

# Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products

## *DRAFT GUIDANCE*

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## **Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products<sup>1</sup>**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### **I. Introduction**

This guidance describes and explains the final rule on CGMP requirements for combination products (final rule as codified in 21 CFR part 4) that FDA issued on January 22, 2013.<sup>2</sup> Prior to issuance of the final rule, although CGMP regulations were in place to establish requirements for drugs, devices, biological products, and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), there were no regulations to clarify and explain the application of these CGMP requirements to combination products. The final rule was intended to provide such clarification and specify how compliance with applicable CGMP requirements may be demonstrated.

Section II of this document provides the definition of a combination product, an overview of the final rule, and the role of the lead center and other agency components with respect to combination product CGMP issues. Section III addresses certain general considerations for CGMP compliance for combination products, and Section IV presents the purpose and content of specific CGMP requirements addressed in the final rule, and Section V analyzes hypothetical scenarios intended to clarify how to comply with certain CGMP requirements addressed in the final rule. Throughout this guidance, the agency also refers to existing guidance and additional sources of information that address CGMP requirements for drugs, devices, biological products, and HCT/Ps, as further inform combination product manufacturers on how to comply with CGMP requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

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<sup>1</sup> This guidance was prepared by the Office of Combination Products in the Office of the Commissioner in conjunction with the Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and the Office of Regulatory Affairs.

<sup>2</sup> See the Current Good Manufacturing Practice Requirements for Combination Products, 78 FR 4307 (January 22, 2013).

cited. The use of the word *should* in agency guidance means that something is suggested or recommended, but not required.

## **II. Background**

### **A. Definition of a combination product**

As set forth in 21 CFR part 3, a combination product is a product composed of any combination of a drug, device, or biological product.<sup>3</sup> The drugs, devices, and biological products included in combination products are referred to as “constituent parts” of the combination product.

Under 21 CFR 3.2(e), a combination product includes:

- 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 (a “single entity” combination product, such as a prefilled syringe or drug-eluting stent);
- 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 (a “co-packaged” combination product, such as a surgical or first-aid kit);
- 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 “cross-labeled” combination product, as might be the case for a light-emitting device and a light-activated drug); or

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<sup>3</sup> For purposes of 21 CFR part 3 and the CGMP rule for combination products, 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). Any reference in this guidance to CGMP requirements as applicable to a combination product that includes a drug constituent part should be understood to refer as well to any combination product that includes a biological product constituent part that is also subject to regulation under the FD&C Act as a drug, and any reference to CGMP requirements as applicable to a combination product that includes a device constituent part should be understood to refer as well to combination products that include a biological product constituent part that is also subject to regulation as a device under the FD&C Act.

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

### **B. Overview of the final rule**

As stated in the final rule, the constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. The final rule clarifies that the CGMP requirements that apply to each of the constituent parts apply to the combination product they constitute.

The final rule on CGMP requirements for combination products applies to all combination products. As stated in the preamble to the final rule, the CGMP requirements for constituent parts of cross-labeled combination products that are manufactured separately and not co-packaged are the same as those that would apply if these constituent parts were not part of a combination product (e.g., for a drug/device combination product, 21 CFR parts 210 and 211 would apply to the manufacture of the drug constituent part(s) of the cross-labeled combination product, and 21 CFR part 820 would apply to the device constituent part(s)).

For single-entity and co-packaged combination products, part 4 offers two ways to demonstrate compliance with CGMP requirements. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product.<sup>4</sup> Under the second option, manufacturers implement a streamlined approach, demonstrating compliance with either the drug CGMPs (21 CFR part 211) or the quality system (QS) regulation (21 CFR part 820) rather than demonstrating full compliance with both, when the combination product contains both a drug and a device, under certain conditions.<sup>5</sup> These conditions include demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements. In addition, for a combination product that includes a biological product, the CGMP requirements for biological products in parts 600 through 680 (21 CFR parts 600 through 680) would apply, and, for a combination product that includes any HCT/Ps, the regulations in part 1271 (21 CFR part 1271)—including the current good tissue practice (CGTP) requirements and donor eligibility requirements—would apply.<sup>6,7, 8</sup>

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<sup>4</sup> See 21 CFR 4.4(a)

<sup>5</sup> See 21 CFR 4.4(b).

<sup>6</sup> See 21 CFR 4.4(a) and (b).

<sup>7</sup> As discussed later in section IV.C, an HCT/P may be a “constituent part” of a combination product when the HCT/P is not regulated solely under section 361 of the PHS Act because it fails to meet one or more of the criteria in 21 CFR 1271.10 and is regulated as a drug, device, and/or biological product. See also 21 CFR 1271.20.

<sup>8</sup> For the purposes of part 4, 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. We note that biological products and combination products that include biological product constituent parts must comply with all applicable requirements in parts 600 through 680. Because many of the requirements in parts 600 through 680 are not considered CGMP requirements, such requirements are not covered by the final rule and are not a focus of this guidance.

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Specifically, the streamlined approach under 21 CFR 4.4(b) provides that combination product manufacturers may meet the requirements of both the drug CGMPs and device QS regulation by designing and implementing a CGMP operating system that is demonstrated to comply with either of the following:

- The drug CGMPs and the following provisions from the QS regulation in accordance with 21 CFR 4.4(b)(1) (considered a drug CGMP-based streamlining approach):

(i) 21 CFR 820.20.	Management responsibility
(ii) 21 CFR 820.30.	Design controls
(iii) 21 CFR 820.50.	Purchasing controls
(iv) 21 CFR 820.100.	Corrective and preventive action
(v) 21 CFR 820.170.	Installation
(vi) 21 CFR 820.200.	Servicing

*OR*

- The QS regulation and the following provisions from the drug CGMPs in accordance with 21 CFR 4.4(b)(2) (considered a QS regulation-based streamlining approach):

(i) 21 CFR 211.84.	Testing and approval or rejection of components, drug product containers, and closures
(ii) 21 CFR 211.103.	Calculation of yield
(iii) 21 CFR 211.132.	Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
(iv) 21 CFR 211.137.	Expiration dating
(v) 21 CFR 211.165.	Testing and release for distribution
(vi) 21 CFR 211.166.	Stability testing
(vii) 21 CFR 211.167.	Special testing requirements
(viii) 21 CFR 211.170.	Reserve samples

21 CFR 4.4(c) provides that if a facility manufactures only a constituent part of a co-packaged or single-entity combination product, that facility is subject only to the CGMP regulations applicable to that constituent part (e.g., 21 CFR part 211 for a drug or 21 CFR part 820 for a device). 21 CFR 4.4(d) provides that 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 occurring at the same facility, that facility must comply with all CGMP requirements described in 21 CFR part 4 applicable to the manufacturing activities at that facility, and a streamlined approach under 21 CFR 4.4(b) may be used to demonstrate compliance with these requirements.

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As described above, facilities subject to section 4.4(d) may opt to implement a streamlined approach under 21 CFR 4.4(b) by either adopting a drug CGMP-based or QS regulation-based streamlining approach. A manufacturer may prefer one approach over the other based, for example, on the details of the manufacturing process used at the facility or in light of other manufacturing activities undertaken at the facility. Regardless, manufacturers should consider how to manage internal documentation to demonstrate compliance with all applicable CGMP requirements.

The agency intends to apply the same policies when inspecting combination product manufacturers regardless of whether the manufacturer chooses to adopt a streamlined approach or to implement both the drug CGMPs and the device QS regulation in their entirety. To facilitate efficient inspection, the agency recommends that manufacturers who choose to operate under a streamlined approach clearly identify in their premarket submissions and at the initiation of an inspection whether they are operating under the drug CGMP-based or QS regulation-based streamlining approach. Manufacturers using either a streamlined approach or opting to implement all applicable CGMP requirements should be able to identify and readily access for FDA inspection all documentation needed to demonstrate compliance with 21 CFR part 4.

### **C. The role of the lead center and other agency components**

A combination product is assigned to an agency center that will have primary jurisdiction (i.e., the lead) for that combination product's premarket review and regulation. Under section 503(g)(1) of the FD&C Act, assignment of a combination product to a center with primary jurisdiction is based on a determination of which constituent part provides the primary mode of action (PMOA) of the combination product.<sup>9</sup>

If the PMOA of a device-biological product combination product is attributable to the biological product, for example, the agency component responsible for premarket review of that biological product would have primary jurisdiction for the regulation of the combination product. The lead center for premarket review of the combination product also has the lead for ensuring compliance with CGMP regulatory requirements. Regardless of the PMOA, agency components will coordinate as appropriate to enable efficient, effective CGMP regulatory oversight, including appropriate CGMP inspections.

It is important to note that if a manufacturer adopts a streamlined approach, the manufacturer is not required to choose the CGMP regulations associated with the constituent part that provides the PMOA of the combination product as the base system. For example, if the drug constituent part of a drug-device combination product provides the product's PMOA, the manufacturer of that combination product may choose to adopt the QS regulation-based streamlining approach.

For a combination product, the lead center is a manufacturer's primary point of contact. Manufacturers may also contact the Office of Combination Products (OCP) for assistance as needed,

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<sup>9</sup> The "primary mode of action" of a combination product is the single mode of action (drug, device, or biological product) that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. See 21 CFR 3.2(k) and (m).

to identify appropriate contact points, help resolve substantive issues, or otherwise facilitate interactions with the agency for combination products.

### **III. General Considerations for CGMP Compliance**

As described above and in the final rule, a combination product must comply with all applicable CGMP regulations. This section addresses some general considerations for CGMP compliance for combination products.

#### **A. Demonstrating compliance**

As discussed in section II above, the final rule offers two ways for co-packaged and single-entity combination product manufacturers to demonstrate compliance with applicable CGMP requirements. As noted in the preamble to the final rule, the term “demonstrate” is not intended to have a new meaning for purposes of part 4. The agency intends for it to be interpreted in the same manner as it would be for purposes of the CGMP regulations listed in 21 CFR 4.3. Manufacturers must demonstrate that each applicable CGMP requirement is complied with for constituent parts and the combination product, if appropriate.<sup>10</sup>

If a streamlined approach is used, the manufacturer must demonstrate compliance with all of the relevant provisions of either the drug CGMPs or QS regulation, and the provisions specified in 21 CFR 4.4(b) for the other set(s) of CGMP requirements applicable to its product. Further guidance on how to demonstrate compliance with the other constituent part’s regulations specified in 21 CFR 4.4(b) is provided in section IV of this guidance. As that discussion explains, some of these specified provisions address issues focusing on one type of constituent part (e.g., reserve sampling). Others address issues that may concern multiple constituent parts or the combination product as a whole (e.g., design controls or corrective and preventive action (CAPA)).

This guidance does not focus on how to demonstrate compliance with the provisions of the drug CGMPs and device QS regulation that are not specified in 21 CFR 4.4(b)). Such provisions address a variety of manufacturing considerations regarding, for example, in-process materials, facility and equipment, record-keeping, labeling, personnel, inputs, testing, and distribution.

#### **B. Investigational products**

Part 4 does not alter the scope of the underlying CGMP regulations for drugs, devices, biological products, and HCT/Ps. In particular, part 4 does not alter the applicability of these CGMP regulations to investigational products.

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 generally exempt from

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<sup>10</sup> 21 CFR part 4.

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compliance with the regulations in 21 CFR parts 210 and 211<sup>11</sup> and, therefore, so is an investigational combination product that includes a drug constituent part for use in a phase 1 study. This exemption does not apply to an investigational combination product or drug constituent part, however, once it has been made available for use by or for the sponsor in phase 2 or phase 3 studies, nor does the exemption apply to a drug product that has been lawfully marketed.

