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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210 and 211

[Docket No. FDA-2007-N-0379] (formerly Docket No. 2007N-0280)

Amendments to the Current Good Manufacturing Practice Regulations for Finished
Pharmaceuticals

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending certain of its regulations on current good manufacturing practice (CGMP) requirements for finished pharmaceuticals as the culmination of the first phase of an incremental approach to modifying the CGMP regulations for these products. This rule revises CGMP requirements primarily concerning aseptic processing, verification of performance of operations by a second individual, and the use of asbestos filters. We are amending the regulations to modernize or clarify some of the requirements as well as to harmonize them with other FDA regulations and international CGMP standards.

DATES: This rule is effective [insert date 90 days after date of publication in the FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

II. Summary of the Final Rule

A. Aseptic Processing

B. Asbestos Filters

C. Verification by a Second Individual

D. Other Minor Changes

III. Comments on the Proposed Rule and FDA's Response

A. General Comments

B. Plumbing

C. Aseptic Processing

D. Asbestos Filters

E. Verification by a Second Individual

F. Miscellaneous Minor Changes Based on 1996 Proposal

IV. Analysis of Impacts

V. Environmental Impact

VI. Federalism

VII. Paperwork Reduction Act of 1995

I. Background

Since the development of the CGMP regulations for drug products 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 to the entire industry, minimize the potential for harm, or achieve some other CGMP objective. We periodically reassess and revise the CGMP regulations to accommodate advances in technology and other scientific knowledge that further safeguard the drug manufacturing process and the public health.

In 1996, as part of this reassessment process, we proposed to: (1) Amend certain requirements of the CGMP regulations for finished pharmaceuticals to clarify certain

manufacturing, quality control, and documentation requirements and (2) ensure that the regulations more accurately encompassed current industry practice (61 FR 20104, May 3, 1996) (1996 proposed rule). Subsequently, as a part of the risk-based Pharmaceutical CGMPs for the 21st Century initiative, we 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) with the CGMPs 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.

Because of this change in approach, we decided not to finalize the 1996 proposed rule. On December 4, 2007, we published a document withdrawing the 1996 proposed rule (72 FR 68111) (the December 2007 proposed rule). On the same date, we published a direct final rule (72 FR 68064) and companion proposed rule (72 FR 68113) to clarify and modernize certain provisions of the CGMP regulations. The comment period for the direct final rule closed on February 19, 2008. On April 4, 2008, we published a document withdrawing the direct final rule because we received significant adverse comments (73 FR 18440). In the document withdrawing the direct final rule, we explained that the comments received would be considered under our usual procedures for notice and comment in connection with the notice of proposed rulemaking that was published as a companion to the direct final rule.

After careful consideration of all comments received, we are now publishing this final rule. The final rule represents the culmination of the first increment of modifications to parts 210 and 211.

II. Summary of the Final Rule

The final rule revises the drug CGMP regulations primarily in three areas: Aseptic processing, use of asbestos filters, and verification of operations by a second individual.

A. Aseptic Processing

The final rule revises § 211.113(b) to clarify that required written procedures designed to prevent microbiological contamination of sterile drug products must include procedures on the validation of all aseptic processes in addition to sterilization processes. Other changes related to aseptic processing include the following:

- Revised § 211.67(a) requires that equipment and utensils be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized “and/or sterilized” at appropriate intervals to prevent malfunction or contamination. This change recognizes that for sterile drug products, sterilization (sometimes in addition to sanitization) is appropriate.

- Revised § 211.84(d)(6) requires microbiological tests before use of each lot of a component, drug product container, or closure “with potential for microbiological contamination” that is objectionable in view of its intended use, consistent with longstanding agency interpretation of this regulation.

- Revised § 211.94(c) requires validation of depyrogenation processes for drug product containers and closures, consistent with longstanding industry practice and agency interpretation of this regulation.

- Revised § 211.110(a) adds bioburden testing to the list (which is not all-inclusive) of in-process control procedures relating to the sampling and testing of in-process materials, which again is consistent with industry practice.

B. Asbestos Filters

We revised §§ 210.3(b)(6) and 211.72 to eliminate provisions permitting limited use of asbestos-containing filters used in processing injectable drug products. We had proposed to simply delete references to asbestos filters in these provisions. However, in response to comments, we also added to § 211.72 the statement “The use of an asbestos-containing filter is prohibited.” Also in response to comments, we revised § 211.72 to reflect appropriate technical standards for nonfiber-releasing filters.

C. Verification by a Second Individual

The final rule makes several changes to the regulations to acknowledge, consistent with our longstanding interpretation, that certain operations may be performed by automated equipment and verified by a person, rather than one person performing an operation and another person verifying that the operation was correctly performed. In particular, we added new paragraph (c) to § 211.68 stating that automated equipment used to perform operations addressed in §§ 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements in those sections for the performance of an operation by one person and checking by another person if the equipment is used in conformity with § 211.68 and one person checks that the operations are properly performed. In response to comments, we revised the paragraph to minimize the possibility that the provision might be misinterpreted as requiring a person to repeat by hand all calculations performed by automated equipment.

In accordance with the addition of § 211.68(c), we are adopting corresponding changes to the following provisions:

- Section 211.101(c) and (d) (concerning charge-in of components and containers),
- Section 211.103 (calculation of yields),
- Section 211.182 (equipment cleaning and maintenance), and
- Section 211.188(b)(11) (batch production and control records).

D. Other Minor Changes

In addition to the revisions to the regulations previously noted, we have made minor revisions to the following provisions to provide greater clarity without changing meaning or intent:

- Section 211.82(b) (storage of components, containers, and closures),
- Section 211.84(c)(1) and (d)(3) (collection and testing of samples of components, containers, and closures), and
- Section 211.160(b)(1) (laboratory controls for determining conformity to specifications).

III. Comments on the Proposed Rule and FDA's Response

We received comments on the proposed rule from drug and biologic manufacturers, industry associations, consultants, and other interested persons. A summary of the comments received and our responses follow. We first respond to comments of a general nature and then to comments on the five topics set forth in the preamble of the direct final rule.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, appears before the comment's description, and the word "Response," in parentheses, appears before our response. We have numbered each comment to help distinguish

between different comments. Similar comments are grouped together under the same number if the same response would be given for each. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received.

A. General Comments

(Comment 1) One comment stated that it will be very important for FDA to ensure clarity and consistency in the understanding of the final rule among agency staff, including both product reviewers and CGMP inspectors, to minimize different interpretations and applications of these regulations.

(Response) We agree that it is important that FDA employees who perform application reviews, as well as conduct CGMP inspections and other compliance activities, understand these regulations and apply them in a consistent manner in the performance of their duties. Therefore, we will take appropriate steps to ensure that agency staff receive adequate training regarding the new regulations.

(Comment 2) One comment stated that we should not withdraw the 1996 proposed rule because it contained many good features with respect to test method validation and the out-of-specification test result problem. The comment maintained that the guidance for industry entitled "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" (71 FR 60158, October 12, 2006) is not helpful to people working with biological drugs and other products. Another comment stated that the December 2007 proposed rule should have incorporated many of the changes in the 1996 proposed rule regarding such matters as validation, quality control unit responsibilities, batch failure investigations, and stability samples because they involve some of the most common CGMP deficiencies.

