Guidance for Industry and FDA Staff:

Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

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Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page of this guidance.

I. Introduction

This guidance describes and explains the final rule on current good manufacturing practice (CGMP) requirements for combination products that FDA issued on January 22, 2013 (final rule).[2] (21 Code of Federal Regulations (CFR) part 4). 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 did not establish any new requirements; it was intended to clarify which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products, and to set forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with applicable CGMP requirements.[3]

Section II of this document provides the definition of "combination product," an overview of the final rule, and describes the role of the lead center and other Agency components[4] with respect to combination product CGMP issues. Section III addresses certain general considerations for CGMP compliance for combination products. Section IV presents the purpose and content of specific CGMP requirements addressed in the final rule. Finally, Section V analyzes hypothetical scenarios that illustrate how to comply with certain CGMP requirements

[1] 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.

[2] See the Current Good Manufacturing Practice Requirements for Combination Products, 78 FR 4307 (January 22, 2013).

[3] As stated in the preamble to the final rule, combination products were subject to CGMP requirements that apply to each constituent part of their combination product prior to promulgation of 21 CFR part 4. Although products developed prior to promulgation of part 4 are frequently termed "legacy" combination products, FDA deliberately does not use this terminology in this guidance because it could be inappropriately interpreted to indicate that products developed prior to promulgation of part 4 are therefore subject to fewer CGMP obligations than products developed after promulgation of part 4.

[4] "Agency component" is defined at 21 CFR 3.2(b) as "the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, or alternative organizational component of the agency."

for specific types of combination products. Throughout this guidance, the Agency also refers to existing guidance and additional resources that address CGMP requirements for drugs, devices, biological products, and HCT/Ps, to 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, this guidance describes the Agency's current thinking on a topic that should be viewed only as recommendations, unless specific regulatory or statutory requirements are 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 part 3 (21 CFR part 3), a combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another).[5] 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,

[5] 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 Federal Food, Drug, and Cosmetic Act (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.

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

- 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. Quality and Current Good Manufacturing Practice

One of FDA's goals is to assure the availability of quality drugs, biologics, devices, and combination products that consistently meet applicable requirements and specifications. The drug CGMP and device QS regulations, as well as the CGMPs for biologics and current good tissue practices for HCT/Ps, provide a framework of minimum requirements to help assure product quality. The core requirements embedded in these regulations provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. This includes establishing a strong quality management system, using appropriate quality raw materials, establishing robust manufacturing and control procedures based on sound design principles, and detecting and investigating product quality deviations. In addition, these regulations call for ongoing assessment of systems and the implementation of corrective actions where appropriate.

C. Overview of the final rule

1. Summary of 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. This guidance refers to a "CGMP operating system" to mean the operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements applicable to the manufacture of a combination product.

The final rule on CGMP requirements for combination products applies to all combination products. The CGMP requirements for constituent parts of cross-labeled combination products that are entirely manufactured at separate facilities 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, only parts 210 and 211 (21 CFR parts 210 and 211) would apply to the manufacture of the drug constituent part(s) of the cross-labeled combination product, and only part 820 (21 CFR part 820) would apply to the device constituent part(s)). With regard to cross-labeled combination products, part 4 was intended to clarify only that the CGMP obligations applicable to the drugs, devices, or biological products also apply to these types of articles when they are constituent parts of cross-labeled combination products.

Because constituent parts of cross-labeled combination products need only comply with the requirements otherwise applicable to that type of product (e.g, part 211 for a drug constituent part or part 820 for a device constituent part), the "streamlined approach" (discussed below) is generally not relevant or applicable to them. However, to the extent that the constituent parts of a cross-labeled combination product are manufactured at the same facility, the manufacturing process would be akin to when the manufacture of the constituent parts of a co-packaged combination product occurs at the same facility. Accordingly, for cross-labeled combination products when manufactured at the same facility, the Agency does not intend to object to the use of a streamlined CGMP operating system for the manufacture of the combination product rather than distinct systems for the manufacture of each constituent part that is occurring at that facility. We believe this approach is consistent with the principles of part 4.

For single-entity combination products and co-packaged combination products, part 4 identifies 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.[6] Under the second option, manufacturers implement a streamlined approach for combination products that include both a drug and a device by demonstrating compliance with either the drug CGMPs (21 CFR parts 210 and 211) or the device Quality System (QS) regulation (21 CFR part 820) and also demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements.[7, 8] In addition, for a combination product that includes a biological product, the manufacturer must demonstrate compliance with the CGMP requirements specific to biological products in parts 600 through 680 (21 CFR parts 600 through 680). For a combination product that includes any HCT/P, the manufacturer must demonstrate compliance with the regulations in part 1271 (21 CFR part 1271)—including the current good tissue practice (CGTP) requirements and donor eligibility requirements.[9, 10, 11]

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 demonstrates compliance with either of the following:

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[6] See 21 CFR 4.4(a)

[7] See 21 CFR 4.4(b).

[8] While 21 CFR 211 requirements apply to all combination products because combination products always contain a drug and/or a biological product, 21 CFR 820 requirements apply only to combination products which include a device constituent part.

[9] See 21 CFR 4.4(a) and (b).

[10] 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, therefore, regulated as a drug, device, and/or biological product. See also 21 CFR 1271.20.

[11] 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 addressed in part 4 and are not a focus of this guidance.

- The drug CGMPs and the following provisions from the device QS regulation in accordance with 21 CFR 4.4(b)(1) (drug CGMP-based streamlined 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 device QS regulation and the following provisions from the drug CGMPs in accordance with 21 CFR 4.4(b)(2) (device QS regulation-based streamlined 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

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. The manufacturer is not required to choose a streamlined approach based on the CGMP regulations for the constituent part that provides the primary mode of action (PMOA) of the combination product (see II.D below). 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 either the device QS regulation-based or drug CGMP-based streamlined approach, or choose to develop a CGMP operating system that wholly complies with the specifics of applicable provisions of both the drug CGMPs and the device QS regulation.