Under 21 CFR 812.1, investigational devices are exempt from part 820 except for design control requirements under 21 CFR 820.30.<sup>12</sup> This exemption also applies to investigational combination products that include an investigational device constituent part.

The agency considers these exemptions from requirements under parts 211 and 820 applicable to combination products and constituent parts of combination products, whether being studied under an investigational device exemption (IDE) or an investigational new drug application (IND). Even when these regulatory CGMP exemptions apply, however, methods, facilities, and manufacturing controls that are appropriate for the investigational products should be used. When applying appropriate manufacturing practices, the agency recommends that the hazards and associated risks from the manufacturing environment that might adversely affect an investigational combination product be considered.

For further information on CGMP for investigational products, see 21 CFR 210.2(c), 21 CFR 820.1, and 61 FR 52,616-52,617, and the Guidance for Industry on *CGMP for Phase I Investigational Drugs* (July 2008).

### **C. 4.2 Definitions**

Unless part 4 expressly states otherwise, terms used have the same meaning as when used in the underlying, referenced regulations. This section addresses the meaning and significance for combination products of the terms “manufacture” and “manufacturer,” “constituent part,” “component,” “device,” and drug “container” and “closure.” It also addresses the meaning of “convenience kit” as a type of combination product.

#### ***1. “Manufacture” and “manufacturer”***

The definition of the term “manufacture” in 21 CFR 4 is intended to include all of the activities considered within the scope of manufacturing for drugs, devices, biological products, and HCT/Ps. Accordingly, the definition of “manufacture” in 21 CFR 4.2 includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage. Therefore, an entity that undertakes any of these activities for

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<sup>11</sup> See 21 CFR 210.2(c).

<sup>12</sup> The preamble to the QS regulation (61 FR 52602) provides additional detail on when design controls apply for products early in the design life-cycle: “The design control requirements are not intended to apply to the development of concepts and feasibility studies. However, once it is decided that a design will be developed, a plan must be established to determine the adequacy of the design requirements and to ensure that the design that will eventually be released to production meets the approved requirements.” (61 FR 52616, Comment 62)

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a combination product is a manufacturer under 21 CFR part 4. For example, if a company designs a drug-device combination product, that activity constitutes the manufacture of that product, thus the facility at which the design work occurs is a manufacturing facility and that entity is a manufacturer, even if all other aspects of the combination product's manufacture (e.g., fabricating, labeling, or packaging) are performed by a third-party contractor.

### ***2. “Constituent part” versus “component”***

As discussed in the preamble to the final rule, the term “constituent part” is used by the agency as a succinct way to identify a drug, device, or biological product included in a combination product. Under the drug CGMPs (21 CFR 210.3), “component” is defined as “any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.” Under the QS regulation (21 CFR 820.3(c)), the term “component” is defined as “any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.”

In short, the terms “constituent part” in 21 CFR part 4 and “component” in the CGMP regulations serve different regulatory purposes. The use of the term “constituent part” in part 4 to refer to drugs, devices, and biological products included in combination products does not alter the meaning of the term “component” or alter the applicability of the regulations listed in 21 CFR 4.3 to components.

Accordingly, if a facility is solely manufacturing an article that would be considered a device component (not a finished device) and is not otherwise subject to the QS regulation (see 21 CFR 820.1(a)), it is not subject to the QS regulation for the manufacture of that component solely because of 21 CFR part 4.

### ***3. Drug containers and closures versus delivery devices***

The agency draws a distinction between drug containers and closures and delivery devices. The essential distinction is whether the article is designed to deliver the drug it contains or merely to hold it.

If the article merely holds the drug, it is only subject to drug CGMPs as a container or closure. A container closure system is the sum of packaging components that together contain and protect the drug product. This includes primary and secondary packaging components if the latter are intended to provide additional protection to the drug product.<sup>13</sup> A packaging system may be considered a container closure system. A packaging component is any single part of a container closure system. Examples of packaging components are containers, ampules, vials, screw caps, stoppers, and stopper overseals.

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<sup>13</sup> See the Guidance for Industry on *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (May 1999).

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An article that does not merely hold or contain the drug, but also delivers it, is not merely a container or closure and may also be subject to the QS regulation. A piston syringe, for example, is not only a container or closure. A piston syringe is a device used to deliver another medical product, as described in 21 CFR 880.5860, and is subject to the QS regulation. Accordingly, a syringe filled with a drug, for example, is a combination product and must demonstrate compliance with both the drug CGMPs and QS regulation.

There are other delivery devices, such as simple liquid medication dispensing devices regulated under 21 CFR 880.6430, that are Class I devices exempt from the QS regulation except for the requirements of 21 CFR 820.180 (general requirements for records) and 21 CFR 820.198 (complaint files), neither of which is a specified provision under 21 CFR 4.4(b)(1). If such a liquid medication dispenser is co-packaged with a drug as a “convenience kit” (see III.C.4 below), generally speaking no additional CGMP requirements would apply to that dispenser or to the combination product under part 820 simply because that dispenser is included in the kit. Note, however, that a device constituent part incorporated into a drug container raises additional considerations. For example, when establishing batch testing and release and product stability testing criteria under 21 CFR 211.165 and 211.166, a dropper incorporated into a drug container’s cap would need to be addressed as part of the drug container because it would come into contact with the drug product. Similarly, when such a dropper is used in conjunction with the drug, the dropper may need to meet certain specifications for dosing of the specific drug product or for maintaining its integrity while in contact with the drug product, for example. As a result, design controls specific to the use of the dropper and its contact with the drug product may be needed and apply under 21 CFR 820.30.

### ***4. Convenience kits***

As explained in the preamble to the final rule, a kit that includes two or more types of medical products (e.g., a device and a drug) is a co-packaged combination product and, therefore, the manufacture of the kit is subject to part 4. The CGMP requirements applicable to a kit manufacturer depend on what products are included in the kit. The preamble to the final rule also states that if the kit includes only 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 required for independent marketing, it is a “convenience kit,” and the only manufacturing steps for the combination product would be the assembly, packaging, labeling, any sterilization, or further processing of the kit itself. Accordingly, the kit manufacturer would only have to demonstrate compliance with CGMP requirements with respect to those manufacturing activities. However, if a kit includes any products that are repackaged, relabeled, or otherwise modified for purposes of their inclusion in the kit, these activities for the constituent parts would be additional aspects of the manufacture of the combination product, thus the kit manufacturer would also have to demonstrate compliance with CGMP requirements with respect to these manufacturing steps.<sup>14</sup>

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<sup>14</sup> Co-packaged combination product manufacturers, including manufacturers of kits, should carefully consider the impact of any sterilization process on the items in the co-package. For example, a constituent part may be sensitive to further processing, as may be the case for surgical sutures. Similarly, some sterilization methods suitable for devices, such as irradiation, are not suitable for many drugs. Also, additional verification to confirm no degradation

## **D. What CGMP requirements apply to a product or facility?**

While combination product manufacturers must demonstrate compliance with all of the CGMP regulations applicable to their combination product under 21 CFR 4.3, as discussed above, they may demonstrate compliance with the drug CGMPs and device QS regulation requirements through one of the streamlined approaches under 21 CFR 4.4(b). Further, not all the provisions of the CGMP regulations listed in 21 CFR 4.3 may be applicable to a specific combination product or constituent part.

### ***1. Are all CGMP regulations applicable to a product?***

The preamble to the proposed rule addressed which CGMP requirements apply to which combination products (see 74 FR at 48426), noting, for example, that only an over-the-counter (OTC) combination product must comply with the tamper-evident packaging requirements in the drug CGMPs and only combination products that include a type of device constituent part that is installed or serviced must comply with installation and servicing requirements in the QS regulation. The preamble to the final rule addressed similar considerations for combination products that include a biological product constituent part, explaining that many of the requirements for biological products 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. In addition, a vaccine manufactured using a spore-forming microorganism would be subject to 21 CFR 600.11(e)(3).

Similarly, not all CGMP requirements may apply at a facility that performs only certain aspects of the manufacture of a combination product. As 21 CFR 210.2(b) and 820.1(a)(1) describe, 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. For example, a facility that manufactures a co-packaged combination product that includes a finished, packaged drug manufactured under the drug CGMPs and received from another facility need not calculate yield for that drug constituent part.

### ***2. What is the meaning of “where appropriate” in the CGMP, QS, and CGTP regulations?***

Firms must demonstrate compliance with all regulations applicable to their product or facility under part 4. However, the drug CGMPs, QS regulation, and CGTPs for HCT/Ps use the term “where appropriate” and similar language to acknowledge that certain measures may not be necessary under certain circumstances. Such language indicates that firms have the opportunity

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in safety and effectiveness after any re-sterilization may be necessary. Furthermore additional sterilization issues may need to be considered, including complete validation of the sterilization process to insure sterility for each constituent part within the kit, and evaluation of the impact of the sterilization process on the constituent parts. See, for example, the Guidance for Industry on *Sterilized Convenience Kits for Clinical and Surgical Use* (January 2002).

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to document justifications for determining that such a measure or approach is not appropriate for a particular product or the specific manufacturing activity they are undertaking.<sup>15</sup>

For instance, 21 CFR 820.30(i) stipulates that each manufacturer establishes<sup>16</sup> and maintains procedures for the identification, documentation, validation, or—where appropriate—verification, review, and approval of design changes before their implementation. Design changes may include both modifications to the product itself and changes to the process used to manufacture the product. Changes to the design, such as changes to properties of the material or dimensional specifications that can be verified through appropriate measurement and test methods, may not need to be validated. However, changes that could impact user needs, such as changes to the user interface, may require validation.

Also, in some cases not expressly identified in the final rule, CGMP requirements in different regulations may be similar, and actions sufficient to demonstrate compliance with one may be sufficient to demonstrate compliance in whole or in part with the other. For example, 21 CFR 211.192 and associated provisions of part 211 require thorough investigation of any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, and then taking appropriate action to address any such discrepancy or failure. Similarly, 21 CFR 820.100 in the QS regulation requires each manufacturer to establish and maintain procedures for implementing corrective and preventive action, including investigating the cause of nonconformities relating to the product, processes, or quality system.

### ***3. What CGMP responsibilities apply to specific manufacturers and facilities, and how should CGMP compliance be coordinated across facilities?***

The combination product sponsor<sup>17</sup> is responsible for ensuring that the manufacturing activities for its product occurring at all facilities, including facilities operated by third parties, are in compliance with CGMP requirements. Each of these manufacturing facilities must be in full compliance with the CGMP requirements applicable to each manufacturing process that occurs at that specific facility.

A facility that manufactures only a finished device intended to be a constituent part of a combination product (i.e., does not engage in any other manufacturing of the combination product) must comply only with the QS regulation. Similarly, a facility that manufactures only a drug intended to be a constituent part of a combination product (i.e., does not engage in any other manufacturing of the combination product), must comply only with the drug CGMPs. Even if a facility is manufacturing only one type of constituent part for a combination product, the CGMP

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<sup>15</sup> Under both 21 CFR 820.1(a)(3) and 1271.150(e), a requirement that is qualified by “where appropriate,” is “appropriate” if, for example, non-implementation of the requirement could reasonably be expected to result in the product not meeting its specified requirements. In the case of an HCT/P, these may be requirements related to prevention of introduction, transmission, or spread of communicable diseases, or a manufacturer’s inability to carry out any necessary corrective action. Under both provisions, a requirement is deemed to be appropriate unless the manufacturer can document justification that it is not.

<sup>16</sup> Per 21 CFR 820.3(k), “*Establish* means define, document (in writing or electronically), and implement.”