(Response) As we stated in the December 4, 2007, document, we withdrew the 1996 proposed rule because we concluded that, given our new approach to CGMP under the 21st century initiative, it would be preferable to revise the CGMP regulations incrementally rather than in a one-time, comprehensive fashion. Furthermore, we believe that it is appropriate to reevaluate some of the matters considered in the 1996 proposed rule in light of recent scientific and technological advances. We appreciate the comments' interest in the specified CGMP issues, and we will consider these issues in future phases of our CGMP modernization efforts.

(Comment 3) One comment encouraged FDA to consider other CGMP regulations that need modernization or clarification, or are no longer necessary due to technological advances, such as aspects of 21 CFR 610.12 concerning the requirements for bulk sterility testing and allowance for sterility retesting for biological products.

(Response) We appreciate the comment's interest in modernizing CGMP regulations. As previously stated, this final rule represents only our first step in updating the drug CGMP regulations to reflect current industry practice and harmonize the regulations with international CGMP requirements. We will consider other aspects of CGMP in future rulemaking proceedings.

B. Plumbing

Section 211.48(a) requires that potable water be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. It further requires that potable water meet the standards established by the U.S. Environmental Protection Agency (EPA) for primary drinking water in 40 CFR part 141. Proposed § 211.48(a) would have deleted the requirement that the potable water used in a plumbing system meet EPA's standards for primary drinking water, and instead required that the

water be “safe for human consumption.” This proposed revision was intended to improve harmonization with foreign regulations (particularly those of the EU and Japan) and to make the U.S. regulation more consistent with the United States Pharmacopeia standard. In the preamble of the direct final rule, we stated that the revised requirement could be met by compliance with the standards in the EPA regulations or in the current regulations of the EU or Japan for potable water used to prepare water for pharmaceutical purposes.

(Comment 4) Four comments objected to the proposed change. Among other things, the comments stated that the standard of “safe for human consumption” is not sufficiently prescriptive.

(Response) Because of the comments received and other considerations, we have decided not to revise § 211.48(a) at this time. We will address the issue of standards for water used in a facility’s plumbing system when we consider proposing regulations for water used as a drug product component in the next phase of our CGMP initiative.

C. Aseptic Processing

In the proposed rule, we sought to amend several regulations on aseptic processing to reflect current industry standards and practices. Some of the proposed revisions would also affect other types of processes and operations. We noted that the proposed changes would not affect the applicability of the guidance for industry entitled “Sterile Drug Products Produced by Aseptic Processing--Current Good Manufacturing Practice” (Aseptic Processing Guidance), issued on October 4, 2004 (69 FR 59258).

1. Equipment Cleaning and Maintenance (§ 211.67(a))

The version of § 211.67(a) amended by this final rule stated: “Equipment and utensils shall be cleaned, maintained, and sanitized 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.” We proposed to add the phrase “and/or sterilized” after the word “sanitized” in § 211.67(a) to reflect the fact that sterilization is appropriate for sterile drug products.

On our own initiative, we have revised § 211.67(a) to state that equipment and utensils shall be cleaned, maintained, “and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals * * *.” This revision does not alter the meaning of the proposed rule change, but clarifies that for some equipment and utensils used in the production of certain drug products, sanitization is appropriate; for other equipment and utensils, sterilization is appropriate; and for still others, both sanitization and sterilization are appropriate.

(Comment 5) One comment stated that it is not appropriate to address sterilization in § 211.67(a). Instead, the comment recommended that a reference to sterilization of equipment and utensils be added to § 211.113(b), which requires the adoption of written procedures designed to prevent microbiological contamination of drug products purporting to be sterile.

(Response) We do not agree with the comment because, as previously noted, equipment and utensils used in the production of sterile drug products must be sterilized, not merely sanitized. In addition, we have revised § 211.113(b) as discussed in section III.C.5 of this final rule.

(Comment 6) One comment suggested that we could simplify the language in this regulation by changing the phrase “beyond the official or other established requirements” to “beyond the established (or other official) requirements.”

(Response) We do not believe that the suggested change simplifies the current phrase, which we believe is clear. Therefore, we do not believe that the suggested change is necessary.

(Comment 7) One comment stated that § 211.67(a) should not apply to the production of medical gases because most medical gas manufacturing lines are product-specific, closed systems that are not subject to cleaning or sanitation as part of an established periodic cycle, but instead are specially cleaned to be “oxygen ready” and carefully handled in accordance with established procedures. The comment maintained that additional cleaning efforts beyond the initial cleaning regimen substantially increase the risk of introducing contaminants into the system. Therefore, the comment stated, it is not necessary to require cleaning of equipment at “appropriate intervals” for medical gas manufacturing. The comment suggested that, alternatively, it might be appropriate for the agency to state that medical gases may represent unique circumstances that will be reflected in a separate guidance.

(Response) We decline to exempt medical gases from the requirements of § 211.67(a) as recommended because this would exceed the scope of our proposed change to clarify that sterilization is appropriate for sterile drug products and would instead focus on whether there is any need for periodic cleaning of medical gas systems. We might consider in a future CGMP rulemaking whether it is appropriate to revise § 211.67(a) to address its application to medical gases.

2. Microbiological Testing of Objectionable Lots of Components, Drug Product Containers, and Closures (§ 211.84(d)(6))

The version of § 211.84(d)(6) amended by this final rule stated: “Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.” We proposed to change the phrase “that is liable to microbiological contamination” to “with potential for microbiological contamination.”

(Comment 8) One comment stated that the proposed change was unnecessarily restrictive and might lead to testing every lot when the risk of microbial contamination is low and the impact on the intended use is insignificant. This comment suggested replacing “that is liable to microbial contamination” with “prone to microbial contamination.” One comment stated that the proposed change could make it more difficult for drug manufacturers to replace a less effective, quality control-based inspection and test method with a more modern and effective quality audit method. The comment stated that because the bioburden of dry items such as vials and stoppers is often heterogeneous, improved assurance of this quality attribute is better achieved through the audit, selection, and control by the manufacturers of these items. This comment maintained that knowledge of and control over the manufacturing processes for containers and closures might fall short of justifying that those products do not have a “potential for contamination.”

(Response) We decline to adopt the recommended change to § 211.84(d)(6) from “that is liable to microbial contamination” to “prone to microbiological contamination.” We believe that our proposed change to “with potential for microbiological contamination” clarifies our longstanding interpretation of the regulation that each lot of component, drug product container, or closure that is susceptible to contamination must undergo microbiological testing before use. Therefore, we have revised § 211.84(d)(6) to refer to components, containers, or closures “with potential for microbiological contamination” as proposed.

3. Validation of Depyrogenation of Drug Product Containers and Closures (§ 211.94(c))

The version of § 211.94(c) amended by this final rule stated: “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.” In the preamble to the direct final rule, we stated that it has been longstanding industry practice

validate the sterilization and depyrogenation processes used for drug product containers and closures to ensure consistent removal of microbial contamination and pyrogens or endotoxins. Therefore, we proposed to add a provision to § 211.94(c) requiring the validation of these depyrogenation processes.

(Comment 9) One comment suggested that we require validation of “sterilization” as well as depyrogenation processes.

