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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210 and 211

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[Docket No. 2007N-0280]

Amendment to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending certain regulations as the first phase of an incremental approach to modifying the current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. We are amending the regulations to modernize or clarify some of the CGMP requirements, as well as harmonize some of the CGMP requirements with those of other foreign regulators and other FDA regulations. These amendments are also consistent with current industry practice. We are taking this action as part of our continuing effort to revise outdated regulations without diminishing public health protection. We are issuing a direct final rule for this action because FDA expects there will be no significant adverse comments on these amendments. Elsewhere in this issue of the **Federal Register**, we are publishing a companion proposed rule, under our usual notice-and-comment rulemaking procedures, to provide a procedural framework to finalize the rule in the event the agency receives any significant adverse comments and withdraws this direct final rule. The companion proposed rule and direct final rule are substantively identical.

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DATES: This rule is effective [*insert date 135 days after date of publication in the **Federal Register***]. Submit written or electronic comments on or before [*insert date 75 days after date of publication in the **Federal Register***]. If we receive no significant adverse comments during the specified comment period, we intend to publish a notice in the **Federal Register** no later than [*insert date 105 days after date of publication in the **Federal Register***], confirming the effective date of the direct final rule. If we receive any timely significant adverse comments during the comment period, we will publish a notice of significant adverse comment in the **Federal Register** withdrawing this direct final rule before its effective date.

ADDRESSES: You may submit comments, identified by Docket No. 2007N-0280, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulation.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(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) 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 “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.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), 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:

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SUPPLEMENTARY INFORMATION:

I. Background

Since the development of the CGMP regulations in 1962, FDA has balanced the need for easily understood minimum standards with the need to encourage innovation and the development of improved manufacturing technologies. We strive to give manufacturers latitude to determine how to achieve the level of control necessary for CGMP compliance, recognizing that, in some instances, more direction from FDA is necessary to provide a uniform standard for the entire industry or because of the potential for harm, or the narrow range of acceptable means to accomplish a particular CGMP objective. FDA periodically reassesses and revises the CGMP regulations to accommodate advances in technology that further safeguard the drug manufacturing process and the public health. As technology and scientific knowledge related to CGMP evolve, so does understanding of the material, equipment, and process variables, as well as the operational procedures and oversight methods that must be defined and controlled to achieve assurance of drug product quality.

In 1996, as part of this reassessment process, FDA proposed a significant revision to the CGMP regulations for finished pharmaceuticals to clarify certain manufacturing, quality control, and documentation requirements, and to ensure that the regulations more accurately encompass current industry practice (61 FR 20103, May 3, 1996) (1996 proposed rule). Subsequently, as a part of the risk-based pharmaceutical CGMPs for the 21st century initiative, FDA created a CGMP Harmonization Analysis Working Group (CGMP Working Group) to analyze related CGMP requirements in effect in the United States and internationally, including those related to quality systems. The CGMP Working Group compared parts 210 and 211 (21 CFR parts 210 and 211) to the GMPs of the European Union (EU), as well as other FDA regulations (e.g.,

the Quality Systems Regulation, 21 CFR part 820) to identify the differences and consider the value of supplementing or changing the current regulations. Based on the CGMP Working Group's analysis, we decided to take an incremental approach to modifying parts 210 and 211 (see http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065744).

Because of this change in approach, FDA decided not to finalize the 1996 proposed rule. Therefore, elsewhere in this issue of the **Federal Register**, we are publishing a notice withdrawing the 1996 proposed rule.

This direct final rule is intended to clarify and modernize the CGMP regulations, as well as harmonize the regulations with international GMP requirements and other FDA regulations. This direct final rule represents the first increment of modifications to parts 210 and 211. We believe that these updating changes are noncontroversial.