21 CFR 4.4(c) provides that if a facility manufactures only one type of constituent part (e.g., a drug or device 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 (i.e., part 211 for a drug or part 820 for a device, as well as those under parts 600 through 680 for a biological product and part 1271 for an HCT/P). 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 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.

Similarly, if a facility manufactures a drug or device that is not a constituent part of a combination product and also manufactures a combination product, the CGMP requirements for the independently marketed drug or device do not change (compliance with parts 210/211 or part 820, respectively). Accordingly, if a facility manufactures an independently marketed device that is subject to part 820 and a combination product, it cannot manufacture the device under a drug CGMP-based streamlined operating system, even if it is used for the combination product, because this operating system only includes limited, specified provisions from the QS regulation. However, both the device and the combination product may be manufactured under a device QS regulation-based streamlined operating system, with the device that is not part of a combination product then being subject only to part 820.

2. Documentation of CGMP Approach

Combination product manufacturers should be able to identify all documentation needed to demonstrate compliance with part 4, and make it readily accessible for an FDA inspection. The facility's quality system documentation should identify the CGMP operating system for the combination product(s) manufactured at that facility, and the manufacturer should share this information with investigators at the initiation of an inspection. For combination product manufacturers implementing a streamlined approach (See Section II.B.1 above), inspection of the base CGMP operating system (i.e., 21 CFR part 210/211 or 21 CFR part 820) will typically be consistent with existing compliance programs and policies associated with it. For specified provisions from the non-base system, FDA intends to utilize the compliance program and policy elements specific to these provisions.[12]

Prior to the promulgation of part 4, manufacturers of combination products already had to demonstrate compliance with the applicable CGMP requirements for each constituent part of their combination product. Manufacturers should ensure that their CGMP procedures and processes are compliant with the regulatory framework provided in part 4. If the operating system requires changes to come into compliance, manufacturers should document the steps they take to ensure ongoing product safety and effectiveness. Manufacturers should be prepared to discuss their approach during inspections.

Combination product manufacturers who are required to address CGMP issues as part of premarket review should identify in premarket submissions whether they are operating under a streamlined approach, and if so, whether it is a drug CGMP-based or device QS regulation-based streamlined approach.[13] In premarket submissions, the CGMP approach should be identified for each relevant facility. For NDAs, BLAs and ANDAs, the CGMP approach should be described

[12] For a listing of existing Compliance Program Guidance Manuals (CPGMs) for drugs, devices, and biologics, see http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm2005382.htm.

[13] Submission of CGMP information is not routinely required prior to clearance of 510(k)'s. As discussed, manufacturers of 510(k) combination products should identify their CGMP operating system in the quality system documentation at their facilities.

in the Common Technical Document. For additional details on placement within the CTD, see *eCTD Technical Conformance Guide*, Section 3.3.2.[14] For PMAs, the CGMP approach should be documented in the manufacturing section of the PMA (the manufacturing module for a modular PMA).

D. 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 Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(g)), assignment of a combination product to a lead center is based on a determination of which constituent part provides the PMOA of the combination product.[15]

If the PMOA of a device-biological product combination product is attributable to the biological product, for example, the center responsible for premarket review of such a 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.

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, in identifying appropriate contact points (including those in the lead center), resolving substantive issues, or otherwise facilitating interactions with the Agency and collaboration among Agency components, including centers and the Office of Regulatory Affairs (ORA).

III. General Considerations for CGMP Compliance

This section addresses some general considerations for CGMP compliance for combination products. Note that this guidance addresses only CGMP requirements. Additional requirements may apply including the need for premarket submissions as a result of changes to product design, intended use, or manufacture.

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[14] Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

[15] 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) (which defines "mode of action" and "therapeutic") and (m) (which defines primary mode of action). For more information on product classification, assignment, and PMOA, see the guidance for industry *How to Write a Request for Designation (RFD)*(April 2011).

A. Demonstrating compliance

The final rule identifies two ways for co-packaged and single-entity combination product manufacturers to demonstrate compliance with applicable CGMP requirements. The Agency intends for the term "demonstrate" to apply for part 4 as it would be for purposes of fulfilling the underlying CGMP regulations listed in 21 CFR 4.3. Manufacturers must demonstrate compliance with each applicable CGMP requirement for constituent parts and combination products.[16]

If a streamlined approach is used, the manufacturer must demonstrate compliance with all of the relevant provisions of either the drug CGMPs or device QS regulation, and the provisions specified in 21 CFR 4.4(b) for the other set(s) of CGMP requirements applicable to the product. Further guidance on how to demonstrate compliance with the regulations specified in 21 CFR 4.4(b) is provided in section IV of this guidance. A manufacturer who implements a streamlined approach is not expected to demonstrate compliance with the specific provisions of the non-base set of requirements other than those specified in 21 CFR 4.4(b) (e.g., for a drug CGMP-based streamlined approach, the manufacturer must demonstrate compliance with applicable drug CGMPs plus the six specified provisions from part 820, as applicable, but the manufacturer does not need to demonstrate compliance with the other specific provisions in part 820).

As provided in 21 CFR 4.4(e), in the event of a conflict between regulations applicable under part 4, the regulations most specifically applicable to the constituent part in question supersede the more general. The intent of this provision is to address any potential conflicts between regulations. This provision does not provide a basis for the Agency to require manufacturers to demonstrate compliance with provisions not otherwise identified in part 4 as applicable to them.

Some of the provisions specified in part 4 from the drug CGMPs and device QS regulation cross-reference other provisions of parts 211 and 820, respectively. This raises the question of whether manufacturers must specifically demonstrate compliance with these cross-referenced provisions. FDA believes that manufacturers can adequately address the expectations of these cross-referenced provisions through implementation of either a drug CGMP-based or device QS regulation-based CGMP streamlined approach.