<sup>17</sup> For purposes of this guidance, “sponsor” means the entity that holds the marketing authorization for a co-packaged or single entity combination product.

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operating system should take into consideration the combination product as a whole, as appropriate. For example, the design controls for a device constituent part may include inputs to address design characteristics to ensure that the combination product as a whole meets specified requirements.

Some CGMP requirements may concern the combination product as a whole, such as design controls, and some may concern overarching responsibilities for the quality system as a whole, such as CAPA requirements. Take, for example, a manufacturing facility collecting nonconformance data that are trended as an input to the CAPA system for a combination product. If a problem is detected that requires a product or process design change, the expertise to develop and implement the change may reside at a different facility. To address such circumstances, a sponsor may have a CAPA system that is shared between facilities, or facility-specific CAPA systems with established links between them to handle issues requiring multi-facility collaboration.

Manufacturing activities that occur at multiple facilities and associated CGMP operating systems should be coordinated appropriately. Each manufacturing facility for a combination product should have documentation specifying its respective responsibilities, and the manufacturer of the finished combination product should have access to this documentation. For example, if a combination product manufacturer uses a specification developer to design the finished product, the manufacturer of the combination product should have the design control records or have access to them if they are held by the specification developer. In addition, the manufacturer should have assurances that the specification developer maintained an adequate design control system. To give another example, if product testing occurs at a contract testing facility, the manufacturer of the combination product should have documentation of the testing conducted and controls applied at the contract facility or have access to the documentation if held at the contract facility. Accordingly, manufacturers should address access to such records among other issues as part of supplier evaluation and oversight.

Measures the sponsor might take to ensure CGMP compliance at all manufacturing facilities for the combination product include auditing and other oversight activities. For example, when multiple facilities participate in the manufacturing process, the sponsor may facilitate CGMP compliance by coordinating interactions among the facilities. A sponsor can enter into comprehensive quality agreements with the various facilities and suppliers involved and coordinate development of such agreements among these entities. These quality agreements may, for instance, specify expectations as to which facility will perform what activities and develop and maintain what documentation needed to demonstrate compliance with which CGMP requirements (based, for example, on which aspects of manufacture each facility conducts). These agreements may also detail what measures a facility will take to ensure compliance with CGMP requirements and any other relevant duties established by the sponsor for that facility.

## **E. Control of changes to a combination product**

As discussed in the preamble to the final rule, while not an issue unique to combination products, coordination of changes among manufacturers participating in the manufacture of a combination product is an important CGMP issue. The manufacturer of a co-packaged or single-entity combination product should ensure appropriate consideration of any implications for the safety or effectiveness of its combination product that might arise from changes to it, including to any constituent part of it. Therefore, the manufacturer should establish arrangements with its suppliers to receive notice of changes. The manufacturer should also establish procedures for acceptance of components, containers/closures, and constituent parts to ensure both detection and evaluation of any changes that are critical to the safety and effectiveness of the combination product prior to incorporating them into the finished combination product.

Similarly, if one entity manufactures one constituent part of a cross-labeled combination product and another entity manufactures the other constituent part, both should have procedures in place to inform one another of changes that may affect the safety or effectiveness of the combination product, and to confirm that the specifications for the respective constituent parts remain appropriate or are updated as needed to ensure that the combination product remains safe and effective. For example, a change to the drug constituent part of a cross-labeled combination product might require a design change to the device constituent part for the combination product to remain safe and effective. Accordingly, awareness and assessment of drug changes to determine whether they require, in this example, a change to the device constituent part(s) may be important to compliance with design control requirements for the device under 21 CFR 820.30. Similarly, a change to a device constituent part of a cross-labeled combination product may necessitate a change to a drug constituent part that would then need to be reflected in the chemistry, manufacturing, and controls specifications and testing procedures for the drug.

## **IV. What do I need to know about the CGMP requirements specified in 21 CFR 4.4(b)?**

### **A. Provisions from the QS regulation specified in 21 CFR 4.4(b)(1)**

This section provides summary descriptions of the provisions from the QS regulation with which manufacturers must demonstrate compliance when using the drug CGMP-based streamlining approach established under section 4.4(b)(1). This discussion is not meant to provide a comprehensive analysis, but rather to help manufacturers—particularly drug and biological product manufacturers who may be less familiar with the QS regulation—understand the purpose and basic content of the specified QS regulation provisions. This section also includes references to some additional guidance documents that may be helpful.<sup>18</sup> Section V

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<sup>18</sup> This section does not address 21 CFR 4.4(b)(1)(v) and (vi), which require manufacturers to demonstrate compliance with installation and servicing requirements under 21 CFR 820.170 and 820.200, respectively. These requirements are included in section 4.4(b)(1) to ensure manufacturers comply with them when applicable to a single-entity or co-packaged combination product. However, the agency anticipates that installed and serviced

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presents hypothetical examples offering additional guidance on how to address these provisions for a combination product.

### ***1. Management responsibility (21 CFR 820.20)***

Statutory CGMP provisions, as well as the drug CGMP regulations, establish requirements relating to management responsibility.<sup>19</sup> While there are specific requirements in 21 CFR 820.20 that are not explicitly addressed in 21 CFR part 211, section 501(a)(2)(B) of the FD&C Act requires oversight and controls to ensure product quality, including to manage risks and establish the safety of raw materials, in-process materials, and the finished drug product. In addition, guidance documents for drug manufacturers describe how to use quality systems to comply with drug CGMPs.<sup>20</sup> A manufacturer of a combination product that includes a device constituent part must ensure that the elements required under 21 CFR 820.20 are satisfied.

For example, among other requirements, a manufacturer must establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality; provide adequate resources for management, performance of work, and assessment activities; and appoint a management member who is responsible for ensuring that quality system requirements are effectively established and maintained, and for reporting on the performance of the quality system to management with executive responsibility.<sup>21</sup> A manufacturer must establish and maintain an adequate organizational structure to ensure that the product is designed and produced in conformance with CGMP requirements.<sup>22</sup> The technical, administrative, and human resources functions affecting the quality of the product should be controlled, whether these functions involve hardware, software, equipment, processed materials, product components, or services. All such controls should be designed to reduce, eliminate, or, ideally, prevent quality nonconformities.

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devices will rarely be constituent parts of such combination products. They are more likely to be separately manufactured and marketed constituent parts of cross-labeled combination products. In such cases, as discussed at 78 FR 4308, each such constituent part would be subject to the CGMP requirements associated with that product. Accordingly, the device constituent part of such a cross-labeled combination product would be subject to installation and servicing requirements.

<sup>19</sup> See, for example, 21 USC 351 (establishing that “current good manufacturing practice” includes management oversight of manufacturing and control to ensure quality and lifecycle risk management); 21 CFR 211.22, 211.25, and 211.180; the Guidance for Industry on *Q10 Pharmaceutical Quality System* (April 2009); and the Guidance for Industry on *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006).

<sup>20</sup> See the Guidances for Industry on *Q10 Pharmaceutical Quality System* and *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

<sup>21</sup> “Management with executive responsibility is that level of management that has the authority to establish and make changes to the company quality policy. The establishment of quality objectives, the translation of such objectives into actual methods and procedures, and the implementation of the quality system may be delegated. The regulation does not prohibit the delegation. However, it is the responsibility of the highest level of management to establish the quality policy and to ensure that it is followed ... It is without question management’s responsibility to undertake appropriate actions to ensure that employees understand management’s policies and objectives. Understanding is a learning process achieved through training and reinforcement. Management reinforces understanding of policies and objectives by demonstrating a commitment to the quality system visibly and actively on a continuous basis. Such commitment can be demonstrated by providing adequate resources and training to support quality system development and implementation.” (61 FR. 52602 at 52612)

<sup>22</sup> See 21 CFR 820.20(b).

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21 CFR 820.20 requires that a manufacturer establish and maintain management responsibility for product quality. Management with executive responsibility must establish its policy and objectives for and commitment to quality, pursuant to 21 CFR 820.20(a). Manufacturers are also responsible for establishing a quality plan and quality system procedures in accordance with 21 CFR 820.20(d) and (e). The quality plan must define the quality practices, resources, and activities relevant to the combination product that is being designed and manufactured and must establish how the quality requirements will be met. The plan can either be an independent document, or it can reference elements of the manufacturer's quality system.

The quality system procedures should ensure compliance with each aspect of the CGMPs applicable to the combination product. Accordingly, under a drug CGMP-based streamlining approach, these procedures and instructions should address the drug CGMPs and those provisions from the QS regulation identified in 21 CFR 4.4(b)(1). The number, complexity, and structure of the manufacturer's procedures and instructions may vary depending on factors such as the size of the manufacturer, organizational structure, and type of combination product being manufactured. Drug manufacturers may already have some of these procedures in place as part of the requirements for a quality control unit under 21 CFR 211.22 and can reference these procedures and augment them as needed to meet the requirements of 21 CFR 820.20.

Management with executive responsibility must review the suitability and effectiveness of the quality system, in accordance with 21 CFR 820.20(c), including to ensure that the quality system satisfies the established quality policy and objectives. These reviews must be conducted at defined intervals and with sufficient frequency.

## ***2. Design controls (21 CFR 820.30)***

The preamble to the proposed rule discusses design control requirements for combination products at some length.<sup>23</sup> As specified in the final rule, design controls apply to any combination product that includes a device constituent part. Guidance for industry on pharmaceutical development addresses product design and development procedures, reflecting "quality by design" principles.<sup>24</sup> The QS regulation includes requirements for design development with which compliance must be demonstrated (21 CFR 820.30(b)). The following is a description of design control requirements and the documentation that must be maintained for co-packaged and single-entity combination products.<sup>25</sup>

Design control procedures apply to activities undertaken during product development and premarket assessment, as well as to postmarket changes to the design or manufacturing process. Accordingly, in some cases, the activities described below may be conducted as part of

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<sup>23</sup> See 78 FR 4314-4315.

<sup>24</sup> See the Guidance for Industry on *Q8(R2) Pharmaceutical Development* (November 2009).

<sup>25</sup> While outside the scope of 21 CFR 4.4(b)(1), it bears noting that the design control process and design history file for the device constituent parts of cross-labeled combination products should address the suitability of the device for use as part of the combination product, including the interactions and interrelationships between it and other constituent parts of the combination product.

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premarket development and the marketing authorization process. As noted above, regardless of when the activity occurs or where related records may reside, the CGMP operating system should include appropriate documentation or reference it, to ensure readily available access to this documentation for FDA inspection.<sup>26</sup>

Design input requirements for the combination product should include considerations such as performance characteristics, safety and reliability requirements, and expected product users. Once the design inputs have been established, the design outputs (e.g., specifications and engineering drawings) must be developed based on those inputs.<sup>27</sup> Once design outputs have been established for all design inputs, design verification and validation activities must be performed to ensure that the combination product design output meets design input requirements, including user needs and intended uses. These activities must be documented in the design history file<sup>28</sup> and must be subjected to design reviews.<sup>29</sup>

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.<sup>30</sup> Design verification is demonstrating that a manufacturer has designed the product it intended to; such testing confirms that the product developed is consistent with the assumptions made by the design team when developing design inputs, but does not necessarily confirm that the product is safe and effective for its intended use. Design verification activities may include, for example, performance tests, safety tests, or visual inspections.

