
(2) Contacting the Manufacturer: For any requirement in this AD to obtain corrective actions from a manufacturer, the action must be accomplished using a method approved by the Manager, International Branch, ANM–116, Transport Airplane Directorate, FAA; or the European Aviation Safety Agency (EASA); or Airbus’s EASA Design Organization Approval (DOA). If approved by the DOA, the approval must include the DOA-authorized signature.

(3) Reporting Requirements: A federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with a collection of information subject to the requirements of the Paperwork Reduction Act unless that collection of information displays a current valid OMB Control Number. The OMB Control Number for this collection is 1210–0056. Public reporting for this collection of information is estimated to be approximately 5 minutes per response, including the time for reviewing instructions, completing and reviewing the collection of information. All responses to this collection of information are mandatory. Comments concerning the accuracy of this burden and suggestions for reducing the burden should be directed to the FAA at: 800 Independence Ave. SW., Washington, DC 20591, Attn: Information Collection Clearance Officer, AES–200.

(p) Related Information


(2) For service information identified in this AD, contact Airbus, Airworthiness Assistance Center, 8401 Corporate Ave., Renton, WA. For information on the availability of this material at the FAA, call 425–227–1221.

Issued in Renton, Washington, on August 15, 2014.

Jeffrey E. Duven, Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 2014–19979 Filed 8–21–14; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 610 and 6180
[Docket No. FDA–2014–N–1110]

Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biological License Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations by removing the general safety test (GST) requirements for biological products. FDA is proposing this action because the existing codified GST regulations are duplicative of requirements that are also specified in biologics licenses, or are no longer necessary or appropriate to help ensure the safety, purity, and potency of licensed biological products. FDA is taking this action as part of its retrospective review of its regulations to promote improvement and innovation, in response to an Executive order.

DATES: Submit either electronic or written comments on this proposed rule by November 20, 2014. See section V of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

• Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

• Mail/Hand Delivery/Courier (for paper submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include Docket No. FDA–2014–N–
Executive Summary

The proposed rule would eliminate the codified GST requirements for biological products. FDA is proposing this action because the existing codified GST regulations are duplicative of requirements that are also specified in biologics license applications (BLAs) or are no longer necessary or appropriate to help ensure the safety, purity, and potency of licensed biological products. Because this proposed rule would impose no additional regulatory burdens, this regulation is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

I. Background

On January 18, 2011, President Barack Obama issued E.O. 13563, “Improving Regulation and Regulatory Review” (76 FR 3821, January 21, 2011). One of the provisions in the E.O. is the affirmation for drug manufacture in the CFR, which occurred in 1963. The GST was subsequently revised to, among other things, “reflect the best current testing procedures established by the scientific community as well as to promote uniformity and specificity in the safety testing of licensed biological products” (March 15, 1976, 41 FR 10888).

A product that meets the requirements for general safety will comply with the criteria found in § 610.11(d) of the GST regulation, i.e., injected animals survive the test period; they do not exhibit any response that is not specific for or expected from the product and which 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.

While originally a useful approach, as time passes, the Agency has periodically explored the utility and efficiency of this approach. In the Federal Register of May 14, 1996 (61 FR 24227), FDA published a final rule exempting certain biotechnology-derived and synthetic biological products from a number of regulations applicable to biological products, including the GST (see § 601.2(c)). This action was in response to technical advances that greatly increased the ability of manufacturers to control the manufacture of, and to more fully analyze the physical and biological characteristics of, many biotechnology-derived biological products.

1 For purposes of this proposed rulemaking, the term “general safety test” or “GST” refer to the requirements found under Title 21 of the Code of Federal Regulations (CFR), subchapter F, parts 600 through 680 (21 CFR parts 600 through 680), specifically 21 CFR 610.11, 21 CFR 610.11a and 21 CFR 680.3(b).
Approximately 2 years later, in the Federal Register of April 20, 1998, FDA issued a direct final rule (DFR) and a companion proposed rule (63 FR 19399 and 19431, respectively) to expand the exceptions in § 610.11(g) to include “cellular therapy products” because, among other reasons, the Agency believed that the procedures and materials used to manufacture these products are stringently controlled and monitored. In addition, FDA provided for in the DFR and the companion proposed rule an administrative procedure for manufacturers of other biological products to request and obtain exemptions from conducting the GST. FDA took this action “. . . because the GST may not be relevant or necessary for biological products . . . currently in various stages of development” and as part of FDA’s continuing efforts at that time “to reduce the burden of unnecessary regulations on biological products without diminishing the protection of the public health” (63 FR 19399 at 19400) (FDA refers readers to the preamble of the April 20, 1998, proposed rule should they wish to obtain additional details on the history of this rulemaking).

