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David A. Stawick,

Secretary of the Commission.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. FDA–2010–N–0099]

RIN 0910–AG15

Revision of the Requirements for Constituent Materials

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations to permit the Director of the Center for Biologics Evaluation and Research (CBER) or the Director of the Center for Drug Evaluation and Research (CDER), as appropriate, to approve exceptions or alternatives to the regulation for constituent materials. FDA is taking this action due to advances in developing and manufacturing safe, pure, and potent biological products licensed under a section of the Public Health Service Act (the PHS Act) that, in some instances, render the existing constituent materials regulation too prescriptive and unnecessarily restrictive. This rule provides manufacturers of licensed biological products with flexibility, as appropriate, to employ advances in science and technology as they become available, without diminishing public health protections.

DATES: Submit electronic or written comments on the proposed rule on or before June 28, 2010. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by April 29, 2010, (see the "Paperwork Reduction Act of 1995" section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA–2010–N–0099 and/or RIN number 0910–AG15, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the "Paperwork Reduction Act of 1995" section of this document).

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:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM 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 the agency name and Docket No. and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Information Collection Provision: The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by April 29, 2010, to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–7285.

FOR FURTHER INFORMATION CONTACT: Paul E. Levine, Jr., Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

Constituent materials regulated under § 610.15 (21 CFR 610.15) include ingredients, preservatives, diluents, adjuvants, extraneous protein and antibiotics that are contained in a biological product. FDA is proposing to amend the regulation for constituent materials at § 610.15 to allow the Director of CBER or the Director of CDER, as appropriate, to approve an exception or alternative to the requirements under § 610.15, when data submitted with the exception or alternative establish the safety, purity, and potency of the biological product. This proposed rule provides manufacturers of biological products with flexibility, as appropriate, to employ advances in science and technology as they become available, without diminishing public health protections. Examples of how the proposed rule would provide flexibility to manufacturers in the use of preservatives and aluminum in biological products are provided below. However, the proposed rule would also provide flexibility to the existing requirements regarding extraneous protein and antibiotics (§ 610.15(b) and (c)), provided that each request for an alternative or exception to these requirements is submitted with data that establish the safety, purity, and potency of the biological product.

Standards for certain constituent materials present in biological products are provided under § 610.15. Section 610.15(a) requires that all ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.

These regulations also require that the amount of aluminum in the recommended individual dose of a biological product not exceed the following:

• 0.85 milligrams if determined by assay;

• 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

• 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director of CBER or the Director of CDER.

This regulation establishes requirements for the presence of certain constituent materials in final licensed, biological products and/or strictly limits the amount of certain constituent materials present in licensed biological products. For example, the regulation contains requirements as to preservatives. Preservatives are compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi. In the **Federal Register** of January 10, 1968 (33 FR 367 at 369), the National Institutes of Health (NIH) issued the precursor regulation to constituent materials (§ 610.15) (the 1968 regulation).[1] This regulation, in part, set forth the requirements for preservatives in biological products in multiple-dose containers and included exceptions to this requirement. Prior to NIH's issuance of the 1968 regulation, there had been reports in the scientific literature of serious injuries and deaths associated with bacterial contamination of multiple-dose containers of vaccines that did not contain a preservative. This concern regarding contamination was the scientific basis for the requirement that products in multiple-dose containers contain a preservative.[2] However, the regulation also provided for certain exceptions from the preservative requirement. These exceptions included live viral vaccines that had been licensed under section 351 of the PHS Act (42 U.S.C. 262) and that were in production when NIH issued the 1968 regulation.[3]

Preservatives in multiple-dose containers have a long record of safe and effective use in preventing microbial growth in the event that the vaccine is accidentally contaminated, as might occur with repeated punctures of multiple-dose containers. The use of preservatives has significantly declined in recent years with the development of new products presented in single-dose containers. However, some biological products, such as inactivated influenza virus vaccines, are still presented in multi-dose containers and contain a preservative.

However, the requirements in connection with preservatives are too prescriptive and unnecessarily restrictive because, for example, state-of-the art technologies, such as the development of devices to ensure aseptic withdrawing, offer an alternative to the use of preservatives in multiple-dose containers. FDA believes that providing the option to manufacture vaccine in multiple-dose containers without use of a preservative would be acceptable, provided that appropriate safeguards, such as adequate storage, aseptic withdrawing techniques and timely use of the product (e.g., use of the vaccine within a defined period of time) are followed to ensure that the safety, purity, and potency of the product are not compromised. Furthermore, the current regulation under § 610.15(a) does not provide FDA with flexibility to consider situations (outside of the listed exceptions) in which to allow the use of preservative-free vaccines in multiple-dose containers. The proposed rule would permit the Director of CBER or the Director of CDER, as appropriate, to approve a request to market a biological product in multiple-dose containers without use of a preservative, if the manufacturer demonstrates the safety, purity, and potency of the product.