Design validation means establishing by objective evidence that product specifications conform to user needs and intended use(s).<sup>31</sup> Design validation ensures that the product is designed correctly to achieve its intended purposes. Specifically, design validation must ensure that the product conforms to defined user needs and intended uses and includes testing of production units under actual or simulated use conditions. Design validation activities, for example, may include simulated use testing or clinical/nonclinical evaluations, including human factors testing and software validation.<sup>32</sup>

In addition, 21 CFR 820.30(g) requires that the manufacturer complete risk analysis, where appropriate, which should begin early in the design process and continue throughout the lifecycle for the product. Risk analysis influences other aspects of design control and additional activities including purchasing controls. Risk analysis should be completed on the combination product as a whole to identify risks associated with its design, manufacturing processes, and intended uses. Some risks may be identifiable during initial design development and addressed in design inputs, while others may become apparent based on postmarket experience (including

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<sup>26</sup> See 21 CFR 820.30(j), 820.180, and 211.180

<sup>27</sup> See 21 CFR 820.30(d).

<sup>28</sup> See 21 CFR 820.30(j).

<sup>29</sup> See 21 CFR 820.30(e).

<sup>30</sup> See 21 CFR 820.3(aa).

<sup>31</sup> See 21 CFR 820.3(z)(2).

<sup>32</sup> For further information about human factor considerations and testing, see FDA's Human Factors and Medical Devices web page at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm>.

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adverse event reporting) and used to determine whether any aspect of the design should be adjusted or revised. Any unacceptable risk(s) should be reduced or mitigated.

In accordance with 21 CFR 820.30(i), manufacturers are also required to have procedures to ensure that any changes to design requirements are identified, documented, validated or verified where appropriate, reviewed, and approved prior to implementation. A change control process is essential to incorporate design changes appropriately both during the original design process for the combination product and after the design has been transferred to manufacturing. The records of these changes must be maintained as part of the design history file. They create a history of the evolution of the design, which can be important when investigating failures or evaluating the appropriateness of proposed modifications or changes to the product.

The design history file for a combination product should address all design issues relating to the combined use of the constituent parts. The design history file may not need to document design and development planning for established characteristics of the individual constituent parts, such as the safety and effectiveness of a drug constituent part of a co-packaged combination product if that drug constituent part was previously approved for the same indication. If a finished device, drug, or biological product is purchased, the combination product manufacturer is not required to retrospectively “design” that constituent part with respect to such previously reviewed characteristics. Rather, the combination product manufacturer should understand the constituent part’s existing design specifications thoroughly in order to perform design controls properly for its use in the combination product.<sup>33</sup> In addition, the combination product manufacturer must comply with design control requirements for any modifications that need to be made to a constituent part for use in the combination product (e.g., new formulation of the drug or new features of a device) under 21 CFR 820.30(i).

It is appropriate to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls. For example, existing specifications may become part of the required design output documentation. Similarly, testing performed prior to distribution of the combination product may be included as documentation of design verification and validation. The combination product manufacturer is responsible for assembling available information and assessing what, if any, additional information and evidence may be needed, such as additional testing or documentation of the design control activities, to address all aspects of design control that are needed to support the manufacture of the product as currently marketed, ensure its safety and effectiveness, and support any future changes to that product. However, manufacturers do not need to prepare a development plan or conduct design review meetings for the product as currently marketed because the development stages that these activities would support have already occurred.

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<sup>33</sup> Similarly, if a combination product manufacturer is purchasing device components for inclusion in a combination product, and the device component supplier is manufacturing a finished device from the same or similar components and is therefore subject to the QS regulation, the combination product manufacturer may be able to leverage elements of that supplier’s design controls in developing the overall design controls for the combination product. If the component supplier does not manufacture a related finished device, the combination product manufacturer’s design control activities for the device constituent part will likely need to be more extensive.

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FDA encourages combination product manufacturers to direct specific questions on the adequacy of their design control measures and documentation to the lead center for their products, or OCP as needed, for assistance. For further information on design controls, see the preamble for the final QS regulation.<sup>34</sup>

### ***3. Purchasing controls (21 CFR 820.50)***

Combination product manufacturers must control purchased products<sup>35</sup> and services as described in 21 CFR 820.50. They must establish such controls for products received at their facility for use in the manufacture of the combination product, for all suppliers of these products, and for suppliers of services obtained (such as terminal sterilization conducted by an outside entity). Facilities that have previously manufactured only drugs, rather than devices or combination products, likely will have relevant procedures in place in accordance with 21 CFR part 211, subpart E, but these procedures may need to be augmented to demonstrate compliance with the specific requirements of 21 CFR 820.50.

Manufacturers must evaluate potential suppliers and define the type and extent of control to be exercised over them based on the evaluation results.<sup>36</sup> They may conduct such evaluations based on factors such as the risks associated with the supplied product or service and complexity of the specifications for it. They must establish and maintain records of acceptable suppliers for purchased products and services, pursuant to 21 CFR 820.50(a)(3), and establish and maintain data that clearly describe or reference the specified requirements for received products (e.g., contracts with relevant terms) pursuant to 21 CFR 820.50(b).

One mechanism by which to facilitate purchasing control is the careful structuring of purchasing agreements with suppliers. Where possible, such agreements must be used to ensure that the manufacturer is notified of changes to the products or services being provided.<sup>37</sup> Such notice of changes facilitates compliance not only with purchasing control duties, but potentially other regulatory requirements as well, including design control obligations to complete additional design verification testing (e.g., to ensure that the purity and stability of a drug constituent part is maintained). If it is not possible to obtain such notice, the combination product manufacturer should implement additional controls to ensure that changes are identified and appropriate measures are taken.<sup>38</sup>

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<sup>34</sup> See Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation, 61 FR 52602-52662 (October 7, 1996).

<sup>35</sup> Under 21 CFR 820.3(r), The term “product” includes components and manufacturing materials, in addition to in-process and finished articles.

<sup>36</sup> See 21 CFR 820.50(a)(2).

<sup>37</sup> See 21 CFR 820.50(b).

<sup>38</sup> While beyond the scope of this guidance, it bears noting that product sponsors may be obligated to notify the agency of changes or seek agency approval prior to making them, depending upon the nature of the change. See, for example, 21 CFR 314.70, 601.12, and 814.39. Accordingly, controlling changes to the materials included in the combination product and the processes and facilities used for their manufacture can be important to ensure compliance with other regulatory duties (in addition to CGMP requirements).

#### **4. Corrective and Preventive Actions (21 CFR 820.100)**

Sponsors for co-packaged or single-entity combination products that have a device constituent part must establish and maintain procedures for implementing CAPA, in accordance with 21 CFR 820.100. Relevant requirements in the drug CGMPs include 21 CFR 211.192 and 21 CFR 211.180(e).

The sponsor should ensure that an appropriately comprehensive review of activities is undertaken at whatever facilities may be relevant to determine the cause of existing or potential problems, which could include manufacturing problems, deviations, or nonconformities for the combination product. The sponsor must identify the action(s) needed to correct and prevent recurrence, then implement such changes. The sponsor should take appropriate measures, which may include CAPAs, with regard to all relevant manufacturing steps at all relevant facilities so that the problem is corrected and problems will be prevented or mitigated going forward. Manufacturers of the combination product must undertake CAPA measures, when required, for issues arising at their facilities. All relevant manufacturers should participate in cross-facility efforts, as appropriate, to determine the cause of problems and the appropriate measures to correct and prevent such problems, as well as document these activities.<sup>39</sup>

#### **B. Provisions from the drug CGMPs specified in 21 CFR 4.4(b)(2)**

This section provides a brief description of the provisions from the drug CGMPs with which manufacturers must demonstrate compliance when using the QS regulation-based streamlining approach established under 21 CFR 4.4(b)(2). This discussion is not meant to be a comprehensive analysis, but rather to help manufacturers—particularly device manufacturers, who may be less familiar with the drug CGMPs—understand the purpose and basic content of the specified provisions of the drug CGMPs, as well as where to find additional guidance.

The specified provisions of the drug CGMPs include requirements for testing and other verification procedures for batches or lots, whether of drug components, drug containers and closures, drug constituent parts, or the whole combination product. As discussed in the preamble to the final rule, combination product manufacturers should establish procedures defining a “batch” or “lot” in all phases of production and describe all batch and lot numbering systems used for incoming material, in-process material, and finished products. These procedures allow manufacturers to connect specific lots or batches of constituent parts, components, and in-process material to the specific batches or lots of the combination product for which they are used. These procedures also enable traceability of sampling and testing, packaging, and labeling activities. Master production and control records should be designed to enable this traceability. An explanation of batch and lot definitions, controls, and tracking should be available for review on inspection.

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<sup>39</sup> For further guidance, see the preamble to the QS regulation at 61 Fed. Reg. at 52633-52635, Comments 158-166, and the Guidances for Industry on *Q10 Pharmaceutical Quality System* and *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

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### **1. Testing and approval or rejection of drug product components, containers, and closures (21 CFR 211.84)**

Drug product components, containers, and closures must be tested in accordance with 21 CFR 211.84. A drug component is any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the drug product.<sup>40</sup> As explained in section III.C.3, a container closure system is the sum of packaging components that together contain and protect the drug product. Combination product manufacturers would not need to demonstrate compliance with this provision for device constituent parts or materials used in the manufacture of a device constituent part, except if the device constituent part or component thereof is also a drug component or constitutes the drug container or closure or a part thereof. For CGMP operating systems established in accordance with 21 CFR 4.4(b)(2) (QS regulation-based streamlining approach), if materials are used solely for manufacture of a device constituent part that is not part of the drug container or closure (e.g., a co-packaged device), the manufacturer need only demonstrate compliance with applicable provisions of 21 CFR part 820 to show appropriate control of such materials for that device constituent part (including 21 CFR 820.30, 820.50, 820.80, and 820.86).

21 CFR 211.84 details how to sample, test, examine, and accept or reject drug product components, containers, and closures from other facilities, including other facilities owned or controlled by the manufacturer. In lieu of such testing, 21 CFR 211.84 allows for some reliance on a supplier's written analysis, provided that certain identity testing is conducted and that the reliability of the supplier's analysis is established by the manufacturer through appropriate validation of the testing results at appropriate intervals. These duties augment and elaborate upon acceptance activities requirements expressly established under 21 CFR 820.80. Accordingly, if a facility already has 820.80-based acceptance procedures, it would be appropriate to provide for compliance with 21 CFR 211.84 requirements by augmenting these existing procedures as needed to incorporate 21 CFR 211.84 compliance measures.

Each lot of drug components, containers, and closures must be withheld from use until it has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.<sup>41</sup> The samples collected for each lot must be representative of the entire lot.<sup>42</sup> These representative samples must be collected and tested or examined in accordance with the procedures specified in 21 CFR 211.84. These procedures require, among other things, appropriate sampling technique to prevent the introduction of contaminants into the sampled component and contamination across multiple sampled components.<sup>43</sup> In addition, the number of containers to sample and the amount of material to be taken from each container must be based on appropriate criteria (e.g., component variability, confidence levels, degree of precision desired, past quality history of the supplier, and the quantity needed for analysis).<sup>44</sup>

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<sup>40</sup> See 21 CFR 210.3(b)(3).

<sup>41</sup> See 21 CFR 211.84(a).

<sup>42</sup> See 21 CFR 211.84(b).

<sup>43</sup> See 21 CFR 211.84(c).

<sup>44</sup> See 21 CFR 211.84(b).

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Some references that may be useful for sampling by variables and sampling by attributes include “ASTM Standard E2709, Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure” and “ASTM Standard E2334, Standard Practice for Setting an Upper Confidence Bound For a Fraction or Number of Non-conforming Items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When there is a Zero Response in the Sample,” respectively.

### ***2. Calculation of Yield (21 CFR 211.103)***

Actual yields and percentages of theoretical yield for the drug constituent part(s) of a combination product must be determined as described in 21 CFR 211.103. Excess or low yields suggest errors in the production process. All discrepancies in yield should be investigated.