For example, 21 CFR 211.170 (Reserve samples) references 21 CFR 211.192 (Production record review). However, 21 CFR 211.192 is not a specified provision in 21 CFR 4.4(b)(2) because part 820 encompasses the requirements of that section. In particular, under the CAPA requirements in 21 CFR 820.100, a manufacturer operating under a device QS-based streamlined approach should have the systems in place that would satisfy the requirements of 21 CFR 211.192. Similarly, 21 CFR 211.103 (Calculation of yield) references 21 CFR 211.68 (Automatic, mechanical, and electronic equipment) in relation to using automated equipment for yield calculations and maintaining appropriate controls over such equipment. Corresponding provisions in 21 CFR 820.70(i), applicable under a QS-regulation based streamlined approach,

[16] 21 CFR part 4.

require that automated data processing systems be validated for their intended uses. To take another example, the definition of design output in 21 CFR 820.3 makes reference to "device master record." Both part 211 and part 820 have requirements for "master records" (21 CFR 211.186, Master Production and Control Records and 21 CFR 820.181, Device Master Record). FDA believes the substantive expectations of these master record provisions are aligned and needed to control product development and manufacture.

This guidance does not focus on how to demonstrate compliance with provisions of the drug CGMPs and device QS regulation other than those specified in 21 CFR 4.4(b). Other provisions of these regulations 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 compliance with the regulations in parts 210 and 211[17] 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. For additional information on study phases, see 21 CFR 312.21.

Under 21 CFR 812.1, investigational devices are exempt from part 820 except for design control requirements under 21 CFR 820.30. This exemption also applies to the manufacturing of investigational combination products that include device constituent parts. Investigational combination products that include a device constituent part are subject to design controls (except when the device constituent part is exempt from design controls, see III.C.3 below), but not to the other provisions of part 820. Design controls should start as early as possible, once a company has determined that a product appears to have clinical utility and management has committed to further development (see also IV.A.2 below).[18]

The Agency considers these exemptions from requirements under parts 211 and 820 applicable to combination products and constituent parts of combination products whether they

[17] See 21 CFR 210.2(c).

[18] The preamble to the device 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)

are being studied under an investigational device exemption (IDE) or an investigational new drug application (IND). Even when these exemptions apply, however, methods, facilities, and manufacturing controls that are appropriate for the investigational products should be used. When developing and 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 the CGMP requirements for investigational products, see 21 CFR 210.2(c), 21 CFR 820.1, 61 Federal Register (FR) 52,616-52,617, and the Guidance for Industry on *CGMP for Phase 1 Investigational Drugs* (July 2008). Manufacturers who have questions about IDE or IND requirements for their combination product should contact the lead center or OCP, if needed, for assistance.

C. Definitions and terminology

Unless 21 CFR 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" and "component," "device," and drug "container" and "closure." It also addresses the meaning of "convenience kit" as a type of co-packaged combination product. Other relevant definitions can be found in part 4 and the underlying CGMP regulations (see, e.g., 21 CFR 210.3, 21 CFR 211.3, 21 CFR 600.3, 21 CFR 606.3, 21 CFR 820.3, and 21 CFR 1271.3)

1. "Manufacture" and "manufacturer"

The definition of the term "manufacture" in part 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. For example, if a company designs a drug-device combination product, that activity constitutes manufacture of that product, and the facility at which the design work occurs is a manufacturing facility. That company is a manufacturer subject to part 4 for the design activities it performs, even if all other aspects of the combination product's manufacture (e.g., fabricating, labeling, or packaging) are performed by another entity. Similarly, a facility responsible for the holding and storage of a combination product would be subject to related CGMP requirements such as 21 CFR 211.142 (Warehousing procedures) and/or 21 CFR 820.150 (Storage), depending upon whether the facility applies a streamlined approach and if so, which approach it applies.

2. "Constituent part" versus "component"

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, "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."[19] Under the device QS regulation, 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."[20] Components can include sub-assemblies that are further processed to make a finished device. In contrast, a finished device is "suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized,"[21] as would be the case for a device constituent part as incorporated into a combination product.[22]

A facility that manufactures only device components, including device components used in a combination product, is not made subject to the device QS regulation by part 4.[23] Similarly, a facility that manufactures solely active pharmaceutical ingredients (APIs) is not subject to part 211, though it is subject to statutory CGMP requirements under Section 501 of the FD&C Act (21 U.S.C. 351). Part 4 does not make such a drug component manufacturing facility subject to part 211 if those components are for use in a combination product. However, a facility that manufacturers a drug-device combination product formed from components is subject to parts 211 and 820, and must comply with these two sets of regulations as provided in part 4.[24]

In short, the terms "constituent part" in part 4 and "component" in the CGMP regulations serve different regulatory purposes. The use of the term "constituent part" in part 4 refers to drugs, devices, and biological products included in combination products and does not alter the meaning of the term "component" or alter whether the regulations listed in 21 CFR 4.3 apply to component manufacturers.

3. Drug containers and closures versus delivery devices

The Agency draws a distinction between mere drug containers and closures and containers and closures that are also devices. The essential difference is generally 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. An article that holds or contains a drug, but also delivers it, may also be a device subject to the device QS regulation in addition to the requirements relating to drug containers and closures.

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.[25] Elements of container closure systems that are device constituent parts include piston syringes, metered dose inhalers (MDIs), and containers for intravenously-administered (IV) fluids (such as IV bags containing

[19] 21 CFR 210.3.
[20] 21 CFR 820.3(c).
[21] 21 CFR 820.3(l).
[22] 21 CFR 4.2.
[23] See 21 CFR 820.1(a).
[24] See 78 FR 4313-4314, Comment 15.
[25] See the Guidance for Industry on *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (May 1999).

saline or anti-coagulants), which both hold and deliver the drugs or biological products they contain.[26] In the case of an IV container, the drug is delivered to the patient via the IV line.

