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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 4

[Docket No. FDA-2009-N-0435]

Current Good Manufacturing Practice Requirements for Combination Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is issuing this regulation on the current good manufacturing practice (CGMP) requirements applicable to combination products. This rule is intended to promote the public health by clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products. In addition, the rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with CGMP requirements for “single-entity” and “co-packaged” combination products.

DATES: This rule is effective July 22, 2013.

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SUPPLEMENTARY INFORMATION:

Table of Contents

- I. Background
 - A. Rationale for the Rulemaking
 - B. The Proposed Rule
 - C. The Final Rule
- II. Comments on the Proposed Rule
 - A. General
 - B. What is the scope of this subpart? (§ 4.1)
 - C. How does FDA define key terms and phrases in this subpart? (§ 4.2)
 - D. What current good manufacturing practice requirements apply to my combination product? (§ 4.3)
 - E. How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product? (§ 4.4)
 - E.1. How To Comply With QS Regulation Requirements Under § 4.4(b)(1)
 - E.2. How To Comply With Drug CGMP Requirements Under § 4.4(b)(2)
 - E.3. How To Comply With Biological Product and HCT/P Requirements Under § 4.4(b)(3)
 - F. Enforcement and Effective Date
 - G. Alternate Approaches
 - H. Guidance
 - I. Other
- III. Legal Authority
- IV. Analysis of Economic Impacts
 - A. Introduction
 - B. Rationale for Final Rule
 - C. Response to Comments
 - D. Impact of Final Rule
- V. Environmental Impact
- VI. Paperwork Reduction Act of 1995
- VII. Executive Order 13132: Federalism

I. Background

A. Rationale for the Rulemaking

As set forth in part 3 (21 CFR part 3), a combination product is a product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product.¹ Under § 3.2(e), a combination product includes:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (single-entity combination products);

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (co-packaged combination products);

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose (a type of cross-labeled combination product); or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling

¹ For purposes of part 3 and this rule, a “biological product” means a biological product subject to regulation under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). All biological products regulated under the PHS Act meet the definitions of drug or device in section 201 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321).

is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another type of cross-labeled combination product).

The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. Accordingly, the CGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products.² To date, however, the Agency has not issued specific regulations clarifying the applicability of the CGMP requirements to combination products. While CGMP regulations are in place that establish requirements for drugs, devices, and biological products, there are currently no regulations that clarify and explain the application of these CGMP requirements when these drugs, devices, and biological products are constituent parts of a combination product. FDA believes that the absence of clear CGMP requirements for combination products could result in inconsistent or differing application of the various CGMP requirements applicable to the constituent parts, which could affect product safety and the public health. In addition, the absence of clear requirements could lead some manufacturers to develop and document manufacturing practices that are redundant and overly burdensome.

In the **Federal Register** of October 4, 2004 (69 FR 59239), the Agency announced the availability of a Draft Guidance for Industry and FDA entitled “Current Good Manufacturing Practices for Combination Products.” The Agency received 15 comments, which were largely supportive of the regulatory approach described in the draft guidance. A common theme that emerged from these comments was the need to develop a clear regulatory framework that takes account of the fact that combination products are made up of drug, device, and biological product constituent parts. At the same time, commenters wanted to ensure that the framework would not lead to unnecessary redundancy in the operating systems used to meet CGMP

² Section 501 of the FD&C Act (21 U.S.C. 351) states circumstances under which drugs and devices (including biological products, which also meet the definition of either drug or device) are deemed adulterated. Adulteration includes the failure to manufacture a product in accordance with applicable CGMP requirements, regardless of whether the product appears to meet its final specifications. See, generally, 21 U.S.C. 351(a)(2)(B) and (h).

requirements (CGMP operating systems).

After careful consideration of the comments, and of how best to ensure that CGMPs for combination products are consistent and appropriate, FDA determined that rulemaking was warranted. We concluded that rulemaking would best facilitate the manufacture of safe and effective combination products by providing a clear and transparent regulatory roadmap for the application of CGMP requirements to these products. Accordingly, the Agency published a proposed rule in the **Federal Register** of September 23, 2009 (74 FR 48423), as part of FDA's ongoing effort to improve the consistency and aid implementation of the regulatory requirements for combination products.

B. The Proposed Rule

The proposed rule addressed CGMP requirements for all combination products. However, for certain types of combination products, the application of CGMP requirements is fairly straightforward. Specifically, the constituent parts of a combination product are each subject only to the CGMP regulations applicable to that type of constituent part (e.g., drug or device) if the constituent parts are manufactured and marketed separately, as may be the case for constituent parts of cross-labeled combination products. Because these constituent parts, while part of a combination product, are separately manufactured and marketed, they remain separate for purposes of applying the CGMP regulations. Therefore, the proposed rule merely provided that all such constituent parts must be manufactured in accordance with the CGMP requirements that would apply to them if they were not part of a combination product.

The application of CGMP requirements to single-entity and co-packaged combination products is less straightforward. Consequently, the proposed rule expressly addressed the practical application of CGMP requirements to these two categories of combination products. The proposed rule reflected Agency recognition that, in most instances, for single-entity and co-packaged combination products, a CGMP operating system that satisfies the CGMP regulations applicable to one constituent part will also satisfy most of the CGMP requirements applicable to the other constituent part. In particular, we explained that compliance with either the CGMP regulations for drugs at parts 210 and 211 (21 CFR parts 210 and 211) (drug CGMPs) or the quality system (QS) regulation for devices at part 820

(21 CFR part 820) will satisfy many, though not all, of the CGMP requirements applicable to both drug and device constituent parts.

In developing the proposed rule, the Agency reviewed the drug CGMPs and QS regulation. We identified specific provisions from the drug CGMPs and QS regulation that a firm would need to satisfy in addition to complying with the other of these two sets of CGMP requirements to demonstrate compliance with both of these sets of requirements. Based on this assessment, the proposed rule offered two options for demonstrating compliance with the CGMP requirements applicable to a co-packaged or single-entity combination product. These options were either: (1) To demonstrate compliance with the specifics of all CGMP regulations applicable to each of the constituent parts included in the combination product or (2) to demonstrate compliance with the specifics of either the drug CGMPs or the QS regulation, rather than both, when the combination contains both a drug and a device, under certain conditions. These conditions included demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements. In addition, for a combination product that included a biological product, the CGMPs requirements for biological products in parts 600 through 680 (21 CFR parts 600 through 680) would apply, and, for a combination product that included any human cell, tissue, and cellular and tissue-based products (HCT/Ps), the regulations in part 1271 (21 CFR part 1271) would apply.³

We intended for the proposed rule to help ensure that CGMP requirements that apply to single-entity and co-packaged combination products are clear and consistent, regardless of which Agency component has lead jurisdiction for the combination product, or which type of application is submitted for marketing authorization. The proposed rule was also intended to streamline demonstrating compliance with CGMP requirements for these types of combination products and to help ensure appropriate implementation of these requirements while avoiding

³ For the purposes of this rule, FDA uses the term "CGMP requirements" to include all such requirements found in the standards in parts 600 through 680 that may apply to biological products. FDA notes that biological products, including biological product constituent parts of combination products, must comply with all applicable requirements in parts 600 through 680, but many of the requirements in parts 600 through 680 are not considered CGMP requirements and are therefore not covered by this rule.

unnecessary redundancy in CGMP operating systems for these products.

After publication of the proposed rule, to facilitate development of comments on the rule, FDA co-sponsored a workshop in January 2010. At this workshop, the Agency provided a summary of the proposed rule and stakeholders then worked in groups to identify issues on which it might be helpful to develop comments.

C. The Final Rule

The final rule is largely identical to the proposed rule. It is organized in the same four sections addressing scope (§ 4.1), definitions (§ 4.2), the CGMPs that apply to combination products (§ 4.3), and how to comply with these CGMP requirements for a single-entity or co-packaged combination product (§ 4.4).

Section 4.1. Section 4.1 states that the rule establishes which CGMP requirements apply to combination products, clarifies the application of these requirements, and provides a regulatory framework for designing and implementing CGMP operating systems at facilities that manufacture copackaged or single-entity combination products.

Section 4.2. Section 4.2 provides definitions for terms used in the regulation. Some of these definitions are included for convenience, for example, cross-referencing an existing definition (such as for "combination product") or to establish the meaning for a reference term (such as "drug CGMP"). Other definitions include content specific to the rule. In addition to cross-referencing the definition for "device" in § 3.2(f), the rule states that a device that is a constituent part of a combination product is considered a finished device within the meaning of the QS regulation; and the definition for "drug" cross-references § 3.2(g) and also states that a drug that is a constituent part of a combination product is a drug product within the meaning of the drug CGMPs. The definition for "current good manufacturing practice operating system" states that such a system is the operating system within an establishment that is designed and implemented to address and meet the CGMP requirements for a combination product.

Section 4.3. Section 4.3 lists all of the requirements that may apply to a combination product under this rule, depending on the types of constituent parts the combination product includes. The CGMP requirements listed are those found in parts 210 and 211 for drugs, part 820 for devices, and parts 600 through 680 for biological products, and

the current good tissue practices found in part 1271 for HCT/Ps. We have removed the specific reference to part 606 because it is already reflected in the reference to parts 600 through 680.

Section 4.4. Section 4.4 addresses how to comply with these CGMP requirements for co-packaged and single-entity combination products, as summarized in the subsections that follow.

Section 4.4(a). This subsection states that the CGMP requirements applicable to a combination product can be satisfied in one of two ways. Under § 4.4(a)(1), a manufacturer can demonstrate compliance with each applicable regulation in its entirety (e.g., with all of the drug CGMPs and the QS regulation, for a drug-device combination product). Alternatively, under § 4.4(a)(2), if the combination product is subject to the drug CGMPs and QS regulation, these two sets of requirements can be met by demonstrating compliance with: (1) Either the drug CGMPs or QS regulation and (2) those provisions specified in § 4.4(b) from the other of these two sets of regulations.

Section 4.4(b)(1). This subsection states that if a manufacturer chooses to demonstrate compliance with the drug CGMPs per § 4.4(a)(2), that manufacturer must also demonstrate compliance with the following provisions of the QS regulation to demonstrate compliance with both sets of regulations:

- § 820.20. Management responsibility.
- § 820.30. Design controls.
- § 820.50. Purchasing controls.
- § 820.100. Corrective and preventive action.

- § 820.170. Installation.
- § 820.200. Servicing.

