biological products. FDA anticipates that manufacturers requesting exemptions would have a demonstrated record of GST compliance supported by long-term compliance with CGMP's, well-documented in-process safety controls, and use sophisticated analytical techniques to adequately characterize the final product and validate its safety. Manufacturers would submit their request and documentation to the Director, CBER, who may grant the exemption if it is determined that the manufacturer's submission justifies an exemption.

*Description of Respondents:* Manufacturers of biological products.

The proposed rule would require only those manufacturers requesting an exemption from the GST under § 610.11(g)(2) to submit additional information as part of a license application or supplement to an approved license application. Manufacturers of ''cellular therapy products'' would be excepted from the GST under § 610.11(g)(2) and thus, would not have to submit an exemption request. In fact, manufacturers of cellular therapy products would be relieved of significant burdens because they would no longer be required to perform the GST and report the results to FDA. FDA estimates that annually it will receive approximately 10 requests for administrative exemption from the GST under 21 CFR 610.11(g)(2). FDA estimates that 40 hours will be required for an applicant to complete and submit the appropriate information for the exemption request. Since that information is ordinarily compiled and organized by the manufacturer while performing the GST, FDA anticipates that the additional time needed to submit an exemption request will be minimal.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

| 21 CFR Section | No. of Respondents | Annual Frequency per Response | Total Annual Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|
| 610.11(g)(2) | 10 | 1 | 10 | 40 | 400 |
| Total | 10 | 1 | 10 | 40 | 400 |

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

For consistency with the direct final rule to which this proposed rule is a companion, FDA is following the PRA comment procedures for direct final rules in this proposed rule. As provided in 5 CFR 1320.5(c)(1), collection of information in a direct final is subject to the procedures set forth in 5 CFR 1320.10. Interested persons and organizations may submit comments on the information collection requirements of this direct final rule by June 19, 1998 to the Dockets Management Branch (address above).

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of the direct final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions. 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.

## V. Request for Comments

Interested persons may, on or before July 6, 1998, submit to the Docket Management Branch (address above) written comments regarding this proposal. This comment period runs concurrently with the comment period for the direct final rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. All comments received will be considered as comments regarding this companion proposed rule and the direct final rule. In the event the direct final rule is withdrawn, all comments received regarding the direct final rule and this companion proposed rule, will be considered under this proposed rule.

## List of Subjects in 21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

Therefore under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and the authority delegated by the Commissioner of Food and Drugs, 21 CFR part 610 is amended as follows:

## PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

1. The authority citation for 21 CFR part 610 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

2. Section 610.11 is amended by revising paragraph (g) to read as follows:

### § 610.11 General safety.

* * * * *

(g) *Exceptions*—(1) The test prescribed in this section need not be performed for Whole Blood, Red Blood Cells, Cryoprecipitated AHF, Platelets, Plasma or Cellular Therapy Products.

(2) For products other than those identified in paragraph (g)(1) of this section, a manufacturer may request from the Director, CBER, an exemption from the general safety test. The manufacturer shall submit information as part of a license application submission or supplement to an approved license application establishing that because of the mode of administration, the method of preparation, or the special nature of the product a test of general safety is unnecessary to assure the safety, purity, and potency of the product or cannot be performed. The request shall include any alternate procedures, if any, to be performed. The Director, CBER, upon finding that the manufacturer's request justifies an exemption, may exempt the product from the general safety test subject to any condition necessary to assure the safety, purity, and potency of the product.

Dated: April 10, 1998.

**William B. Schultz,**

*Deputy Commissioner for Policy.*

[FR Doc. 98–10313 Filed 4–17–98; 8:45 am]

BILLING CODE 4160–01–F