DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 97N–0449]

RIN 0910–AB51

Revision to the General Safety Requirements for Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations regarding general biological products standards by adding an administrative procedure for obtaining exemptions from the general safety test (GST) requirements. We are taking this action because the GST may not be relevant or necessary for certain biological products. The rule will permit manufacturers of biological products to apply for an exemption from the GST requirement provided they submit information to demonstrate that they use appropriate production controls and quality assurance safeguards.

DATES: This rule is effective [*insert date 60 days after date of publication in the* **Federal Register**].

FOR FURTHER INFORMATION CONTACT: Stephen M. Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

Under § 610.11 (21 CFR 610.11), manufacturers of biological products must perform a test for general safety on biological products intended for administration to humans. The GST is one of several tests listed 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 the product in the final container from every final filling of each lot of the biological product.

The source of such toxic contaminants may be bacterial and fungal by-products that persist after the bacteria are removed by filtration or killed by sterilization, or formulation errors that result in harmful levels of certain substances, e.g., preservatives. The test serves as a safety net to detect harmful contaminants.

Technological advances have increased the ability of manufacturers to control and analyze the manufacture of many biotechnology derived biological products. After more then a decade of experience with these products, we found that we 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** on May 14, 1996 (61 FR 24227), a final rule exempting certain biotechnology and synthetic biological products from a number of regulations applicable to biological products, including the GST (see 21 CFR 601.2(c)).

In the **Federal Register** of April 20, 1998, we published a direct final rule and a companion proposed rule (63 FR 19399 and 19431, respectively) to revise the general safety requirements for biological products. The direct final

rule amended the regulations to exempt cellular therapy products from the GST requirement and added an administrative procedure for manufacturers of other biological products to request exemptions from performing the GST. We published a companion proposed rule to provide a procedural framework within which the rule could be finalized in the event we received any significant adverse comments regarding the direct final rule and we withdrew or severed the direct final rule.

We received six comments. We did not receive any significant adverse comments to the amendment to specifically exempt ‘‘cellular therapy products’’ in § 610.11(g)(1). We received significant adverse comments on the administrative procedure provision § 610.11(g)(2). In this rulemaking, we respond to all comments received.

Accordingly, we published a notice in the **Federal Register** of August 5, 1998 (63 FR 41718), confirming in part and withdrawing in part the direct final rule amending the GST requirements. We confirmed a revision to § 610.11(g)(1) to add ‘‘cellular therapy products’’ to the list of products excepted from the GST. Based on receipt of adverse comments, we withdrew the revision of § 610.11(g)(2) that provided a general administrative procedure for requesting and obtaining exemptions from the GST. We applied the comments regarding the withdrawn portion of the rule to the companion proposed rule and considered them in developing this final rule.

II. Highlights of the Final Rule

The final rule codifies, at § 610.11(g)(2), an administrative procedure under which manufacturers of biological products may 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 § 610.11(g)(2) we will permit biological product manufacturers who employ appropriate production and final filling controls and quality assurance safeguards to apply for an exemption from the GST requirement. Manufacturers who request an exemption must provide supporting documentation to the Director, Center for Biologics Evaluation and Research (CBER), as to why a product should not be subject to the GST requirement. The request must 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 must describe alternate procedures, if any, to be employed. The Director of CBER may grant an exemption if he/she finds that the manufacturer's submission justifies an exemption.

Manufacturers wishing to obtain an exemption to the GST for a particular product should contact the appropriate CBER product division for specific information regarding how to apply and what information should be included in the application or supplemental application.

III. Comments on the Proposed Rule

(Comment 1) Proposed § 610.11(g)(1) would add ''cellular therapy products'' to the list of products excepted from the GST.

One comment supported the amendment, and none of the comments objected to the amendment to add ''cellular therapy products'' to the list of exceptions.

We confirmed a revision to § 610.11(g)(1) in the **Federal Register** of August 5, 1998, notice to add ''cellular therapy products'' to the list of products excepted from the GST.

(Comment 2) Proposed § 610.11(g)(2) would add an administrative procedure for manufacturers to request and obtain an exemption from the GST. The proposal would require manufacturers to submit information as part of a biologics license application submission or a supplement to an approved biologics license application.

One comment opposed proposed § 610.11(g)(2) because the mechanism for requiring each licensed manufacturer to submit a license supplement to gain an exemption from the GST was too restrictive and alternative mechanisms should be available by which all manufacturers of a specific product or a group of products could be exempted.

We disagree with this comment. The comment did not suggest an alternate mechanism for our consideration. We believe such changes should be addressed on a case-by-case basis through a biologics license application or supplement so that we can ensure appropriate controls are in place to detect contaminants ordinarily found by the GST.

(Comment 3) One comment specifically objected that the administrative procedure in proposed § 610.11(g)(2) would codify FDA's use of the biologics licensure process to achieve the regulatory objectives that should be achieved instead only through notice and comment rulemaking.