In the Federal Register of August 5, 1998 (63 FR 41718) (August 1998 Notice), FDA published a DFR confirming in part, and withdrawing in part, the provisions in the DFR that published April 20, 1998. Specifically, FDA confirmed a revision to § 610.11(g) to add “cellular therapy products” to the list of products exempted from the GST. However, because the Agency received significant adverse comments concerning § 610.11(g)(2), the provision of the rule that required administrative procedures for requesting an exemption from the GST regulations, § 610.11(g)(2) was withdrawn. As discussed in the August 1998 Notice, the comments were applied to the corresponding portion of the companion proposed rule and considered in developing the final rule. After considering the comments to the DFR and companion proposed rule, in the Federal Register of March 4, 2003 (68 FR 10157 at 10158) (March 2003 Final Rule), FDA again provided for an administrative procedure under which manufacturers of biological products may request and obtain exemptions from conducting the GST (§ 610.11(g)(2)). In the preamble to the March 2003 Final Rule, FDA again noted that the GST may not be relevant or necessary for certain biological products (68 FR 10157).

Accordingly, § 610.11 currently includes a provision allowing manufacturers to request an exemption from the GST. Note that this exemption provision requires manufacturers to provide supporting documentation when making their request (see 68 FR 10157 through 10159). Specifically, when requesting such an exemption, manufacturers must submit information as part of a BLA or supplement to an approved BLA establishing that because of the mode of administration, the method of preparation, or the special nature of the product, a test for general safety is unnecessary to assure the safety, purity, and potency of the product, or cannot be performed (§ 610.11(g)(2)).

Since FDA issued the March 2003 Final Rule, it has become increasingly clear that the codified GST regulations are too restrictive for certain additional biological products because they specify particular methodologies or requirements when alternatives may be available that provide the same or greater level of assurance of safety. Thus, the Agency believes that the regulations may no longer reflect the best current testing procedures established by the scientific community as a general matter (although the testing procedures may still be appropriate in certain circumstances) and that the more efficient way of prescribing testing requirements for particular products would be to allow such requirements to be specified in the BLA to enhance flexibility to make appropriate changes to testing methods.

II. Appropriate Controls Would Remain in Place

FDA believes that if this rulemaking becomes finalized as proposed, we would be able to continue to ensure that appropriate controls remain in place. For example, manufacturers of all products derived from inherently toxic substances would be required to continue to use the safety tests that are prescribed in their BLAs to control and monitor toxicity. These product-specific tests (performed in animals, cell cultures, or other systems) in conjunction with physical, chemical, and biological characterization tests define and monitor the production process and alert manufacturers to potential problems. These products are tailored to the proprietary manufacturing process and are appropriate for the detection of intrinsic or extraneous toxic contaminants for a particular product or product class, they are more appropriately specified in the manufacturer’s BLA or BLA supplement than codified as regulations.

Furthermore, we anticipate that the proposal to eliminate the codified GST regulations would encourage the implementation of the principles of the “3Rs,” to reduce, refine, and replace animal use in testing, thus addressing the need to minimize the use of animals in such testing and promoting more humane, appropriate, and specific test methods for assuring the safety of biological products.2

If the proposed rule is finalized and the GST regulations are eliminated, manufacturers would continue to be required to perform a particular safety test for certain products that present specific safety concerns, for example, testing for a specific toxicity, as set forth in an approved BLA or BLA supplement. As discussed previously, although this rulemaking proposes to eliminate the codified GST from the biologics regulations, FDA recognizes that all manufacturers that currently conduct a GST have this test described in their BLAs for their licensed products. As a result, if this proposed rule is finalized, these manufacturers would continue to be required to perform the GST unless the manufacturer’s BLA were revised through a supplement to eliminate or modify the test. FDA would review these proposed changes to a manufacturer’s approved BLA on a case-by-case basis so that we could ensure that any such action is appropriate. Thus, the removal of these biologics regulations, should this proposed rule be finalized, would not automatically revise a manufacturer’s BLA or BLA supplement.