Yield determinations must be made at the conclusion of each appropriate phase of manufacturing, processing, packaging, and holding for the drug constituent part(s) and for the combination product as a whole.<sup>45</sup> Accordingly, calculation of yield should be determined at each phase at which component, in-process material, or product loss may occur, during the formulation of the drug prior to incorporation into the combination product, during incorporation (e.g., filling or coating), and during the packaging process. These calculations must be performed by one person and independently verified by a second person, unless the yield is calculated by automated equipment in accordance with section 21 CFR 211.68, in which case it must be independently verified by one person.<sup>46</sup>

For each appropriate phase of the manufacturing process performed, the formula used and the data generated for the yield calculation in a manufacturing or production record should be documented. These records should include actual yields and percentages of theoretical yields for the drug product, including as it is processed and combined with the other constituent part(s) of the combination product. If a third party is manufacturing the drug for the combination product, that manufacturer is responsible for complying with the calculation of yield requirement at the appropriate phases of the drug manufacturing process it performs, but the combination product manufacturer is responsible for ensuring that the supplier satisfies these requirements as a part of the purchasing controls for its combination product in accordance with 21 CFR 820.50.

### ***3. Tamper-evident packaging requirements for over-the-counter human drug products (21 CFR 211.132)***

Manufacturers of OTC combination products must comply with the requirements of 21 CFR 211.132. The required controls include tamper-evident packaging and labeling alerting customers to these protective features of the product’s packaging. These controls are important to help improve the security of OTC combination product packaging and help ensure the safety and effectiveness of OTC combination products.

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<sup>45</sup> See 21 CFR 211.103.

<sup>46</sup> See 21 CFR 211.103.

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For single-entity combination products, tamper-evident packaging requirements apply to the packaging for the combination product as a whole. For co-packaged combination products, these requirements can be met through appropriate packaging of the drug constituent part(s) within the larger co-package so long as such an approach is otherwise permissible under the packaging and labeling requirements applicable to that combination product.

An exemption from tamper-evident packaging and labeling requirements for an OTC combination product, may be requested in accordance with 21 CFR 211.132(d). If the manufacturer makes changes to packaging and labeling of an approved OTC product to comply with the requirements of 21 CFR 211.132, it must notify the lead center for the combination product before distributing it.<sup>47</sup>

### ***4. Expiration dating (21 CFR 211.137)***

Section 211.137 helps assure that drug products (drug constituent parts in the case of combination products) meet applicable standards of identity, strength, quality, and purity at the time of use by requiring that the product labeling bear an expiration date. This date must take into account any storage conditions stated in the labeling and be based on appropriate stability testing as described in 21 CFR 211.166.<sup>48</sup>

The expiration dating for a combination product also should take into account any other applicable shelf-life considerations (e.g., for a product that is to be provided sterile, the length of time that its packaging material can be assured to retain its integrity and, thereby, maintain a sterile barrier). The expiration date for a combination product may be shorter than the expiration date or shelf life for its drug constituent part(s) if marketed independently. Reasons for a shorter expiration period could include interactions between the constituent parts when combined, the effects of additional manufacturing steps, or other differences arising from the combination of the constituent parts.

### ***5. Testing and release for distribution (21 CFR 211.165)***

Testing and release for distribution are critical in drug product manufacture and quality control. Section 211.165 requires that an appropriate laboratory determination of satisfactory conformance to final specifications (including the identity and strength of each active ingredient) is made for each batch of drug product prior to release. Section 211.165 also requires appropriate laboratory testing, as necessary, of each batch of a drug product required to be free of objectionable microorganisms. In addition, sampling and testing plans must be described by written procedures.<sup>49</sup>

Accordingly, manufacturers must test each batch of their combination product to determine satisfactory conformance to final written specifications for the drug constituent part.<sup>50</sup>

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<sup>47</sup> See 21 CFR 211.132(e).

<sup>48</sup> See 21 CFR 211.137(b).

<sup>49</sup> See 21 CFR 211.165(c).

<sup>50</sup> See 21 CFR 211.165(a).

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Laboratory testing must be performed on every batch of a single-entity combination product and of the drug constituent part(s) of a co-packaged combination product, to ensure that all batches meet appropriate specifications for their approval and release.<sup>51</sup> A detailed listing of all the tests performed and the acceptance criteria should be maintained and available for inspection.<sup>52</sup>

If one facility is manufacturing a drug product as a constituent part to be supplied to another facility or manufacturer for inclusion in a co-packaged combination product, appropriate and adequate laboratory testing should be conducted by the drug product manufacturing facility prior to release of the drug constituent part(s) for distribution in accordance with 21 CFR 211.165. Appropriate testing or examination (such as visual inspection) should also be conducted throughout the remaining manufacture of the finished co-packaged combination product to ensure that the drug constituent part(s) continues to conform to its final specifications.

### ***6. Stability testing (21 CFR 211.166)***

Section 211.166 requires a written testing program designed to assess the stability characteristics of drug products. Furthermore, 21 CFR 211.166 sets forth required elements of the testing program, including elements concerning sample size, storage conditions for samples retained for testing, and other elements related to testing methodology and frequency. Manufacturers are responsible for establishing and managing the stability program.

Stability testing is performed to determine appropriate storage conditions and expiration dates (see section IV.B.4). Among other considerations, this testing must enable evaluation of any effects on the stability of the drug due to storage in a container closure system, which may be a device constituent part (or component of the device constituent part).<sup>53</sup> For a single-entity combination product, testing must be performed on the drug constituent part in the finished combination product.<sup>54</sup>

If a combination product manufacturer purchases a drug product manufactured by a third-party manufacturer for inclusion in its co-packaged combination product, that third-party manufacturer is responsible for stability testing for that drug product. The combination product manufacturer is responsible for ensuring the stability of the drug product as marketed in the co-

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<sup>51</sup> See 21 CFR 211.165(a), (b).

<sup>52</sup> 21 CFR 211.165 addresses testing and release for “drug products”; appropriate controls for intermediate stages (e.g., in process materials) in the manufacture of combination products are addressed under separate provisions of the drug CGMPs and QS regulation that are not specified in 21 CFR part 4. Accordingly, if the manufacturer operates under a streamlined approach under 21 CFR 4.4(b), it should take into consideration the materials and manufacturing steps for the combination product as a whole in determining how to demonstrate compliance with obligations for in-process materials, and may find it helpful to refer to the corresponding requirements of the other regulation. For example, if the facility operates under a QS regulation-based streamlining approach, in determining how to comply with duties under 21 CFR 820.70, 820.80, and 820.86 for the combination product as a whole, reference to 21 CFR 211.110 and guidance relating to it may facilitate appropriate consideration of issues related to such materials for drug constituent parts.

<sup>53</sup> See 21 CFR 211.166(a)(4).

<sup>54</sup> See 21 CFR 4.3, 4.4, and 211.166. In addition, under the design control requirements, testing must be performed to demonstrate that the device functionality (i.e., mechanical performance of the device constituent part) is maintained until the specified expiration date. See 21 CFR 820.30.

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package through appropriate mechanisms, such as purchasing controls or conducting additional stability testing. Documentation of such oversight should be included in the CGMP records.<sup>55</sup>

### ***7. Special testing requirements (21 CFR 211.167)***

21 CFR 211.167 establishes requirements for batch testing applicable to drug products having particular characteristics. Specifically, 21 CFR 211.167(a) requires appropriate laboratory testing of drug products purporting to be sterile and/or pyrogen-free to determine conformance with such requirements; 21 CFR 211.167(b) requires appropriate testing of ophthalmic ointments to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances; and 21 CFR 211.167(c) requires appropriate laboratory testing of controlled-release dosage forms to determine conformance to the specifications for the rate of release of each active ingredient. A special testing requirement specified in 21 CFR 211.167 applies to a combination product only if the combination product or a drug constituent part of it falls into one or more of these three categories. Special testing may be required for the drug constituent part, or the combination product as a whole, depending on the product.

With respect to 21 CFR 211.167(a), batch testing requirements would apply both to the drug constituent part and to the finished combination product for a single-entity combination product (such as a prefilled syringe) to ensure the combination product is sterile and pyrogen-free when distributed. In contrast, if a vial of a vaccine were co-packaged with an empty syringe, the requirements in 21 CFR 211.167(a) would apply only to the vial of vaccine. The requirements related to sterility and non-pyrogenicity of the empty syringe would be addressed through compliance with process controls under 21 CFR part 211 and the provisions of 21 CFR part 820 specified in 21 CFR part 4 (for example, design control requirements under 21 CFR 820.30 and purchasing control requirements under 21 CFR 820.50), rather than batch testing under 21 CFR 211.167(a).<sup>56</sup> A similar analysis would apply for compliance with 21 CFR 211.167(b) for a single-entity versus a co-packaged combination product that includes an ophthalmic ointment. 21 CFR 211.167(c) would apply to a controlled release drug constituent part of a co-packaged combination product and also to a controlled release single-entity combination product, to confirm rate of release of the active ingredient. For example, a transdermal drug patch or drug-eluting disc or stent would be subject to 21 CFR 211.167(c).

### ***8. Reserve samples (21 CFR 211.170)***

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. The reserve sampling requirements of 21 CFR 211.170 must be met to ensure appropriate sampling systems for the drug constituent parts of combination products.

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<sup>55</sup> For further information on stability testing considerations, see, for example, the Guidance for Industry on *QIA(R2) Stability Testing of New Drug Substances and Products* (November 2003).

<sup>56</sup> For additional information on pyrogen and endotoxin testing, see the Guidance for Industry on *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012).

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Accordingly, as explained below, for co-packaged combination products, manufacturers should maintain samples of the drug constituent part, and for single-entity combination products, they should maintain samples that include the device constituent part or components thereof as appropriate.

Under 21 CFR 211.170, reserve samples must be kept that are representative of each lot of the active ingredient and of each lot or batch of the drug product. Furthermore, reserve samples of drug products must be retained and stored under conditions consistent with product labeling and stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics.<sup>57</sup> All reserve samples must consist of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens.<sup>58</sup> Manufacturers must examine drug product samples for deterioration, investigate evidence of deterioration, and record and maintain the results of such examination.<sup>59</sup> Drug product reserve samples generally must be maintained for 1 year after the expiration date for the drug product; different time periods apply to certain radioactive and OTC products.<sup>60</sup> Active ingredient samples generally must be kept for 1 year after the expiration date for the last lot of the combination product containing the active ingredient.<sup>61</sup> Accordingly, manufacturers should retain samples from each lot of the bulk drug substance for 1 year after the expiration date of the last lot of the combination product to use that lot of the active ingredient.

For co-packaged combination products, it is generally sufficient to maintain the appropriate number of samples from each lot of the active ingredient and from each lot of the drug product in the immediate container/closure in which it is marketed. For single-entity combination products, manufacturers also should maintain reserve samples of the active ingredient and of the drug product within its container/closure. In some cases, the container/closure may be the entire device constituent part. In others, it may be a part of the device or distinct from the device constituent part. For a drug-eluting stent or disc, or a prefilled syringe, for example, reserve samples should be kept of the entire combination product. In contrast, if, for example, the combination product consists of an injector system (device constituent part) into which the user inserts cartridges containing the drug reserve samples of the filled cartridge alone would suffice to comply with drug product sample retention duties. A complete injector system may be needed to conduct testing of the samples.

Manufacturers with questions regarding their duties under section 211.170, including what may constitute a representative sample or a sufficient number of samples to keep, may contact the lead center for their combination product, as well as OCP as needed, for assistance.

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<sup>57</sup> See 21 CFR 211.170(b).