The Agency has exempted some devices from all or certain provisions of the device QS regulations. For example, 21 CFR 880.6430 exempts liquid medication dispensers (cups, droppers, etc.) from all provisions of the device QS regulation with the exception of 820.180 and 820.198. Such exemptions may extend to device constituent parts of combination products and to the combination products of which they are a part. If the exemptions for a device constituent part of a drug-device combination product cover all of the part 820 provisions included in 21 CFR 4.4(b)(1), then the Agency will consider the combination product manufacturer CGMP compliant so long as the CGMP operating system is compliant with part 211 (no demonstration of compliance with part 820 will be necessary). However, if a device that would ordinarily be exempt from all or certain provisions in part 820 is incorporated into a container closure system, for example if a dropper is incorporated into the cap of a bottle of a drug, this may be a new use of the device such that the exemptions from part 820 may not be applicable.[27] In any event, when incorporated into a container closure system, the device must be addressed as part of the container closure system for purposes of part 211 (e.g., requirements under 21 CFR 211.84, 211.165, and 211.166, discussed in section IV.B).

Manufacturers should document their evaluation if they believe a container closure system that has delivery attributes is not a device, or if they believe a device constituent part is exempt from any or all provisions under the device QS regulation. Manufacturers who have questions about whether their container closure system, or an element thereof, is regulated as a device, or whether exemptions from part 820 apply, are encouraged to discuss the issue with the lead center or OCP, as needed.

4. Convenience kits

A kit that includes two or more different types of medical products (e.g., a device and a drug) is a co-packaged combination product and, therefore, part 4 applies to the manufacture of the kit. The CGMP requirements applicable to a kit manufacturer depend on what products are included in the kit.

If the kit includes only products that are 1) legally marketed independently and 2) packaged in the kit as they are when independently marketed (including any labeling used for

[26] The Agency notes that other Agency guidance addresses syringes and other devices that contain a drug as "container closures" for the drug, and focuses on considerations related to their use as container closures, while addressing only in a summary manner other requirements applicable because these container closures are also regulated as devices. *See, e.g., Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics[1999]*. As reflected in this section and elsewhere in this guidance, such devices are subject to container closure requirements because they hold a drug. However, because they are also devices, they and the combination product of which they are a part are subject to additional requirements, including under part 820.

[27] Although outside the scope of this guidance, we note that changes to the intended use of constituent parts of a combination product may require premarket review by FDA.

independent marketing), it is a "convenience kit,"[28] and the only manufacturing steps for the combination product would be the assembly, packaging, labeling, any sterilization, and 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.

Kit manufacturers should carefully analyze what CGMP requirements apply to a kit.[27] If a kit includes any products that are repackaged, relabeled, or otherwise modified from the independently marketed product, then the kit is not a convenience kit. Likewise, if the kit manufacturer includes labeling for the kit that modifies the intended use for a constituent part, then the kit is not a convenience kit. In these cases, the manufacturer would have to demonstrate compliance with CGMP requirements for the constituent parts and the overall product. Also, if a device constituent part would be considered exempt from the device QS regulation if marketed outside the kit, the kit manufacturer may not be able to claim this exemption from part 820 if the intended use of the device constituent part in the kit is new.

Co-packaged combination product manufacturers, including manufacturers of convenience kits, should carefully consider the impact of any sterilization process on the items in the co-package.[29] 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 in safety and effectiveness after any re-sterilization may be necessary. For example, manufacturers should consider whether re-sterilization affects stability, material properties, and expiration dating/shelf-life of any of the products within the kit. Additional issues may need to be considered, including validation of the sterilization process to ensure sterility for each constituent part within the kit, as appropriate.[30]

Manufacturers should document their evaluation if they believe a kit qualifies as a convenience kit or that a device constituent part (and, therefore, a kit) should not be subject to requirements under part 820. Kit manufacturers who have questions about whether their kit is a convenience kit, or about the applicability of part 820 requirements, are encouraged to contact the lead center or OCP, as needed.

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, they may, as discussed above, 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

[28] The term "convenience kit" as used in this guidance embraces solely the definition presented in this section, initially provided in the preamble to the part 4 regulation (see 78 FR 4310). The term "convenience kit" is used in other FDA regulations for different purposes. See, for example, 21 CFR 801.3.
[29] See, e.g., 21 CFR 211.166.
[30] See, for example, the Guidance for Industry on *Sterilized Convenience Kits for Clinical and Surgical Use* (January 2002).

the provisions of the CGMP regulations listed in 21 CFR 4.3 may be applicable to a specific combination product or constituent part.

1. Applicability of CGMP requirements 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 device 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 (21 CFR 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, already-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 and facility under part 4. However, the drug CGMPs, device QS regulation, and CGTPs for HCT/Ps use language such as "where appropriate" or "as necessary" to acknowledge that certain measures may not be necessary or applicable under certain circumstances and that manufacturers must pursue such measures if they are needed. Such language indicates that firms have the opportunity to document justifications for determining that such a measure or approach is not appropriate or necessary for a particular product or the specific manufacturing activity they are undertaking.[31] Such justifications should generally be maintained within the quality system documentation and may warrant Agency review prior to implementation depending on the product type and relevant premarket submission obligations.

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[31] 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 preventing 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.

For example, 21 CFR 820.30(i) stipulates that each manufacturer establish[32] and maintain procedures for "the identification, documentation, validation or *where appropriate* verification, review, and approval of design changes before their implementation" (emphasis added). Changes to the design, such as changes to properties of the material or dimensional specifications, may not need to be validated if they can be verified through appropriate measurement and test methods. However, changes that could impact user needs, such as changes to the user interface, may require validation. Similarly, part 211 requires compliance with certain duties "as appropriate" (e.g., 21 CFR 211.84(a) addressing the sampling, testing, or examining of components, containers, and closures prior to release by the quality control unit). Containers may not need to be tested, for example, if visual examination is sufficient to evaluate critical attributes.

