1. Thayer, D. W., G. Boyd, W.S. Muller, et al. "Radiation resistance of *Salmonella,*" *Journal of Industrial Microbiology,* 5: 383–390, 1990.
2. Memorandum for FAP 8M4584 from V. K. Bunning, FDA, to W. Trotter, FDA, April 4, 2000.
3. Memorandum for FAP 8M4584 from K. Morehouse, FDA, to W. Trotter, FDA, April 11, 2000.
4. Memorandum for FAP 8M4584 from K. Morehouse, FDA, to W. Trotter, FDA, May 14, 1999.
5. Memorandum for FAP 8M4584 from I. Chen, FDA, to W. Trotter, FDA, December 11, 1998.
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7. U.S. Department of Agriculture, Agricultural Research Service, USDA National Nutrient Database for Standard Reference, Release 23, Nutrient Data Laboratory Home Page (*http://www.ars.usda.gov/ba/bhnrc/ndl*), 2010.
8. Bureau of Foods Irradiated Foods Committee, *Recommendations for Evaluating the Safety of Irradiated Food,* Prepared for the Director, Bureau of Foods, FDA, July 1980.

Dated: April 8, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011–8815 Filed 4–12–11; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. FDA–2010–N–0099]

Revision of the Requirements for Constituent Materials

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending 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. A request for an exception or alternative will be considered for approval when the data submitted in support of such a request establish the safety, purity, and potency of the biological product for the conditions of use, including indication and patient population, for which the applicant is seeking approval. FDA is taking this action due to advances in developing and manufacturing safe, pure, and potent biological products licensed under 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 biological products with flexibility, as appropriate, to employ advances in science and technology as they become available, without diminishing public health protections.

DATES: This rule is effective May 13, 2011.

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

In the **Federal Register** of March 30, 2010 (75 FR 15639), FDA published a proposed rule to amend the regulations for constituent materials under § 610.15 (21 CFR 610.15). Constituent materials include ingredients, preservatives, diluents, adjuvants, extraneous protein and antibiotics that are contained in a biological product. FDA is amending the regulation for constituent materials 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. An exception or alternative will be considered for approval when the data submitted in support of such a request establish the safety, purity, and potency of the biological product for the conditions for which the applicant is seeking approval. Under the final rule, the Director of CBER or CDER would not approve an exception or alternative when the data or the conditions of use, including indication and patient population, for which the applicant is seeking approval, do not provide a sufficient scientific and regulatory basis for such an approval.

The final rule provides manufacturers of biological products with flexibility, as appropriate, to employ advances in science and technology, as they become available. However, the final rule does not diminish public health protections that are provided by existing laws and regulations. The final rule gives manufacturers the potential to employ advances in science and technology if the data provide a sufficient regulatory basis for approval of the product. This means that each manufacturer's request for an exception or alternative will be considered on a case-by-case basis to determine whether the product at issue meets the statutory and regulatory criteria for safety, purity, and potency for use in the intended population. The Director of CBER or CDER will only approve a request for an exception or alternative after determining that the particular request meets this prescribed criteria for the intended population. Examples of how the final rule provides flexibility (such as alternatives to the use of preservatives and modifications to the amount of aluminum permitted in certain biological products), without diminishing public health protections, are provided in the paragraphs that follow.[1]

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 must 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 must 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 must 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 (v/v) glycerin. Furthermore, under § 610.15, an adjuvant must not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.

Section 610.15(a) also requires that the amount of aluminum in the recommended individual dose of a biological product not exceed:

1. 0.85 milligrams if determined by assay;

[1] Although specific examples for use of extraneous protein and antibiotics are not provided, the final rule also allows for flexibility in applying the existing standards for extraneous proteins and antibiotics (§ 610.15(b) and (c)); provided that each request for an alternative or exception to these requirements is supported by data that establish the safety, purity, and potency of the biological product.

2. 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

3. 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.

Section 610.15 establishes standards for the presence of certain constituent materials in licensed, biological products and/or strictly limits the amount of certain constituent materials present in licensed biological products. However, in order to employ advancements in science and technology to benefit the public health, flexibility in applying these regulatory standards is needed.

