

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 600

[Docket No. 2007N-0284]

Revision of the Requirements for Live Vaccine Processing

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations by providing options to the existing requirement for the processing of live vaccines. FDA is amending the regulations due to advances in technology that will allow processing of live vaccines to be performed in multiproduct manufacturing areas. We are publishing this rule because the existing requirement regarding facilities and equipment for live vaccine processing is too prescriptive and is no longer necessary. We are taking this action as part of our continuing effort to reduce the burden of unnecessary regulations on industry and to revise outdated regulations without diminishing public health protection. Elsewhere in this issue of the FEDERAL REGISTER, we are publishing a companion proposed rule under our usual procedures for notice and comment in the event that we receive any significant adverse comments on the direct final rule. If we receive any significant adverse comments that warrant terminating the direct final rule, we will consider such comments on the proposed rule in developing the final rule.

DATES: This rule is effective [insert date 5 months after date of publication in the FEDERAL REGISTER]. Submit written or electronic comments by [insert date 75 days after date of publication in the FEDERAL REGISTER]. If we receive no significant adverse comments

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during the specified comment period, we intend to publish a confirmation document on or before the effective date of this direct final rule confirming that the direct final rule will go into effect on [insert date 5 months after date of publication in the FEDERAL REGISTER]. If we receive any significant adverse comments during the comment period, we intend to withdraw this direct final rule before its effective date by publication of a notice in the FEDERAL REGISTER.

ADDRESSES: You may submit comments, identified by Docket No. 2007N-0284, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

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.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described previously, in the ADDRESSES portion of this document under Electronic Submissions.

Instructions: All submissions received must include the agency name and Docket No. 2007N-0284 for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For additional information on submitting comments see the "Request for Comments" heading in section VII 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.fda.gov/ohrms/dockets/default.htm> 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.

FOR FURTHER INFORMATION CONTACT:

Nathaniel L. Geary,

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Rockville, MD 20852-1448,

301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

Live organisms are used in the production of certain vaccine products. These live organisms are generally used as source material for further manufacture into final products used in the prevention, treatment, or cure of a disease or condition of human beings. Live organisms pose a challenge to manufacturers in the prevention of cross contamination of other products and manufacturing areas. Some live organisms used in manufacturing may be harmful to humans,

especially immunocompromised patients. To ensure the safety of a biological product manufactured in the same building or area in which live organisms are utilized, tight controls are needed to avoid the release of any live organisms into the manufacturing environment and to prevent cross contamination of other products manufactured in the same building or area.

Current FDA regulations strictly limit how live vaccine processing may be performed. Current § 600.11(e)(4) (21 CFR 600.11(e)(4)) requires that: (1) Space used for processing a live vaccine must be decontaminated before processing is started and must not be used for any other purpose during the vaccine processing; (2) live vaccine processing areas must be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor; (3) the processing area must include adequate space and equipment for all processing steps up to, but not including, filling into final containers; and (4) test procedures that potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, must not be conducted in space used for processing live vaccine.

We are revising § 600.11(e)(4) to allow greater flexibility for vaccine manufacturers regarding the buildings and equipment used for live vaccine processing. The revisions provide for the use of modern manufacturing approaches to assist vaccine manufacturers who engage in live vaccine processing, e.g., manufacturers of influenza virus vaccines. The revisions provide that live vaccine processing steps may be performed in multiproduct manufacturing buildings and areas when appropriate controls exist to prevent cross contamination of other products and areas. We recognize that advances in facility, utility, system, and equipment design, as well as in sterilization, decontamination, and disinfection technologies have increased the ability of manufacturers to control the manufacture of biological products and the equipment used in their

manufacture. The use of appropriate controls, procedures, and processes provides an adequate degree of confidence that a product meets the expected levels of safety, purity, and potency. Areas of special concern, such as containment, decontamination, sterilization, and disinfection can be addressed using currently available controls, procedures, and processes. The scope of this regulation is limited to all live vaccine processing steps up to, but not including, filling into final containers. In section II of this document, we identify each of the changes included in this direct final rule.

II. Highlights of the Direct Final Rule

We are revising § 600.11(e)(4) to require that live vaccine processing be performed under appropriate controls to prevent cross contamination of other products and other manufacturing areas within the building. We regard an area as a specific room or set of rooms within a building associated with the manufacturing of any one product or multiple products.

Revised § 600.11(e)(4)(i) is analogous to the preexisting § 600.11(e)(4). In revised § 600.11(e)(4)(i)(A), we provide that a manufacturer can use an area that is either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and includes adequate space and equipment for all processing steps up to, but not including, filling into final containers. In revised § 600.11(e)(4)(i)(B), we require that a manufacturer not use the manufacturing space for conducting test procedures that potentially involve the presence of microorganisms other than the vaccine strains or the use of tissue culture cell lines other than primary cultures.

