4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 601, 610, and 680

[Docket No. FDA-2014-N-1110]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations by removing the general safety test (GST) requirements for biological products. FDA is finalizing 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. FDA is taking this action as part of its retrospective review of its regulations to promote improvement and innovation, in response to the Executive order.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Lori J. Churchyard, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose and Coverage of the Final Rule

The final rule removes the codified GST[1] regulations for biological products which will update outdated requirements and accommodate new and evolving technology and testing capabilities without diminishing public health protections. FDA is finalizing this action because the existing codified GST regulations are duplicative of requirements that are also specified in BLAs, 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 Executive Order (E.O.) 13563 of January 18, 2011.

Summary of the Major Provisions of the Final Rule

The final rule removes the requirements contained in §§ 610.11, 610.11a, and 680.3(b) (21 CFR 610.11, 610.11a, and 680.3(b)) from the regulations. Section 610.11 requires a GST for the detection of extraneous toxic contaminants in certain biological products intended for administration to humans. Section 610.11a concerns the GST requirements for inactivated influenza vaccine. Section 680.3(b) concerns GST requirements for allergenic products. Removal of these regulations, however, would not remove GST requirements specified in individual BLAs. A biological product

[1] For purposes of this final rule, the terms "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, 610.11a, and 680.3(b).

manufacturer would continue to be required to follow the GST requirements specified in its BLA unless the manufacturer advised FDA of its elimination or modification of the test by a submission filed in accordance with § 601.12 (21 CFR 601.12). FDA would review proposed changes to a manufacturer's approved biologics license on a case-by-case basis so that FDA can ensure that any such action is appropriate.

Costs and Benefits

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

I. Background

As part of FDA's retrospective review of its regulations to promote improvement and innovation under Executive Order 13563, FDA is removing the codified GST requirements as specified in this rule. We believe this action is appropriate because in many instances, the GST regulations duplicate requirements that are also specified in the BLA requirements for biological products intended for human use under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), or they are outmoded or otherwise unnecessary to help ensure the continued safety, purity, and potency of biological products. FDA published the proposed rule "Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biological License Applications" in the Federal Register of August 22, 2014 (79 FR 49727). FDA corrected

the title of that proposed rule to "Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biologics License Applications" in the Federal Register of September 10, 2014 (79 FR 53670).

For a number of years, FDA has not codified specific test methods as standards for licensed biological products, in part because codifying specific test methods as standards can diminish the ability of the Agency and industry to respond to technological developments. Instead the Agency has required manufacturers to provide a full description of manufacturing methods, including test methods, in manufacturers' BLAs (§ 601.2(a) (21 CFR 601.2(a))). Since FDA issued the March 2003 final rule "Revision to the General Safety Requirements for Biological Products" in the Federal Register of March 4, 2003 (68 FR 10157), it has become increasingly clear that the codified GST regulations are too restrictive for certain biological products because alternatives may be available which provide the same or greater level of assurance of safety as the GST. Thus, the Agency believes that the GST regulations may not always reflect the scientific community's assessment of the best current testing procedures, although in certain circumstances the GST may still be appropriate. The Agency believes that a more efficient way of prescribing testing requirements for particular products would be to allow such requirements to be specified in the BLA, which will enhance flexibility to make appropriate changes to testing methods.

II. Summary of the Final Rule

FDA is adopting as final, without material change, the proposed revocation of general safety test requirements that are duplicative of requirements in BLAs.

- The final rule is removing §§ 610.11, 610.11a, and 680.3(b), the regulations that require that manufacturers of biological products perform a specified test for general safety of biological products. FDA is taking this action because the existing codified GST regulations are duplicative, outmoded, or are otherwise unnecessary to help ensure the continued safety, purity, and potency of licensed biological products.
- As set forth in an approved BLA or BLA supplement, for products that present specific safety concerns, manufacturers will be required to perform appropriate safety test(s) to address those concerns. For example, the BLA may require testing for a specific toxicity.
- The appropriate tests will be specified in the manufacturer's BLA or BLA supplement rather than codified as regulations.
- Elimination of the codified GST regulations would encourage the implementation of the principles of the "3Rs," to reduce, refine, and replace animal use in testing. This addresses the need to minimize the use of animals in such testing and promotes more humane, appropriate and specific test methods for assuring the safety of biological products.[2]
- The finalization of this rule does not automatically revise a manufacturer's BLA or BLA supplement.
- 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 in accordance with § 601.12.

[2] Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 285l-3). 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.

- 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 § 601.12, 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.
- FDA anticipates that changes involving the discontinuance of the GST or the reliance on a test other than the GST would have 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 or effectiveness of the product. Such changes must be identified in a supplement submitted under § 601.12(c) (changes requiring supplement submission at least 30 days prior to distribution of the product made using the change).

III. Legal Authority

FDA is issuing this regulation under the biological products and communicable disease provisions of the PHS Act (42 U.S.C. 262 and 264), and the provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321 et seq.) applicable to drugs. Under these provisions of the PHS Act and the FD&C Act, we have the authority to issue and enforce regulations designed to ensure, among other things, that

biological products are safe, pure, and potent and manufactured in accordance with current Good Manufacturing Practice, and to prevent the introduction, transmission, or spread of communicable disease.

IV. Comments on the Proposed Rule and FDA Response

The Agency received two letters of comments on the proposed rule. Comments were received from a trade association, and an animal welfare organization.