Section 4.4(b)(2). This subsection states that if a manufacturer chooses to demonstrate compliance with the QS regulation per § 4.4(a)(2), that manufacturer must also demonstrate compliance with the following provisions of the drug CGMPs to demonstrate compliance with both sets of regulations:

- § 211.84. Testing and approval or rejection of components, drug product containers, and closures.
- § 211.103. Calculation of yield.
- § 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
- § 211.137. Expiration dating.
- § 211.165. Testing and release for distribution.
- § 211.166. Stability testing.
- § 211.167. Special testing requirements.
- § 211.170. Reserve samples.

Section 4.4(b)(3). This subsection states that manufacturers must also demonstrate compliance with the CGMPs among the requirements (including standards) for biological products listed in § 4.3(c) if the combination product includes a biological product, and with the requirements for HCT/Ps listed in § 4.3(d) if the combination product includes an HCT/P.

Section 4.4(c). This subsection states that a facility at which a single type of constituent part is manufactured must demonstrate compliance with the CGMP requirements applicable to that type of constituent part.

Section 4.4(d). This subsection states that a facility at which two or more types of constituent parts have arrived or continue to be manufactured may apply a CGMP system that complies with § 4.4(b).

Section 4.4(e). This subsection states that, in the event of a conflict between CGMP requirements applicable to a combination product, the regulations most specifically applicable to the constituent part at issue shall prevail.

II. Comments on the Proposed Rule

FDA received 25 sets of comments from regulated entities, trade associations, and individuals. To make it easier to identify comments and our responses, the word “Comment” appears before the comment’s description, and the word “Response” appears before our response. We have also numbered the comments to help distinguish among them. 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. Certain comments were grouped together under a single number because the subject matter of the comments was similar.

A. General

(Comment 1) Some commenters sought clarification of what manufacturers must do to “demonstrate” compliance for purposes of this rule. Commenters proposed that the Agency confirm that “demonstrate” is used in this rule as “it always has been with respect to GMPs.” Specifically, commenters stated that the requirements for firms to demonstrate compliance are set forth in the rules and include, for example, the implementation of written procedures, internal auditing and other requirements. Commenters noted that “ ‘demonstrate’ also encompasses demonstrating and justifying that

specific provisions are inapplicable to a facility.”

(Response) We confirm that the term “demonstrate” is not intended to have a new meaning for purposes of this rule. The Agency intends for it to be interpreted in the same manner as it would be for purposes of the CGMP regulations listed in § 4.3. As the commenters state, depending on the circumstances and requirements at issue, appropriate means by which to demonstrate compliance with these CGMP requirements may include development of written procedures and maintenance of records documenting use and verification of CGMPs.

B. What is the scope of this subpart? (§ 4.1)

(Comment 2) Some comments stated that the rule is unclear as to whether it applies only to commercial production or also during product development and to investigational products. One commenter proposed including information on the stages of a product’s life cycle during which the rule applies. Another requested further guidance on this issue.

(Response) Section 4.3 lists all of the CGMP regulations that apply to a combination product under the rule. The rule does not modify these regulations; rather it addresses how to comply with them for a combination product.

An investigational drug for use in a phase 1 study is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such a drug is exempt from compliance with the regulations in part 211. This exemption does not apply to an investigational combination product or constituent part of a combination product for use by or for the sponsor in phase 2 or phase 3 studies, or when the drug has been lawfully marketed.⁴ Similarly, while device sponsors must ensure that investigational devices are manufactured under a state of control, 21 CFR 812.1 provides that investigational devices are exempt from part 820 except for design control requirements under § 820.30. (See 21 CFR 812.30(b)(5)(ii)). The Agency considers both these exemptions, from parts 211 and 820 obligations, to apply to combination products and constituent parts of combination products, whether being studied under an approved investigational device exemption (IDE) or an approved investigational new drug application (IND).

⁴ See § 210.2(c).

(Comment 3) One comment noted that the rule does not address products that produce another product on site at the point of care, which the commenter notes are typically devices that produce a drug. The commenter requests that the final rule clarify that the manufacturer is subject only to the CGMP requirements applicable to the product that makes the other product on site.

(Response) This rule applies to combination products. Accordingly, questions regarding CGMPs for non-combination products are beyond its scope. However, this comment raises the question of whether medical products that make other medical products at the point of care are regulated as combination products and, therefore, subject to this rule.

There are two potential scenarios to consider. The first is where a single medical product (e.g., a device) makes another medical product (e.g., a drug) at the point of care. In this case, the medical product that makes the other medical product at the point of care and the medical product manufactured at the point of care would not be regulated as a combination product. Rather, the medical product that makes the other medical product would be regulated in accordance with its own classification and, therefore, subject to the CGMP requirements applicable to that type of article. For example, if the product that makes the other product is a device, it would be subject to the QS regulation.

The second scenario is where two or more different types of medical products (e.g., a device and a biological product) are used together at the point of care to make another medical product. The medical products used to make the other medical product might comprise a combination product. In such cases, the CGMP requirements applicable under this rule to the type of combination product that they constitute (e.g., cross-labeled or co-packaged) may apply. See §§ 4.3 and 4.4. The Agency has not published general guidance on the issue of when two medical products used at the point of care to make another product constitute a combination product. Accordingly, product sponsors are encouraged to contact the Office of Combination Products (OCP) with any questions on this topic.

(Comment 4) One commenter asked for Agency guidance on whether products on the market prior to the establishment of OCP are considered combination products by the Agency and, therefore, subject to the rule. Several commenters stated that the proposed rule did not clearly address its applicability to approved products

already being marketed. Commenters requested that the Agency limit application of the rule to new products and to existing products only when a design change, or significant design change, is made to the product, and not be applied retroactively to existing products. One commenter stated that existing manufacturers should be exempt from pre-manufacturing design control requirements. One commenter stated there was a need for guidance regarding how the rule would affect CGMP requirements for products addressed in master files. One stated that the Agency should identify which currently marketed products are subject to this rule.

(Response) This rule does not create new CGMP requirements, but rather attempts to clarify how to apply them to combination products. Compliance with all applicable CGMP requirements is required for all products and appropriate to ensure consistent manufacture of products that meet the safety and effectiveness and quality standards that form the basis for product marketing authorization, regardless of when a product was first marketed or approved.

As noted elsewhere in this document, we intend to provide further information in related guidance, on how to comply with this rule and the underlying regulations to which it refers, including with respect to coming into compliance with pre-manufacturing design control requirements for products currently being marketed.

Regarding the issue of master files, we note that, as discussed throughout this preamble, this rule is not intended to change existing CGMP requirements established under the regulations listed in § 4.3. Rather, this rule is intended to clarify how to comply with those requirements for a combination product. Accordingly, if the manufacture of an item addressed in a master file would be subject to CGMP requirements under a rule listed in § 4.3, those CGMP requirements must be met under this rule, including as provided in § 4.4. If the manufacture of the item would not be subject to CGMP requirements under a rule listed in § 4.3, then no CGMP requirements apply to the manufacture of that item under this rule. For example, if the item is a component of a device and its manufacture, therefore, would not be subject to the QS regulation, the manufacture of that item is not made subject to the QS regulation by this rule. However, the CGMP requirements for manufacturers of combination products and constituent parts of combination products that include items addressed in master files

may include duties with respect to such items (e.g., purchasing control requirements under the QS regulation for a combination product that includes a device).

(Comment 5) Some commenters raised concerns regarding application of the rule to co-packaged combination products, arguing that the rule as written would be overly burdensome for these products. One commenter proposed that “Convenience kits that contain device(s) and drugs or biologics would be governed under 21 CFR 4 only if the device(s) included in the kit are Class II or III.” The commenter offered as a rationale for this change that application of the approach in the proposed rule to such products would represent “an unnecessarily burdensome approach to the industry and in most instances will not provide greater protection of the public health.” Other commenters asked for guidance on the application of CGMP requirements to a drug manufacturer who purchases a finished, “off-the-shelf” medical device to include in a kit. A commenter stated that the control, packaging and release of kits can be adequately handled by current parts 210, 211, and 600 CGMP regulations, and that existing guidance and supplement approval requirements (design verification testing for container closure) are adequate to address any additional considerations necessitated by the packaging and labeling of a kit.

(Response) We do not agree that the rule represents an unnecessarily burdensome approach to CGMP compliance for “convenience kits” or other kits and do not find it necessary to alter the application of the rule to “convenience kits.”

This rule is not intended to create new CGMP requirements, and instead seeks to clarify how to apply them to combination products. A kit that includes two or more types of medical products (e.g., a device and a drug), is a combination product and subject to this rule. Accordingly, the manufacture of the products in the kit would also be subject to this rule.

An important question, however, in responding to this comment is how to define the term “convenience kit.” For purposes of this rule, we define the term to include only kits that solely include products that are: (1) Also legally marketed independently and (2) included in the kit as already packaged for independent marketing and with the same labeling as for independent marketing. This is an important question because no additional CGMP requirements generally would apply to the products in such a “convenience

kit” simply because they have been included in the kit. The only additional CGMP requirements that would generally apply to such a convenience kit would be those applicable to the assembly, packaging, labeling, any sterilization, or further processing of the kit itself. In contrast, if any products to be included in a kit are repackaged, relabeled or otherwise modified for purposes of their inclusion in the kit, the kit is not a “convenience kit” for purposes of this rule and all the CGMP requirements applicable under this rule based on any changes made to the constituent parts would apply.

Accordingly, no additional CGMP requirements would apply to an “off-the-shelf” device that is packaged and labeled in accordance with its existing marketing authorization for the independent sale solely because of its inclusion in a convenience kit. However, if an off-the-shelf device is included in a co-packaged combination product for an intended use that differs from the intended use for which that device is marketed separately, additional CGMP requirements may apply, including design controls to ensure that the device is appropriate for the specific use to which it is put in the combination product.

C. How does FDA define key terms and phrases in this subpart? (§ 4.2)

(Comment 6) One commenter asked whether a device combined with a medical device accessory would be considered a combination product.

(Response) A combination product must include two or more different types of constituent parts (e.g., a drug and device, or biological product and a drug). The definition of device at section 201(h) of the FD&C Act (21 U.S.C. 321(h)) includes devices that are an “accessory” to another device. A device and such an accessory to it are, therefore, both devices and when combined would not constitute a combination product.

(Comment 7) One commenter requested clarification relating to the definition of the term “manufacture.” This commenter sought confirmation that the rule is intended to encompass the types of activities included in the definition of manufacture under drug CGMPs and the QS regulation, and to cover the entities undertaking these activities. This commenter also sought clarification of what parties must do to comply with CGMPs, for example, if the manufacture of a combination product involves a specification developer, contract manufacturer, and component manufacturer. This commenter proposed that the responsibility for

ensuring that all requirements are met should fall to the manufacturer who holds the marketing application.