In revised § 600.11(e)(4)(ii), if manufacturing is conducted in a multiproduct manufacturing building or area, we require appropriate controls including procedural controls, and where necessary, process containment, to prevent cross contamination of other products and

other manufacturing areas within the building. In addition, we are requiring that all product, equipment, and personnel movement between distinct live vaccine processing areas and between live vaccine processing areas and other manufacturing areas up to, but not including, filling in containers, must be conducted under conditions that will prevent cross contamination of other products and manufacturing areas within the building, including the introduction of live vaccine organisms into these other areas. Process containment is a system designed to mechanically isolate equipment or an area that involves manufacturing using live vaccine organisms. Procedural controls establish and perform effective decontamination, sterilization, and disinfection, as well as execute manufacturing procedures in such a manner as to prevent cross contamination with live vaccine organisms.

As part of their procedural controls, manufacturers must have written procedures and effective processes in place to adequately remove or decontaminate live vaccine organisms from manufacturing areas and from equipment for subsequent manufacture of other products. Written procedures must be in place for verification that processes to remove or decontaminate live vaccine organisms have been followed. All potential routes of cross contamination to other manufacturing areas should be addressed, including movement of persons (e.g., technical, maintenance, delivery, management personnel, and visitors), equipment, and in-process materials. Live vaccine organisms should not be removed from designated areas unless this can be done in a manner that prevents the cross contamination of other products and manufacturing areas. These procedural controls will provide a level of assurance that products made in areas where live vaccines are manufactured remain safe, pure, and potent.

III. Legal Authority

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

IV. Rulemaking Action

In the FEDERAL REGISTER of November 21, 1997 (62 FR 62466), FDA described its procedures on when and how the agency will employ direct final rulemaking. We have determined that this rule is appropriate for direct final rulemaking because we believe that it includes only noncontroversial amendments and we anticipate no significant adverse comments. Consistent with our procedures on direct final rulemaking, FDA is publishing elsewhere in this issue of the FEDERAL REGISTER a companion proposed rule to amend FDA's regulations to allow greater flexibility in live vaccine processing. The companion proposed rule provides a procedural framework within which the rule may be finalized in the event that the direct final rule is withdrawn because of any significant adverse comments. The comment period for the direct final rule runs concurrently with the companion proposed rule. Any comments received in response to the companion proposed rule will be considered as comments regarding the direct final rule.

We are providing a comment period on the direct final rule of 75 days after the date of publication in the FEDERAL REGISTER. If we receive any significant adverse comments, we

intend to withdraw this direct final rule before its effective date by publication of a notice in the FEDERAL REGISTER. A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether an adverse comment is significant and warrants terminating a direct final rulemaking, we will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process in accordance with section 553 of the Administrative Procedure Act (5 U.S.C. 553). Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a regulation change in addition to those in the rule would not be considered a significant adverse comment unless the comment states why the rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this rule and that provision can be severed from the remainder of the rule, we may adopt as final those provisions of the rule that are not the subject of a significant adverse comment.

If any significant adverse comments are received during the comment period, FDA will publish, before the effective date of this direct final rule, a document withdrawing the direct final rule. If we withdraw the direct final rule, any comments received will be applied to the proposed rule and will be considered in developing a final rule using the usual notice-and-comment procedures.

If FDA receives no significant adverse comments during the specified comment period, FDA intends to publish a confirmation document, before the effective date of the direct final rule, confirming the effective date.

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 direct 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 (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 direct final rule is not an economically significant regulatory action as defined by 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 this direct final rule will provide increased flexibility for the processing of live vaccines, it would decrease overall compliance costs. Therefore, the agency certifies that this direct 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 \$127 million, using the most current (2006) Implicit Price

Deflator for the Gross Domestic Product. FDA does not expect this direct final rule to result in any 1-year expenditure that would meet or exceed this amount.

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

C. Federalism

FDA has analyzed this direct final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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 direct 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. The Paperwork Reduction Act of 1995

This direct final rule contains no new collections of information. The collection of information under § 600.11(e)(4) is covered by OMB control numbers 0910-0139 (expires September 30, 2008) and 0910-0308 (expires July 31, 2008). Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) is not required.

VII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) written or electronic 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 600

Biologics, 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 600 is amended as follows:

PART 600--BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

2. Section 600.11 is amended by revising paragraph (e)(4) to read as follows:

§ 600.11 Physical establishment, equipment, animals, and care.