The requirements for a licensed biological product manufacturer to report changes in its product, product labeling, production process, quality controls, equipment, facilities, or responsible personnel, as established in its approved BLA, are detailed in § 601.12. Under this regulation, manufacturers must report each change to the Agency in one of several different types of submissions. The applicable submission category depends on the potential for the change(s) at issue to have an adverse effect on the identity, strength, quality, purity, or potency of the particular biological product as it may relate to the safety or effectiveness of the product. A BLA supplement for a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as it may relate to the safety


Additional information on the Federal Government’s implementation of the principles of the 3Rs may be found at the ICCVAM Web site at http://ntp.niehs.nih.gov/go/iccvam.
or effectiveness of the product must be submitted under § 601.12(c) (Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change).

As a general matter, should a manufacturer wish to no longer perform the GST" described in its BLA, the Agency would consider the discontinuation of the GST to have a moderate potential to have an adverse effect on the identity, strength, purity, or potency of the product as it may relate to the safety or effectiveness of the product. Accordingly, a manufacturer who desires to discontinue the GST in the approved BLA of its certified biological products. FDA is proposing that any final rule that may issue based on this proposal be effective 90 days after the date of its publication in the Federal Register.

IV. Legal Authority
FDA is issuing this regulation under the biological products provisions of the PHS Act (42 U.S.C. 262 and 264), and the drugs and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321 et seq.). Under these provisions of the PHS Act and the FD&C Act, we have the authority to issue and enforce regulations designed to ensure that biological products are safe, effective, pure, and potent, and to prevent the introduction, transmission, and spread of communicable disease.

V. Proposed Effective Date
FDA is proposing that any final rule that may issue based on this proposal be effective 90 days after the date of its publication in the Federal Register.

VI. Analysis of Impacts
FDA has examined the impacts of the proposed rule under E.O. 12866, E.O. 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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 proposed rule is not a significant regulatory action as defined by E.O. 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule generally increases flexibility for safety testing and would result in the reduction of certain regulatory burdens and does not add any new regulatory responsibilities, the Agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

This rule proposes to amend the biologics regulations by removing GST regulations for biological products found in §§ 610.11, 610.11a and 680.3(b). FDA is proposing this action because the current codified GST regulations are duplicative of requirements that are also specified in biologics licenses, or are no longer necessary or appropriate to help ensure the safety, purity, and potency of licensed biological products. The removal of the GST regulations for biological products would not remove GST requirements specified in individual biologics license applications, however. All manufacturers that currently conduct a GST are already required, as part of the requirements specified in their biologics license applications, to perform the GST and would thus continue to be required perform the GST unless the BLA were revised to eliminate or modify the test through a supplement in accordance with § 601.12(c). Because this proposed rule would impose no additional regulatory burdens, this regulation is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

VII. The Paperwork Reduction Act of 1995
This proposed rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3520). The collections of information in § 601.12 have been approved under OMB control number 0910–0338. Therefore, FDA tentatively concludes that the proposed requirements in this document are not subject to review by OMB because they do not constitute a "new collection of information" under the PRA.

VIII. Environmental Impact
The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Federalism
FDA has analyzed this proposed rule in accordance with the principles set forth in E.O. 13132. FDA has
determined that the proposed rule, if finalized, would not contain policies that would 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 tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the E.O. and, consequently, a federalism summary impact statement is not required.

X. Request for Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

XI. Reference

FDA has placed the following reference on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday and are available electronically at http://www.regulations.gov.


List of Subjects

21 CFR Part 610
- Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 680
- Biologics, Blood, 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, it is proposed that 21 CFR parts 610 and 680 be amended as follows:

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

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


§ 610.11 [Removed and Reserved]

2. Remove and reserve § 610.11.

§ 610.11a [Removed and Reserved]

3. Remove and reserve § 610.11a.

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

4. The authority citation for 21 CFR part 680 continues to read as follows:


§ 680.3 [Amended]

5. Remove and reserve paragraph (b). Dated: August 18, 2014.

Peter Lurie,
Associate Commissioner for Policy and Planning.

[FR Doc. 2014–19888 Filed 8–21–14; 8:45 am]