(Response) The term “manufacture” for purposes of the rule is intended to encompass all activities defined as manufacturing under the drug CGMPs and QS regulation and also under the biological product and HCT/P regulations listed in § 4.3. Both specification developers and contract manufacturers “manufacture” and are considered manufacturers for purposes of these underlying CGMP regulations and are, therefore, subject to this rule if they manufacture combination products or constituent parts of combination products. However, an entity that is not considered a manufacturer for purposes of the QS regulation, which manufactures a device component, is not subject to this rule even if that component will be incorporated into a combination product or constituent part of a combination product at some other facility. See Quality System (QS) Regulation/Medical Device Good Manufacturing Practices (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/qualitysystemregulations/default.htm>).

As discussed in response to Comments 13 and 14 of this document, the CGMP requirements applicable to a particular manufacturer for the work done at its facility may vary based upon the type or types of constituent parts being manufactured and the aspects of their manufacture that are being performed. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product (hereafter referred to as the applicant for purposes of the preamble to this rule) is responsible for compliance with all aspects of the CGMP requirements applicable to the entire manufacturing process and across all facilities.

(Comment 8) Some commenters sought confirmation that containers and closures, which they asserted are currently treated as drug components, would continue to be treated as such. Some commenters sought guidance on whether a prefilled syringe would be considered a combination product.

(Response) The suggestion that containers and closures are treated as drug components for purposes of CGMPs is incorrect. Components are defined under § 210.3 as “any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.” It is true that containers and closures are subject to

the drug CGMPs rather than the device QS regulation. While some CGMP requirements apply to both drug components and containers/closures, containers/closures are separately addressed in the drug CGMPs, and distinct CGMP requirements apply to them (see § 211.84).

The Agency will continue to regulate drug containers and closures in accordance with parts 210 and 211. A syringe, however, is not a mere container/closure. A syringe is a device used to deliver another medical product (e.g., a drug) (see, e.g., 21 CFR 880.5860). Accordingly, a prefilled syringe is a combination product and subject to this rule. See also response to Comment 15 of this document distinguishing complete syringe constituent parts from components of syringes. We plan to address distinctions between devices and containers/closures in further detail in later guidance.

(Comment 9) Several commenters asked that the Agency revise and clarify the term “constituent part,” arguing that its interpretation is important to understanding the scope of the rule. Some commenters proposed inclusion of a definition for component or language in the codified regarding how manufacturers should address components in their CGMP systems. These and other commenters sought clarification of how the rule might apply to components of devices and ingredients for drugs and biological products. Some commenters also sought clarification of how the definition of constituent part might relate to whether an article should be considered a drug component as opposed to a device, citing container closures as an example. Some commenters also asked that the Agency provide guidance, including examples, of articles the Agency considers constituent parts and articles that we consider components.

(Response) We have declined to revise the definition of constituent part, or to include a definition of component, in the rule. The current definition of constituent part found in § 4.2 provides a succinct way to identify a drug, device, or biological product as included in a combination product. Such a term of reference is needed not only for this rule but in relation to virtually all regulatory activity for combination products.

The rule does not change the scope of the regulations listed in § 4.3. Rather, it expressly codifies the applicability of these requirements to combination products and clarifies how to comply with these regulations for combination products. Accordingly, articles not

otherwise subject to the regulations listed in § 4.3 are not made subject to those regulations by this rule. Therefore, for example, if an article would be considered a device component, and it would not be subject to the QS regulations in the absence of this rule, that device component does not become subject to the QS regulations because of this rule.

In addition, we note that the term component is defined for a drug at § 210.3(b)(3) and for a device at § 820.3(c). The existing definitions appropriately characterize the components of drugs and devices, respectively, and we see no need to develop a distinct definition in relation to combination products.

The Agency appreciates the value of guidance to ensure understanding of this rule by both industry and FDA staff. The Agency is developing guidance on the application of the rule, including examples to illustrate these and other concepts addressed.

(Comment 10) One commenter sought clarification of the definitions for “co-packaged” and “single-entity” combination products. This commenter also requested a list of examples to clarify these definitions.

(Response) The definitions for co-packaged and single-entity combination product are quoted in part I.A. of this preamble and are found in § 3.2(e). This rule merely cross-references those existing definitions. We note, however, that the term “component” as used in the definition for single-entity combination product in § 3.2(e) and this rule, is synonymous with “constituent part” under this rule. We recommend visiting the Web page for OCP on the Agency’s Web site at <http://www.fda.gov/CombinationProducts/default.htm>, for further information relating to these definitions and examples of combination products.

(Comment 11) One commenter urged the Agency to take care to ensure that stakeholders understand the terminology being used in the rule and its preamble.

(Response) We have been mindful of this consideration in attempting to make the rule and this preamble as clear as possible, including in the selection and manner of defining key terms in § 4.2.

D. What current good manufacturing practice requirements apply to my combination product? (§ 4.3)

(Comment 12) One commenter sought clarification of the CGMP requirements applicable to combination products comprised of constituent parts that are manufactured and marketed separately. This commenter proposed revising § 4.3

to address this issue by replacing “The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part * * *” with “The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to the drug constituent part of a combination product” and parallel changes with respect to device and biologic constituent parts.

(Response) The preamble to the proposed rule discussed in some detail the issue of what CGMP requirements apply to the manufacture of constituent parts that are manufactured and marketed separately from one another (see 74 FR 48423 at 48424 to 48425). We do not see a need to revise § 4.3 to provide further clarity as requested by the commenter. Section 4.3 lists the CGMP regulations applicable to combination products. This rule does not change the requirements of these listed regulations. In § 4.4, this rule addresses how to comply with these requirements for single-entity and co-packaged combination products because of the complexity of applying these requirements to these types of combination products. The rule does not expressly address how to comply with these requirements for separately manufactured and marketed constituent parts of combination products because each of these separately manufactured constituent parts is subject only to the regulations listed in § 4.3 that are applicable to that type of constituent part. We note that we have modified § 4.3(c) for clarity.

E. How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product? (§ 4.4)

(Comment 13) Some commenters noted that not all requirements of the CGMP regulations applicable to combination products may be relevant to a particular product or to when and where particular aspects of the manufacturing process are undertaken. Commenters offered recommendations for addressing this variation in guidance or through revision of the rule.

(Response) This rule does not alter the regulations listed in § 4.3. All of the CGMP requirements applicable to a combination product or constituent part must be met where and when required.

We agree that not all the provisions of the CGMP regulations listed in § 4.3 as applicable to a class of combination product (e.g., drug-device or biological product-drug combination product) or constituent part (drug, device, or

biological product) may be relevant to a specific type of combination product or constituent part. The preamble to the proposed rule addressed this point (see 74 FR 48423 at 48426). For example, only combination products that include an OTC drug must comply with tamper-evident packaging requirements, and only combination products that include a type of device that is installed or serviced must comply with installation and servicing requirements.

Similarly, we agree that not all CGMP requirements may apply at a facility that is performing only certain aspects of the manufacture of a combination product. As §§ 210.2(b) and 820.1(a)(1) reflect, an entity that engages in only some operations subject to the regulations in parts 210, 211, 600 through 680, 820, and 1271, need only comply with the regulations applicable to those operations. In addition, manufacturers retain the ability to demonstrate that a departure from stipulated CGMP requirements is appropriate, to the extent that the CGMP regulations for drugs, devices, biological products, and HCT/Ps permit such showings (see, for example, § 820.1(a)(3), providing manufacturers an opportunity to document justifications for determining that requirements qualified by “where appropriate” in part 820 are not appropriate for the particular product).

Many, but not all, CGMP requirements are facility specific. Examples of such requirements include requirements for testing of the product by a facility or controls over the supplies brought into the facility. Other requirements, however, are not facility-specific. For example, some concern the product as a whole, such as design controls, and some concern overarching duties for the manufacturing process as a whole, such as Corrective and Preventive Action (CAPA) and management responsibility. Duties associated with such cross-cutting CGMP requirements may be shared by several facilities.

All manufacturers are responsible for ensuring compliance with all CGMP requirements applicable to the manufacturing activities at their facilities. In addition, the applicant is responsible for ensuring compliance with all of the CGMP requirements applicable to the product, taking into account all of the activities occurring at all facilities involved with the manufacturing process.

Section 4.3 of the rule lists all of the CGMP requirements that may apply to a combination product and its constituent parts. Section 4.4 addresses how manufacturers may comply with these requirements for single-entity and

co-packaged combination products. Section 4.4 states that manufacturers may comply with these requirements through the design and implementation of a CGMP operating system that meets all applicable CGMP requirements. Section 4.2 defines CGMP operating system as the operating system within an establishment that is designed and implemented to address and meet the CGMP requirements for a combination product. Accordingly, if the combination product is manufactured at multiple facilities, each facility would need such an operating system, including the facility from which the applicant oversees all of the manufacturing activities and compliance with all CGMP requirements related to the product.

The issues raised in these comments are not peculiar to combination products or their constituent parts, though addressing them may present some added complexity because of the number of sets of regulations that may apply to a combination product, the relatively complex nature of these products, and the multiple Agency components that may have an interest in ensuring compliance with CGMP requirements for these products. Examples and clarification to aid compliance will be provided in subsequent guidance.

(Comment 14) Some commenters sought clarification of § 4.4(b)(1) and (b)(2) and confirmation of whether the rule requires compliance with both the drug CGMPs and with the QS regulation throughout the entire manufacturing process for combination products and their constituent parts, or only at facilities where constituent parts subject to both of these two sets of requirements are being made. Commenters asserted that applying both sets of requirements throughout the entire manufacturing process of a combination product would result in a more demanding and complex CGMP system than currently expected for non-combination medical products. Other commenters proposed that the rule should be revised to have a “product-based” rather than a “facility-based” approach.

(Response) As discussed in response to Comment 13 of this document, the applicability of some CGMP requirements will vary depending on the circumstances, including what aspect of a product’s manufacture takes place at a facility and whether multiple facilities are involved in the manufacture of a combination product. Accordingly, we do not agree that the rule should be either “product-based” or “facility-based.” A manufacturer must comply with the requirements

applicable to the activities undertaken at its facility, including applicable aspects of requirements that apply to multiple facilities or the overall manufacturing process for the product, and a product applicant must ensure compliance with all CGMP requirements for its product.