We intend to revise our regulations only when a group of products which can be defined as a product type, such as ''cellular therapy products,'' can be excepted from a regulatory provision. Rulemaking is not an efficient vehicle for exempting specific or individual products or specific manufacturers, or when there are limitations to the exemptions, which should be outlined in some detail. We believe the biologics licensure process is a more efficient process than rulemaking for granting exemptions to the GST.

(Comment 4) Proposed § 610.11(g)(2) would allow manufacturers to request an exemption from the GST; it would not allow other entities to request such exemptions.

One comment argued that a letter from a trade association should suffice to obtain such an exemption.

We disagree with this comment. The request for exemption represents an alternative to the regulations to establish a firm, enforceable commitment by the manufacturer to FDA as to specific obligations. Submissions by an association would not be suitable because it is the manufacturer that must follow the regulations. Trade associations cannot compel specific actions by their member manufacturers. In addition, trade associations do not have the authority to change an applicant's submission.

However, anyone may submit a request to FDA, with supporting information, to revise the regulations to provide for exceptions from GST requirements.

(Comment 5) One comment noted that the proposal did not create a procedural mechanism to allow for partial exemptions. The comment explained that partial exemptions could be appropriate for specific subclasses of products.

We decline to amend the rule as suggested by the comment. The comment did not provide enough information that would allow us to determine the merits of or need for partial exemptions. However, under § 610.11(g)(2), we may accept a request for an exemption in the form of a biologics license supplement for a limited group of products after a case-by-case evaluation. Section 610.11(g)(2) gives manufacturers a mechanism for obtaining exemptions for specific biological products on an individual basis, rather than

for whole ‘‘classes’’ of products, such as are excepted in § 610.11(g)(1). We believe such exemptions should be addressed on a case-by-case basis through a biologics license application or supplement.

(Comment 6) Two comments would revise the proposal to exempt allergenic products if each lot of stock concentrates of allergenic extracts and each lot of diluent contained in the final product satisfies the GST requirements. The comments requested that we modify 21 CFR 680.3(b)(1) to exempt allergenic extracts from the requirement to perform the repeat GST on final products when a GST is performed on a stock concentrate. The comments explained that the suggested amendment would eliminate an unnecessary burden on the allergenic product industry that would result from separate rulemaking procedures.

The issue of exempting allergenic products is outside the scope of this rulemaking. Consequently, we decline to amend the rule as suggested by the comment.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles set forth in the Executive order. OMB

has determined that the final rule is a significant regulatory action as defined by the Executive order and is subject to review under the Executive order.

In accordance with the principles of Executive Order 12866, the final rule will provide increased flexibility for applications with approved biological products and may substantially reduce the burdens on some applicants seeking 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 the final rule has no compliance costs and does not result in any new requirements, the agency certifies that the final 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 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.

V. Environmental Impact

This agency has determined under 21 CFR 25.31(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork

Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting 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.

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

Description: FDA is revising the requirements for GST set forth in § 610.11. The test may detect harmful contaminants that may enter or be introduced through undetected failures in the manufacture of biological products. The revision would add an administrative procedure for obtaining exemptions from the GST requirements for biological products not already excepted under § 610.11(g)(1). FDA is codifying the new administrative procedure because alternatives to the GST may be feasible or appropriate for some biological products. FDA anticipates that manufacturers requesting exemptions would have demonstrated a record of the GST compliance, well-documented in-process safety controls, and use sophisticated analytical techniques to adequately characterize the product and validate its safety. Manufacturers would submit their requests and documentation to the Director, CBER, who may grant the exemption if it is determined that the manufacturer's submission justifies such an action.

Description of Respondents: Manufacturers of biological products.

This final rule requires only those manufacturers requesting an exemption from the GST under § 610.11(g)(2) to submit additional information as part of a biologics license application or supplement to an approved biologics license

application. Based on our experience, we estimate that we will receive approximately 10 requests for administrative exemption from the GST under § 610.11(g)(2) annually. We also estimate that an applicant will take 40 hours to complete and submit the appropriate information for the exemption request. Since the applicant ordinarily compiles and organizes the information while performing the GST, we anticipate 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

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

The direct final rule and companion proposed rule of April 20, 1998 (63 FR 19399 and 19431, respectively) provided a 60-day public comment period on the information collection provisions reflected in this final rule. Although some comments objected to the license supplement mechanism of gaining approval for an exemption as being too burdensome, we received no comments on the actual burden estimates for submitting such supplements.

VII. Federalism

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

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 under authority delegated to 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, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

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

§ 610.11 General safety.

* * * * *

(g) * * *

(2) For products other than those identified in paragraph (g)(1) of this section, a manufacturer may request from the Director, Center for Biologics Evaluation and Research, an exemption from the general safety test. The manufacturer must submit information as part of a biologics license application submission or supplement to an approved biologics 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 must include alternate procedures, if any, to be performed. The Director, Center for Biologics Evaluation and Research, 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: February 26, 2003.

William K. Hubbard,

Associate Commissioner for Policy and Planning.

[FR Doc. 03–????? Filed ??–??–03; 8:45 am]

BILLING CODE 4160–01–S