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

A facility that manufacturers a constituent part of a combination product or a complete combination product must be compliant with the CGMP requirements applicable to each manufacturing process that occurs at that specific facility. In addition, the combination product owner (the holder of the marketing authorization for the product) retains overall responsibility for the product, even if the owner is not directly engaged in its manufacture. As outlined below, quality agreements and audits can be helpful in assuring compliance with applicable CGMP requirements.

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 device 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 operating system should take into account considerations for the combination product as a whole as appropriate. Before changes are made to the manufacturing process of a constituent part, the CGMP operating system should ensure consideration of whether such changes could affect performance and/or interaction with the other constituent part(s) and, if so, whether the safety and effectiveness of the combination product could be impacted. Quality agreements with constituent part manufacturer(s) are one way to ensure that changes to a constituent part are transparent to a combination product manufacturer or owner.

Some CGMP requirements concern the product as a whole, such as design controls, and some concern overarching considerations for the manufacturing process 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 change may require modification of manufacturing activities at another facility or the expertise to develop and implement the change may reside at a different facility. Similarly, a facility that only handles customer calls

[32] 21 CFR 820.3(k) states that "*Establish* means define, document (in writing or electronically), and implement."

may provide relevant complaint data to another facility responsible for trending all quality data and managing the CAPA system. A CAPA system that is shared between facilities, or facility-specific CAPA systems with established links between them, may facilitate handling of issues requiring multi-facility collaboration. Regardless of the approach, the CAPA system(s) should allow for adequate flow of information between facilities and manufacturers for the combination product and appropriate investigation and resolution of identified CAPA issues.

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 the manufacturer of the finished combination product uses a specification developer to design the finished product, that manufacturer 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 finished 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 that might be taken 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 owner may facilitate CGMP compliance by coordinating interactions among the facilities, including by entering into comprehensive quality agreements with the various facilities and suppliers. 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 particular 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 owner for that facility. For example, an owner may contract for the manufacture of the final combination product with a contract manufacturing facility, and detail in the supplier agreements the CGMP responsibilities and approaches for that facility.

E. Control of changes to a combination product

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. Appropriate consideration should be given to any implications for the safety or effectiveness of the combination product that might arise from changes to the combination product or its constituent parts.

Single-entity and co-packaged combination product manufacturers must establish arrangements with their suppliers, contractors, and consultants to receive notice of changes in the product or service, where possible, in accordance with 21 CFR 820.50. This notice should

address changes the supplier makes to its process or product—including to an API, other drug components, or a container-closure system—that it manufactures, if the change might affect the downstream manufacturing process or the quality of the combination product itself. These combination product manufacturers 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 or effectiveness of the combination product prior to incorporating them into the finished combination product.[33]

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 a change to the device constituent part(s) of such a combination product 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, which may require a change in its chemistry, manufacturing, and controls (CMC).[34, 35]

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

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

This section provides summary descriptions of the provisions from the device QS regulation with which manufacturers of single-entity and co-packaged combination products that include a device constituent part must demonstrate compliance when using the drug CGMP-based streamlined approach established under 21 CFR 4.4(b)(1), including considerations specific to applying these device QS regulation requirements to combination products. 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 device QS regulation—understand the purpose and basic elements of the device QS regulation

[33] 21 CFR 211.84 details how a manufacturer must sample, test, examine, and accept or reject drug product components, containers, and closures.

[34] For additional information on guidance related to CMC topics, see FDA's webpage: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm.

[35] While beyond the scope of this guidance, it bears noting that product owners 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, 807.81(a)(3) and 814.39. Accordingly, controlling changes to combination products and the processes and facilities used for their manufacture can be important to ensure compliance with other regulatory requirements (in addition to CGMP requirements).

provisions specified in 21 CFR 4.4(b)(1). This section also includes references to additional guidance documents that may be helpful.[36] Section V presents hypothetical examples offering additional guidance on how to address these provisions for a combination product.

1. Management responsibility (21 CFR 820.20)

Requirements under 21 CFR 820.20 ensure that management with executive responsibility (i.e., senior employees of a manufacturer who have the authority to establish or make changes to the quality policy and quality system)[37] are actively engaged in oversight of the quality system, and reflect the expectation that management with executive responsibility demonstrate an active, ongoing commitment to quality system development and implementation.[38] Statutory CGMP provisions and regulations for drugs establish requirements related to management responsibility, and the Agency has also issued guidance on this topic.[39] However, there are specific requirements in 21 CFR 820.20 that are not explicitly addressed in drug CGMP requirements, and 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.

A combination product manufacturer must establish and maintain an adequate organizational structure to ensure that the product is designed and produced in accordance with CGMP requirements. This structure 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 include

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[36] 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 21 CFR 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 devices will rarely be constituent parts of such combination products. If they are constituent parts of a combination product, they are more likely to be separately manufactured and marketed as constituent parts of cross-labeled combination products. In such cases, as discussed in Section II.C.1 II.B, each constituent part manufacturer would be subject to the CGMP requirements associated with the constituent part it manufactures. Accordingly, the device constituent part of such a cross-labeled combination product would be subject to installation and servicing requirements.

[37] 21 CFR 820.3(n).

[38] As stated in the preamble to the device QS regulation, "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 52602-52612)

[39] See Section 501 of the FD&C Act [21 USC 351], which 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 (establishing that "current good manufacturing practice" includes management oversight of manufacturing and controls to ensure quality and lifecycle risk management). See also 21 CFR 211.22, 211.25, and 211.180; and the Guidance for Industry *Q10 Pharmaceutical Quality System* (April 2009).

an appointed 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.[40] Management with executive responsibility must establish the policy and objectives for and commitment to quality.[41] These policies and objectives are reflected in the quality plan and quality system procedures.[42]

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.[43] The plan can either be an independent document, or it can reference elements of the manufacturer's quality system.