II. Description of the Direct Final Rule

A. Plumbing

This rule deletes from § 211.48(a) the current requirement of adherence to a specific U.S. Environmental Protection Agency (EPA) water standard and instead simply requires that the plumbing system contain water that is “safe for human consumption.” In an effort to improve harmonization with foreign regulations (particularly the European Union and Japan) and to make the U.S. regulation more consistent with that of the United States Pharmacopeia standard, which is satisfied by compliance with the regulations of the European Union (EU) and Japan, this revision requires that water supplied by the plumbing system and used to prepare water for pharmaceutical purposes be “safe for human consumption,” and continues the requirement that it “be supplied under continuous positive pressure in a plumbing system free of

defects that could contribute contamination to any drug product.” Compliance with the standards set forth in the regulations currently prescribed by the EPA would be acceptable under this revision, as would compliance with the standards set forth in the current regulations of the EU or Japan for potable water used to prepare water for pharmaceutical purposes.

B. Aseptic Processing

The current regulations related to aseptic processing have not been updated to reflect current industry standards and practices. In September 2004, we issued “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice” (see <http://www.fda.gov/cder/guidance/5882.fnl.htm>). The issuance of this document was the culmination of several years of work, including soliciting input from external stakeholders, such as described below.

In 2002, we began work on a draft guidance that was intended to replace the 1987 Guideline on Sterile Drug Products Produced by Aseptic Processing. A concept paper was presented to FDA’s Advisory Committee on Pharmaceutical Science on October 22, 2002, for comment. Among other things, the Committee recommended that we work with the Pharmaceutical Quality Research Institute (PQRI) for resolution of major issues. The PQRI Aseptic Processing Working Group (Aseptic Processing Working Group), composed of members from FDA, industry, and academia, was formed to provide scientifically based input targeting specific aseptic processing topics (e.g., media fills). PQRI performed a survey of the industry on these topics, the results of which were presented to the Aseptic Processing Working Group for consideration. The Aseptic Processing Working Group also considered scientific publications and other regulatory documents in preparing

recommendations concerning specific aseptic processing topics. These recommendations were discussed by the Aseptic Processing Working Group on February 27 and 28, 2003 (www.pqri.org/commworking/minutes/mtc.asp) and presented to the Manufacturing Subcommittee of FDA's Advisory Committee on Pharmaceutical Science on May 22, 2003.

In its September 2003, "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach: Second Progress Report and Implementation Plan," FDA announced the issuance of the draft guidance. See http://www.fda.gov/cder/gmp/2ndProgressRept_Plan.htm. At the time, the agency noted that the guidance was intended to clarify regulatory expectations, including relevant regulatory standards for sterile drug products. FDA believed the guidance would help reduce the incidence of manufacturing problems with sterile drug products and related drug shortages. The guidance was also consistent with agency efforts to harmonize with international regulatory standards and develop more science-based guidance documents. As noted previously, FDA issued the final guidance in September 2004.

After the GMP Harmonization Analysis Working Group completed its formal analysis comparing parts 210 and 211 with the GMPs of the EU as well as with other FDA current good manufacturing practice regulations, it recommended that part 211 be modernized by adding more clarification about aseptic processing in an effort to harmonize with current industry standards and practices. Therefore, we are now amending several regulations related to aseptic processing to clarify the regulatory requirements to reflect currently accepted industry practice as well as, in some cases, to harmonize with international regulatory standards. The revision to § 211.113(b) applies specifically to validation of aseptic processes, but the revisions to the other

four sections discussed below apply, as appropriate, to both aseptic and other types of processes and operations. These revisions clarify and reflect longstanding agency interpretation of these regulations and industry practices. The agency notes that these clarifications of the regulations with respect to aseptic processing do not affect the applicability of the final guidance issued in September 2004. The guidance's recommendations on the ways in which manufacturers can satisfy certain aseptic processing regulatory requirements still apply.

Section 211.67(a) *Equipment cleaning and maintenance* is being revised to add the phrase "and/or sterilized" after the word "sanitized" in the current regulation. This change updates the terminology to reflect the fact that, in the context of sterile drug products, the appropriate form of sanitization would be sterilization. This is consistent with our interpretation of this regulation for more than 20 years and reflects the currently accepted industry practice.

Section 211.84(d)(6) *Testing and approval or rejection of components drug product containers, and closures*, is being revised to change the phrase "that is liable to microbiological contamination," to "with potential for microbiological contamination." We believe this revision provides additional clarity without changing the meaning or intent of the regulation.