(Response) We do not believe that the suggested change is needed because § 211.113(b) already requires validation of sterilization processes for the prevention of microbiological contamination of drug products purporting to be sterile.

(Comment 10) Four comments objected to the requirement in existing § 211.94(c) because it requires depyrogenation of components based on the nature of the drug and does not take into account the fact that some containers and closures are inherently nonpyrogenic, have been qualified not to require active depyrogenation, or do not require depyrogenation because of handling procedures. Three of the comments proposed that in addition to the nature of the drug, the drug’s manufacturing process be included as a factor in determining when containers and closures must be sterilized and processed to remove pyrogenic properties. Two of the comments recommended that the requirement to validate depyrogenation processes be limited to containers and closures that are made nonpyrogenic by a designated depyrogenation process (thus excluding inherently nonpyrogenic containers and closures from the regulation).

(Response) We decline to adopt the suggested revisions because they go beyond the scope of our proposed change to require validation of depyrogenation processes and instead focus on the need for depyrogenation itself.

4. Inclusion of Bioburden Testing in In-Process Testing (§ 211.110(a))

Section 211.110(a) requires that written procedures be established and followed that describe in-process controls and tests or examinations to be conducted on samples of in-process materials of each batch of a drug product. The regulation specifies five control procedures that must be established, 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 the drug product. We proposed to add bioburden testing to this list (which is not all-inclusive) because testing for bioburden is standard industry practice for in-process materials and drug products that are produced by aseptic processing.

(Comment 11) Three comments objected to the addition of bioburden testing to § 211.110(a). One comment objected to the inclusion of any specific test and suggested that specific tests be addressed in agency guidance. One comment stated that bioburden testing is not conducted at the same time as other tests specified in § 211.110(a) and is not an in-process test or control because it does not yield immediate results that allow for process adjustment. The comment stated that it would be more appropriate to address bioburden testing in § 211.84. One comment suggested that because § 211.110 covers the sampling and testing of all in-process materials and drug products, adding bioburden testing as a mandatory control procedure could expand current industry validation procedure and produce diversity among the industry and regulators on the circumstances in which validation of bioburden testing is appropriate.

(Response) We do not agree with the comments. As stated in the direct final rule, testing for bioburden is an important in-process control, particularly for drug products that are produced through aseptic processing. Section 211.110(a) provides flexibility to manufacturers so that they need only conduct bioburden testing where the testing is appropriate to assure batch uniformity

and drug product integrity. We believe that manufacturers understand for which types of drug products, and at what point in the manufacturing process for these drugs, bioburden testing is appropriate. Accordingly, we have added bioburden testing to § 211.110(a).

5. Control of Microbiological Contamination (§ 211.113(b))

Section 211.113(b) states that appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, must be established and followed. The version of § 211.113(b) amended by this final rule further stated: “Such procedures shall include validation of any sterilization process.” We proposed to substitute “all aseptic and sterilization processes” for “any sterilization process.” As noted in the preamble of the direct final rule, even before we issued the now-replaced guidance on “Sterile Drug Products Produced by Aseptic Processing” in 1987, industry routinely conducted validation studies (often referred to as media fills) that substituted microbiological media for the actual product to demonstrate that its aseptic processes were validated (72 FR 68064 at 68066). The proposed change was intended to clarify existing practice and to harmonize § 211.113 with Annex 1 of the EU CGMPs.

(Comment 12) Several comments objected to the proposed change to § 211.113(b) on the basis that aseptic processing cannot be validated. One comment stated that validation of aseptic processing technically cannot be done, although the manufacturer can ensure tight control over the process. One comment stated that aseptic processing simulations demonstrate the capability of a facility, equipment, and operational controls to provide a minimal microbial contamination rate in a single event, but they cannot predict the outcome of a similar process performed at a different time. The comment maintained that to consider aseptic processing to be validated overstates the ability to measure and control the process and could be interpreted as approval to

relax the controls necessary for its success. The comment recommended that § 211.113(b) be revised to require validation of “all sterilization/depyrogenation processes” and to direct that aseptic processes “be subjected to periodic assessment to demonstrate the capability of the control strategy to adequately support end product sterility.”

One comment stated that there is currently no means to comply with the proposed requirement to validate aseptic processes. The comment maintained that the microbiological and decontamination methods used in aseptic processing lack the sensitivity, recoverability, and accuracy of the physical and chemical measurement systems normally associated with process validation. The comment further claimed that media fills do not validate aseptic processing because they measure only detectable micro-organisms and do not verify that no micro-organisms exist. The comment stated that although aseptic processing cannot be validated, a state of control can be established, ensuring that the aseptically produced drug consistently meets its specifications and quality attributes. The comment recommended that rather than validation of aseptic processes, § 211.113(b) require “a formalized quality risk management and control strategy for aseptic processes to provide assurance of requisite and continued process capability and product quality.”

One comment stated that although media fills can evaluate an aseptic process, they cannot be considered to validate the process. The comment recommended that we either not adopt the proposed requirement to validate aseptic processes or provide more clarity on what is expected for validation of aseptic processes. Similarly, another comment recommended that we not revise § 211.113(b) as proposed unless we clarify that more than media fills are required to validate an aseptic process. The comment stated that a well-controlled, robust process is

required for aseptic processes and that once a state of control has been established for the process, media fills can be useful in confirming the state of control.

(Response) Although we acknowledge that aseptic process validation does not provide absolute assurance of product sterility, we do not agree that aseptic processes cannot be validated. Validation of aseptic processes, which is a common practice throughout the pharmaceutical industry, means establishing documented evidence that provides a high degree of assurance that a particular process will consistently produce a product meeting its predetermined specifications and quality attributes. Media fills, together with operational controls, environmental controls, and product sterility testing, provide a sufficient level of assurance that drugs purported to be sterile are in fact sterile.

(Comment 13) One comment suggested adding a definition of aseptic processing to part 210.

(Response) We do not believe that it is necessary to define aseptic processing in the regulation. The Aseptic Processing Guidance makes it clear to manufacturers what aseptic processing entails.

(Comment 14) One comment requested confirmation that it is acceptable to follow the current FDA guidance and use media fills to meet the requirement to validate aseptic processes.

(Response) As stated in the preamble to the direct final rule and reiterated previously in this document, manufacturers can follow the recommendations in the Aseptic Processing Guidance to comply with CGMP requirements for aseptic processing, including validation. However, as with any guidance, the Aseptic Processing Guidance is not binding on industry or the agency, and manufacturers may use an alternative approach to achieve compliance if the approach meets the requirements of the act and FDA regulations.

(Comment 15) One comment sought clarification that the requirement to validate aseptic processing would not inhibit implementation of novel technologies recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the ICH Q8, Q9, and Q10 guidances, or other innovative approaches in these areas.

(Response) We do not believe that the requirement to validate aseptic processing will interfere with the implementation of new technologies either as part of following ICH recommendations or as part of other efforts to meet CGMP requirements. As stated in section I of this document, we have always attempted to balance the need for easily understood minimum CGMP standards with the desire to encourage innovation and the development of improved manufacturing technologies. We are confident that industry can meet the requirement to validate aseptic processing with no adverse impact on technological innovation in drug product manufacturing.