The quality system procedures (21 CFR 820.20(e)) ensure compliance with each aspect of the CGMPs applicable to the combination product.[44] The number, complexity, and structure of a combination product manufacturer's procedures and instructions may vary depending on factors such as the manufacturer's organizational structure and the complexity of the combination product being manufactured. Drug manufacturers may already have some such 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 periodically review the suitability and effectiveness of the quality system, including to ensure that the quality system satisfies the established quality policy and objectives.[45] These reviews must be conducted at defined intervals and with sufficient frequency. Management review procedures should ensure that management has adequate access to relevant information from facilities contracted to perform manufacturing activities for the combination product.

2. Design controls (21 CFR 820.30)

The preamble to the rule discusses design control requirements for combination products at some length.[46] This section discusses the design controls that apply to single-entity or co-packaged combination products that include a device constituent part that is subject to them.[47] Design control activities confirm that there are no negative interactions between constituent parts, and ensure that their combined use results in a combination product that is safe and effective and performs as expected.

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[40] 21 CFR 820.20(b).
[41] 21 CFR 820.20(a).
[42] See 21 CFR 820.20(d) and (e).
[43] 21 CFR 820.20(d).
[44] 21 CFR 820.20(e)
[45] 21 CFR 820.20(c).
[46] See 78 FR 4314-4315.
[47] If a manufacturer claims that the device constituent part or combination product is exempt from 21 CFR 820.30, the manufacturer should document its evaluation to support this determination. See sections III.C.3 and C.4 of this guidance; see also 21 CFR 820.30(a)(1).

The following is a description of design control requirements and the documentation that must be maintained for co-packaged and single-entity combination products.[48] While pharmaceutical development focuses on drug considerations, if broadened to take into account the other constituent parts of combination products and how they interrelate, many pharmaceutical development practices (for example, Quality by Design principles[49]) can be leveraged and built upon when demonstrating compliance with design controls for a combination product. The Agency recognizes that the terminology used in 21 CFR 820.30 can differ from that used for pharmaceutical development. Manufacturers should be able to communicate to the Agency how the terminology they use relates to design control principles and requirements.

Design control requirements apply to activities during product development as well as to postmarket changes to the design or manufacturing process. Accordingly, the activities described below may be conducted as part of premarket development and reflected in documentation submitted as part of the marketing authorization process. Regardless of when the activity occurs or where related records may reside, the CGMP operating system should include or reference appropriate documentation to ensure readily available access to this documentation for FDA inspection.[50]

The extent and complexity of the design controls process and associated documentation will vary based on the product. For example, consider a drug product that is already legally marketed independently that will have the same formulation, route of administration and intended use when marketed as part of a combination product that also incorporates a delivery device. Design controls would begin when the delivery device configuration is judged to be feasible and appropriate to develop. The drug properties would be inputs for design control activities that would focus on ensuring that the device appropriately delivers the drug and that the drug quality is not adversely affected by its contact with the device. Conversely, for a novel combination product with novel drug and device constituent parts, design controls ensure coordinated development of the drug and device resulting in a final combination product that meets user needs and achieves intended uses. The extensiveness of design control activities and related documentation for products should also be commensurate with the phase of product development.

As part of the design controls, a design and development plan must be established to describe or reference the design and development activities and define responsibility for implementation. The plans must identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process.[51]

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[48] 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.

[49] See the Guidance for Industry on *Q8(R2) Pharmaceutical Development* (November 2009), http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073507.pdf.

[50] See 21 CFR 820.30(j), 820.180, and 211.180.

[51] 21 CFR 820.30(b).

Design input requirements for the combination product should include considerations such as performance characteristics, safety and reliability requirements, and expected needs of product users and patients.[52] Design inputs should be considered early in product development to ensure that development efforts are consistent with the product's intended use, including the needs of users, including patients. Once the design inputs have been established, the design outputs (e.g., specifications and engineering drawings) must be developed based on those inputs.[53] 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. Design review is also required to ensure that formal and documented reviews of the design are planned and conducted at appropriate stages of the product's design development,[54] and all of these activities must be documented in the design history file.[55]

Design inputs ensure that design requirements are appropriate to address the intended use of the product, and design outputs include documentation of the product specifications that can be evaluated against the design inputs as development progresses. Similarly, Quality Target Product Profile (QTPP) in pharmaceutical development involves prospective consideration of the quality characteristics of a drug product to ensure desired quality taking into account safety and efficacy of the drug product. A manufacturer may identify potential Critical Quality Attributes (CQAs) or properties of a drug product that should be within appropriate limits, ranges, or distributions to ensure product quality and refine these CQAs as product development continues. QTPP and CQA principles may be applied for combination products in a manner consistent with design input and output requirements. In addition, when developing a combination product, the QTPP and CQA for the drug constituent part may be helpful in establishing design inputs and design outputs for the combination product.

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.[56] Design verification 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).[57] Design validation ensures that the product is designed correctly to achieve its intended purpose(s), and includes testing of production units or their equivalents (with appropriate justification[58]) under actual or simulated use conditions.

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[52] See 21 CFR 820.30(c).
[53] See 21 CFR 820.30(d).
[54] See 21 CFR 820.30(e).
[55] See 21 CFR 820.30(j).
[56] See 21 CFR 820.30(f) and 21 CFR 820.3(aa).
[57] See 21 CFR 820.30(g) and 21 CFR 820.3(z)(2).
[58] The preamble to the device QS regulation (61 FR 52619) provides additional detail on use of equivalents: "When equivalent devices are used in the final design validation, the manufacturer must document in detail how the device was manufactured and how the manufacturing is similar to and possibly different from initial production. Where

Design validation activities, for example, may include simulated use testing or clinical/nonclinical evaluation, including human factors[59] and software validation. Some design verification (e.g., bench and/or pre-clinical testing) and validation (e.g., human factors testing, when appropriate) will typically be completed prior to the initiation of clinical studies of safety and efficacy for the combination product, which are also part of design validation. Clinical studies conducted to support safety and/or efficacy of the constituent parts of a combination product may be appropriate to be leveraged as part of the cumulative design validation efforts for the overall combination product.