Section 211.94(c) *Drug product containers and closures* is being revised to clarify that validation is required for the processes used to remove pyrogenic properties (depyrogenation processes). The revision reflects currently accepted industry practice and the agency's longstanding interpretation of this regulation. To assure that certain drug products are suitable for their intended use, drug product containers and closures are required to be sterilized and depyrogenated to remove microbial contamination and pyrogens or endotoxin.

It has been longstanding industry practice to validate the sterilization and depyrogenation processes used for drug product containers and closures to assure consistent removal of microbial contamination and pyrogens or endotoxin. Lack of evidence of such validation and inadequacies in the validation studies have been cited in FDA actions throughout the years based on this regulation. Accordingly, this rule simply clarifies § 211.94(c) by adding a new sentence at the end which states; “Such depyrogenation processes shall be validated.”

Paragraph (a) of § 211.110 *Sampling and testing of in-process materials and drug products* is being revised to include bioburden process control procedures and tests, where appropriate. The existing regulation provides five examples of control procedures and tests that must be addressed, where appropriate, to monitor the output and to validate the performance of manufacturing processes that may be responsible for causing variation in the characteristics of in-process material and drug product. The existing regulation also acknowledges that the examples are not an all inclusive list of necessary process control procedures and tests. For in-process materials and drug products that are produced by aseptic processing, testing for bioburden is a well established industry standard to ensure that the finished dosage form will be sterile and that the process is not shifting from established limits that may affect control. The revised regulation will add bioburden testing as the sixth example of process control procedures.

Paragraph (b) of § 211.113 *Control of microbiological contamination* is being revised to include validation of aseptic processes for drug products that are purported to be sterile. The current regulation mentions only validation of sterilization processes, not aseptic processes. Even before 1987, when the

Guideline for Sterile Drug Products Produced by Aseptic Processing was issued, industry routinely conducted validation studies that substituted microbiological media for the actual product to demonstrate that its aseptic processes were validated. These parts of validation studies are often referred to as media fills. We believe that this revision clarifies existing practices and serves to harmonize the CGMP requirements with Annex 1 of the EU GMPs, which requires such validation.

C. Asbestos Filters

Our current regulations for filters used in processing liquid injectable products need to be updated. The current regulations require manufacturers, before using asbestos-containing filters, to submit proof to FDA that an alternative filter will or is more likely to result in product contamination. However, we are not aware that asbestos filters are currently commercially manufactured for pharmaceutical use or that they are currently used in the production of pharmaceuticals. Indeed, their use would no longer be considered a good manufacturing practice. Therefore, we are revising §§ 210.3(b)(6) and 211.72 to remove an outdated regulation permitting limited use of asbestos-containing filters. This revision also provides consistency with international standards.

We removed from the definition of “non-fiber releasing filter,” the statement that “All filters composed of asbestos are deemed to be fiber-releasing filters”; because the revised regulation does not permit any use of asbestos-containing filters. Thus, this sentence is no longer necessary. Because other nonasbestos, fiber-releasing filters may still be used, the revised regulation retains the current requirement that allows the use of fiber-releasing

filters only when necessary, and only if another filter is also used specifically to reduce the amount of shed fibers in the finished pharmaceutical.

It is noteworthy that the current CGMP regulation at paragraph (a) of § 211.65 *Equipment construction*, requires equipment, including filters, to be constructed so that “surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.” We are not changing this requirement, which also restricts the amount and type of objectionable particulates in drug products resulting from contact with equipment.

D. Verification by Second Individual

Under the current CGMP regulations, several regulations include requirements that certain activities be performed by one person and checked as specified by a second person. Section 211.101(c) requires that each container of component dispensed for use in manufacturing be examined by a second person to assure that it was released by the quality control unit, that the weight or measure is correct as stated in the batch production records, and that the containers are properly identified. Section 211.101(d) requires that each component shall be added to the batch by one person and verified by a second person. Section 211.103 requires that specified yield calculations shall be performed by one person and independently verified by a second person. Section 211.182 requires that the persons performing and double-checking the cleaning and maintenance of major equipment shall date and sign or initial equipment logs indicating that the work was performed. Finally, § 211.188(b)(11) requires that batch production and control records shall

include identification of the persons performing and directly supervising or checking each significant step in the operation.