D. Asbestos Filters

As stated in the preamble to the direct final rule, we need to update our regulations on filters used in processing liquid injectable products. The version of § 211.72 amended by this final rule required manufacturers, before using an asbestos-containing filter, to submit proof to FDA that an alternative nonfiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the product. However, we are not aware that asbestos filters are currently commercially manufactured for pharmaceutical use or are used in drug production, and their use is not considered a good manufacturing practice. Therefore, we proposed to delete the reference to the use of asbestos-containing filters from § 211.72 and to delete the reference to asbestos filters from the definition of “nonfiber-releasing filter” in § 210.3(b)(6).

(Comment 16) Two comments stated that the regulations should state that the use of asbestos filters is prohibited. One comment stated that if asbestos-containing filters are in fact available and the proposed changes were interpreted as permitting their use, this might pose a risk to patients.

(Response) We agree with the comments. Therefore, in addition to deleting the reference to asbestos-containing filters in § 210.3(b)(6), we have revised the last sentence of § 211.72 to state that the use of an asbestos-containing filter is prohibited.

(Comment 17) One comment recommended that we clarify the second sentence in proposed § 211.72, which stated: “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.” The comment recommended that this sentence be revised to state as follows: “Fiber-releasing filters may be used when/where it is not possible to manufacture such drug products without the use of such filters.”

(Response) We agree with this proposed change and have revised § 211.72 accordingly.

(Comment 18) Four comments recommended revising the following provision in proposed § 211.72: “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.” Each of these comments stated that it is technically more accurate to describe a filter in terms of its nominal pore size rating than its mean porosity. One comment stated that the filter pore size standard of 0.22 micron is outdated and should be changed to 0.2 micron.

(Response) These suggested technical changes are consistent with statements in our guidances for industry (e.g., the Aseptic Processing Guidance) concerning filters. Therefore, we have revised § 211.72 to require that if use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron be used.

E. Verification by a Second Individual

The current CGMP regulations include several provisions requiring that certain activities be performed by one person and checked as specified by a second person.

- Section 211.101(c) requires that: (1) 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, (2) the weight or measure is correct as stated in the batch production records, and (3) the containers are properly identified.

- Section 211.101(d) requires that each component be added to the batch by one person and verified by a second person.

- Section 211.103 requires that specified yield calculations be performed by one person and independently verified by a second person.

- Section 211.182 requires the persons performing and double-checking the cleaning and maintenance of major equipment to date and sign or initial equipment logs indicating that the work was performed.

- Section 211.188(b)(11) requires that batch production and control records include identification of the persons performing and directly supervising or checking each significant step in the operation.

When we amended the CGMP regulations in 1978, we established § 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 the following requirements:

- Equipment is routinely checked according to a program designed to assure proper performance,
- Changes to records are made only by authorized personnel,
- Input and output are checked for accuracy, and
- Appropriate backup of data is maintained.

In the preamble to the 1978 final rule, we stated that the verification requirements in § 211.101 for charge-in of components when automated systems are used would be met if a person verified that the automated system was working properly (43 FR 45014 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.

Because we have received questions about the performance and checking requirements in §§ 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) when the operations are performed by automated equipment, such as the widespread and increasing use of computer-controlled operations, we proposed to revise these sections. We proposed to amend these regulations to indicate that when automated equipment is used to perform certain operations, only one person is needed to verify that the automated equipment is functioning adequately. Correspondingly, proposed § 211.68(c) stated that 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 § 211.68 and one person verifies that the operations addressed in those sections are performed accurately by such equipment. We stated in the preamble of the direct final rule that these revisions would clarify our longstanding policy that verification by a second individual may not be necessary when automatic equipment is used under § 211.68.

1. General Comments on Verification

(Comment 19) One comment stated that validated, automated systems equipped with real time alarms that do not require any human intervention should not require human verification. Another comment stated that such systems should not require human verification with each use and, when human verification is needed, the level of verification required should be consistent with the level of automation used. Both of these comments maintained that requiring operator verification of automated, validated equipment under §§ 211.68(c), 211.101(c)(3) and (d), 211.103, and 211.188(b)(11) might hinder the implementation of process analytical technology (PAT) in the drug industry.

(Response) In the FEDERAL REGISTER of February 12, 1991 (56 FR 5671) (the 1991 proposal), we issued a proposed rule in part to amend § 211.68 to add what is now the third sentence of § 211.68(b): “The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system.” This revision was adopted as part of the final rule issued on January 20, 1995 (60 FR 4087) (the 1995 final rule).

In the 1995 final rule, we responded to several comments on the proposed revision. Two comments suggested that the revised regulation did not accommodate the accepted use of validated computerized drug production and control systems. We declined to change the

revision as proposed, stating our belief that the wording in the revised rule adequately encompasses the use of these systems (60 FR 4087 at 4089).

Two comments on the 1991 proposal questioned the need for human verification of operations that are performed by validated computer systems. The comments listed other regulations that were not the subject of the proposed rule that required more than one person to verify certain manufacturing operations, apparently to show that additional personnel would be needed to comply with proposed § 211.68. We noted in the 1995 final rule that the revisions to § 211.68 do not impose any specific personnel requirements. We also noted that the agency is aware that computers are subject to malfunctions, some of which could possibly result in the loss of critical information regarding the manufacturing process or a serious production error and the possible distribution of an adulterated product. Therefore, we stated that while increasingly sophisticated system safeguards and computerized monitoring of essential equipment and programs help protect data, no automated system exists that can completely substitute for human oversight and supervision. We further indicated that while the degree of verification is left to the manufacturer's discretion, the exercise of such discretion under § 211.68 requires the use of routine accuracy checks to provide a high degree of assurance that input to and output from a computer or related system are reliable and accurate. We stated our intent that each manufacturer exercise reasonable judgment based on a variety of factors, including, but not limited to, the complexity of the computer or related system, in developing a method to prevent inaccurate data input and output (60 FR 4087 at 4089).

The December 4, 2007, direct final rule and companion proposed rule were intended to amend the regulations involving second-person checks only to clarify our longstanding policy that verification by a second individual may not be necessary when automatic equipment is used

under § 211.68, and that in such situations only one person is needed to verify that the automated equipment is functioning adequately. The amendments were not intended to either add to or detract from any existing requirements in this regard, but only to clarify our longstanding interpretation and policy for these requirements. We note that the same basic considerations apply in this regard today as we expressed in the 1995 final rule. Although increasingly sophisticated controls and safeguards have been implemented for some automated systems, our policy has been that some degree of human oversight, supervision, verification, monitoring, or checking is still necessary to verify proper performance as part of assuring the identity, strength, quality, and purity of drug products. For suitably validated automated systems, even with real time alarms, it is still necessary for a human to verify that the systems are operating as planned and to monitor for abnormalities. We agree that the level, nature, and frequency of such human verification will vary depending on the level of automation used as well as the nature of the system and controls, and the manufacturer has the flexibility and responsibility to determine what is suitable and necessary. Contrary to the comments, we believe that manufacturers can conduct human verification of automated operations in conjunction with the use of PAT in drug production.

For these reasons, we continue to believe that human verification is necessary to ensure that automated systems are functioning properly.