In addition, manufacturers must perform risk analysis where appropriate,[60] which should begin early in the design process and continue throughout the lifecycle for the product. Risk analysis should enable identification of unacceptable risks so that they can be mitigated. It influences other aspects of design control and additional activities including purchasing controls (see section IV.A.3). Although existing risk analysis for products used as constituent parts of the combination products may be relevant, risk analysis should include considerations for 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 later in product development, during premarket review, or based on postmarket experience (including adverse event reporting) and used to determine whether any aspect of the design should be modified. Standards and guidance addressing conduct of risk management activities such as risk assessment, risk control, risk reporting, and risk review for devices and drugs are appropriate references to inform these activities for a combination product.[61] Also, risk assessment and management activities performed for a drug constituent part under pharmaceutical development practices may become elements of the overall risk analysis for a combination product.

Manufacturers must establish and maintain design transfer procedures to ensure effective translation of design specifications into production methods and procedures.[62] Design transfer is the bridge between the design of the product and the manufacturing process to make the commercial product.

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there are differences, the manufacturer must justify why design validation results are valid for the production units, lots, or batches." For a combination product, this documentation and justification must account for considerations arising from inclusion of a drug or biological product, including equivalence of the manufacturing process for the drug/biologic constituent part or the combination product as a whole. The rationale for equivalence should be documented and may require bridging studies, completion of comparability protocols, or other test data to support that products used for design validation are representative of the combination product that the manufacturer intends to market.

[59] For more information on human factors for combination products, see Draft Guidance for Industry an FDA Staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When finalized, this document will represent the Agency's current thinking on this topic.

[60] 21 CFR 820.30(g).

[61] For more information on risk analysis and risk management see, e.g., ISO 14971 *Risk Management – Medical Devices* and FDA Guidance for Industry *Q9 Quality Risk Management* (June 2006).

[62] 21 CFR 820.30(h).

Manufacturers are 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.[63] Change controls apply once initial design inputs have been approved by the manufacturer.[64] A change control process is essential to manage design changes both during the original design process for the combination product and after the design has been transferred to manufacturing.[65] The records of these changes must be maintained as part of the design history file (21 CFR 820.30(j)). They create a history of the evolution of the design, which can be important when investigating failures or evaluating the appropriateness of proposed, additional changes to the product. A manufacturer may choose to use different processes for premarket (as opposed to postmarket) changes to accommodate the rapid, iterative design process that is often present during investigational stages, so long as the design change and transfer process is compliant with 21 CFR 820.30.

The Design History File (DHF) for a combination product captures all design issues relating to the combined use of the constituent parts. The DHF may not need to document design and development planning for established characteristics of the individual constituent parts, for example 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.[66] If a separately developed drug, device, or biological product constituent part needs to be modified to be used in the combination product, the manufacturer must assess what design control activities must be performed to ensure safety and effectiveness of the combination product (e.g., new formulation of a drug or new features of a device).[67]

It is appropriate for a DHF for a combination product to leverage and cross-reference developmental data and data systems. Manufacturers transitioning from drug development to combination product development should evaluate existing development documentation and systems and assess what, if any, changes may be needed to demonstrate compliance with 21 CFR 820.30. Manufacturers should be able to explain to FDA in premarket submissions and in inspections how their practices and terminology align with the requirements in 21 CFR 820.30,

[63] 21 CFR 820.30(i).
[64] 61 FR 52621, Comment 87.
[65] 21 CFR 820.30(h).
[66] 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 device 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. The information leveraged should typically be covered by a formal agreement between the combination product manufacturer and supplier defining maintenance and sharing of design information. If the component supplier does not itself comply with the device QS regulation, the combination product manufacturer's design control activities for the device constituent part will likely need to be more extensive.
[67] 21 CFR 820.30(c).

and be able to identify and readily access for FDA inspection all documentation needed to demonstrate compliance with design control requirements.

If a manufacturer is evaluating the adequacy of their design controls and documentation for a currently marketed combination product, it may be helpful to review premarket submissions, the product risk profile, and postmarket experience for the combination product. The results of this review can inform decisions on whether additional testing and documentation is required. 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, and OCP as needed, for assistance. For further information on design controls, see the preamble to the final device QS regulation.[68]

3. Purchasing controls (21 CFR 820.50)

Manufacturers of single-entity and co-packaged combination products that include a device constituent part must control purchased products[69] and services as described in 21 CFR 820.50. They must establish such purchasing 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) (21 CFR 820.50(a)). Facilities that have previously manufactured only drugs, rather than devices or combination products, will likely have relevant procedures in place in accordance with part 211, subpart E. However, if these procedures do not demonstrate compliance with the specific requirements of 21 CFR 820.50, they must be augmented to do so.

Manufacturers must evaluate potential suppliers and define the type and extent of control to be exercised over them based on the evaluation results.[70] Manufacturers may design and conduct such evaluations based on factors such as the risks associated with the supplied product or service and complexity of the specifications for it. Manufacturers must establish and maintain records of acceptable suppliers for purchased products and services,[71] and establish and maintain data that clearly describe or reference the specified requirements for products and services received (e.g., contracts with relevant terms).[72]

One way to facilitate purchasing control is the careful structuring of purchasing agreements with suppliers. Where possible, such agreements are used to ensure that the combination product manufacturer is notified of changes to the products, the manufacturing process, or the services being provided.[73] Such notice of changes facilitates compliance not only with purchasing control duties, but also, potentially, with other regulatory requirements, including design control obligations to complete additional design verification testing to address

[68] See Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation, 61 FR 52602-52662 (October 7, 1996).
[69] Under 21 CFR 820.3(r), the term "product" includes components and manufacturing materials, in addition to in-process and finished articles.
[70] See 21 CFR 820.50(a)(2).
[71] See 21 CFR 820.50(a)(3).
[72] See 21 CFR 820.50(b).
[73] See 21 CFR 820.50(b).

the change (e.g., to ensure that the purity and stability of a drug constituent part is maintained when the materials change in a device constituent part that is also a container closure). 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. The combination product manufacturer should ensure agreements are appropriately structured, whether through direct agreements with suppliers and contract manufacturers or through confirmation that such parties have adequate agreements between themselves. For example, a combination product manufacturer may choose to maintain a change agreement with a material supplier who provides material directly to a contract manufacturing facility.

