

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 June 1, 2004. If we receive any significant adverse comments during the comment period, we intend to withdraw the direct final rule before its effective date by publication of a document in the **Federal Register**.

ADDRESSES: Submit written comments on the direct final rule to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT:

Valerie A. Butler, 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

Spore-forming microorganisms are used in the production of certain biological products. These microorganisms may be 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. By their very nature, these microorganisms pose a great challenge to manufacturers. Bacteria produce spores as a means to survive adverse environmental conditions, while some fungi use them as a form of reproduction. Spores show great resistance to high temperature, freezing, dryness, antibacterial agents, radiation, and toxic chemicals. Under favorable conditions, spores can germinate into actively growing bacteria and fungi. Many of these spore-forming microorganisms are pathogenic to humans and have been implicated in causing morbidity and mortality. To ensure the safety of a biological product manufactured in a facility in which spore-forming microorganisms are present, these microorganisms must be kept under tight control to avoid the release of spores into the manufacturing atmosphere and potential contamination of other products.

Due to the unique survival properties of spore-forming microorganisms, current FDA regulations require that work with these microorganisms be conducted separately from manufacturing operations for other products. (Currently, FDA regulations use the term "spore-bearing" microorganisms. In this rulemaking, we are revising these regulations to use the

term "spore-forming" because it is a more commonly used term. For the purposes of these regulations, spore-forming microorganisms include both the spore and vegetative cells.) Under § 600.11(e)(3) (21 CFR 600.11(e)(3)), all work with spore-forming microorganisms must be performed in an entirely separate building, or in a completely walled-off portion of a if that portion is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. Section 600.11(e)(3) further requires that all vessels, apparatus, and equipment used for spore-forming microorganisms be permanently identified and reserved exclusively for use with those organisms. This provision also states that any materials destined for further manufacturing may be removed from this area only under conditions that will prevent the introduction of spores into other manufacturing areas.

In accordance with Executive Order 12866, which directs Federal agencies to review their regulations and eliminate or modify those that are outdated or otherwise in need of reform, we are revising § 600.11(e)(3) to allow greater manufacturing flexibility regarding work with spore-forming microorganisms. The revisions provide that work with spore-forming microorganisms may be performed in multiproduct manufacturing areas when appropriate controls to prevent contamination of other products and areas exist. We recognize that advances in facility, system, and equipment design and in sterilization technologies have increased the ability of manufacturers to control and analyze the manufacture of biological products and the equipment used in their manufacture. The use of appropriate controls and procedures and processes provide an adequate degree of confidence that a product meets the expected levels of safety and purity. Areas of special concern, such as containment, contamination with pathogenic and/or toxic agents, sterilization, and disinfection can be addressed using currently available and required procedures and processes.

This direct final rule does not apply to spore-forming microorganisms used for testing of biological products to determine the growth-promoting qualities of test media used to ensure the sterility of each lot of product or as biological indicators for validation of steam sterilization cycles. The rule also does not change the requirements for those products set forth in

§§ 600.11(e)(2) and 610.12 (21 CFR 610.12).

II. Highlights of the Direct Final Rule

We are amending our regulations involving spore-forming microorganisms as set forth below.

A. Work With Spore-Forming Microorganisms

We are revising § 600.11(e)(3) to provide greater flexibility in production facilities and procedures for work with spore-forming microorganisms.

Revised § 600.11(e)(3)(i) states that manufacturing processes using spore-forming microorganisms conducted in a multiproduct manufacturing site must be performed under appropriate controls to prevent contamination of other products and areas within the site. We regard a manufacturing site as an entire complex of buildings, connected or separate, that belongs to one entity engaged in the manufacture of any one product or multiple products. An area within a manufacturing site is a specified location within a facility (physical structure) associated with the manufacturing of any one product or multiple products. Revised § 600.11(e)(3)(i) further states that prevention of spore contamination can be achieved by using a separate, dedicated building or, if manufacturing is conducted in a multiproduct manufacturing building, by using process containment. Finally, revised § 600.11(e)(3)(i) states that all product and personnel movement between the area where the spore-forming microorganisms are manufactured and other manufacturing areas must be conducted under conditions that will prevent the introduction of spores into other areas of the facility.

Revised § 600.11(e)(3)(ii) states that if process containment is employed in a multiproduct manufacturing area, procedures must be in place to demonstrate adequate removal of the spore-forming microorganism(s) from the manufacturing area for subsequent manufacture of other products. Revised § 600.11(e)(3)(ii) further states that these procedures must provide for adequate removal or decontamination of the spore-forming microorganisms on and within manufacturing equipment, facilities, and ancillary room items as well as the removal of disposable or product dedicated items from the manufacturing area. Finally, revised § 600.11(e)(3)(ii) states that environmental monitoring specific for the spore-forming microorganism(s) must be conducted in adjacent areas during manufacturing operations and in