<sup>58</sup> See 21 CFR 211.170(a) and (b).

<sup>59</sup> See 21 CFR 211.170(b).

<sup>60</sup> See 21 CFR 211.170(b). Active ingredient samples generally must be kept for 1 year after the expiration date for the last lot of the combination product containing the active ingredient. See 21 CFR 211.170(a).

<sup>61</sup> See 21 CFR 211.170(a).

## **C. Combination products that include biological products and HCT/Ps**

In addition to all other CGMP requirements applicable to the combination product under 21 CFR 4.3 and 4.4, a manufacturer of a combination product that contains a biological product or an HCT/P must comply with the requirements that would apply to the biological product or HCT/P if it were not part of a combination product.

### ***1. Complying with CGMP requirements for biological products***

It is important to remember that a biological product is also by definition a drug or a device. Accordingly, in addition to the requirements in 21 CFR parts 600 through 680, a biological product is always either subject to the drug CGMPs or the QS regulation, regardless of whether the biological product is a constituent part of a combination product. The CGMP requirements for biological products in 21 CFR parts 600 through 680 augment the drug CGMPs and QS regulation to ensure adequate consideration of issues for biological products. The CGMP requirements for biological products in 21 CFR parts 600 through 680 address the particular challenges biological products pose, including challenges arising from their relative complexity. For biological products, consistency of manufacturing procedures can, in fact, be a primary means by which to ensure the safety, purity, and potency of the product.

The CGMP requirements for biological products in 21 CFR parts 600 through 680 augment the drug and device CGMPs and must be satisfied if a combination product includes a biological product constituent part. However, as noted in the preamble to the final rule, many requirements in parts 600 through 680 are applicable only to certain types of biological products. For example, while part 600 facially addresses biological products in general, only products manufactured using a spore-forming microorganism would be subject to 21 CFR 600.11(e)(3) (Work with Spore-forming microorganisms). Similarly, only blood and blood components are subject to the CGMP requirements for such products under part 606. In addition, the CGMP requirements for biological products applicable to a given product can vary based on product-specific considerations.

In short, the specific requirements in 21 CFR parts 600 through 680 that must be met to comply with 21 CFR 4.3 and 4.4(c) for a particular combination product that includes a biological product constituent part will depend on the type of biological product it includes. The agency welcomes the opportunity to discuss these requirements with manufacturers to ensure sound, effective CGMP operating systems. If manufacturers have questions regarding these requirements, they may contact the lead center for the combination product, as well as OCP as needed, for assistance.

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## ***2. Complying with CGMPs for HCT/Ps***

An HCT/P that is not regulated solely under section 361 of the PHS Act is also regulated as a drug, device, and/or biological product.<sup>62</sup> As explained in the preamble to the final rule, the drug CGMPs, QS regulation, and the requirements in 21 CFR parts 600 through 680 may apply to an HCT/P depending on whether the product is regulated as a drug, device, or biological product.<sup>63</sup> The current CGTPs, including donor eligibility requirements for HCT/Ps in part 1271, apply to a combination product that includes an HCT/P.

These CGMPs and the CGTPs supplement one another for such products and do not supersede each other unless the regulation specifically provides otherwise. In the event that a regulation in 21 CFR part 1271 is in conflict with a requirement in 21 CFR parts 210, 211, 600 through 680, or 820, the regulations more specifically applicable to the product in question will supersede the more general.<sup>64</sup>

The requirements for the manufacture of HCT/Ps under part 1271 are designed to prevent the introduction, transmission, and spread of communicable diseases, and thereby are essential to protecting the public health. However, requirements under some sections of part 1271 overlap with the requirements under the drug CGMPs and the QS regulation. The agency has addressed these overlaps in part 1271 and in the Guidance for Industry on *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)* (CGTP Guidance).

21 CFR 1271.150(d) explains, in part, that for HCT/Ps regulated as biological products, drugs or devices, the procedures contained in subpart D and in subpart C of part 1271 and the procedures contained in 21 CFR parts 210, 211, and 820, supplement one another. As a consequence, compliance with certain provisions of 21 CFR part 211 or 820 may also constitute partial or complete compliance with certain provisions of 21 CFR part 1271. However, for certain CGTP requirements, the CGTP requirements would require additional manufacturing practices because the CGTP requirements would not be partly or completely covered by a corresponding CGMP or QS regulation requiring the same practice. Accordingly, the adjustments that might need to be made to an existing CGMP operating system to be fully compliant with the 21 CFR part 1271 CGTP requirements for a combination product that includes an HCT/P may differ if the system being augmented is a drug manufacturing system

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<sup>62</sup> The HCT/P regulations at part 1271 distinguish between HCT/Ps regulated solely under section 361 of the PHS Act (42 U.S.C. 264) and those that are also regulated as drugs, devices, and/or biological products. Section 1271.10 provides that an HCT/P that is more than minimally manipulated or 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. Refer to 21 CFR 3.2(e), 1271.10, 1271.15, and 1271.20, to determine whether an HCT/P is regulated as a drug, device, or biological product constituent part of a combination product or is excepted from the requirements in part 1271.

<sup>63</sup> See 78 FR 4317.

<sup>64</sup> See 21 CFR 1271.150(d). Also see the Guidance for Industry on *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)* (December 2011).

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under 21 CFR part 211, a device manufacturing system under 21 CFR part 820, or a combination product manufacturing system that demonstrates compliance with 21 CFR part 211 and 21 CFR part 820 in accordance with 21 CFR 4.4(a)(1), 4.4(b)(1), or 4.4(b)(2).

For further information, see the CGTP Guidance. FDA understands the complexity of manufacturing considerations and duties for combination products that contain an HCT/P that is a biological product (or drug or device) constituent part. Accordingly, the agency encourage manufacturers to contact the lead center for your product, or OCP as needed, if manufacturers have questions about how to comply with CGMP requirements for their particular product.

### **V. Application of CGMP requirements to specific types of combination products**

The hypothetical scenarios addressed in this section focus on three types of combination products. While each of these types of combination products is subject both to the drug CGMPs and to the QS regulation, each example is used to focus on specific CGMP considerations relating to CGMP provisions specified in 21 CFR 4.4(b). Specifically:

- Section A, a prefilled syringe example, focuses on how to comply with the QS regulation provisions specified in 21 CFR 4.4(b)(1) if a manufacturer adopts a drug CGMP-based streamlining approach for its CGMP operating system (by demonstrating compliance with the drug CGMPs and with the specified provisions from the QS regulation).
- Section B, a drug-coated mesh example, focuses on specific provisions of the QS regulation specified in 21 CFR 4.4(b)(1) to highlight some additional issues not raised in the prefilled syringe scenario.
- Section C, a drug-eluting stent (DES) example, focuses on how to comply with the drug CGMP provisions specified in 21 CFR 4.4(b)(2) if a manufacturer adopts a QS regulation-based streamlining approach for its CGMP operating system (demonstrating compliance with the QS regulation and the specified provisions from the drug CGMPs).

This discussion is intended to highlight only certain issues that a combination product might raise, and considerations for addressing them, relating to the CGMP provisions specified in 21 CFR 4.4(b). This discussion is not intended to reflect a complete analysis of the CGMP issues that need to be addressed for such products, whether under the specific CGMP provisions discussed or any other CGMP requirements also applicable to such products. In addition, specific products may raise distinct issues that are not taken into account in the hypothetical scenarios presented below. If manufacturers have specific questions relating to their particular products, the agency recommends that they contact the lead center for the product, as well as OCP as needed, for assistance.

## **A. Prefilled syringe**

### ***1. Scenario Description***

A drug manufacturer (Manufacturer A) plans to sell a drug in a prefilled syringe presentation. Manufacturer A already has marketing approval for the drug product and would apply for the marketing approval for this prefilled syringe presentation. No other changes to the drug will be made. Manufacturer A will buy off-the-shelf syringe components from a supplier (Manufacturer B) who also manufactures finished syringes using the same components. Manufacturer A will assemble the syringe components, prefill the syringe at a facility it operates, and then package, label, and distribute the prefilled syringe from this facility.

Manufacturer A's facility has an existing drug CGMP operating system. As the prefilled syringe is a single-entity combination product under 21 CFR 3.2(e)(1), Manufacturer A must demonstrate compliance with both the drug CGMPs and device QS regulation.<sup>65</sup> To do so, Manufacturer A opts to establish a CGMP operating system using the drug CGMP-based streamlining approach in accordance with 21 CFR 4.4(b)(1). While Manufacturer A must ensure that its operating system fully complies with the drug CGMPs for this product, taking into account all of the issues raised by inclusion of the device constituent part, this example focuses on considerations for demonstrating compliance with the provisions from the QS regulation specified in 21 CFR 4.4(b)(1).

### ***2. Compliance with QS regulation requirements***

Having chosen to use the drug CGMP-based streamlining approach, under 21 CFR 4.4(b)(1), in addition to demonstrating compliance with the drug CGMPs, Manufacturer A must comply with the applicable specified provisions of the Quality System (QS) regulation as discussed below. For each such provision, this discussion offers exemplary considerations and activities for the combination product manufacturer to meet the QS regulation requirements.

#### ***a) 820.20, Management Responsibility***

While 21 CFR 211.22, 211.25, and 211.180 establish requirements relevant to management responsibility, Manufacturer A must ensure that its CGMP operating system demonstrates compliance with the specific requirements in 21 CFR 820.20 (discussed in greater detail in section IV.A.1).

Manufacturer A should, for example, review its existing CGMP operating system to determine how to demonstrate compliance with these requirements. Management with executive responsibility for Manufacturer A should review the facility's quality policy and develop and implement appropriate oversight procedures, if such procedures are not already in place, to ensure both the policy and oversight are adequate. The oversight procedures should include

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<sup>65</sup> See 21 CFR 4.4.

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clear delineation of the personnel to whom management with executive responsibility is delegating responsibility for implementing the quality policy (including translation into methods and procedures) and for implementation of the CGMP operating system for this product at the facility.

### *b) 820.30, Design Controls*

Manufacturer A is responsible for establishing and maintaining procedures for design control activities for the combination product. In this scenario, Manufacturer A is the product sponsor and is manufacturing the prefilled syringe. Accordingly, Manufacturer A is responsible for the design control activities for the syringe as part of the combination product, as well as for the combination product. However, Manufacturer A is buying the syringe components from Manufacturer B, another manufacturer, which uses the same components to manufacture finished syringes. As a result, Manufacturer A may be able to leverage syringe-specific design control activities, procedures, and documentation from the design controls Manufacturer B uses for its finished syringes. Because no changes are to be made to the drug other than being prefilled into the syringe, design considerations for the drug should serve as inputs for controlling the design of the syringe to ensure its design reflects adequate consideration of the drug's characteristics, as indicated below.

#### *i. Design inputs and outputs*

The table below includes illustrative examples of design inputs and user needs and related design outputs for this prefilled syringe.

<i>Design Input/User Needs</i>	<i>Design Output</i>
Required minimum/maximum delivery dose for drug	Drawing/specification for syringe minimum/maximum volume
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, for example
Expected use condition (e.g., expected user experience/education level)	Content, reading level, for example, for the prefilled syringe's labeling
Maximum allowable temperature of drug	Packaging/labeling specifications for the prefilled syringe
No degradation of drug or syringe over the expected shelf-life as a result of contact with one another	Specifications for drug-contacting syringe materials
Expected shipping method and appropriate storage conditions	Design drawings/specifications for primary and secondary packaging
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

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### ii. Design verification and validation

Once Manufacturer A has established design outputs for all design inputs, it must perform design verification and validation activities to ensure that the combination product meets design input requirements, including user needs and intended uses.<sup>66</sup> Examples of appropriate testing of the prefilled syringe include: bench testing of the delivery of the drug from the syringe to ensure repeatable and accurate drug delivery; shock and vibration testing of the packaged prefilled syringe to ensure no damage or loss of integrity in shipping; validation that expected users can adequately follow the instructions for use; other human factors studies; biocompatibility testing; drug and syringe compatibility studies; leachables and extractables testing; and verification that the prefilled syringe works with all expected delivery methods (i.e., needle, needleless). These activities would be documented in the design history file pursuant to 21 CFR 820.30(j) and would be subject to design change and review requirements pursuant to 21 CFR 820.30(e and (i).