(Comment 20) One comment stated that many current biotech processes include component additions and deletions in a continuous or periodic manner over long periods of time. The comment stated that there would be no added value in requiring a manual verification of this component management scheme in a fully automated scenario.

(Response) For the reasons stated in our response to comment 19, we believe that some degree of human oversight, supervision, verification, monitoring, or checking is a necessary part of CGMP for such processes and that there is added value in having greater assurance that the automated systems are operating properly as intended. We do not expect that each individual component change must be witnessed in person, but rather that a suitable system of human oversight be established and followed to effectively verify that the automated processes are indeed operating correctly in the performance of these operations.

(Comment 21) One comment maintained that our statement in the preamble of the direct final rule that the verifying individual may be, but is not required to be, the operator is a contradiction of the CGMP regulations, which require (in § 211.25(a)) that all individuals have the education, training, and experience to enable them to perform their assigned functions. The comment asked why the agency would allow an untrained operator to perform a sole verification of a critical step if an automated system is used and recommended that we retract the noted preamble statement.

(Response) The comment incorrectly concluded that allowing the verifying individual to be a person other than the operator would thereby allow an untrained individual to perform the function of verifying a critical step. Section 211.25(a) requires each person performing an assigned function to have the education, training, and experience, or any combination thereof, to enable that person to perform the function. Thus, any person, whether the operator or not, who performs such a verification step would necessarily be required to have the knowledge, training, and experience needed to perform that function. Therefore, our preamble statement does not conflict with the regulations.

(Comment 22) One comment stated that the proposed changes regarding second person verification should be extended to include § 211.188(a), which requires the preparation of batch production and control records that include an accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed. The comment stated that when there is only one signature needed, but the system is automated, it would also follow that no human signature or signature equivalent would be necessary, such as in issuance of a batch record under § 211.188(a), when the record is electronic. The comment also stated that in this case, it is impossible to check the pages for a true and accurate copy. The comment recommended revising § 211.68(c) to include § 211.188(a) in the listing of sections affected and to state that there could be single performance verification under § 211.188(a).

(Response) We do not agree with the recommended changes to § 211.188(a), which would eliminate any human verification of the records. As previously stated, we are clarifying in this rule that the checking of automated equipment by one person can satisfy the requirements of those regulations that address the performance of a step by one person and the verification of the step by a second person. Our proposal regarding verification of operations was intended to make clear that only one person is needed to verify that automated equipment for a processing step is functioning properly; we did not propose deleting all human verification of the step. In addition, we disagree with the comment's apparent contention that no human signature would be needed for issuance of electronic batch production and control records. If such records are generated and issued electronically as part of an automated system, a person must verify that the correct records were issued and that they are still accurate and complete. We believe it is clear that § 211.188(a) requires only one check for accuracy, with date and signature (which could be

electronic), and that it does not require a separate second check of this step. Therefore, no changes to § 211.188(a) are necessary or appropriate.

(Comment 23) Three comments addressed second-person verification in § 211.194. Section 211.194(a) requires that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards as specified in that subsection. Section 211.194(a)(7) requires that laboratory records include the initials or signature of the person who performs each test and the date(s) the tests were performed. Section 211.194(a)(8) requires the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards. Two of the comments stated that the principle behind the proposed second-person verification revisions should be extended to § 211.194 to include checking laboratory records involving automated laboratory equipment. The first comment recommended revising § 211.194 generally. The second comment specifically recommended that § 211.194(a)(8) be revised to add that if laboratory tests have been performed by automated equipment under § 211.68, the laboratory record need only include the identification of one person conducting the review of the tests performed by the automated system. The comment also asked that § 211.194(a)(8) be added to the list of sections affected in § 211.68(c). The third comment stated that the failure to include § 211.194(a)(7) and (a)(8) in the proposed revisions implies that the use of automated systems to perform or check testing is not allowed.

(Response) We decline to include § 211.194 among the sections enumerated in § 211.68(c) concerning second-person verification of operations performed by automated equipment. We acknowledge that automated equipment may be used to conduct certain laboratory testing operations. However, when automated equipment is used to perform a

laboratory test, typically a person initiates the test and ensures that the correct equipment is used and that it operates properly. In this situation, one person assists in or oversees the performance of the laboratory test and a second person reviews the records for accuracy, completeness, and compliance with established standards. Thus, the use of equipment to perform laboratory tests, though permissible, is not a situation in which automated equipment (rather than a person) performs an operation and a person verifies that performance, which is the situation addressed in revised § 211.68(c). Therefore, it would not be appropriate to include a reference to § 211.194 (or to § 211.194(a)(8) specifically) in revised § 211.68(c).

2. Automatic, Mechanical, and Electronic Equipment (§ 211.68)

(Comment 24) One comment stated that § 211.68 is no longer in line with the technological improvements of the past 30 years and with the increasing knowledge of computer validation by industry and regulators. The comment recommended that § 211.68 be aligned with 21 CFR 820.70(i), section 5.4 of the ICH Q7A guidance entitled “Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,” and the Pharmaceutical Inspection Cooperation Scheme’s Annex 11 on computerized systems.

(Response) We decline to adopt the suggested revisions because they exceed the scope of our proposed revision of § 211.68, which only addressed second-person verification of operations performed by automated equipment. We might consider revising other provisions of § 211.68 as part of a future rulemaking to update the CGMP regulations and make them consistent with international CGMP provisions.

(Comment 25) One comment recommended that instead of our proposed changes to § 211.68(c) and other regulations concerning second-person verification, we revise § 211.68(a), which permits the use of automatic, mechanical, or electronic equipment in the manufacture,

processing, packing, and holding of drug products. The comment stated that the wording of our proposed changes only allows for actions to be performed by automated equipment and checked by a person, which would prevent the introduction of automated systems to check operations performed by a person. The comment also stated that our proposed changes would still require the involvement of at least one person in each of these circumstances and prevent the use of a controlled system or systems that both perform and independently verify the relevant operations. One comment suggested that rather than our proposed revisions, the desired clarification concerning automated equipment and second-person checks would be better achieved by adding to § 211.68(a) the following sentence: “Automated equipment can satisfy the requirements for the performance of an operation by one person and/or checking by another person.”

(Response) We do not agree with the recommended change. The proposed rule simply clarified our longstanding position that only one human check is necessary to verify a processing step performed by automated equipment. The suggested revision of § 211.68(a), however, would allow manufacturers to rely solely on automated equipment to verify the human performance of certain processing steps and allow automated equipment to both perform and check operational steps, which would constitute a significant change from the current regulations. As stated in our response to comment 19, we believe that human verification of certain processing steps, even when those steps are performed by automated equipment, is still necessary.

(Comment 26) One comment stated that although proposed § 211.68(c) implies that the automated equipment is doing the work and a person can verify that the work is done, there are cases in which a person does the work and automated equipment might be able to verify the person's work. The comment cited as an example the case in which an automated system scans

the bar codes of ingredients and equipment to ensure that the ingredient is correct for use with the equipment for that step in the process, but the physical addition of the ingredient is by the human operator (followed by the automated system scanning). The comment recommended, therefore, that § 211.68(c) be modified to allow both the automated system and the person to do either the performance or the verification tasks for the operations addressed by §§ 211.101(c) or (d), 211.103, 211.182, 211.188(b)(11), or 211.194(a)(8), or a single performance verification in the case of § 211.188(a).