For example, § 610.15 contains specific requirements as to preservatives. Preservatives are compounds that kill or prevent the growth of micro-organisms, particularly bacteria and fungi. The current requirements for preservatives were based, at least in part, on reports from scientific literature concerning serious injuries and deaths associated with bacterial contamination of multiple-dose containers of vaccines that did not contain a preservative.[2] As discussed previously, § 610.15 provides for limited exceptions from the preservative requirement. These exceptions include 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 the National Institutes of Health (NIH) issued the 1968 regulation.[3] [4]

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 a multiple-dose container. Even though the use of preservatives has significantly declined in recent years with the use of products filled in single-dose containers that do not require addition of a preservative, some biological products such as inactivated influenza virus vaccines are still presented in multi-dose containers with a preservative. The use of preservatives could also decline further as manufacturers develop and employ new technologies, such as multi-dose adaptors to prevent contamination of products in multiple-dose containers, without the use of preservative.

However, 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. It is necessary for FDA to have flexibility in applying the regulatory requirements for preservatives when, for example, state-of-the art technologies, such as the development of devices to ensure aseptic withdrawing offer a safe alternative to the use of preservatives in multiple-dose containers. The final rule permits the Director of CBER or the Director of CDER to approve a request to market a biological product in multiple-dose containers without the use of a preservative, if the manufacturer demonstrates that sufficient measures, such as an aseptic withdrawing technique through the use of an appropriate device, ensure that the product continues to meet the statutory and regulatory requirements for safety, purity, and potency. Thus, the final rule allows flexibility in the use of advancements in technology to provide a public benefit, while continuing to ensure the safety, purity, and potency of the product.

Another example where it is necessary for FDA to have flexibility in applying current regulatory requirements 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 1981, FDA 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,[5] 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 "General Biological Products Standards; Aluminum in Biological Products," 46 FR 51903, October 23, 1981. 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) [6] and Tetanus Toxoid (1952).[7] The final rule does 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 1981, involving the groups who were at high risk of contracting hepatitis, the final rule allows 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 for the conditions for which the applicant is seeking approval, but contains an amount of aluminum that is higher than currently permitted by § 610.15. For example, the final rule permits the Director of CBER or CDER to approve a manufacturer's request for an exception to use a proposed therapeutic vaccine for treating individuals with cancer, when the proposed vaccine contains aluminum levels higher than currently allowed but still meets the requirements of safety, purity, and potency.

II. Clarifications to the Preamble of the Proposed Rule

FDA received comments on the rule from manufacturers, private and public interest groups, and the general public. In response to comments expressing concerns about the safety of a licensed product for which FDA grants an exception or alternative to current regulations, FDA emphasizes that a manufacturer's request for an exception or alternative will not be approved unless the submitted data meet the

[2] See "The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal Vaccines," pp. 21–25, August 11, 1999. See also Wilson, Graham S., *Hazards of Immunization,* 1967.

[3] With the creation of NIH, NIH had regulatory authority over biological products until 1972, at which time they were transferred to FDA. NIH issued the precursor regulation to constituent materials, § 610.15, in the **Federal Register** of January 10, 1968 (33 FR 367 at 369). See the **Federal Register** notice of June 29, 1972 (37 FR 12865) and the **Federal Register** notice of August 9, 1972 (37 FR 15993), for more information concerning the transfer of authority from NIH to FDA and how the regulations pertaining to biological products under 21 CFR part 73 were transferred to the then newly established 21 CFR part 273.

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

[5] More specifically, the amendment permitted the use of up to 1.25 mg per dose 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. "General Biological Products Standards; Aluminum in Biological Products," (46 FR 51903, October 23, 1981).

[6] NIH, Minimum Requirements for Diphtheria Toxoid, 4th Revision, 1947.

[7] NIH, Minimum Requirements for Tetanus Toxoid, 4th Revision, 1952.

statutory and regulatory criteria for safety, purity, and potency for use in the intended population. FDA also emphasizes that the product at issue must be shown to be safe, pure, and potent for the conditions of use, including proposed indication and patient population, for which the applicant is seeking approval, in determining whether the product may be approved. FDA further clarifies that consideration for approval of a request will be done case-by-case and will be based on review of the data submitted in support of a request.

In addition, in response to comments, FDA clarifies that there is both a need for FDA to have flexibility in applying the regulatory standards in § 610.15, and a need for manufacturers to have flexibility in employing advancements in science and technology for developing new safe, pure, and potent alternatives to current products. FDA provides more discussion on the need for flexibility in the responses to comments on the proposed rule.