The rule provides that a facility that is manufacturing only one type of constituent part of a co-packaged or single-entity combination product need only comply with the CGMP requirements applicable to that constituent part type (§ 4.4(c)). Facilities that perform manufacturing activities for more than one type of constituent part of such a combination product must comply with the CGMP requirements applicable to each type of constituent part being manufactured at that facility (§ 4.4(d)). The rule permits the use of the streamlined approach to demonstrate compliance with the drug CGMP and device QS regulation requirements when both are applicable to a facility’s manufacturing activities for a single-entity or co-packaged combination product (§ 4.4(a) and (b)).

With regard to CAPA requirements and the parallel requirements of the drug CGMPs, for example, the applicant and any other manufacturer(s) for a single-entity or co-packaged combination product must ensure that an appropriately comprehensive review of activities is undertaken at whatever facilities may be relevant to determine the root cause of manufacturing problems, deviations, or nonconformities. These requirements also call for corrective actions and preventive measures to be taken with regard to all relevant manufacturing steps at all relevant facilities, so that the problem is corrected and potential problems will be prevented or mitigated going forward. In the case of the product applicant these duties are comprehensive, applying to all relevant facilities and all appropriate measures for the product. For products with multiple manufacturers, the scope of the duties for each manufacturer parallels and depends upon the scope of the activity undertaken at that manufacturer’s facility. The related guidance for this rule will address these issues further.

(Comment 15) Some commenters sought clarification of the language of § 4.4(d) that states that a facility where two or more different types of constituent parts have arrived or at which their manufacture is proceeding may apply the streamlined approach provided for under § 4.4(a)(2) and (b). One commenter proposed that this streamlined system should only have to

be met once two or more types of constituent parts have been assembled. Some commenters proposed that once initiated, the system should apply on a “forward-looking” basis and should not reach back to manufacturing operations that occurred prior to when the constituent parts begin being manufactured together at the same facility.

(Response) As discussed previously in response to Comment 13 of this document, there are various types of CGMP requirements, some of which are facility-specific, and some that apply to multiple facilities or the overall manufacturing process for the product. All of these requirements must be met for a combination product. As these comments suggest, the requirements applicable to a particular manufacturer depend on the activities undertaken at the facility or facilities that manufacturer operates, with the applicant having responsibilities for compliance with all CGMP requirements for its product.

Section 4.4(d) concerns the CGMP operating system for a specific facility participating in the manufacture of a single-entity or co-packaged combination product. If a facility manufactures only one type of constituent part of such a combination product, it must comply with the CGMPs for that type of product (e.g., the QS regulation if the constituent part is a device). In contrast, when two or more constituent parts of a combination product are being manufactured at the same facility, the manufacturer must comply with the CGMPs applicable to each type of constituent part (e.g., the drug CGMPs and device QS regulation if the facility is combining or otherwise manufacturing both drug and device constituent parts). Accordingly, § 4.4(d) states that a facility may initiate a CGMP operating system that complies with § 4.4(b) when the manufacture of two or more different types of constituent parts is being conducted at that facility. Section 4.4(d) is intended to clarify that when a facility must comply with the CGMP requirements for more than one type of constituent part, a § 4.4(b)-compliant CGMP operating system is available as a means of demonstrating compliance.

We reject the proposal that the CGMP requirements applicable to a constituent part come into effect only after that constituent part has been formed. Such an approach would be inconsistent with the application of the underlying CGMP regulations listed in § 4.3. The trigger is whether the facility is conducting manufacturing operations that would be subject to the underlying CGMP

requirements. For example, if a facility is manufacturing only device components, it might not be subject to CGMP requirements under the QS regulation. However, a facility that is manufacturing a finished device from such components is subject to the QS regulation. Therefore, for example, if a facility is manufacturing a finished combination product, a prefilled syringe for instance, from device components and drug components, that facility is subject to both the QS regulation and drug CGMPs.

(Comment 16) One commenter asserted that due to ambiguities associated with an out-of-specification (OOS) investigation, excessive work may be involved if there is a need to perform a device component review.

(Response) FDA disagrees with this comment. Medical device In Vitro Diagnostic (IVD) product manufacturers routinely perform OOS investigations successfully. OOS investigation is conducted under § 211.192 for drugs and under §§ 820.80(d) and 820.90 for devices. In some cases, as for IVD devices, OOS for a device may be similar to OOS for a drug. In others, the approach may differ. This rule is not intended to alter the scope of such investigations for drugs or devices. Accordingly, whether a combination product manufacturer opts to institute a CGMP operating system that implements the QS regulation plus the called-out provisions from part 211, or one that implements the drug CGMPs plus the specified provisions of the QS regulation, OOS for the combination product should be appropriate to address the considerations articulated in § 211.192 for the drug constituent part and in §§ 820.80(d) and 820.90 for the device constituent part. For example, unexplained discrepancies (or the failure of a batch or any components to meet any specifications) shall be thoroughly investigated as appropriate.

(Comment 17) Some commenters requested that the Agency clarify selection criteria for whether to adopt the approach under § 4.4(b)(1) that calls for implementation of the drug CGMPs plus specified provisions of the QS regulation or the approach under § 4.4(b)(2) that calls for implementation of the QS regulation plus specified provisions of the drug CGMPs. One commenter suggested the primary mode of action of the combination product as one possible basis for selection.

(Response) We do not see a need to limit under what circumstances a manufacturer may or should select the approach under § 4.4(b)(1) or (b)(2). It is appropriate to leave the decision of whether to implement a system in

accordance with § 4.4(b)(1) or (b)(2) to the discretion of the manufacturer. Some facilities, for example, may already operate under either the drug CGMPs or QS regulation in manufacturing other products, and may prefer to demonstrate compliance with both sets of regulations by taking the steps necessary to demonstrate compliance with the called out provisions of the regulation under which they do not otherwise operate. Other facilities may have no pre-existing manufacturing approach, for example, and select an option on other grounds. Both the approaches permitted in § 4.4(b) are permissible under the rule, and neither is considered preferable by the Agency.

(Comment 18) One commenter sought guidance on how to implement a CGMP system in accordance with § 4.4(a)(1), which permits establishment of a system that fully implements all of the CGMP regulations applicable to the combination product under § 4.3. Specifically, this commenter sought guidance on how to resolve conflicts among requirements of the regulations applicable to a combination product if implemented in accordance with § 4.4(a)(1).

(Response) As discussed previously in this document, the requirements of the drug CGMP and QS regulation are similar in many respects. Further, the various regulations listed in § 4.3 are generally compatible with one another. Nonetheless, we appreciate that questions as to how to reconcile them and actual conflicts may arise. Accordingly, regulations listed in § 4.3 and this regulation include provisions addressing how to resolve any conflicts among them. These provisions essentially call for following whichever requirement is more specifically applicable. See §§ 211.1(b), 820.1(b), and 4.4(e) of this rule. This determination may be based on such factors such as which regulation addresses a manufacturing issue most precisely and which requirement arises from the regulation most specifically applicable to the constituent part. Should we become aware of potential conflicts with respect to combination products in general or classes of combination products, we intend to address them in guidance. However, we are not aware of any such potential conflicts at this time.

(Comment 19) One commenter requested that the following language be added to § 4.4(c): “Device components and constituent parts are governed under QSR. The drug components and constituent parts are governed under CGMPs. The components of constituent

parts would be governed under the quality system in which they are specified.” A second commenter proposed a similar change to § 4.3(a) to state that drug CGMPs “apply to the drug constituent part of a combination product,” and corresponding changes to § 4.3(b) through (d).

(Response) We have not made either proposed revision because we do not agree that they would clarify the rule, and also because they could cause confusion. Section 4.4(c) provides that all CGMP requirements applicable to a constituent part of a single-entity or co-packaged combination product must be satisfied during any period in which that constituent part is manufactured at a separate facility. In some cases, the CGMPs applicable to that constituent part may arise from only one of the regulations listed in § 4.3. In other cases, the applicable CGMPs may arise from several of these listed regulations. Similarly, as explained in sections E.1 and E.2 of this document, the CGMP requirements listed in § 4.3 apply to the combination product, and compliance with them may involve policies, procedures, and practices applicable to the combination product as a whole or to multiple constituent parts.

E.1. How To Comply With QS Regulation Requirements Under § 4.4(b)(1)

(Comment 20) As discussed previously in this document, some commenters sought guidance concerning the applicability of the requirements specified in § 4.4(b) as a general matter. The great majority of comments addressing in particular the application of the QS regulation requirements specified under § 4.4(b)(1) focused on § 820.30 (design controls). Some commenters asked for clarification of how to apply design controls to combination products. Some questioned whether design controls should apply other than to the device constituent part of a combination product. Some asked for guidance regarding how to apply design controls to non-device constituent parts of a combination product, noting that the decision to incorporate such an article into a combination product may occur after that article has already been developed.

(Response) Design controls apply when a device constituent part is used in a combination product. Design controls require the manufacturer of a combination product which includes a device constituent part to establish and maintain procedures to ensure that the design requirements for the combination product are appropriate and address the

intended use of the combination product, including the needs of the user and patient. The design control process may rely on existing information for the constituent parts, such as information provided in support of the combination product's marketing authorization.

The design history file for a combination product with device and drug or biological product constituent part must address all design issues resulting from the combination of the constituent parts, regardless of whether the manufacturer chooses to apply a CGMP operating system that implements part 820 plus the provisions of part 211 specified in § 4.4(b)(2) of this rule or implements part 211 plus the provisions of part 820 specified in § 4.4(b)(1) of this rule. For example, with regard to a drug or biologic product constituent part in a combination product, the design history file would document and provide objective evidence that the drug or biologic is appropriate for use with the device (e.g., why the formulation of the drug constituent part is appropriate for use in a drug-eluting stent given the need to ensure controlled elution, resistance to flaking, etc.). Similarly, with regard to a device constituent part in a combination product, the design history file would document and provide objective evidence that the device constituent part is appropriate for use with the drug or biological product (e.g., that a syringe is appropriate for use as a delivery device for a drug by providing assurance that there is no interaction with the drug, that the syringe will deliver the drug properly, and that container closure integrity and shelf life can be maintained, etc.).

The combination product manufacturer is responsible for design and development planning, including the design of processes for the manufacture of the combination product. For products manufactured by multiple manufacturers, the finished combination product manufacturer and the application holder (if they are not the same entity), each are responsible for these duties. The design inputs must ensure that the design requirements are appropriate and address the intended use of the combination product, including the needs of the patient and the user of that combination product. Design output procedures must ensure that those design outputs that are essential for the proper functioning of the combination product are identified. The total finished design output consists of the combination product, its packaging, and its labeling. In addition, design control requirements for review, verification, validation, design changes

and design history file apply. If a sponsor wishes to use an existing or off-the-shelf product as a constituent part of a combination product, the design controls must ensure that the existing product meets appropriate design requirements for the combination product to be safe and effective, which may require modification of the existing product for use as part of the combination product. See § 820.30. Further explanation will be provided in the related guidance.