When the CGMP regulations were amended in 1978, FDA issued § 211.68, which provides that automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product, subject to certain requirements that the controls used are designed to assure proper performance of such equipment, to assure that changes to records are made only by authorized personnel, to check the input and output for accuracy, and to provide for appropriate backup of data.

FDA has periodically been asked whether the requirements for verification by a second individual in §§ 211.101(c) and (d), 211.103, 211.182, and 211.188(b)(11) are applicable in situations where operations are performed by various types of automated equipment rather than by an individual. When these regulations were adopted in 1978, the preamble addressed this issue in response to several comments about the second checking requirements of § 211.101 for charge-in of components when automated systems are used. We specifically noted that the use of automated systems is permitted under section 211.68 and that the requirement of 211.101 would be met if the second individual verifies that the automated system is working properly (43 FR 45013 to 45087 at 45051, September 29, 1978). Thus, in this situation, the first individual is replaced by a machine or other automated process, and only one person is necessary to verify that the automated system is functioning as intended.

Due to periodic questions received by FDA about the performance and checking requirements required by §§ 211.101(c) and (d), 211.103, 211.182, and

211.188(b)(11) when the operations are performed by automated equipment, such as the widespread and increasing use of computer-controlled operations, we are revising these sections. The revisions will clarify our long-standing interpretation and policy that verification by a second individual may not be necessary when automatic equipment is used under § 211.68. Rather, in these situations, only one person is needed to verify that the automated equipment is functioning adequately. In cases where there is an operator for the automated equipment, the verifying individual may be, but is not required to be, the operator.

Thus, we are amending §§ 211.101(c) and (d), 211.103, 211.182, and 211.188(b)(11) to indicate that the use of automated equipment under § 211.68 may eliminate the need for verification by a second individual and that in those situations only one person is needed to verify that the automated equipment is functioning properly. In addition, we are amending section 211.68 to provide a consistent clarification of this point.

E. Miscellaneous Minor Changes Based on 1996 Proposal

We are revising § 211.82(b) by replacing the phrase “as appropriate” by the phrase “whichever is appropriate” to eliminate any ambiguity in the regulation and to emphasize that it is, in fact, accepted industry practice to conduct some testing or examination before the components, drug product containers, or closures are released from quarantine.

We are revising § 211.84(c)(1) by replacing the phrases “where necessary, by appropriate means” with “when necessary in a manner to prevent introduction of contaminants into the component.” This change will clarify that the act of cleaning is done for a particular purpose, to prevent the

introduction of contaminants, and must be done unless such cleaning is not necessary to prevent such an introduction of contaminants.

In addition, two editorial changes are being made to § 211.84(d)(3) by replacing the word “conformance” with “conformity” and “procedure” with “specifications.” Similarly, two minor editorial changes are being made to the first sentence of § 211.160(b)(1) by replacing the word “conformance” with “conformity” and “appropriate” with “applicable.” We believe that these revisions provide clarity without changing the meaning or intent of the regulations.

III. Direct Final Rulemaking

In the **Federal Register** of November 21, 1997 (62 FR 62466), FDA published a notice of availability of a guidance document that explains when and how we intend to 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 revise the CGMP regulations for finished pharmaceuticals. 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 as a result 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 either of these rules will be considered as comments to the other.

We are providing a comment period on the direct final rule of 75 days after the date of the 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 subjects of a significant adverse comment.

If any significant adverse comments are received during the comment period, FDA will publish, within 30 days after the close of the comment period, a notice of significant adverse comment and will withdraw 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 document confirming the effective date of the direct final rule within 30 days after the comment period ends.

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 this 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 a significant regulatory action as defined by the Executive order, because the rule generally either clarifies the agency’s longstanding interpretation of, or increases latitude for manufacturers in complying with, preexisting CGMP requirements. 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 does not impose any new regulatory obligations, the agency certifies that it would 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 \$122 million, using the most current (2005) 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.

