

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 than 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