E.2. How To Comply With Drug CGMP Requirements Under § 4.4(b)(2)

(Comment 21) Some commenters proposed adding the requirements from §§ 211.160 (general requirements) and 211.194 (laboratory records) of the drug CGMP requirements to the list of requirements with which manufacturers must demonstrate compliance under § 4.4(b)(2).

(Response) We do not find that it is necessary to add §§ 211.160 and 211.194 to § 4.4(b)(2). The topics addressed in these sections are adequately addressed in part 820, including, for example, in §§ 820.70 (production and process controls), 820.72 (calibration), 820.80 (acceptance activities), 820.180 (general requirements), and 820.250 (statistical techniques).

Section 211.160 is primarily concerned with the "establishment of * * * specifications, standards, sampling plans, test procedures, or other * * * control mechanisms" with respect to the laboratory. This section also states that these control mechanisms and changes to them shall be drafted by the appropriate organizational unit and reviewed by the quality control unit. These requirements shall be followed and documented, and any deviation shall be recorded and justified. Also, appropriate "instruments, apparatus, gauges, and recording devices" shall be calibrated. While we recognize that pharmaceutical laboratory control is critical to the quality of drug components, in-process materials, and the final product, this section's requirements are broad enough to be comparable to requirements specified in §§ 820.70(a) and (b) (general requirements and changes to production and process controls), 820.80(c) (in-process acceptance activities), 820.250 (statistical techniques), 820.20(a)(1) (responsibility and authority), and 820.72(b) (calibration).

Section 211.194 is primarily concerned with the management and maintenance of official records with respect to the laboratory. This section's requirements are comparable to requirements specified in § 820.180

(general requirements for official records). While § 211.194 specifies some requirements for testing of laboratory samples, "complete records" of all data generated within a laboratory is comparable to "all records" as described in § 820.180. Section 211.194 can be used as a source of information for specific pharmaceutical laboratory testing records needing to be managed and maintained, as well as relevant CGMP guidance with respect to pharmaceutical and microbiological laboratories.

(Comment 22) Some commenters sought clarification of circumstances under which § 211.103 (calculation of yield) should be satisfied and questioned whether determining yield would provide meaningful information beyond what the QS regulation requires regarding whether processes are under control. One sought clarification of whether the requirement applies only to drug constituent parts.

(Response) Section 211.103 states that calculation of yield "shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding" for a drug product. This may provide valuable information and insight to the status of a manufacturing process at significant evaluation points, not just for the final product. In addition, § 211.103 provides an important quality check both for a pharmaceutical production process as a whole and for individual unit operations of the process. It is important to account for any increase or decrease in expected yield of materials during the manufacturing process. When either occurs, it is important to conduct a prompt and thorough investigation. Appropriate manufacturing controls can help prevent deviations from expected process yield, which can be important to the success of manufacturing steps and to ensuring that the final product meets specifications. Any phase of the pharmaceutical process that is subject to potential component, in-process material, or product loss, due to physical or chemical means, should be evaluated with respect to actual and theoretical yield of these materials. Section 211.103 does not apply to device constituent parts of combination products.

(Comment 23) Some commenters sought clarification of the application of § 211.170 (reserve samples). Some argued that reserve sample requirements should apply only to drug constituent parts of combination products and not to device constituent parts or the entire combination product, asserting that keeping samples of devices or complete

combination products would be cost prohibitive. Others sought guidance regarding how to comply with reserve sampling requirements for “small lot” products with less than 100 products in a lot, or products that come in multiple sizes and shapes.

(Response) Reserve samples are needed to help ensure the postmarket safety and effectiveness of combination products, as they are for drugs and biological products. They are used, for example, to address certain product complaints, evaluate stability concerns, and assess the causes of adverse events. Under § 211.170, reserve samples must be maintained for each lot of a drug (or biological product) “under conditions consistent with product labeling,” “stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics,” and must consist of “at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens.”

For a single-entity combination product, such as a prefilled syringe or a drug-eluting disc or stent, it would be appropriate to retain samples of the complete product from each lot and, in any event, the samples should include the drug and all device components that come into direct contact with the drug. For co-packaged and cross-labeled combination products, it generally should be sufficient to maintain samples of each lot of the drug or biological product in the immediate container/closure in which it is marketed. Specific questions or concerns about reserve samples should be discussed with the lead review center for the combination product. We will provide further information regarding how to comply with sample retention requirements for combination products in related guidance for this rule.

(Comment 24) Some commenters sought guidance on compliance with batch release testing requirements under § 211.165. One asserted that such “testing-in” requirements are in conflict with “design-in” requirements of the QS regulation. Some sought clarification of who is responsible for batch release for drug constituent parts, and whether the release is under a Certificate of Analysis or based on actual approval of the batch records. One asked how “batch” would be defined, specifically whether the batching of the device constituent part or the drug would prevail in determining what is a “batch.” One noted that a different approach might be appropriate for smaller production batches (for example, of less than 100) as opposed to batches that might

contain 100,000 units. One asked if the Agency agreed that flexibility in applying the requirements would be appropriate if the combination product has a device primary mode of action. One asked if the Agency would consider testing of selected batches appropriate for small batch, high-cost combination products. One asked whether the Agency would permit combining sub-batches or testing of representative samples of the finished product. One asked, with regard to devices that contain antimicrobials, whether testing of antimicrobial activity could be considered a suitable surrogate endpoint for the determination of strength of the active ingredient.

(Response) Section 4.4 applies to single-entity and co-packaged combination products. Testing and release for distribution of finished pharmaceuticals is a critical step in drug product manufacture and quality control. This applies to all single entity and co-packaged combination products that contain a drug constituent part. Such testing requirements do not conflict with design-based controls. Rather, the two work hand-in-hand to ensure appropriate manufacture and product performance.

Each combination product manufacturer should establish procedures defining “a batch” in all phases of production, and describe all batch numbering systems used for incoming material, in-process material, and finished products. These procedures allow the manufacturer to connect specific lots of constituent parts, components and in-process material to the specific lot of combination product in which they were used as well as provide traceability of sampling and testing, packaging and labeling activities. Master production and control records should be designed to enable this traceability. Batch definition, control, and tracking procedures should be explained in product applications and available for review on inspection.

All proposed testing and sampling plans of drug constituent parts should be conducted in accordance with §§ 211.160 and 211.165. Sampling plans should be designed to assure appropriate statistical quality control criteria are met as a condition for the drug constituent part’s approval and release. The acceptance criteria for all sampling and testing of a drug constituent part for product release should be reviewed and approved by the firm’s quality unit.

“Release” of pharmaceutical ingredients, excipients, and/or products may mean different things depending on

where in the manufacturing process the materials are being tested. Incoming ingredients, excipients, and supplies from suppliers must be tested, controlled, and documented in accordance with § 211.84. Reliance on reports of analysis and certificates of testing may be permitted under certain circumstances as provided at § 211.84(d) so long as at least one specific identity test is conducted for each component of a drug constituent part. Acceptable materials can be “released” into the drug constituent part or combination product production system. Finished drug constituent parts or combination products must also be tested, controlled, and documented before they can be “released” for distribution to other clients or the market.

Regarding the issue of whether verification and testing of antimicrobial activity could be a suitable surrogate for the determination of strength, we note that it would not be appropriate to use a qualitative activity determination (such as a determination of general antimicrobial activity) in place of a quantitative determination of biological activity (such as a determination of microbial inhibitory concentration (MIC)). Further, what type of test to conduct can depend on the purpose of the antimicrobial. For example, if a device is coated with an antimicrobial drug, and the intended use of the combination product involves dissemination of the drug to produce a pharmacologic effect, then “strength” could be determined by chemical analysis (reflecting chemical content) or by MIC (reflecting biological activity). However, if the antimicrobial coating serves only to inhibit or prevent microbial colonization of the device, then an antimicrobial preservative effectiveness test might be more appropriate.

We plan to discuss batch release testing further in the related guidance for this rule.

(Comment 25) Some commenters sought clarification of how to comply with §§ 211.166 (stability testing) and 211.137 (expiration dating) requirements. Two comments sought clarification of stability testing and expiration testing for kits, and one questioned the practicality of annual stability testing for each “size and shape” of a combination product.

(Response) Combination products that include drug constituent parts must comply with § 211.166. A written testing program must be established to verify the stability of the drug constituent part. These stability testing programs are critical in determining appropriate storage conditions and

expiration dating. Any drug product manufactured for commercial distribution should be subjected to stability testing, including each type of drug constituent part included in a kit. Among other considerations, this testing must enable evaluation of any effects of storage in a container closure system, which may be a device constituent part, on the stability of the drug. See § 211.166(a)(4). As stated in § 211.137, expiration dating must comply with 21 CFR 201.17. We plan to provide additional information on how to comply with the requirements of §§ 211.166 and 211.137 in the related guidance for this rule.

E.3. How To Comply With Biological Product and HCT/P Requirements Under § 4.4(b)(3)

(Comment 26) Some commenters sought clarification of which CGMP requirements for biological products and HCT/Ps might apply to a combination product. Some noted that the proposed rule provided that manufacturers of drug-device combination products could demonstrate compliance with both the drug CGMPs and device QS regulation by demonstrating compliance with one of these regulations in its entirety and with specified provisions of the other regulation. In contrast, they noted, the proposed rule stated that manufacturers of combination products that include a biological product or HCT/P must demonstrate compliance with all of the CGMP requirements applicable to a biological product or HCT/P, respectively. Commenters asked whether the Agency could specify biological product and HCT/P CGMP requirements with which compliance must be demonstrated if a manufacturer has demonstrated compliance with the drug CGMPs or device QS regulation.

(Response) As noted previously in this document, and stated in the definition for biological product at § 4.2, a biological product is also by definition a drug or a device. Accordingly, a biological product is always either subject to the drug CGMP regulations described in parts 210 and 211, or to the QS regulation described in part 820, as appropriate, regardless of whether the biological product is a constituent part of a combination product. Furthermore, biological products, including those that are constituent parts of combination products, must comply with all applicable requirements in parts 600 through 680. To the extent that requirements in parts 600 through 680 pertain to manufacturing for biological products, these requirements apply in conjunction with the CGMP regulations

in parts 210, 211, and 820 and do not create a separate CGMP operating system. Therefore, the additional requirements that pertain to manufacturing for biological products in parts 600 through 680 that would otherwise apply to a biological product if it were not part of a combination product must still be met when that biological product is a constituent part of a combination product.