To make it easier to identify the comments and our responses, the word "Comment" and a comment number appear in parentheses before each comment's description, and the word "Response" in parentheses precedes each response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received. Certain comments were grouped together because the subject matter of the comments was similar.

A. General Comments

(Comment 1) Both letters of comments support the proposed rule.

(Response) FDA acknowledges and appreciates that the comments we received agree with the need for this rulemaking. As stated previously, the rule removes the requirements contained in §§ 610.11, 610.11a, and 680.3(b) from the regulations because the existing codified GST regulations are duplicative of requirements that are also specified in BLAs, or are no longer necessary or appropriate to help ensure the safety, purity, and potency of licensed biological products. Removal of these regulations

provides a more efficient way of prescribing testing requirements and enhances flexibility to make appropriate changes to testing methods.

B. Comments on Specific Topics

(Comment 2) One comment requests that FDA encourage manufacturers who have a GST described in their BLAs for their licensed products to submit supplements to their BLAs to eliminate or modify the test and that FDA take additional steps to ensure that the final rule will have the intended effect of eliminating the use of animals in safety testing.

(Response) As stated in the preamble of the proposed rule (79 FR 49727 at 49729), we anticipate that the elimination of the codified GST regulations will encourage the implementation of the principles of the "3Rs," to reduce, refine, and replace animal use in testing. Moreover, on our own initiative, as discussed elsewhere in this document, we have determined that the effective date of the final rule will be 30 days after the date of its publication in the Federal Register to give manufacturers the flexibility to submit supplements to their BLAs for their licensed products as soon as possible.

(Comment 3) One comment requests that we add language to § 601.2 or other relevant biologics regulation to clarify our intent to encourage the implementation of the principles of the 3Rs.

(Response) FDA declines to adopt this recommended change because the request to add language to § 601.2 or other relevant biologics regulations is outside the scope of this rulemaking.

(Comment 4) One comment requests that FDA establish user fees with respect to the continued use of the GST after the effective date of this final rule, or that FDA

establish other clear policies that will provide economic incentives to discontinue the use of the GST. Further, the comment refers to Executive Order 13563, which encourages Federal Agencies to "…assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees...."

(Response) We decline to adopt these suggested changes because they are beyond the scope of this rule. The proposed rule did not address user fees or economic incentives. This rule allows, but does not require, current BLA holders to submit to FDA supplements to their BLAs to eliminate or modify the GST.

(Comment 5) One comment states that a manufacturer who submits a supplement to eliminate or modify a GST in its BLA will not be able to stop conducting the GST until FDA determines that the manufacturer has appropriately reported this change.

(Response) We disagree in part. As stated in the preamble to the proposed rule (79 FR 49727 at 49730), a manufacturer who desires to discontinue the GST in its approved BLA or utilize an alternative method other than the GST approved in its BLA must submit a BLA supplement reporting the change in accordance with § 601.12. Should a manufacturer wish to discontinue the GST described in the approved BLA, or to utilize an alternative method other than the GST approved in its BLA, FDA anticipates that the change would have 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 or effectiveness of the product. Accordingly, a manufacturer who desires to make such a change must submit a BLA supplement reporting the change in accordance with § 601.12(c). Within 30 days of the date FDA receives the submission, FDA will determine if the change has been reported in the proper category and if any of the

required information is missing, and will inform the applicant accordingly. If FDA does not so notify the applicant, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

V. Conforming Amendments

As part of this final rule, we need to make conforming changes when the removed provisions are referenced elsewhere in the CFR. The final rule removes "§ 610.11" from § 601.2(c)(1) and 21 CFR 601.22.

VI. Effective Date

We are making this rule effective 30 days after the date of publication in the Federal Register. We are making this change in the interest of reducing unnecessary regulatory burden to give manufacturers the flexibility to submit supplements right away, should they wish to do so.

VII. Economic Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 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 final rule is not a significant regulatory action as defined under Executive Order 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 final

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 certifies 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 $144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

This final rule amends the biologics regulations by removing the GST requirements for biological products found in §§ 610.11, 610.11a and 680.3(b). FDA is finalizing 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, however, would not remove GST requirements specified in individual BLAs. All manufacturers that currently conduct a GST are already required, as part of the standards specified in their BLAs, to perform the GST and would thus continue to be required to perform the GST unless the BLA were revised to eliminate or modify the test through a supplement in accordance

with § 601.12. Because this 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.

VIII. The Paperwork Reduction Act of 1995

This final 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 requirements in this document are not subject to review by OMB because they do not constitute a "new collection of information" under the PRA.

IX. 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.

X. 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 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 has concluded that the rule does not contain policies that have federalism implications as defined in the

Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

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, 21 CFR parts 601, 610, and 680 are amended as follows:

PART 601--LICENSING

1. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.2 [Amended]

2. Section 601.2 is amended in paragraph (c)(1) by removing “610.11,”.

§ 601.22 [Amended]

3. Section 601.22 is amended in the third sentence by removing “610.11,”.

PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS

4. 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.

§ 610.11 [Removed and Reserved]

5. Remove and reserve § 610.11.

§ 610.11a [Removed and Reserved]

6. Remove and reserve § 610.11a.

PART 680--ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

7. The authority citation for 21 CFR part 680 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.

§ 680.3 [Amended]

8. In § 680.3, remove and reserve paragraph (b).

Dated: June 26, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-16366 Filed: 7/1/2015 08:45 am; Publication Date: 7/2/2015]