FDA considered all comments received in response to the proposed rule and has determined that the proposed rule should be issued as a final rule. Accordingly, FDA is issuing as a final rule the amendment to § 610.15 under paragraph (d) to permit the Director of CBER or the Director of CDER, as appropriate, to approve an exception or alternative to the regulatory requirements for constituent materials, when the data submitted with the request for approval of an exception or alternative establish the safety, purity, and potency of the biological product, and is acceptable for use in the intended population. All requirements under § 610.15 remain in effect, except those for which the Director approves an exception or alternative. FDA approval of an exception or alternative will be done case-by-case, based on the data submitted for a specific product. Manufacturers seeking approval of an exception or alternative must submit a request in writing. The request may be submitted as part of the original biologics license application (BLA) or as an amendment to the original, pending application or as a prior approval supplement to an approved application.

III. Comments on the Proposed Rule

FDA received 15 letters of comment on the proposed rule, not including 1 duplicate letter from the same commenter. As stated previously, these comments were received from manufacturers, private and public interest groups, and the general public. Several of the comments supported the proposed rule and several comments disagreed with the proposed rule. Some of the comments on the proposed rule were similar to or duplicates of other comments received, and have been grouped together, where appropriate, to facilitate a uniform response.

To make it easier to identify the comments and our corresponding responses, the word "Comment" followed by a number is placed in parentheses and is used to indicate a particular comment or set of similar comments, as appropriate. The word "Response" in parentheses precedes FDA's response to a comment. The order of comments and responses, as listed, do not represent a value assigned to the comment but is used for organizational purposes only.

(Comment 1) Several comments supported the proposed rule. One such comment praised the rule for broadening the potential capacity for biologics manufacturers to provide medicines to the public without compromising the high level expectation of demonstrating safety, purity, and potency. Another comment supported the proposed rule for providing a means to advance "innovative science" and applications of use. Yet another comment expressed interest in seeing the "reasonable flexibility" provided in the proposed rule extended to other biopharmaceutical fields. Still another comment found the conditions and recommendations in the proposed rule to be comprehensible and useful.

(Response) FDA acknowledges and appreciates the supportive comments. As previously stated, the rule allows FDA the flexibility to approve an exception or alternative to the constituent materials regulation, without diminishing public health protections. As such, the final rule provides patients safe access to important products resulting from advances in science and technology. FDA continues to review existing regulations and may propose modification of these regulations as appropriate for public health and safety.

(Comment 2) One comment requests clarification as to whether a request for an exception or alternative to the requirements under § 610.15 can be made earlier in clinical development rather than waiting until submitting the original BLA.

(Response) FDA clarifies that although a manufacturer may submit a request for an exception or alternative early in the clinical development of a biological product, FDA considers such a request to be timely when the data intended to support the request establish the safety, purity, and potency of the biological product for its intended use. In developing data necessary to support a request for an exception or alternative, manufacturers must comply with all applicable laws and regulations, including the procedures and requirements for investigational new drug applications (INDs) and BLAs under parts 312 and 601 (21 CFR parts 312 and 601). Only after FDA determines that the biological product meets the statutory and regulatory criteria for safety, purity, and potency, and is acceptable for use in the intended population, may the Director of CBER or CDER approve a request for an exception or alternative.

However, FDA strongly encourages early communication from manufacturers intending to submit a request for an exception or alternative to the requirements under § 610.15. This includes pre-IND and IND communications by which manufacturers may seek FDA advice concerning issues such as data needed to support the rationale for testing a biological product in humans, the design of nonclinical pharmacology, toxicology, and drug activity studies, initial development plans for the biological product, and regulatory requirements for demonstrating safety, purity, and potency. Early communications between FDA and manufacturers, as described previously, are intended to be advisory and are not to be interpreted as approval of a request for an exception or alternative.

(Comment 3) One comment requests agreement from FDA that sponsors may administer multiple doses taken from individual preservative-free multi-dose vials in clinical trials prior to licensure, as long as the sponsor follows pre-approved aseptic procedures in defined time periods to support this format as part of the original license application.