As noted in the preamble to the proposed rule, many requirements in parts 600 through 680 are not considered CGMP requirements. Moreover, many requirements in parts 600 through 680 are applicable only to certain types of biological products. For example, blood and blood components are subject to the CGMP requirements for such products under part 606. Additionally, a vaccine manufactured using a spore-forming microorganism would be subject to § 600.11(e)(3) (work with Spore-forming microorganisms). As a result, the specific requirements in parts 600 through 680 that apply will depend on the type of biological product.

An HCT/P that is not regulated solely under section 361 of the PHS Act (42 U.S.C. 264) is regulated as a drug, device, and/or biological product (see §§ 1271.10 and 1271.20).⁵ The requirements for HCT/Ps under part 1271 are designed to prevent the introduction, transmission, and spread of communicable diseases. These requirements must be met for HCT/Ps, and are essential to protecting the public health. However, the Agency recognizes that there are some sections of part 1271 that overlap with the requirements under the drug CGMPs and the QS regulation, and has addressed these overlaps in draft guidance. See “Guidance for Industry; Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory>

⁵ The HCT/P regulation at part 1271 distinguishes between HCT/Ps regulated solely under section 361 of the PHS Act (42 U.S.C. 264) and those that are regulated as drugs, devices and/or biological products under the PHS Act. The HCT/P regulation provides that an HCT/P that is combined with another article (other than water, crystalloids, or a sterilizing, preserving or storage agent) does not meet the criteria for regulation solely under section 361 of the PHS Act, but would be regulated as a drug, device and/or biological product. Refer to §§ 1271.10 and 1271.20 when considering what regulations apply to a combination product with an HCT/P constituent part.

Information/Guidances/Tissue/UCM285223.pdf.

(Comment 27) One commenter sought clarification of how to reconcile conflicts between HCT/P manufacturing requirements and drug CGMP and QS regulation requirements. This commenter stated that some HCT/Ps are also considered xenotransplantation products due to their exposure to animal materials (mouse, insects) during manufacturing and that FDA should consider addressing this topic in the final rule and/or associated guidance.

(Response) Based on experience to date, the Agency believes that conflicts are unlikely to occur between the HCT/Ps manufacturing requirements listed in § 4.3(d) and the drug CGMPs or device QS regulation. Further, as discussed in response to Comment 18 of this document, the rule includes a provision at § 4.4(e) on how to resolve conflicts between CGMP requirements. Accordingly, we do not see a need to revise the rule in respect to this issue or to address it in guidance at this time. Regarding the issue of xenotransplantation products, we note that the Agency has already addressed this topic in guidance (see “Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans,” (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074354.htm>).

F. Enforcement and Effective Date

(Comment 28) Several commenters recommended delaying the effective date, in most cases to 1 year after publication of this rule. Some noted a need to coordinate various functions and conduct extensive communications and analyses in developing a compliant system. Others noted the time the Agency provided for implementation of aspects of other rules, such as the design control requirements of the QS regulation. Some addressed the time and financial costs of making such changes, arguing that the Agency has substantially underestimated the costs of implementing this rule, and should extend the effective date in light of the greater costs they believe will be incurred.

(Response) This final rule serves to clarify options for manufacturers to comply with the sets of CGMPs applicable to their combination product. As stated in the preamble to the proposed rule, manufacturers are responsible for compliance with the CGMP requirements that apply to each constituent part of their combination

products (74 FR 48423 at 48424). This rule does not establish any new requirements. Accordingly, we see no reason to delay its effective date, and consistent with the plan described in the proposed rule, we are issuing this rule to be effective in 180 days. The Agency wants to move forward in providing greater assurance that the streamlined approach outlined in the 2004 draft guidance and codified in § 4.4(b) of this rule may be used to demonstrate compliance with CGMPs for combination products. As noted throughout this notice, we are preparing companion guidance to provide further, general information regarding our expectations for compliance with CGMPs for combination products, and we remain available to work with manufacturers to resolve product-specific questions. We intend to continue to apply a risk-based approach to facility inspection and, consistent with ensuring protection of the public health and in light of the specific circumstances, to offer manufacturers a reasonable opportunity to correct deficiencies before taking further compliance or enforcement actions.

G. Alternate Approaches

(Comment 29) Some commenters proposed alternate approaches, suggesting a more “unified” approach would be preferable or arguing that the drug CGMPs and device QS regulation are not well-suited for application to products including devices and drugs, respectively. Some encouraged reliance on guidance instead.

(Response) As discussed in the preamble to the proposed rule and summarized in section I.A of this document, the Agency undertook an extensive evaluation of the drug CGMPs, device QS regulation, and biological product and HCT/P requirements in developing this rule. This process included consideration of comments received on the draft guidance that proposed an approach much the same as the approach offered in the proposed rule and adopted in this final rule. The comments received on that draft guidance and on the proposed rule were largely supportive of this approach, and the Agency believes that this approach offers an efficient and effective means to ensure that combination products are manufactured in accordance with all appropriate CGMP requirements.

We see no reason to develop an entirely new regime for combination products, but rather find that it is appropriate to utilize the well-established and understood CGMP requirements that already exist for the constituent parts of which combination

products are comprised. At the same time, it is important to establish with clarity and certainty the CGMP requirements that apply to combination products, to ensure effective compliance and consistent, appropriate regulation. Accordingly, we determined that a rulemaking rather than reliance on guidance alone is appropriate to achieve these goals. As discussed throughout this preamble and in the preamble to the proposed rule, we understand that guidance is important to the effective implementation of this rule, and are issuing companion guidance for this reason.

H. Guidance

(Comment 30) Several commenters requested that FDA issue companion guidance for this rule. Some requested that such guidance include relevant case studies or descriptions of what would constitute a demonstration of compliance with requirements for examples of combination products and manufacturing activities. One proposed that the guidance address the application of provisions of the drug CGMPs and QS regulation that are not specified in the rule and their compatibility with those provisions that are specified in § 4.4(b) from the other of these two regulations. One commenter proposed guidance on the application of CGMP requirements for combination products in relation to master files. One commenter proposed a need for a table of key CGMP considerations for developing a streamlined system and for audit instructions and inspection check lists. Some emphasized the need to address what actions existing facilities should take to come into compliance. One encouraged harmonization with international efforts where possible. One stated that FDA should provide additional guidance on how the rule will affect Agency policy on CGMP requirements for investigational device constituent parts in combination products for which the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research has the lead. One requested that guidance provide for the opportunity to discuss CGMP issues with the Agency. Some requested that such guidance issue prior to the final rule. One commenter advised that we review existing guidance to ensure its consistency with this rule.

(Response) As noted in the proposed rulemaking, FDA recognizes that timely, comprehensive guidance is important to help ensure consistent and appropriate implementation of this rule. FDA intends to issue such guidance to

industry and staff, focusing on the implementation of the regulatory requirements for use of a streamlined CGMP operating system for single-entity and co-packaged combination products. We welcome the comments received on this issue and look forward to further feedback in response to the guidance we issue. With regard to the requests that we issue draft guidance prior to issuance of this final rule, we did not believe it would be appropriate to anticipate the content of this rule by publishing guidance concerning its content prior to its finalization.

We remain committed to international harmonization efforts, including those related to CGMP requirements for combination products. A practical challenge for combination products in particular is that international collaboration and harmonization efforts are at an early stage for these products. At the same time, there is a current need to clarify and rationalize our domestic CGMP requirements for this rapidly growing class of products. We have taken an approach that integrates underlying CGMP approaches for drugs, devices, and biological products, which have each benefited in various respects from substantial international harmonization efforts. The approach adopted in this rule will facilitate implementation of streamlined CGMP operating systems for combination products that will integrate as readily as possible with these existing and ongoing harmonization efforts. We are committed to continuing to work with our foreign counterparts on CGMPs and other issues for combination products, and to pursuing domestic regulatory approaches in the United States that will enable such efforts to the extent practicable and appropriate consistent with meeting our domestic regulatory needs.

With regard to the comment concerning review of existing guidance for consistency with this rule, we note that any prior guidance must be read in light of subsequent changes to legal requirements, whether through new statutory law or issuance of new regulations. The Agency will continue to review all guidance to ensure its continued utility and accuracy.

I. Other

(Comment 31) Some commenters recommended using the term “hybrid” rather than “streamlined” in reference to the compliance option under § 4.4(b) for single-entity and co-packaged combination products. One commenter suggested that the rule does not reduce the burden of compliance with both the drug CGMPs and QS regulation. Some

commenters argued that the term streamlined might suggest a relaxation of requirements when § 4.4(b), in fact, does not relax CGMP requirements for such products.

(Response) We appreciate the concerns raised by these commenters. However, we disagree with the conclusion that § 4.4(b) does not provide a means to streamline compliance with the drug CGMPs and device QS regulations for single-entity and co-packaged combination products. The alternative to the approach permitted under § 4.4(b) is that of § 4.4(a), under which a facility would need to demonstrate compliance with all applicable requirements under both of these regulations. Section 4.4(b), in contrast, reflects the Agency's judgment that many provisions of these two regulations are similar to one another and that demonstrating compliance with most requirements of one of these sets of regulations suffices to demonstrate compliance with similar provisions of the other set.

We also disagree that use of the term "streamlined," which is consistent with the rule's removal of redundant requirements for compliance with similar provisions of the drug CGMPs and QS regulation, implies a relaxation of CGMP requirements. Rather, it reflects the provision of a more efficient means to satisfy them.

(Comment 32) Some commenters raised issues concerning training of compliance staff, inspection standards, coordination and allocation of responsibilities among Agency staff, and tracking and oversight for compliance activities within the Agency.

(Response) The Agency recognizes the importance of effective and appropriate training, oversight, and standards for CGMP inspection, and for efficient, effective coordination among staff. We intend to address such matters through appropriate inspectional standards, training, and other mechanisms used in relation to other CGMP inspectional activities. However, these issues are matters of internal Agency operation outside the scope of this rulemaking and we do not address them further here.

(Comment 33) Some commenters stated that the Agency should address how to ensure appropriate change controls for combination products, with one comment highlighting the issue with respect to cross-labeled combination products. Some commenters proposed that the Agency consider requiring constituent part manufacturers to notify one another before making changes to the constituent part. Some commenters also addressed the question of which post-

approval change requirements should apply under what circumstances, proposing that the submission requirements for the change be those applicable to the constituent part being changed, or the most stringent requirement applicable to any of the constituent parts being changed if a change is being made to more than one.