(Response) We acknowledge that it might be possible to design an automated system to verify operations performed by humans, but as stated in our response to comment 19, we continue to believe that some human verification of the processing steps performed by an automated system is necessary.

(Comment 27) One comment suggested revising § 211.68(c) to state that automated equipment can satisfy the requirements for verification of operations addressed by the listed sections as follows: (1) If such unit operation is fully automated, no manual verification is necessary and (2) if there is an operator for the automated equipment, the verifying individual may be, but is not required to be, the operator. The comment gave several reasons for this change:

- Automated, validated systems equipped with real-time alarms that do not require any human intervention should not require human verification because § 211.68(a) adequately addresses the maintenance and verification of performance of these systems.
- The need and type of verification required should be consistent with the level of automation used. For example, operations that are not fully automated and require operator

participation may serve as verification of the operator's activities, while fully manual operations would require a second human verification.

- As proposed, § 211.68(c) might hinder the adoption of PAT (e.g., there would be no value added by manual verification when components are charged in a fully automated manner according to a validated algorithm).

(Response) As stated in our response to comment 19, we do not agree with the contention that no human verification is necessary when fully automated systems are used, and we therefore decline to make these requested changes to § 211.68(c). We also do not believe that § 211.68(c) will hinder the adoption of PAT. As stated in the preamble to the direct final rule, we agree that if there is an operator for the automated equipment, the verifying individual may be, but is not required to be, the operator. However, § 211.68(c) does not require that the verifying individual be the operator, and we do not believe that it is necessary that the provision explicitly state that the verifying individual need not be the operator.

(Comment 28) One comment stated that the proposed revision of § 211.68(c), when applied to § 211.188(b), might be more restrictive than FDA's position in Compliance Policy Guide (CPG) Sec. 425.500, Computerized Drug Processing; Identification of "Persons" on Batch Production and Control Records (formerly CPG 7132a.08). CPG 425.500 states that when significant steps in the manufacturing, processing, packing, or holding of a batch are performed, supervised, or checked by a computerized system, an acceptable means of complying with the identification requirements in § 211.188(b)(11) would consist of conformance to certain requirements. The comment maintained that CPG 425.500 gives companies the flexibility to automate not only the performance of critical actions but also the supervision and checking of these actions if it is shown that the efficacy of these controls would be at least equivalent to the

level of efficacy if the verification were done by a second person. The comment stated that this flexibility should be extended to all CGMP sections in which a verification is requested. The comment therefore asked that § 211.68(c) be revised to state that 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 § 211.68 and one person either performs the operations addressed in those sections under the control of the automated equipment or verifies that these operations are performed accurately by such equipment.

(Response) We do not agree with the comment's apparent interpretation of CPG 425.500 that the CPG allows for elimination of human oversight. The purpose of the CPG is to explain what constitutes "identification" of persons in batch records under § 211.188(b)(11) when automated systems are used for various functions. The CPG states that when an automated system is used to perform, directly supervise, or check significant steps in the production of a drug, the identification requirements in § 211.188(b)(11) are met if there is documentation that the system contains adequate checks (and documentation of the performance of the system itself), validation of the system's performance, and recording of specific checks in batch records (including initial, branching, and final steps). These conditions for applying the identification requirements to steps using automated equipment involve the responsibilities of persons. For example, a person, rather than automated equipment, is needed to record these checks of production steps in batch records. Therefore, contrary to the comment's implication, the CPG does not state that human oversight is unnecessary when an automated system is involved in the performance, supervision, or checking of production steps. All automated systems require some

level (commensurate with the complexity and risk inherent in the system) of human oversight or checking for expected performance at appropriate intervals. Therefore, we decline to revise § 211.68(c) as recommended.

(Comment 29) One comment, although supportive of the proposal to allow initial activities to be performed by automated equipment, objected to requiring that the output of an automated and adequately validated activity be checked for accuracy by a person. The comment maintained that the act of having validated software and its related processes itself constitutes an independent check that operations are being performed accurately and argued that this is more reliable than any contemporaneous check by a person. The comment therefore asked that § 211.68(c) be changed to state that independent checks may consist of contemporaneous analysis and verification by a second person following completion of the activity; or, where the automated process has been validated to a high degree of confidence, the prior validation can satisfy this requirement and a second person's check may then consist of verifying the validated status of the equipment and processes.

(Response) We do not agree with the suggested change. Although we agree that it is an important part of process controls to ensure the validated status of equipment and processes even before they are used, we do not believe that verifying this validated status can satisfy the requirement for checking the actual performance of automated equipment. However, we believe that the requirement in proposed § 211.68(c) that one person "verifies that the operations * * * are performed accurately" by automated equipment may have led some comments to believe that we were requiring a more specific and detailed repetitive type of check than we intended. When automated equipment is used for operations addressed by revised § 211.68(c) in conformance with § 211.68, the person doing the checking must verify that the automated equipment is

functioning properly and that the operations are reliably performed in the intended manner. As discussed in the response to comment 19, the nature and frequency necessary for such verification will vary depending on the level of automation used as well as the nature of the system and controls. We do not expect that it will normally be necessary, under § 211.68(c), for a person to repeat all of the automatic calculations by hand to ensure their accuracy. Therefore, we have revised § 211.68(c) to clarify that automated equipment can be used to perform an operation when the performance is checked by a person provided that “such equipment is used in conformity with this section [§ 211.68] and one person checks that the equipment properly performed the operation.”

3. Verification of Weighing, Measuring, or Subdividing Operations (§ 211.101(c))

Section 211.101 concerns charge-in of components. Proposed § 211.101(c) stated, in part, that if the weighing, measuring, or subdividing operations for components are performed by automated equipment under § 211.68, only one person is needed to ensure that the requirements in § 211.101(c)(1), (c)(2), and (c)(3) are met.

(Comment 30) One comment proposed broadening § 211.101(c) to clarify that the weighing, measuring, and subdividing operations could be either performed by automated equipment or checked by automated equipment after being performed manually.

(Response) We decline to make this suggested change for the reasons provided in response to comments 19 and 25. Revised § 211.101(c) only permits human checking of weighing, measuring, and subdividing operations performed by automated equipment; we did not propose to allow automated checking of these operations. We continue to believe that human verification of these processing steps is necessary.

(Comment 31) One comment stated that with respect to medical gases, there is no measurement of components to be dispensed for manufacturing that needs to be double-checked to ensure that the right quantity of the right component was added, because transfers of pure gases are within product-specific systems. However, the comment stated, with respect to gas mixtures, it is appropriate to have a verification of hook-ups as different components are added unless there is subsequent purity testing for each component.

(Response) We decline to exempt single gas filling operations from certain requirements of § 211.101(c) as recommended because such a change would exceed the scope of our proposed change to § 211.101(c), which only addressed human checking of weighing, measuring, and subdividing operations performed by automated equipment. We might consider in a future rulemaking whether it is appropriate to exempt medical gases from certain requirements of § 211.101(c).

4. Verification of Components Added to the Batch (§ 211.101(d))

Proposed § 211.101(d) would have required that each component be either 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.