The purpose of this direct final rule is to update the codified language to reflect current practice and to harmonize requirements in the CGMP regulations with international GMP requirements and other FDA regulations. It would not impose any additional requirements; therefore, industry would not incur incremental compliance costs for these changes.

B. Environmental Impact

Issuing these clarifying amendments to the CGMP regulations will not have a significant impact on the human environment. Therefore, an environmental impact statement is not 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 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

The provisions of this direct final rule contain 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 0910–0139.

VI. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this direct final rule. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that any 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

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and Containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 210 and 211 are amended as follows:

**PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN
MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS;
GENERAL**

- 1. The authority citation for 21 CFR part 210 continues to read as follows;

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

- 2. Section 210.3 is amended by revising paragraph (b)(6) to read as follows:

§ 210.3 Definitions.

(b) * * *

(6) *Nonfiber releasing filter* means any filter, which after appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered.

* * * * *

**PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED
PHARMACEUTICALS**

- 3. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

- 4. Section 211.48 is amended by revising paragraph (a) to read as follows:

§ 211.48 Plumbing.

(a) Water supplied by the plumbing system of the facility must be safe for human consumption. This water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.

* * * * *

■ 5. Section 211.67 is amended by revising paragraph (a) to read as follows:

§ 211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

* * * * *

■ 6. Section 211.68 is amended by adding paragraph (c) to read as follows:

§ 211.68 Automatic, mechanical, and electronic equipment.

* * * * *

(c) Such automated equipment used for performance of operations addressed by §§ 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections for the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section and one person verifies that the operations addressed in those sections are performed accurately by such equipment.

■ 7. Section 211.72 is revised to read as follows:

§ 211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the

manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product.

■ 8. Section 211.82 is amended by revising paragraph (b) to read as follows:

§ 211.82 Receipt and storage of untested components, drug product containers, and closures.

* * * * *

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of § 211.80.

■ 9. Section 211.84 is amended by revising paragraphs (c)(1), (d)(3), and (d)(6) to read as follows:

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

* * * * *

(c) * * *

(1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.

* * * * *

(d) * * *

(3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of

the supplier’s test results through appropriate validation of the supplier’s test results at appropriate intervals.

* * * * *

(6) Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

* * * * *

■ 10. Section 211.94 is amended by revising paragraph (c) to read as follows:

§ 211.94 Drug product containers and closures.

* * * * *

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.

* * * * *

■ 11. Section 211.101 is amended by revising paragraphs (c) and (d) to read as follows:

§ 211.101 Charge-in of components.

* * * * *

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

- (1) The component was released by the quality control unit;
- (2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under § 211.68,

only one person is needed to assure conditions of paragraphs (c)(1), (c)(2), and (c)(3) of this section have been met.

(d) Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under § 211.68, only verified by one person.

■ 12. Section 211.103 is revised to read as follows:

§ 211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person, or, if the yield is calculated by automated equipment under § 211.68, be independently verified by one person.

■ 13. Section 211.110 is amended by revising paragraph (a) introductory text and by adding paragraph (a)(6) to read as follows:

§ 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

* * * * *

(6) Bioburden testing.

* * * * *

■ 14. Section 211.113 is amended by revising paragraph (b) to read as follows:

§ 211.113 Control of microbiological contamination.

* * * * *

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

■ 15. Section 211.160 is amended by revising paragraph (b)(1) to read as follows:

211.160 General requirements.

* * * * *

(b) * * *

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

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■ 16. Section 211.182 is revised to read as follows:

§ 211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and

lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record.

The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 211.68, only the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

■ 17. Section 211.188 is amended by revising paragraph (b)(11) to read as follows:

§ 211.188 Batch production and control records.

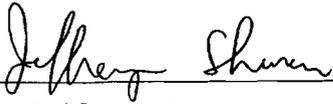
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(b) * * *

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under § 211.68, the identification of the person checking the significant step performed by the automated equipment.

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November 26, 2007.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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