(Response) We agree that coordination with regard to changes among manufacturers participating in the manufacture of a combination product is an important CGMP issue. It is not unique to combination products however, and we do not see a need to establish additional requirements specifically for combination products. Where constituent parts of single-entity or co-packaged combination products are being made by one entity and supplied to another's facility where the finished combination product is made, compliance with purchasing control requirements, for example, would necessitate tracking of changes and confirmation that the change will not prevent the combination product from meeting its specifications.

Similarly, the manufacturers of separately manufactured and marketed constituent parts of cross-labeled combination products are subject to the CGMP requirements applicable to the type of constituent part they are manufacturing. They must ensure that the manufacture of their constituent part complies with the specifications established to ensure the safe and effective use of that constituent part in combination with the other constituent parts for the combination product's intended use(s). Appropriate coordination among manufacturers with respect to CGMP compliance for changes to constituent parts of combination products will be further addressed in later guidance.

The requirements for reporting post-marketing changes to the Agency or for obtaining Agency review of post-marketing changes, when making a post-market change to a combination product or a constituent part of a cross-labeled combination product, are beyond the scope of this rule. The issue of what type of submission to make to the Agency for a post-approval change to a combination product is also beyond the scope of this rule. However, we note that we intend to issue guidance addressing post-marketing change submission requirements.

(Comment 34) One commenter raised an issue regarding reporting of adverse events for "cross-labeled" combination products. One commenter asked for guidance on labeling requirements for combination products. Another

proposed that the Agency develop a new master file category for combination product constituent parts and components to address application and quality requirements for these parts of combination products. Another requested that planned guidance for the rule address establishment registration and product listing for manufacturers and importers of combination products. Another commenter proposed development of a new export certificate program for combination product CGMP compliance. Another sought guidance on needle registration, labeling, and testing.

(Response) We appreciate these comments, which raise issues that we may address in other contexts. However, these issues are beyond the scope of this rule and, therefore, we are not offering substantive responses to them here.

III. Legal Authority

The Agency derives its authority to issue the regulations in 21 CFR part 4, subpart A, from 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b–360f, 360h–360j, 360l, 360hh–360ss, 360aaa–360bbb, 371(a), 372–374, 379e, 381, 383, and 394, Federal Food, Drug, and Cosmetic Act, and 42 U.S.C. 216, 262, 263a, 264, and 271, Public Health Service Act.

Most importantly, the provisions at sections 501(a)(2)(B) and (h) of the FD&C Act (21 U.S.C. 351(a)(2)(B) and (h)) require drugs and devices to be manufactured in accordance with CGMPs. Section 520(f) of the FD&C Act (21 U.S.C. 360j(f)) specifically authorizes the issuance of CGMP regulations for devices. Section 501 of the FD&C Act states that a drug or device is deemed adulterated if it is not manufactured in accordance with CGMPs. This provision applies to biological products including those that are constituent parts of combination products because these products meet the definition of drug or device under section 201 of the FD&C Act. This provision also applies to HCT/Ps that do not meet the criteria for regulation solely as HCT/Ps under section 361 of the PHS Act, because they meet the definition of a drug, or device under section 201 of the FD&C Act. In addition, section 351 of the PHS Act (42 U.S.C. 262) authorizes FDA to issue manufacturing standards for biological products. Section 361 of the PHS Act authorizes the issuance of regulations to prevent the introduction, transmission, or spread of communicable diseases.

Under applicable statutory provisions, the following CGMP regulations were previously issued for drugs, devices, biological products, and HCT/Ps that

may be included in combination products:

- Drug CGMP regulations for finished pharmaceuticals or drug products set forth at parts 210 and 211). Drug products not subject to these regulations (e.g., bulk drugs or active pharmaceutical ingredients) must still meet the current good manufacturing practice general standard required by the statute.

- QS regulation for devices set forth at part 820.

- Requirements that pertain to manufacturing within the requirements (including standards) for biological products in parts 600 through 680.

- Current good tissue practices for HCT/PS set forth in part 1271.

There is considerable overlap in the drug CGMPs and QS regulation, and for the most part the overlap is clear. For example, both establish requirements for management, organization, and personnel; both require documentation and recordkeeping; and both allow flexibility in their application to the manufacture of a particular product. FDA considers the drug CGMPs and the QS regulation to be similar, and they are meant to achieve the same general goals.

Nevertheless, these two sets of regulations differ somewhat because each is tailored to the characteristics of the types of products for which it was designed. Each set of regulations contains certain specific requirements for various CGMP concepts that are only more generally addressed in the other regulation. For example, the QS regulation has detailed CAPA requirements (§ 820.100) while CAPA principles are currently more generally addressed in the drug CGMP regulation as part of Subpart J, Records and Reports, specifically at §§ 211.180(e) and 211.192).

This rule clarifies the applicability of these two regulations to combination products and provides a streamlined option for practical implementation for co-packaged and single-entity combination products. Because the drug and device CGMP requirements are so similar, when using this streamlined approach, demonstrating compliance with the requirements of one of these two sets of regulations (e.g., drug CGMPs), along with demonstrating compliance with the requirements of the specified provisions from the other set (e.g., QS regulation), would be considered to be demonstrating compliance with all requirements from both.

The CGMP requirements specific to each constituent part of a combination product also apply to the combination product itself because, by definition,

combination products consist of drugs, devices, and/or biological products. (See § 3.2(e)). These articles do not lose their discrete regulatory identity when they become constituent parts of a combination product. Therefore, all combination products are subject to at least two sets of CGMP requirements. For example, in the case of a drug-device combination product, the QS regulation in part 820 and the drug CGMP regulations in parts 210 and 211 would apply to the combination product.

Although combination products retain the regulatory identities of their constituent parts, the FD&C Act also recognizes combination products as a category of products that are distinct from products that are solely drugs, devices, or biological products. For example, section 503(g)(4)(A) of the FD&C Act (21 U.S.C. 353(g)(4)(A)) requires OCP to “designate” a product as a combination product as well as to ensure “consistent and appropriate postmarket regulation of like products subject to the same statutory requirements.” Further, section 563(a) of the FD&C Act, (21 U.S.C. 360bbb–2(a)), governs the “classification” of products as “drug, biological product, device, or a combination product subject to section 503(g)” (emphasis added). In this respect, the FD&C Act identifies a combination product as a distinct type of product that could be subject to specialized regulatory controls.

Under the preceding authorities and section 701(a) of the FD&C Act (21 U.S.C. 371), which authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act, FDA has the authority to issue regulations clarifying the applicability of CGMP requirements to combination products. The Agency is also authorized under these authorities to issue regulations specifying how compliance with CGMP requirements for combination products may be demonstrated.

IV. Analysis of Economic Impacts

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). FDA believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule codifies what is currently in effect, the Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Rationale for Final Rule

The final rule has two related purposes. The first is to clarify the CGMP requirements that apply to combination products, and the second is to help ensure the consistent and appropriate application and enforcement of these requirements. Constituent parts and manufacturing practices vary among combination products; different CGMP requirements apply depending upon the constituent parts in the combination product and what manufacturing practices are used. The final rule attempts to streamline the practical implementation of CGMP requirements for co-packaged and single-entity combination products.

C. Response to Comments

A number of comments suggested that the regulatory impact analysis of the proposed rule underestimated the incremental cost to comply with this rule; however they did not suggest alternative estimates or methodologies. There were divergent views as to whether the burden of compliance would be greater for legacy products or for small firms and those new to manufacturing combination products. One comment suggested the rule, as proposed, would inhibit innovation.

FDA disagrees with these comments. The Agency has made its views clear

that all manufacturers are already responsible for compliance with the CGMP requirements that apply to each constituent part of their combination products. This final rule clarifies and codifies this view. The CGMPs for drugs, devices, and biological products all require periodic review and update to the systems to ensure they remain current with advances in technology and regulatory practice. Those manufacturers who choose to streamline their systems for legacy products that are in compliance with current practice, do so voluntarily, and it is assumed would only do so if the private benefits of doing it out-weigh the private costs. Because the final rule clarifies and codifies Agency practice on the application of existing CGMP regulations to combination products, it will make it simpler and less burdensome for all manufacturers to apply the regulations when developing new products. It could even shorten approval times for some products by reducing delays caused by lack of systems in place to comply with all applicable CGMP requirements.

D. Impact of Final Rule

FDA estimates that approximately 300 manufacturers of combination products will be affected by the final rule. These manufacturers of combination products should benefit from the greater clarity provided regarding what regulatory provisions apply to their products and how they may comply with them. For both existing and future products, the streamlined approach set forth in the final rule will help ensure that CGMP requirements for co-packaged and single-entity combination products are consistent and appropriate, without duplicative or otherwise unnecessary aspects. This codification of CGMP requirements for combination products will also help ensure predictability and consistency in the application and enforcement of these regulatory requirements with regard to all combination products across FDA.

Firms must already comply with the CGMP regulations for drugs, devices, and biological products, including the current good tissue practice regulations for HCT/Ps, found at parts 211, 820, 600 through 680, and 1271, that are applicable to the constituent parts of their combination products. The cost of this final rule would be the incremental costs to modify or streamline existing standard operating systems. Because this final rule is codifying our current practice, any firms that choose to streamline or modify existing SOPs are doing so because the private benefits are greater than the private costs. If some

firms choose to modify their SOPs as a result of this final rule, the net benefits of the rule will be greater than the costs.

Some firms may incur one-time incremental costs reassessing compliance with the final rule. Because this final rule codifies Agency practice that is described in current guidance documents and because no new CGMP requirements are proposed, we believe the time required would be small and estimate it to be about 25 hours per product. The amount of these compliance assessment costs for an individual firm, and the impact of any such costs, will depend on the number and nature of the products the firm produces and how the firm has applied current regulations. Nonetheless, because the time required would be limited, the Agency believes the impact will not be significant on entities considered small based on the Small Business Administration's definition of a small entity (500 employees for device and biological product firms and 750 employees for drug firms).

V. Environmental Impact

FDA has determined under 21 CFR 25.30(a), 25.30(h), 25.30(j), 25.31(a), (c), (h), and (j), and 25.34(a) and (d) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

We note that the information collected under the underlying CGMP regulations for drugs, devices, and biological products, including current good tissue practices for HCT/Ps, found at parts 211, 820, 600 through 680, and 1271, have already been approved and are in effect. The provisions of part 211 are approved under the Office of Management and Budget (OMB) control number 0910-0139. The provisions of part 820 are approved under OMB control number 0910-0073. The provisions of parts 606, 640, and 660 are approved under OMB control number 0910-0116. The provisions of part 610 are approved under OMB control number 0910-0116 and OMB control number 0910-0338 (also for part 680). The provisions of part 1271, subparts C and D, are approved under OMB control number 0910-0543. This final rule contains no new collections of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VII. Executive Order 13132: Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required. The sole statutory provision giving preemptive effect to this rule is section 751 of the FD&C Act (21 U.S.C. 379r), which would apply only with respect to OTC drug constituent parts of combination products.