(Comment 32) One comment stated that eliminating a double check for adding materials to a batch is problematic because an error in those operations would be difficult to detect and might not be discovered before the product is distributed, which could result in patient injury and product recall. The comment recommended deleting or modifying the ability to use a sole verifier for operations involving addition of materials.

(Response) The comment appears to suggest that we proposed to eliminate the requirements concerning verification that appropriate components were added to a batch. The

revisions we are adopting do not eliminate the requirement to verify performance in § 211.101(d); they simply codify our longstanding policy that components may be added either by a person or by suitable automated equipment. The addition of components still must be checked by a person.

(Comment 33) One comment stated that under the proposed change to § 211.101(d), if a validated system performs a function, it is acceptable for one person to verify that action, but if an automated system prompts an operator to perform a function, a second person would be required to confirm the proper execution of the action. The comment recommended changing § 211.101(d) to state that each component must be added to the batch by one person and verified by a second person, “unless the components are added by automated equipment under § 211.68, in which case verification can be performed by one person.”

(Response) We decline to accept the suggested change because we do not believe that it constitutes a substantive difference from the language of proposed § 211.101(d). It is irrelevant whether use of a particular automated system for component charge-in requires an operator to perform a related function; in either case, verification of the charge-in operation(s) must be performed by a person.

(Comment 34) One comment recommended changing § 211.101(d) to specify that the weighing, measuring, or subdividing operations might be performed by automated equipment or checked by automated equipment after being performed manually. The comment also stated that in many instances, the verification by a person of actions performed by automated equipment can only be done on the basis of outputs from the equipment. As an example, the comment stated, when the introduction of components in a liquid production line is fully automated, there is no possibility for the operator to check that the correct amount of materials was incorporated into

batch other than by relying on information given by the same automated equipment. The comment stated that in that case, the verification would consist of confirming that the component's incorporation process was completed without errors or alarms.

(Response) We decline to make this suggested change for the reasons stated in response to comments 19 and 25. Revised § 211.101(d) only permits human checking of component additions performed by automated equipment; we did not propose to allow automated checking of component additions performed by humans. In the example given in the comment, human verification that components were properly added to the liquid production line by the automated equipment would be needed to ensure that the equipment performed properly. We continue to believe that human verification of this processing step is necessary.

5. Calculation of Yield (§ 211.103)

We proposed, in § 211.103, to require that calculations of actual yields and percentages of theoretical yields 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.

(Comment 35) One comment stated that it is not necessary to have a person recalculate a yield manually after a validated system does it automatically. The comment asked that § 211.103 be revised to limit the human interaction to data entry and data verification, but not recalculation of yields if yields are calculated by a validated, automated system. A similar comment stated that § 211.103 should be changed to state that if the yield is calculated by automated equipment, a person must verify the data entries, rather than regenerate the calculations.

(Response) We do not believe that the recommended changes are needed or appropriate. Revised § 211.103 does not require that all yield calculations be repeated manually. Manual recalculation might be a suitable approach to verifying yield calculations, but § 211.103 also permits the use of other approaches, including verification that automated equipment functioned properly while performing yield calculations.

(Comment 36) One comment reiterated the views expressed in its comments on the CGMP for medical gases draft guidance. Thus, the comment requested that the requirements for yield calculation in § 211.103 not be applied to medical gases because of the atmospheric-gas-separation and cylinder-filling processes associated with medical gases. In further support of its position, the comment referred to an FDA publication (Human Drug CGMP Notes, vol. 5, no. 2, June 1997) in which the agency stated that it would propose to revise the CGMP regulations to exempt medical gases from the requirements for yield reconciliation.

(Response) We decline to exempt medical gases from the requirements for yield calculation in § 211.103 as recommended because this would exceed the scope of our proposed change to § 211.103, which addressed only human checking of yield calculations performed by automated equipment. We might consider in a future CGMP rulemaking whether it is appropriate to exempt medical gases from certain requirements of § 211.103. In addition, we might consider providing specific recommendations to medical gas manufacturers to help them comply with the requirements for calculating yields in the course of finalizing the draft guidance on CGMP for medical gases.

6. Equipment Cleaning and Use Log (§ 211.182)

We proposed, in § 211.182, to require the persons performing and double-checking equipment 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) to date and sign or initial the log indicating that the work was performed.

(Comment 37) One comment stated that eliminating a double check for cleaning equipment is problematic because an error in those operations would be difficult to detect and might not be discovered before the product is distributed, which could result in patient injury and product recall. The comment recommended deleting or modifying the ability to use a sole verifier for operations involving equipment cleaning.

(Response) The comment appears to suggest that we proposed to eliminate the requirements concerning verification that equipment was appropriately cleaned and maintained. The revisions we are adopting do not eliminate the requirement to verify performance in § 211.182; they simply codify our longstanding policy that equipment may be cleaned and maintained either by a person or by suitable automated equipment. Cleaning and maintenance of equipment must still be checked by a person.

(Comment 38) One comment stated that operations addressed by §§ 211.182 and 211.188(b)(11) are often performed using semi-automated equipment that requires an operator to select the correct menu. The comment stated that major pieces of equipment such as “Clean in Place” (CIP) skids and vial washers often require the operator to select the appropriate process menu before the execution of the actual automated cycle by the equipment’s controller. The comment asked whether, when operator input is necessary to select but not perform an operation, the signature of the operator selecting the menu is required in cases when there is a second signature that verifies the performance of the cycle. One comment requested that we verify in

§ 211.182 or the preamble of the final rule that a single verification remains sufficient when automated but portable cleaning skids are used.

(Response) We do not believe that initiation of the automated cleaning cycle by a human operator constitutes performance of the cleaning process for purposes of revised § 211.182. The revised regulation requires that after an automated cleaning process (such as CIP) is completed, the human operator must date and sign or initial the log verifying that the equipment performed the automated cleaning process properly. The regulation does not require the operator to date and sign or initial the log simply for the initiation of the automated cleaning cycle. This approach applies to both portable equipment skids and fixed equipment.

(Comment 39) One comment stated that in many instances, the human verification of an action performed by automated equipment can only be done on the basis of outputs from the equipment. As an example, the comment stated, when equipment is cleaned through CIP, the verification should consist of confirming that the system reports the cleaning as successfully completed without alarms.

(Response) What constitutes adequate verification that equipment has been properly cleaned or maintained using automated equipment in accordance with revised § 211.182 depends on the particular circumstances. The outputs from the automated equipment will normally be key factors, but not necessarily the only ones. The manufacturer should determine the reliability of the outputs and periodically check them. For example, it might be appropriate to verify that an alarm is working properly and is successfully monitoring the equipment's critical functions. There might be other ways of verifying the adequate performance of cleaning and maintenance by automated equipment, such as by monitoring the usage of cleaning supplies in a cleaning cycle or conducting an independent check of the rinse.

(Comment 40) One comment stated that for most medical gas systems, routine or periodic cleaning is not performed because the industry is characterized by product-specific closed systems that undergo an appropriate cleaning process before initial use. The comment stated that because of the high number of batches produced on a weekly/monthly basis in the medical gas industry, it is more appropriate to keep cleaning and maintenance records separate from batch records. The comment maintained that although requiring documentation of equipment cleaning, maintenance, and use in individual equipment logs may be appropriate for traditional pharmaceuticals (where key processing equipment may be used for multiple products and lot numbers), applying this requirement to medical gases would make retrieval and management of cleaning and maintenance records much more difficult. The comment added that use logs are not appropriate for medical gases because batch record documentation provides a consecutive listing of products manufactured on each system.