### iii. Risk Analysis

Under the risk analysis requirement of 21 CFR 820.30(g), Manufacturer A must identify risks associated with the prefilled syringe design, its manufacturing processes and intended uses, and reduce or mitigate any unacceptable risk(s). The table below lists some potential risks associated with prefilled syringes and potential mitigations for these risks.

<i>Risk</i>	<i>Mitigation</i>
Syringe filled with incorrect drug dose	In-process acceptance testing, process validation
Loss of sterility	Container/closure integrity testing, packaging validation/testing
Drug contamination from materials contained in syringe	Purchasing controls (including receiving acceptance activities with syringe component manufacturer), in-process and finished product testing to ensure no introduction of contaminants during manufacture and over the product shelf-life
Syringe failure during use	Design verification testing on syringe, purchasing controls over syringe component manufacturer

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<sup>66</sup> See 21 CFR 820.30(f) and (g).

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### iv. Design changes

Manufacturer A must also have procedures in place to ensure that any changes to design requirements are identified, documented, validated and/or verified, reviewed, and approved prior to implementation in accordance with 21 CFR 820.30(i). Activities should include review of the original risk analysis, review and approval of the revised design inputs and outputs, and review and approval of the design change. For example, before changing the material used in the syringe that comes into contact with the drug, Manufacturer A should repeat verification activities that were originally performed to ensure that no degradation of the drug or device performance characteristics will occur before the expiration date for the combination product as a result of the change of materials. All of this information would need to become a part of the design history file in accordance with 21 CFR 820.30(j).

#### *c) 820.50, Purchasing Controls*

Manufacturer A is required to control its purchasing activities for the syringe components in accordance with 21 CFR 820.50.

For example, if the syringe barrel and plunger material is critical to ensuring that there is no adverse reaction with the drug, Manufacturer A should structure purchasing agreements with Manufacturer B to ensure that Manufacturer A is notified of any changes in design or materials for any components prior to implementation. In addition, because the device constituent part (syringe) is also a container/closure for the drug, Manufacturer A must perform acceptance testing of the syringe components in accordance with 21 CFR 211.84. Similarly, if Manufacturer A uses an outside facility for terminal sterilization of the prefilled syringe, for example, Manufacturer A must also have appropriate controls over that sterilization service provider in accordance with section 820.50.

#### *d) 820.100, Corrective and Preventive Actions*

Manufacturer A is required to establish and maintain CAPA procedures related to the combination product as discussed above in section IV.A.4. Following are two examples of issues that might arise and exemplary steps for addressing them.

Example 1: Manufacturer A has implemented in-process manufacturing verifications that the syringe is being filled with the correct drug dose, and the data from this process are analyzed for potential nonconformities. Manufacturer A notes an increase in nonconformities relating to the volume of drug being placed in the syringe and in turn opens a CAPA to investigate the problem. Upon investigation of the cause of the improper fill volume, Manufacturer A determines that maintenance procedures on the filling equipment are the cause of the incorrect fill volume. These procedures are updated, and verification testing performed to confirm that the changes correct the problem.

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Example 2: Manufacturer A begins receiving an increased number of customer complaints related to holes or damage to the syringe sterile package and opens a CAPA to investigate the issue. The CAPA reveals that Manufacturer B has made changes to a syringe component such that there are sharp edges that can damage the sterile pouch during shipping. Manufacturer A works with Manufacturer B to eliminate the sharp edge or finds a new supplier. Manufacturer A also augments purchasing specifications and acceptance test steps to perform visual inspection of the syringe components. Manufacturer A repeats related design verification testing to ensure that the new syringe meets all design requirements and does not result in pouch damage during shipping.

*e) 820.170, Installation and 820.200, Servicing*

Installation and servicing requirements would not apply to the prefilled syringe because the product does not require installation or servicing activities.

### **B. Drug-coated mesh**

#### ***1. Scenario Description***

Manufacturer A plans to sell a synthetic surgical mesh coated with a drug. Manufacturer A has a marketing authorization to sell the uncoated mesh. Manufacturer A wants to coat the mesh with the drug to treat infection at the site of the product's implantation. Manufacturer B has an approval to market the drug for local administration treat infection at the site of implantation of this class of device, but not in a formulation suitable for coating onto the mesh. Manufacturer A has established a business relationship with Manufacturer B to use the drug and develop the data needed to support Manufacturer A's marketing authorization for the coated mesh. Manufacturer B will manufacture the drug formulation for spraying onto the mesh, and Manufacturer A will manufacture the finished drug-coated mesh combination product.

#### ***2. Compliance with QS regulation requirements***

The coated mesh product is a single-entity combination product under 21 CFR 3.2(e)(1). Manufacturer A is subject both to the drug CGMPs and the QS regulation for this combination product. Therefore, Manufacturer A must ensure that its CGMP operating system complies with both the QS regulation and drug CGMPs, in accordance with one of the approaches permitted under 21 CFR 4.4, taking into account all of the issues raised by inclusion of the drug constituent part. This discussion, however, focuses on design control and purchasing control considerations arising from inclusion of the drug constituent part in the product.

*a) 820.30, Design Controls*

All of the design control activities required by 21 CFR 820.30, as summarized in IV.A.2 above, must be addressed in the design history file for the drug-coated mesh. Design control considerations likely would be addressed as part of premarket review of this combination product (e.g., regarding the suitability of the drug formulation and the compatibility of the mesh with the drug). Accordingly, much of the information that needs to be included in the design

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history file would be developed and submitted as part of the premarket review process. Manufacturer A may opt to incorporate such information by cross-reference to such premarket submissions. Whatever approach Manufacturer A selects must ensure that all required design history information is readily available to FDA for review.

The design history file for the surgical mesh must include design input, output, verification and validation data, and the results of design reviews for the combination product. In developing the design controls related to the drug constituent part, Manufacturer A may rely on the safety, efficacy, quality and *in situ* dose data for the drug as marketed. These existing data that supported approval of the drug would be available as a reference for the combination product design history file to enable development of design inputs for the drug constituent part and the combination product as a whole, and otherwise facilitate its development process.

A focus of the design control process for the drug constituent part of the combination product is to ensure that the drug-coated mesh will be safe and effective for treating infection at the site of implantation. Accordingly, if the necessary dose of the drug for effective prevention of infection, for example, is already known, it would be an input (if the precise dose is not yet known, then an input would be that the product elute a safe and effective dose); design outputs and validation and verification would need to be established to ensure that this required dose is provided when the drug elutes from the mesh.<sup>67</sup> In addition, risk analysis must be conducted to identify any risks associated with the design, manufacturing, and use of the mesh.<sup>68</sup> Also, mitigation measures should be identified and performed to address any identified risks. Design reviews should incorporate these and other related design considerations for the product and relevant personnel with expertise in both the drug- and device-specific issues (as well as an individual independent from the design stage being reviewed). The transfer of the product design into production specifications should incorporate all important aspects of the drug constituent part for use in the combination product.

### i. Design inputs and outputs

The table below includes illustrative examples of design inputs, including user needs, and related design outputs that may need to be considered in light of the inclusion of the drug constituent part.

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<sup>67</sup> See 21 CFR 820.30(d), (f), and (g).

<sup>68</sup> See 21 CFR 820.30(g).

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<i>Design Input/User Needs</i>	<i>Design Output</i>
Required delivery dose and delivery rate for the drug	Drug formulation and concentration, coating thickness, uniformity of coating, manufacturing process requirements, allowable storage conditions, drug delivery rate
Expected use condition (e.g., anatomical location of use, surgical technique)	Labeling (instructions for use), Material/drug composition to ensure no damage to mesh or coating during surgical placement
Maximum allowable temperature during transportation, handling, and storage for the combination product	Packaging/labeling specifications for the combination product
No unacceptable degradation of the drug over the expected shelf-life	Specifications for the drug-contacting materials, shelf-life labeling
No degradation of the surgical mesh over the expected shelf-life	Specifications for mesh material and drug formulation, shelf-life labeling

### ii. Design verification and validation

Several examples of design verification and validation activities are described below:

- One intended use is that the drug-coated mesh will reduce infections. Manufacturer A must perform a clinical trial (design validation) to ensure that the drug, when combined with the mesh, is effective in preventing infection and does not raise safety concerns.<sup>69</sup> Design outputs from this study would include the drug concentration in the coating formulation to be specified in purchasing controls over Manufacturer B and the coating thickness as specified in process controls over the application of the coating by Manufacturer A.
- A user need is that a physician be able to use the mesh product as labeled without damaging the drug coating or the mesh material. Manufacturer A would also have to verify that the mechanical properties of the coated mesh are such that the product can withstand the stresses anticipated during the surgical procedure and still perform as intended.<sup>70</sup> The results would be used to define and develop the design outputs for the product, including final instructions for use, as well as mechanical product specifications and related in-process acceptance testing criteria.
- Another input to the design process is that the product has a shelf-life consistent with the stability of the drug formulation and the mesh. Manufacturer A would perform

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<sup>69</sup> See 21 CFR 820.30(g).

<sup>70</sup> See 21 CFR 820.30(f).

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design verification testing such as bench testing after accelerated aging to confirm that the critical performance properties of the mesh material are not degraded during storage or as a result of contact with the drug coating and stability studies<sup>71</sup> to ensure that the properties of the drug are not degraded over the expected shelf life. The design outputs arising from this process would include the labeled expiration date and storage conditions of the combination product and packaging design specifications.

### iii. Risk analysis and mitigation

The table below lists some potential risks associated with a surgical mesh coated with a drug, and potential mitigations for these risks.

<i>Risk</i>	<i>Mitigation</i>
Drug concentration in coating not sufficient to treat infection (e.g., due to insufficient thickness, inappropriate delivery rate, or non-uniformity of coating)	In-process acceptance testing, process validation
Mesh erodes or drug degrades during use or storage	Design verification testing (bench), clinical testing, labeling (instructions for use), purchasing controls over drug supplier, specifications and other process controls

### *b) 820.50, Purchasing Controls*

Manufacturer A may already have established procedures for controlling purchasing/supplier activities pursuant to 21 CFR 820.50. Manufacturer A must ensure that appropriate purchasing controls for Manufacturer B are established and maintained. In particular, based on the risk associated with the drug and supplier, Manufacturer A must evaluate Manufacturer B as a potential supplier of the drug and establish the type and extent of control to be exercised over Manufacturer B as a selected supplier.<sup>72</sup>

Purchasing controls (and acceptance activities under 21 CFR part 211) should focus on ensuring that Manufacturer B can supply the drug that meets the specifications that Manufacturer A has established during the design control process. Manufacturer A should establish purchasing agreements with Manufacturer B to ensure that Manufacturer A is notified of any changes that may affect the performance of the combination product prior to their implementation. The notifications should address issues including changes to the composition, manufacturing process or facility, or design of the drug component.

Such proposed changes may require that Manufacturer A complete additional design verification and/or validation. For example, verification testing may be necessary to confirm that

<sup>71</sup> See the Guidance for Industry on *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

<sup>72</sup> See 21 CFR 820.50(a)(2).