List of Subjects in 21 CFR Part 4

Combination products, Biological products, Devices, Drugs, and Human cell, Tissue, and cellular and tissue based products, Regulation of combination products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 4 is added to read as follows:

PART 4—REGULATION OF COMBINATION PRODUCTS

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

Sec.

- 4.1 What is the scope of this subpart?
- 4.2 How does FDA define key terms and phrases in this subpart?
- 4.3 What current good manufacturing practice requirements apply to my combination product?
- 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

Subpart B [Reserved]

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360l, 360hh-360ss, 360aaa-360bbb, 371(a), 372-374, 379e, 381, 383, 394; 42 U.S.C. 216, 262, 263a, 264, 271.

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

§ 4.1 What is the scope of this subpart?

This subpart applies to combination products. It establishes which current good manufacturing practice

requirements apply to these products. This subpart clarifies the application of current good manufacturing practice regulations to combination products, and provides a regulatory framework for designing and implementing the current good manufacturing practice operating system at facilities that manufacture co-packaged or single-entity combination products.

§ 4.2 How does FDA define key terms and phrases in this subpart?

The terms listed in this section have the following meanings for purposes of this subpart:

Biological product has the meaning set forth in § 3.2(d) of this chapter. A biological product also meets the definitions of either a drug or device as these terms are defined under this section.

Combination product has the meaning set forth in § 3.2(e) of this chapter.

Constituent part is a drug, device, or biological product that is part of a combination product.

Co-packaged combination product has the meaning set forth in § 3.2(e)(2) of this chapter.

Current good manufacturing practice operating system means the operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements for a combination product.

Current good manufacturing practice requirements means the requirements set forth under § 4.3(a) through (d).

Device has the meaning set forth in § 3.2(f) of this chapter. A device that is a constituent part of a combination product is considered a finished device within the meaning of the QS regulation.

Drug has the meaning set forth in § 3.2(g) of this chapter. A drug that is a constituent part of a combination product is considered a drug product within the meaning of the drug CGMPs.

Drug CGMPs refers to the current good manufacturing practice regulations set forth in parts 210 and 211 of this chapter.

HCT/Ps refers to human cell, tissue, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter. An HCT/P that is not solely regulated under section 361 of the Public Health Service Act may be a constituent part of a combination product. Such an HCT/P is subject to part 1271 of this chapter and is also regulated as a drug, device, and/or biological product.

Manufacture includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage.

QS regulation refers to the quality system regulation in part 820 of this chapter.

Single-entity combination product has the meaning set forth in § 3.2(e)(1) of this chapter.

Type of constituent part refers to the category of the constituent part, which can be either a biological product, a device, or a drug, as these terms are defined under this section.

§ 4.3 What current good manufacturing practice requirements apply to my combination product?

If you manufacture a combination product, the requirements listed in this section apply as follows:

(a) The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part;

(b) The current good manufacturing practice requirements in part 820 of this chapter apply to a combination product that includes a device constituent part;

(c) The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to which those requirements would apply if that constituent part were not part of a combination product; and

(d) The current good tissue practice requirements including donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P.

§ 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

(a) Under this subpart, for single entity or co-packaged combination products, compliance with all applicable current good manufacturing practice requirements for the combination product shall be achieved through the design and implementation of a current good manufacturing practice operating system that is demonstrated to comply with:

(1) The specifics of each set of current good manufacturing practice regulations listed under § 4.3 as they apply to each constituent part included in the combination product; or

(2) Paragraph (b) of this section.

(b) If you elect to establish a current good manufacturing practice operating system in accordance with paragraph (b) of this section, the following requirements apply:

(1) If the combination product includes a device constituent part and a

drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following provisions of the QS regulation must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QS regulation need be made:

(i) Section 820.20 of this chapter.

Management responsibility.

(ii) Section 820.30 of this chapter.

Design controls.

(iii) Section 820.50 of this chapter.

Purchasing controls.

(iv) Section 820.100 of this chapter.

Corrective and preventive action.

(v) Section 820.170 of this chapter.

Installation.

(vi) Section 820.200 of this chapter.

Servicing.

(2) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the QS regulation, the following provisions of the drug CGMPs must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the drug CGMPs need be made:

(i) Section 211.84 of this chapter.

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

(ii) Section 211.103 of this chapter.

Calculation of yield.

(iii) Section 211.132 of this chapter.

Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(iv) Section 211.137 of this chapter.

Expiration dating.

(v) Section 211.165 of this chapter.

Testing and release for distribution.

(vi) Section 211.166 of this chapter.

Stability testing.

(vii) Section 211.167 of this chapter.

Special testing requirements.

(viii) Section 211.170 of this chapter.

Reserve samples.

(3) In addition to being shown to comply with the other applicable manufacturing requirements listed under § 4.3, if the combination product includes a biological product constituent part, the current good manufacturing practice operating system must also be shown to implement and comply with all manufacturing requirements identified under § 4.3(c) that would apply to that biological product if that constituent part were not part of a combination product.

(4) In addition to being shown to comply with the other applicable current good manufacturing practice requirements listed under § 4.3, if the combination product includes an HCT/P, the current good manufacturing practice operating system must also be shown to implement and comply with all current good tissue practice requirements identified under § 4.3(d) that would apply to that HCT/P if it were not part of a combination product.

(c) During any period in which the manufacture of a constituent part to be included in a co-packaged or single entity combination product occurs at a separate facility from the other constituent part(s) to be included in that single-entity or co-packaged combination product, the current good manufacturing practice operating system for that constituent part at that facility must be demonstrated to comply with all current good manufacturing practice requirements applicable to that type of constituent part.

(d) When two or more types of constituent parts to be included in a single-entity or co-packaged combination product have arrived at the same facility, or the manufacture of these constituent parts is proceeding at the same facility, application of a current good manufacturing process operating system that complies with paragraph (b) of this section may begin.

(e) The requirements set forth in this subpart and in parts 210, 211, 820, 600 through 680, and 1271 of this chapter listed in § 4.3, supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event of a conflict between regulations applicable under this subpart to combination products, including their constituent parts, the regulations most specifically applicable to the constituent part in question shall supersede the more general.

Subpart B [Reserved]

Dated: January 15, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-01068 Filed 1-18-13; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF THE INTERIOR

National Indian Gaming Commission

25 CFR Part 573

Compliance and Enforcement

AGENCY: National Indian Gaming Commission, Interior.

ACTION: Correcting amendments.

SUMMARY: On August 9, 2012, the National Indian Gaming Commission (NIGC) published a final rule amending its enforcement regulation to include a graduated pre-enforcement process for voluntary compliance. That rule referenced a rule that was later withdrawn and also incorrectly referenced an internal citation. This publication corrects the error and makes technical amendments to reference the Commission's recently finalized appeal rules contained in a new subchapter.

DATES: *Effective:* February 6, 2013.

FOR FURTHER INFORMATION CONTACT: Maria Getoff, National Indian Gaming Commission, 1441 L Street NW., Suite 9100, Washington, DC 20005. Email: maria_getoff@nigc.gov; telephone: (202) 632-7003.

SUPPLEMENTARY INFORMATION:

I. Background

The Indian Gaming Regulatory Act (IGRA or Act), Public Law 100-497, 25 U.S.C. 2701 *et seq.*, was signed into law on October 17, 1988. The Act establishes the National Indian Gaming Commission ("Commission") and sets out a comprehensive framework for the regulation of gaming on Indian lands. The purposes of IGRA includes providing a statutory basis for the operation of gaming by Indian tribes as a means of promoting tribal economic development, self-sufficiency, and strong tribal governments; ensuring that the Indian tribe is the primary beneficiary of the gaming operation; and declaring that the establishment of independent federal regulatory authority for gaming on Indian lands, the establishment of federal standards for gaming on Indian lands, and the establishment of a National Indian Gaming Commission are necessary to meet congressional concerns regarding gaming and to protect such gaming as a means of generating tribal revenue. 25 U.S.C. 2702.

On August 9, 2012, the Commission published a final rule amending part 573 (Compliance and Enforcement) to include a graduated pre-enforcement process through which a tribe may come into voluntary compliance. 77 FR 47517, Aug. 9, 2012. The part also sets forth general rules governing the Commission's enforcement of the IGRA, NIGC regulations, and tribal ordinances and resolutions approved by the Chair under 25 CFR part 522.

On September 25, 2012, the Commission published a final rule consolidating all appeal proceedings before the Commission into a new

subchapter H (Appeal Proceedings Before the Commission), thereby removing former parts 524, 539, and 577. 77 FR 58941, Sept. 25, 2012. Thus, any reference in part 573 to appeal rights in former part 577 is obsolete and must be revised to reference the new subchapter H.

This document amends the final rule by making two technical amendments and a correction to the final rule to accurately identify referenced regulations. Specifically, this technical amendment amends § 573.4(c)(3) and § 573.5(a) to accurately reference the new subchapter H in place of part 577. Also, this document corrects an error in § 573.2(c) by replacing a cross reference to paragraph "(b)" with paragraph "(a)."

Regulatory Matters

Regulatory Flexibility Act

The rule will not have a significant impact on a substantial number of small entities as defined under the Regulatory Flexibility Act, 5 U.S.C. 601, *et seq.* Moreover, Indian Tribes are not considered to be small entities for the purposes of the Regulatory Flexibility Act.

Small Business Regulatory Enforcement Fairness Act

The rule is not a major rule under 5 U.S.C. 804(2), the Small Business Regulatory Enforcement Fairness Act. The rule does not have an effect on the economy of \$100 million or more. The rule will not cause a major increase in costs or prices for consumers, individual industries, Federal, State, local government agencies or geographic regions. Nor will the rule have a significant adverse effect on competition, employment, investment, productivity, innovation, or the ability of the enterprises, to compete with foreign based enterprises.

Unfunded Mandate Reform Act

The Commission, as an independent regulatory agency, is exempt from compliance with the Unfunded Mandates Reform Act, 2 U.S.C. 1502(1); 2 U.S.C. 658(1).

Takings

In accordance with Executive Order 12630, the Commission has determined that the rule does not have significant takings implications. A takings implication assessment is not required.

Civil Justice Reform

In accordance with Executive Order 12988, the Commission has determined that the rule does not unduly burden the judicial system and meets the