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(e) * * *

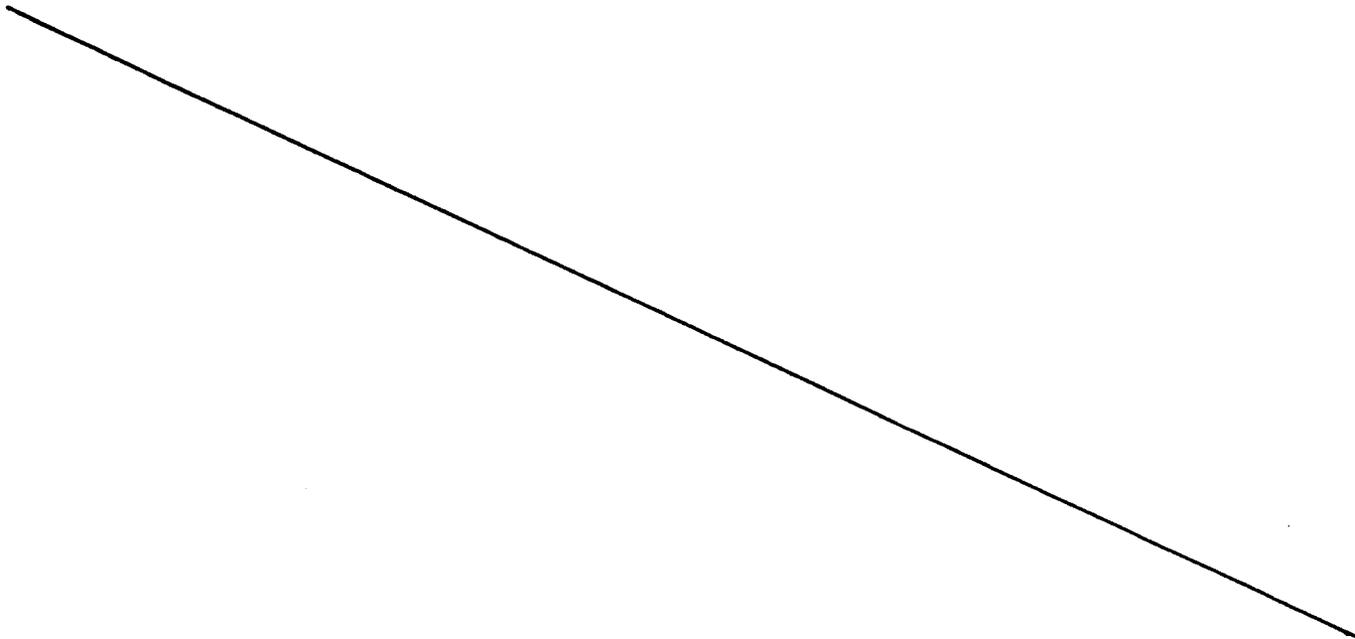
(4) Live vaccine processing. Live vaccine processing must be performed under appropriate controls to prevent cross contamination of other products and other manufacturing areas within the building. Appropriate controls must include, at a minimum:

(i)(A) Using a dedicated manufacturing area that is either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and includes adequate

space and equipment for all processing steps up to, but not including, filling into final containers;
and

(B) Not conducting test procedures that potentially involve the presence of microorganisms other than the vaccine strains or the use of tissue culture cell lines other than primary cultures in space used for processing live vaccine; or

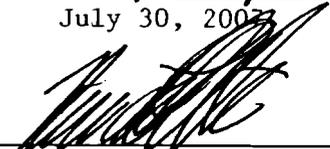
(ii) If manufacturing is conducted in a multiproduct manufacturing building or area, using procedural controls, and where necessary, process containment. Process containment is deemed to be necessary unless procedural controls are sufficient to prevent cross contamination of other products and other manufacturing areas within the building. Process containment is a system designed to mechanically isolate equipment or an area that involves manufacturing using live vaccine organisms. All product, equipment, and personnel movement between distinct live vaccine processing areas and between live vaccine processing areas and other manufacturing areas, up to, but not including, filling in final containers, must be conducted under conditions that will prevent cross contamination of other products and manufacturing areas within the building, including the introduction of live vaccine organisms into other areas. In addition, written procedures and effective processes must be in place to adequately remove or



decontaminate live vaccine organisms from the manufacturing area and equipment for subsequent manufacture of other products. Written procedures must be in place for verification that processes to remove or decontaminate live vaccine organisms have been followed.

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Dated: 7/30/07
July 30, 2007



Randall W. Lutter,
Deputy Commissioner for Policy.

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**CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL**
Dawn P. Hawkins