(Response) FDA does not agree with the comment. The current regulation for preservatives requires that products in multiple-dose containers contain a preservative, with listed exceptions. The final rule provides the Director of CBER or CDER with flexibility to approve a request for an exception or alternative to this requirement. However, FDA will consider each request for an exception or alternative on a case-by-case basis and approval of such a request will be based on the determination that the data submitted with the request establishes a regulatory basis for approval. Sponsors seeking to investigate the use of a new biological product in humans must follow the procedures and requirements for investigational drugs under part 312. (See also Response to Comment 4).

(Comment 4) Several comments opposed the proposed rule because the commenters understood the rule to give the Director of CBER or CDER sole authority in the decisionmaking process to approve a request for an exception or alternative. Another comment stated that the proposed rule does not allow for a deliberative process for vaccine ingredient changes. Other comments stated that the drug industry had too much influence upon government agencies including FDA, and that all decisions about additives should reside with many experts, in order to avoid the potential of undue influence. One comment seeks greater transparency from FDA and manufacturers for all aspects of biologics. Another comment states that all changes to medicine, particularly those "which are proscribed by some government entities, should be subject to a public review."

(Response) FDA acknowledges and appreciates all comments on the proposed rule. FDA agrees with comments supporting public review and transparency. However, FDA disagrees with the comments opposing the authority of the Director of CBER or CDER to approve a biologic product. FDA also disagrees with the comments that the rule places the decisionmaking process in the hands of one person, does not allow for a deliberative process for vaccine ingredient changes, and that manufacturers will have an undue influence in the approval process.

Under the provisions of the PHS Act, and the Federal Food, Drug, and Cosmetic Act (the FD&C Act), FDA has the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, and potent. Through delegations of authority,[8] the Directors of CBER and CDER have been given the authority to approve biological products. Thus, the Directors of CBER and CDER may approve a biologic product determined to be safe, pure, and potent, based on factors that include review of data, and in some cases, taking into account recommendations and input from independent experts (*e.g.,* advisory committees), input from interested parties, and public comments.

The PHS Act and the FD&C Act provide FDA with the authority to issue regulations that not only establish the requirements for product approvals but also establish the requirements for clinical investigations of unapproved biologics (21 U.S.C. 355(i) and 42 U.S.C. 262(a)(2)(A)). In accordance with part 312, manufacturers seeking to investigate the use of a new biological product in humans must follow specified procedures and requirements for investigational biological products. During the IND process, manufacturers must submit, for FDA review, data and proposals for additional studies intended to support the safety, purity, and potency of a biological product. Manufacturers also are required to provide information on patient outcomes and adverse events observed during this investigation. FDA reviews the submitted data and, upon determining that the biological product does not represent an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, will allow a manufacturer to proceed with the investigational use of a biological product. A manufacturer, after developing data to support approval, may submit a BLA to FDA for review and approval.

Under § 601.2, the Director of CBER or CDER may approve a manufacturer's application for a biologics license only after a manufacturer submits an application accompanied by data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets requirements of safety, purity, and potency. These data are reviewed by appropriate experts to determine whether the application meets the statutory and regulatory requirements. In addition to the recommendations made by these experts, the Director of CBER or CDER may seek input from other sources within and outside of FDA to determine whether the application should be approved. Further, FDA closely monitors the safety of a biological product during its pre-approval and post-approval development, and may take corrective action, as necessary to protect the public.

In addition to the review process described previously, a sponsor, applicant, or manufacturer of a biological product regulated under the PHS Act (42 U.S.C. 262), may request review of a scientific controversy by an appropriate scientific advisory panel (§ 10.75(b)(2) (21 CFR 10.75(b)(2)). Also, under § 10.75(c), interested persons outside of FDA may request internal review of a decision through established FDA channels of supervision or review.

Thus, the current regulations establish procedures for review and evaluation of biological products, which include review by appropriate internal and external experts. In addition, the current regulations allow for public and private entities to participate in FDA's review process, as appropriate. This process serves to increase transparency and helps ensure that the public health is protected. The final rule maintains these important regulatory procedures and requirements while increasing FDA's flexibility in employing advances in science and technology.