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the purity and stability of the drug is maintained, pursuant to the requirements of section 820.30(i)<sup>73</sup>

### **C. Drug Eluting Stent (DES)**

#### ***1. Scenario Description***

In this scenario, Manufacturer A is the sponsor and manufacturer for a drug-eluting stent (DES) composed of a stent coated with a drug. Manufacturer B manufactures the active pharmaceutical ingredient (API or bulk drug substance), Manufacturer C manufactures a polymer with which the bulk drug substance will be combined for coating onto the stent, and Manufacturer D manufactures the materials used for the product's packaging. Manufacturer A purchases the bulk drug substance from Manufacturer B and the polymer from Manufacturer C, then formulates the drug coating solution and uses it to coat the stent in its own facility. At the same facility, Manufacturer A packages the DES using the primary packaging materials it purchases from Manufacturer D.

#### ***2. Compliance with drug CGMP requirements***

The DES is a single-entity combination product as defined in 21 CFR 3.2(e)(1) and, therefore, is subject to both the drug CGMPs and device QS regulation. As a device manufacturer, Manufacturer A already has a CGMP operating system designed to comply with the QS regulation and has elected to establish a QS regulation-based CGMP operating system for the DES in accordance with 21 CFR 4.4(b)(2). While Manufacturer A must ensure that this operating system complies with the QS regulation, taking into account all of the issues raised by inclusion of the drug constituent part, this example focuses on considerations for complying with the drug CGMP provisions specified in 21 CFR 4.4(b)(2).<sup>74</sup>

##### ***a) 21 CFR 211.84, Testing and approval or rejection of components, drug product containers, and closures***

As part of its existing CGMP operating system, Manufacturer A has already implemented 21 CFR 820.30, 820.50, 820.80, and 820.86. Accordingly, Manufacturer A has controls in place to evaluate suppliers, contractors, and consultants based on their ability to meet quality and specified requirements. Manufacturer A's purchasing controls for the DES must include evaluation of Manufacturer B as the supplier of the bulk drug substance, Manufacturer C as the supplier of the polymer for the coating, and Manufacturer D as the supplier of the packaging materials in conformance with 21 CFR 820.50(a)(1). Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the entity can consistently provide material meeting specifications. In addition, under its CGMP operating system for the facility, Manufacturer A has controls to identify the acceptance status of

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<sup>73</sup> As the sponsor for the drug-coated mesh, Manufacturer A would also have postmarket duties to notify the agency of such changes and, in some cases, to obtain agency approval of the change depending on the nature of the change.

<sup>74</sup> Control of the device constituent part (i.e., the bare stent) would be undertaken in accordance with the QS regulation.

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manufactured products. Manufacturer A's duties under 21 CFR 211.84 relate to these various obligations and controls arising from the QS regulation. Under 21 CFR 4.4(b)(2), Manufacturer A must augment its existing CGMP operating system as needed to satisfy the requirements of 21 CFR 211.84 for the DES.

In accordance with 21 CFR 211.84, the bulk drug substance, polymer, and packaging materials supplied by manufacturers B, C, and D must be sampled, tested, or examined, as appropriate, by Manufacturer A to determine if they should be approved or rejected for use. Each lot of these incoming materials must be withheld from use until it is determined that it meets appropriate written specifications of identity, strength, quality, and purity and related tests, under 21 CFR 211.84. Designated areas for disposition and sampling of components and materials should be controlled to ensure that all incoming lots are evaluated and not contaminated. Representative samples from each lot must be taken in accordance with 21 CFR 211.84(b) and (c) to make a determination of the quality of the lot.

The packaging materials should be visually inspected to ensure the correct, specified materials have been received from Manufacturer D. The bulk drug substance and polymer each must be tested by Manufacturer A for conformity with all appropriate written specifications for purity and quality, and for strength of the bulk drug substance, unless a report of analysis is appropriately relied on (as described in the paragraph below).<sup>75</sup> Samples used for testing must be representative of the lot of material being assessed.<sup>76</sup> Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based on a statistically valid sampling plan that takes into consideration the material type, degree of precision required, material variability, past quality history of the supplier, and the quantity needed for analysis. Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Under certain circumstances, Manufacturer A may rely on a report of analysis from a supplier in lieu of conducting some of its own testing. If, for example, Manufacturer B performs conformity testing for the bulk drug substance (testing to ensure the material meets appropriate purity, strength, and quality specifications) just prior to the shipment of material to Manufacturer A, then a report of analysis may be accepted by Manufacturer A in lieu of testing for these characteristics by Manufacturer A, if certain conditions are met. Specifically, Manufacturer A is still responsible for the performance of at least one specific identity test upon receipt of a lot of the bulk drug substance, even if a comprehensive report of analysis accompanies the lot. Reliance on reports of analyses is also contingent on Manufacturer A establishing the reliability of the supplier's analyses through appropriate validation of the test results at appropriate intervals.<sup>77</sup> The supplier can be evaluated through initial purchasing controls and at suitable, subsequent intervals. A similar analysis would apply if Manufacturer C were to conduct conformity testing for the polymer it supplies to Manufacturer A.

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<sup>75</sup> See 21 CFR 211.84(d)(2).

<sup>76</sup> See 21 CFR 211.84(b).

<sup>77</sup> See 21 CFR 211.84(d)(2).

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Incoming testing by Manufacturer A (and receipt of a report of analysis with respect to the materials obtained from Manufacturer B, C, or D if tested by them) must occur prior to formulation at Manufacturer A of the finished DES.<sup>78</sup> Due to the nature and intended use of sterile drug eluting stents, testing must include microbiological testing of the bulk drug substance and polymer.<sup>79</sup>

### *b) 21 CFR 211.103, Calculation of yield*

Manufacturer A is responsible for the calculation of yield at appropriate phases throughout the entire manufacturing process of the drug constituent part, including its application to the DES, and the packaging of the DES. The calculation of yield should be determined during appropriate steps in the manufacturing process, including the formulation of the drug constituent part and polymer prior to and after the coating of the stent. The formula used and the data generated for the calculation should be maintained in a manufacturing and/or production record.

### *c) 21 CFR 211.132, Tamper-evident packaging requirements for over-the-counter (OTC) human drug products*

This regulatory requirement is not applicable to drug-eluting stents, as they are not OTC products.

### *d) 21 CFR 211.137, Expiration dating*

As the manufacturer of the combination product, Manufacturer A is responsible for establishing the expiration date on the labeling of the finished combination product. The expiration date must be established based on the data from the stability studies on the finished packaged DES and should also take into account other shelf-life considerations as required under design control. These considerations include the functionality of the stent and polymer and the integrity of the coating and the packaging.<sup>80</sup>

### *e) 21 CFR 211.165, Testing and release for distribution*

Manufacturer A must test each batch of the finished combination product to determine conformance with final written specifications of the product. A detailed listing of all the tests performed on the DES and the acceptance criteria should be incorporated into the documentation for the manufacturing, production, and laboratory systems. A description of each analytical test should be developed and documented in standard operating procedures. A general list of tests for drug-eluting stents is provided below. Additional information on drug-eluting stents is provided in the draft Guidance for Industry on Coronary Drug-Eluting Stents–Nonclinical and Clinical Studies –(March 2008).<sup>81</sup>

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<sup>78</sup> See 21 CFR 211.84(a).

<sup>79</sup> See 21 CFR 211.84(c)(3) and (d)(6).

<sup>80</sup> See 21 CFR 211.137(a) and (b).

<sup>81</sup> When finalized, this guidance will represent FDA's current thinking on DES.

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- Appearance
- Identification
- Assay
- Impurities and Degradation Products
- Content Uniformity
- Drug Release Rate (immediate and/or extended release rates)
- Package Integrity and Sterility
- Endotoxins
- Particulate Matter
- Additional Testing, when applicable (including testing for polymer molecular weight, residual monomers, catalysts, and other additives)

### *f) 21 CFR 211.166, Stability testing*

Stability testing for the final DES product should address the following considerations: appearance, assay/drug content, impurities/degradation products, rate of drug release, particulate matter, sterility, and package integrity. Methods used for batch release under 21 CFR 211.165 may also be suitable for stability testing. Analytical procedures for stability testing should be fully validated as suitable to demonstrate stability.

### *g) 21 CFR 211.167, Special testing requirements*

Manufacturer A must conduct or contract to conduct conformity testing of the DES in accordance with 21 CFR 211.167(a) because this class of product is purported to be sterile and pyrogen-free. In addition, testing in accordance with 21 CFR 211.167(c) must be conducted because the DES constitutes a controlled-release dosage form.

### *h) 21 CFR 211.170, Reserve samples*

Manufacturer A must maintain reserve samples representative of each lot of the bulk drug substance used in the combination product and of each lot or batch of the finished packaged DES.<sup>82</sup> Reserve samples must consist of at least twice the quantity necessary to perform all tests required for the bulk drug substance and the finished DES, excluding sterility and pyrogen testing.<sup>83</sup> The reserve samples must be kept for the time periods required by 21 CFR 211.170. The samples of the bulk drug substance should be kept for 1 year past the expiration date of the last lot of finished drug-eluting stents to use that lot of the bulk drug substance.<sup>84</sup> The samples for each lot of the finished DES must be kept for 1 year after the expiration date for the product.<sup>85</sup>

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<sup>82</sup> See 21 CFR 211.170(a) and (b).

<sup>83</sup> See 21 CFR 211.170(a) and (b).

<sup>84</sup> See 21 CFR 211.170(a)(1).

<sup>85</sup> See 21 CFR 211.170(b)(1).

## **VI. Contact Us**

If you have questions regarding compliance with CGMP requirements for combination products after reviewing this guidance and the other guidance documents cited in this document, we encourage you to contact us. We recommend you contact the lead center for your product in the first instance. However, you may also contact OCP for assistance. Below are contact points for each center and OCP.

### 1. CBER

Mail: Office of Communication, Outreach and Development (OCOD)  
10903 New Hampshire Avenue  
Building 71, Room 3103  
Silver Spring, MD 20993  
Rockville, MD 20852-1448  
Phone: 1-800-835-4709 or 240-402-8010  
Email: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

### 2. CDER

Mail: Division of Drug Information (DDI)  
Hillandale Building  
10001 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 1-855-543-3784 or 301-796-3400  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)

### 3. CDRH

Mail: Division of Industry and Consumer Education (DICE)  
10903 New Hampshire Avenue  
Building 66, Room 4621  
Silver Spring, MD 20993  
Phone: 1-800-638-2041 or 301-796-7100  
Email: [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)

### 4. OCP

Mail: Office of Combination Products, Food and Drug Administration  
10903 New Hampshire Avenue  
Building 32, Hub/Mail Room #5129  
Silver Spring, MD 20993  
Phone: 301-796-8930  
Fax: 301-847-8619  
Email: [combination@fda.gov](mailto:combination@fda.gov)

## VII. References

### *Device*

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2. Sterilized Convenience Kits for Clinical and Surgical Use, Guidance for Industry (Jan. 2002)  
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(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>)
5. Human Factors and Medical Devices(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm>)

### *Drugs*

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8. Q1A(R2) Stability Testing of New Drug Substances and Products, Guidance for Industry (Nov. 2003)  
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10. Quality Systems Approach to Pharmaceutical CGMP Regulations, Guidance for Industry (Sept. 2006)  
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*Biological Products*

16. Cooperative Manufacturing Arrangements for Licensed Biologics, Guidance for Industry (Nov. 2008)  
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*HCT/Ps*

18. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry (Dec. 2011)

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*Combination Products*

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