Another example where the current requirements are too prescriptive and unnecessarily restrictive pertains to the amount of aluminum permitted under § 610.15(a) in the recommended single human dose of a biological product. Aluminum, in the form of an aluminum salt, is used as an adjuvant in certain biological products. The existing regulation limits the amount of aluminum per dose to no more than 0.85 milligrams (mg) if determined by assay or 1.14 mg if determined by calculation on the basis of the amount of aluminum compound added. In the **Federal Register** of October 23, 1981 (46 FR 51903), FDA published a rule entitled "General Biological Products Standards; Aluminum in Biological Products" (the October 1981 rule). The October 1981 rule amended § 610.15(a) to increase the permissible level of aluminum per dose to 1.25 mg both to make the regulation consistent with World Health Organization standards,[4] and because it appeared that certain groups (such as renal dialysis patients), who were understood to be at high risk of contracting hepatitis, might require a higher dosage of the hepatitis B vaccine, which would in turn, require amounts of aluminum as high as 1.25 mg per dose. (See also "General Biological Products Standards for Aluminum in Biological Products" (46 FR 23765, April 28, 1981)).

The aluminum content per dose in the formulation of a licensed biological product, as specified in § 610.15(a), reflects the NIH Minimum Requirements for Diphtheria Toxoid (1947)[5] and Tetanus Toxoid (1952)[6]. The proposed rule would not alter the existing requirements regarding the amount of aluminum in a biological product. Instead, in a change that is analogous to the one FDA issued in the October 1981 rule, involving the groups who were at high risk of contracting hepatitis, the proposed rule would allow either the Director of CBER or the Director of CDER to approve an exception or alternative when the Director determines that a biological product meets the requirements for safety, purity, and potency but contains an amount of aluminum that is higher than currently permitted by § 610.15, such as a therapeutic vaccine for treating patients with cancer that contains aluminum salts at levels higher than currently allowed, but still meets the requirements of safety, purity, and potency.

The proposed rule enables FDA to assess the constituent materials in these and other products and provides sufficient flexibility for FDA to employ advances in science and technology as they become available, without diminishing public health protection.

Manufacturers seeking approval of an exception or alternative to a requirement under § 610.15 would be required to submit a request in writing.

[1] In 1968, NIH regulated biological products, through its Division of Biologics Standards. In the **Federal Register** of June 29, 1972 (37 FR 12865), an amended Statement of Organization, Functions and Delegations of Authority of the Department of Health, Education and Welfare was published reflecting a transfer of the Division of Biologics Standards to the Food and Drug Administration. In the **Federal Register** of August 9, 1972 (37 FR 15993), FDA published regulations that further reflected these organizational changes. As a result of this organizational change, the regulations pertaining to biological products under Part 73 of Title 42 of the Code of Federal Regulations were transferred to the newly established Part 273 of Title 21 of the Code of Federal Regulations.

[2] See "The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal Vaccines" at 21–24 (August 11, 1999). See also Wilson, Hazards of Immunization, 1967.

[3] Biological products had contained preservatives prior to 1968. "The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal Vaccines" at 24 (August 11, 1999).

[4] More specifically, the amendment permitted the use of up to 1.25 mg of aluminum determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Bureau of Biologics.

[5] National Institute of Health, "Minimum Requirements for Diphtheria Toxoid," 4th Revision, 1947.

[6] National Institutes of Health, "Minimum Requirements for Tetanus Toxoid," 4th Revision, 1952.

The request may be submitted as part of the original biologics license application, as an amendment to the original, pending application or as a prior approval supplement to an approved application.

II. Highlights of the Proposed Rule

FDA is proposing to amend § 610.15 by adding new paragraph (d) that would permit the Director of CBER or the Director of CDER, as appropriate, to approve exceptions or alternatives to the regulatory requirements for constituent materials, when the data submitted with the exception or alternative establish the safety, purity, and potency of the biological product. All requirements under § 610.15 would remain in effect, except those for which the Director approves an exception or alternative. Manufacturers seeking approval of an exception or alternative must submit a request in writing, as described in section I of this document.

FDA is proposing this rule to permit the Director of CBER or the Director of CDER, as appropriate, to approve exceptions or alternatives to the regulations for constituent materials, when the data submitted with the exception or alternative establish the safety, purity, and potency of the biological product. All requirements under § 610.15 would remain in effect, except those for which the Director approves an exception or alternative. Manufacturers seeking approval of an exception or alternative must submit a request in writing, as described in section I of this document.