(Comment 5) Several comments opposed the proposed rule because the commenters believe the rule would make the use of vaccines less safe. One commenter stated that FDA is ignoring its mandate to make vaccines safer by any and all means at its disposal; that FDA is making vaccines less safe by removing the certainty as to the minimum standards that a biological product must meet; and that the proposed rule does not require that the written requests for such exemptions or alternatives include the appropriate proofs (toxicological and immunological) of the short-term and long-term safety to the most susceptible humans. A few comments stated that an increase in the amount of aluminum may compromise the safety of vaccines. Another comment stated that families do not feel that the current regulations are "too prescriptive and unnecessarily restrictive," and that families would prefer more stringent rules. Other comments discussed specific concerns with already-approved vaccines.

(Response) FDA acknowledges these comments, as many of the issues were considered in drafting the proposed rule. However, FDA disagrees with the assertion that the rule will result in a decrease in the safety of vaccines and other biological products for which a request for an exception or alternative to any requirement under § 610.15 is made and approved. These regulations will continue to be the criteria by which all license applications will be evaluated. However, in order to employ advancements in treatment for certain populations, such as treatment for individuals suffering from life-threatening conditions (*e.g.,* cancer), FDA needs flexibility in applying the regulations. By analogy, as is stated in the drug regulations at 21 CFR 314.105(c):

> While the statutory standards apply to all drugs, the many kinds of drugs that are subject to statutory standards, and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is

[8] Delegations of authority give certain officials in CBER and CDER the legal authority to take substantive actions and perform certain functions of the Commissioner of Food and Drugs. Staff Manual Guide 1410.702 available on the Internet at *http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049563.htm* (accessed October 22, 2010); "Drug and Biological Product Consolidation," (68 FR 38067, June 26, 2003).

required to provide for a particular drug to meet the statutory standards.

The final rule is consistent with this CDER regulation as it allows the Directors of CBER and CDER flexibility in applying current standards for the approval of an exception or alternative to § 610.15, when data submitted with the request for an exception or alternative, establish the safety, purity, and potency of the biological product.

Further, consistent with existing statutory and regulatory requirements, the Directors of CBER and CDER will not approve a biological product that is unsafe for the intended population. The final rule does not alter these statutory and regulatory requirements nor does it guarantee that a request for an exception or alternative will be approved. The final rule only allows the Director of CBER or CDER the flexibility to approve a manufacturer's request for an exception or alternative if the manufacturer demonstrates that the biological product is safe, pure, and potent for use in the intended population.

With regard to comments expressing concern about the safety of previously licensed vaccines or specific ingredients in previously licensed vaccines, FDA notes that those comments concerning previously licensed vaccines are outside the scope of this rulemaking action because the rule only allows the Director of CBER or CDER to approve a manufacturer's request for an exception or alternative to any requirement in § 610.15, when the data submitted in support of such a request establish the safety, purity, and potency of the biological product.

(Comment 6) One comment opposed the proposed rule because the commenter did not know how FDA would monitor or enforce requirements for adequate storage, aseptic withdrawing techniques, and timely use of vaccines in multiple-dose containers without preservative or if additional training would be given to health care providers.

(Response) In addressing this comment, FDA clarifies that all requests for an exception or alternative are subject to FDA regulations regarding the monitoring and enforcement of regulatory standards. These regulations were established to assure the quality and integrity of data submitted to FDA in support of new product approvals and to protect the rights and welfare of the public. FDA accomplishes this through various means, including conducting onsite inspections, data audits, product testing, and report monitoring. FDA also provides advice through guidances and other communications which are provided to assist interested parties in complying with regulatory standards for the safety, purity, and potency of a product.

(Comment 7) One comment provided alternative revisions to the proposed rule and other subsections within § 610.15. Specifically, the commenter proposed that FDA revise the proposed rule to read as follows:

> Alternatives. Except for the generally accepted standards of purity and quality, in keeping with the vaccine safening mandates set forth in 42 U.S.C. 300aa–27"; * * * "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, provided the manufacturer proves that the exception or alternative would improve the safety of the biological drug product or, failing that, improves the effectiveness, not efficacy, or reduces the per dose cost, of the biological drug product without reducing the safety of said product"; and * * * "include the findings, pro and con, of and the data from all of the studies conducted to support the request.