(Response) We decline to exempt medical gases from certain requirements of § 211.182 as recommended because this would exceed the scope of our proposed change to § 211.182, which addressed human verification of cleaning steps performed by automated equipment. We might consider in a future CGMP rulemaking whether it is appropriate to exempt medical gases from certain requirements of § 211.182.

7. Batch Production and Control Records (§ 211.188(b)(11))

Section 211.188 concerns batch production and control records. Proposed 211.188(b)(11) specified that when a significant step in the operation is performed by automated equipment under § 211.68, the record would need to identify the person checking the significant step performed by the automated equipment.

(Comment 41) One comment stated that § 211.188(b)(11) should be changed to state that a significant manufacturing step could be either performed or checked by automated equipment. The comment stated that this approach is permitted by CPG 425.500.

(Response) We decline to make this suggested change. As stated in our response to comment 28, CPG 425.500 does not, as the comment implies, state that human oversight is unnecessary when an automated system is involved in the performance, supervision, or checking of production steps. To revise § 211.188(b)(11) as recommended by the comment might be interpreted as permitting manufacturers to rely solely on automated equipment to verify the human performance of certain production steps. As stated in our response to comments 19 and 25, we believe that human verification of processing steps is still necessary.

F. Miscellaneous Minor Changes Based on 1996 Proposal

We proposed to make miscellaneous minor changes to CGMP regulations to clarify certain manufacturing, quality control, and documentation requirements and to align the regulations with industry practice.

1. Storage of Untested Components, Drug Product Containers, and Closures (§ 211.82(b))

The version of § 211.82(b) amended by this final rule stated: “Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released.” We proposed to replace the phrase “as appropriate” with the phrase “whichever is appropriate” to eliminate any ambiguity in § 211.82(b) and to emphasize that it is accepted industry practice to conduct some testing or examination before components, drug product containers, or closures are released from quarantine.

(Comment 42) One comment requested that medical gas container-closure assemblies returned from customers and reused be exempted from § 211.82(b). The comment stated that

assembled cylinder/valve medical gas combinations are reused and handled differently than they would be at the time of initial receipt. The comment stated that returned assemblies are individually inspected for all critical quality issues immediately before filling; those assemblies that do not meet the inspection criteria are moved to a quarantine area. The comment stated that this practice satisfies the intention that components, containers, and closures be inspected to ensure that unacceptable assemblies are not used in the manufacturing process.

(Response) Under revised § 211.82(b), manufacturers of medical gases would retain the ability to sequester and inspect returned valve/cylinder assemblies before refilling in accordance with the industry practice described by the comment. The practice described by the comment is to have the assembled valve/cylinders placed in a segregated area (apparently not identified using the word “quarantine”), examined for conformance to quality standards, and, if the criteria are met, immediately made available for refilling. This practice would meet the requirement for a quarantine status if goods in such areas or under such a status are not acceptable for use as-is unless and until they are qualified to be suitable for use. Therefore, we do not believe that the practice as described violates revised § 211.82(b), and there is no need to exempt medical gas manufacturers from this requirement.

2. Cleaning of Component Container Samples (§ 211.84(c)(1))

The version of § 211.84(c)(1) amended by this final rule stated: “The containers of components selected [for sampling] shall be cleaned where necessary, by appropriate means.” We proposed to replace the phrase “where necessary, by appropriate means” with the phrase “when necessary in a manner to prevent introduction of contaminants into the component.” This change was intended to clarify that the act of cleaning is done for a particular purpose--to prevent

the introduction of contaminants--and must be done unless cleaning is not necessary to prevent contamination.

(Comment 43) One comment expressed concern that the proposed change might be interpreted to require validation of this prevention of contamination during sampling. The comment requested that we confirm that our intent is to place the contamination concern into the controls and procedures for sampling and into the training of staff who perform these activities, rather than to require validation of the absence of contamination.

(Response) Revised § 211.84(c)(1) does not require manufacturers to conduct validation studies to prove that the method of sampling prevents contamination. When properly designed and followed, the cleaning procedures, training, and facility and equipment controls, along with supervisory and quality unit oversight, should ensure compliance with § 211.84(c)(1).

3. Editorial Changes (§§ 211.84(d)(3) and 211.160(b)(1))

We proposed minor editorial changes to two regulations, §§ 211.84(d)(3) and 211.160(b)(1). The version of § 211.84(d)(3) amended by this final rule stated: “Containers and closures shall be tested for conformance with all appropriate written procedures.” We proposed to replace the word “conformance” with “conformity” and the word “procedures” with “specifications.” The first sentence of the version of § 211.160(b)(1) amended by this final rule stated: “Determination of conformance to appropriate 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.” We proposed to replace the word “conformance” with “conformity” and the word “appropriate” with “applicable.” We stated in the preamble to the direct final rule that these revisions would

provide clarity without changing the meaning or intent of these regulations. We received no comments on these proposed changes, and we have revised these provisions as proposed.

IV. Analysis of Impacts

FDA has examined the impacts of this 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 final rule is not a significant regulatory action as defined by the Executive order, because the rule either clarifies the agency's longstanding interpretation of, or increases latitude for manufacturers in complying with, existing 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 final rule does not impose any new regulatory obligations, the agency believes that the 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. This rule does not result in any 1-year expenditure that would meet or exceed this amount.

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

V. Environmental Impact

FDA concludes that 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.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have 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, we have 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.

VII. Paperwork Reduction Act of 1995

This final rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) (the PRA). The collections of information (recordkeeping requirements) in part 211 have already been approved by OMB under control number 0910-0139. The final rule

amends certain sections of part 211 as well as § 210.3 (§ 210.3 does not contain information collection requirements). As concluded in section IV of this document, “Analysis of Impacts,” the purpose of the final rule is to update the regulations to reflect current practice and to harmonize requirements in the CGMP regulations with requirements in other regulations and with international CGMP standards. The final rule does not impose any additional requirements. Thus, because the final rule does not substantively revise the information collection requirements in part 211 or add new information collection requirements, there is no need to conduct an analysis under the PRA.

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 211.67 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, as appropriate for the nature of the drug, 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.

* * * * *

5. 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 relating to 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 checks that the equipment properly performed the operation.

6. 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 be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. The use of an asbestos-containing filter is prohibited.

7. 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.

8. 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.

* * * * *

9. Section 211.94 is amended by revising paragraph (c) 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.

* * * * *

10. 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 paragraphs (c)(1), (c)(2), and (c)(3) of this section.

(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.

11. 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.

12. 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.

* * * * *

13. 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.

14. 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.

* * * * *

15. 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, just 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.

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

211.188 Batch production and control records.

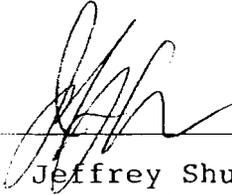
* * * *

(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.

* * * *

dated: August 22, 2008.



Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

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