III. Legal Authority

FDA is issuing this regulation under the biological products provisions of the Public Health Service Act (42 U.S.C. 262 and 264) and the drugs and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (sections 201, 301, 501, 502, 503, 505, 510, 701, and 704 (21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 371, and 374)). Under these provisions of the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, we have the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, and potent; and prevent the introduction, transmission, and spread of communicable disease.

IV. Analysis of Impacts

A. Review Under Executive Order 12866, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995

FDA has examined the impacts of the proposed 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 proposed rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule would allow the Director of CBER or the Director of CDER, as appropriate, to approve exceptions or alternatives to the regulations for constituent materials, this action would increase flexibility and reduce the regulatory burden for affected entities. Therefore, the agency proposes to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. We request detailed comment regarding any potential economic impact of this proposed rule.

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 $133 million, using the most current (2008) 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.

The benefits of this regulatory action are that the proposed rule would reduce burdens on industry (e.g., developers of biological products) due to greater flexibility and reduced regulatory requirements. These issues are discussed in greater detail in section I of this document.

Any costs associated with this regulatory action are expected to be minimal and widely dispersed among affected entities. Based on FDA experience, we estimate that we would receive a total of approximately three requests annually for an exception or alternative under § 610.15. FDA experience with similar information collection requirements suggests that approximately 1 hour would be required to prepare and submit such a request.

B. Environmental Impact

The 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 adverse effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

C. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed 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 proposed 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.

V. 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). A description of these provisions is given below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on the following topics: (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: Revision of the Requirements for Constituent Materials.

Description: The proposed rule would permit the Director of CBER or the Director of CDER, as appropriate, to approve a manufacturer's request for exceptions or alternatives to the regulation for constituent materials. This proposed rule provides manufacturers of biological products with flexibility, as appropriate, to employ advances in science and technology as they become available, without diminishing public health protections. Manufacturers seeking approval of an exception or alternative must submit a request in writing. The request must be clearly identified with a brief statement describing the basis for the request and supporting data. The request may be submitted as part of the original biologics license application, as an amendment to the original, pending application or as a prior approval supplement to an approved application. The information to be collected will assist FDA in identifying and reviewing requests for an exception or alternative to the requirements for constituent materials.

Description of Respondents: Manufacturers of biological products.

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
610.15	3	1	3	1	3

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

Based on FDA experience, we estimate that we will receive a total of approximately 3 requests annually for an exception or alternative under § 610.15. The hours per response are based on FDA experience with similar information collection requirements.

In compliance with the PRA (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection to OMB (see **DATES** and **ADDRESSES**).

VI. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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 Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 610

Biologics, Labeling, Reporting and Recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 610 be 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. Amend § 610.15 by adding new paragraph (d) to read as follows:

§ 610.15 Constituent materials.

* * * * *

(d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.

Dated: March 25, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–7073 Filed 3–29–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–335P]

RIN 1117–AB28

Schedules of Controlled Substances: Exempted Prescription Product; River Edge Pharmaceutical, Servira

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: This Notice of Proposed Rulemaking proposes the amendment of the list of Exempted Prescription Products cited in the Code of Federal Regulations. This action is in response to DEA's review of new applications for exemption. DEA has received one new application for exemption for River Edge Pharmaceutical's Servira®. Having reviewed this application and relevant information, DEA finds that this preparation has no significant potential for abuse. Therefore, DEA hereby proposes that this product be added to the list of Exempted Prescription Products and exempted from the application of certain provisions of the Controlled Substances Act (CSA).

DATES: Written comments must be postmarked and electronic comments must be submitted on or before April 29, 2010. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after Midnight Eastern Time on the last day of the comment period.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA–335" on all written and electronic correspondence. Written comments sent via regular or express mail should be sent to the Drug Enforcement Administration, *Attention:* DEA Federal Register Representative/ODL, 8701 Morrissette Drive, Springfield, VA 22152. Comments may be sent to DEA by sending an electronic message to *dea.diversion.policy@usdoj.gov*. Comments may also be sent electronically through *http://www.regulations.gov* using the electronic comment form provided on that site. An electronic copy of this document is also available at the *http://www.regulations.gov* Web site. DEA will accept attachments to electronic comments in Microsoft word, WordPerfect, Adobe PDF, or Excel file formats only. DEA will not accept any file formats other than those specifically listed here.

Please note that DEA is requesting that electronic comments be submitted before midnight Eastern time on the day the comment period closes because