(Response) FDA acknowledges the comment and appreciates the suggestions for revising § 610.15. However, in accordance with the regulations, FDA is seeking public comment only on the proposed rule to permit the Director of CBER or the Director of CDER, as appropriate, to approve exceptions or alternatives to the regulation for constituent materials. FDA's response to the comments requesting revisions to the proposed rule are discussed in the paragraphs that follow.

FDA disagrees with the commenter's suggested revisions to the proposed rule because the revisions inappropriately limit the application of the rule to vaccines; allow more flexibility than is intended for approving a manufacturer's request for an exception or alternative; may lead to confusion about the rule; and are unnecessary. As discussed previously, the final rule allows the Director of CBER or CDER flexibility to approve a request for an exception or alternative to a requirement under § 610.15 provided that data are submitted that establish the safety, purity, and potency of the specific biological product. These statutory and regulatory requirements apply to the use of constituent materials in all biological products and not just to vaccines as the comment suggests. In addition, FDA may only approve a BLA for a vaccine or other biological product if it has been demonstrated to be "safe, pure, and potent." The commenter's suggestions that FDA should take cost considerations into account when making a decision to approve a vaccine are inconsistent with FDA's regulatory authority. Although FDA is sensitive to issues of cost, current statutory standards for constituent materials are based on the safety, purity, and potency of the product. Furthermore, the suggested revisions to the proposed rule inappropriately limit what FDA may consider with respect to a request for an exception or alternative. Manufacturers are required by current regulations to submit all available data, including adverse event reports, with a BLA. FDA reviews the data to determine whether an application should be approved. The final rule, as consistent with current regulations, does not allow the Director of CBER or CDER to approve an application if the data are not sufficient to establish that the biological product is safe, pure, and potent in relation to the manufacturer's intended use of the product.

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 FD&C 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 PHS Act and the FD&C 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.

V. 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 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 (Pub. L. 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 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 final rule allows the Director of CBER or the Director of CDER, as appropriate, to approve exceptions or alternatives to the regulations for constituent materials, this action increases the flexibility and reduces the regulatory burden for affected entities. Therefore, FDA 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 $135 million, using the most current (2009) 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.

The benefit of this regulatory action is its reduction, through greater flexibility in the regulatory requirements, of burdens on the biological products industry. These issues are discussed in greater detail in section I of this document. Industry cost reductions may result in consumers being offered lower prices or wider availability of existing and new biological products; this would have a positive effect on patients' welfare.

Any administrative and paperwork 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 each such request.

We received comments expressing concern that this rule would generate additional costs in the form of negative public health effects. FDA has considered the potential for adverse consequences, including increased morbidity and mortality, associated with allowing deviations from the constituent materials regulations set forth in § 610.15(a) through (c), and will grant exemptions only in cases where data indicate that biological products in their exempted forms will be safe, pure, and potent for the conditions for which the applicant is seeking approval. As experience with the October 1981 rule has shown, FDA is able to conduct a constituent materials exemption process in a manner that is consistent with its public health mandate. For all these reasons, we believe the final rule will impose no overall public health cost.

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

VI. Paperwork Reduction Act of 1995

Section 610.15(d) of this final rule contains reporting requirements that were submitted for review and approval to the Director of the Office of Management and Budget (OMB), as required by section 3507(d) of the Paperwork Reduction Act of 1995. The requirements were approved and assigned OMB control number 0910–0666.

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, 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. Amend § 610.15 by adding 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: April 7, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011–8885 Filed 4–12–11; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1314

[Docket No. DEA–347I]

RIN 1117–AB30

Self-Certification and Employee Training of Mail-Order Distributors of Scheduled Listed Chemical Products

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

ACTION: Interim final rule with request for comment.

SUMMARY: On October 12, 2010, the President signed the Combat Methamphetamine Enhancement Act of 2010 (MEA). It establishes new requirements for mail-order distributors of scheduled listed chemical products. Mail-order distributors must now self-certify to DEA in order to sell scheduled listed chemical products at retail. Sales at retail are those sales intended for personal use; mail-order distributors that sell scheduled listed chemical products not intended for personal use, *e.g.,* sale to a university, are not affected by the new law. This self-certification must include a statement that the mail-order distributor understands each of the requirements that apply under part 1314 and agrees to comply with these requirements. Additionally, mail-order distributors are now required to train their employees prior to self certification. DEA is promulgating this rule to incorporate the statutory provisions and make its regulations consistent with the new requirements