Note that regardless of the nature of purchasing controls, combination product manufacturers must comply with the testing requirements under 21 CFR 211.84 with respect to drug components, and product containers and closures (see IV.B.1 below).

4. Corrective and Preventive Actions (21 CFR 820.100)

Manufacturers of 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).[74] 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 root-cause of problems and the appropriate measures to correct such problems and prevent recurrence. Manufacturers of combination products should document these activities.[75] The CAPA process for combination products also should consider implications of corrective and preventive actions for all constituent parts and for the combination product as a whole.

While combination product manufacturers have flexibility in coordinating CAPA systems across facilities, they maintain responsibility for ensuring that the 21 CFR 820.100 requirements are met. Manufacturers should ensure that an appropriately comprehensive review of activities is undertaken at relevant facilities to determine the cause of existing or potential problems, which could include manufacturing problems, deviations, or nonconformities for a constituent part or the combination product as a whole. The manufacturer should have appropriate mechanisms in place to ensure that issues are identified, action(s) needed to correct and prevent recurrence are taken, and necessary changes are implemented. The manufacturer should take appropriate measures, which may include CAPAs, with regard to all relevant manufacturing steps at all relevant facilities to correct problems and to prevent or mitigate them going forward.

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[74] See also FDA Guidance for Industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (October 2006), which discusses appropriate identification, assessment, and investigation of OOS results for drug products, including results obtained under 21 CFR 211.165 (a provision specified in 21 CFR part 4). Quality data from OOS investigations and any related corrective actions should be addressed through the combination product manufacturer's quality system. Also, FDA guidance for industry, ICH *Q10 Pharmaceutical Quality System* (April 2009), includes additional recommendations for preventive actions and, when failures or other issues occur, corrective actions.

[75] For further guidance, see the preamble to the device QS regulation at 61 Fed. Reg. at 52633-52635, Comments 158-166.

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 single-entity and co-packaged combination product manufacturers must demonstrate compliance when using the device QS regulation-based streamlined approach established under 21 CFR 4.4(b)(2), including considerations specific to applying these requirements to combination products. This discussion is not meant to be a comprehensive analysis, but rather to help manufacturers—particularly device manufacturers, who may be less familiar with drug CGMPs—understand the purpose and basic elements of the provisions of the drug CGMPs specified in 21 CFR 4.4(b)(2), as well as to direct such manufacturers to 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. 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 batches or lots 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 enable traceability of sampling and testing, packaging, and labeling activities, and can be important when assessing and responding to issues including complaints and adverse events. 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.

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.[76] A container closure system is the sum of packaging components that together contain and protect the drug product. This includes primary packaging components and also secondary packaging components if the latter are intended to provide additional protection to the drug product.[77] Examples of packaging components are ampules, vials, screw caps, stoppers, and stopper overseals. As discussed in section III.C.3, container closure systems and elements of container closure systems may also be regulated as devices.

Combination product manufacturers do not need to demonstrate compliance with this provision for device constituent parts or materials used in the manufacture of a device constituent part, unless the device constituent part is also the drug container or closure or a part thereof. For example, for a CGMP operating system established in accordance with 21 CFR 4.4(b)(2) (device

[76] See 21 CFR 210.3(b)(3).
[77] See the Guidance for Industry on *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (May 1999).

QS regulation-based streamlined 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 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. In lieu of such testing, 21 CFR 211.84 allows for some reliance on a supplier's report of 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 activity requirements expressly established under 21 CFR 820.80. Accordingly, if a facility already has 21 CFR 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 compliant 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.[78] The samples collected for each lot must be representative of the entire lot.[79] 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 contamination of the sampled component or of other materials.[80] 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).[81, 82]

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 may suggest problems in the production process, including equipment failure, that may affect product quality and that may not be discovered, or not be discovered as quickly, using sample-based release testing alone. Actual yield discrepancies outside of established and documented allowable variation from theoretical yield should be investigated.

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[78] See 21 CFR 211.84(a).
[79] See 21 CFR 211.84(b).
[80] See 21 CFR 211.84(c).
[81] See 21 CFR 211.84(b).
[82] Some references that may be useful for sampling by variables and sampling by attributes include "American Standards for Testing and Materials (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.

Yield calculation requirements under 21 CFR 211.103 apply to the drug constituent parts of combination products. Data on the number of device constituent parts and components used and lost during the manufacture of a combination product may be necessary to ensure appropriate control of the manufacturing process in accordance with 21 CFR 211.100 or 21 CFR 820.70, but yield calculation in accordance with 21 CFR 211.103 is not required for device constituent parts. However, problems with the device constituent part during combination product manufacturing may affect drug yield and result in further investigation. For example, prefilled syringes that are rejected due to nonconformity of the syringe needle may result in corresponding loss of drug from the batch/lot. Any loss would be captured as part of the yield calculations for the drug constituent part, and investigation of the cause of that loss should identify the manufacturing problem that is leading to these device nonconformities.

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.[83] Accordingly, calculation of yield should be determined at each phase at which component, in-process material, or product loss may occur, including during the formulation of the drug prior to incorporation into the combination product, during incorporation into the combination product (e.g., filling or coating), and, possibly, 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.[84]

For each appropriate phase of the manufacturing process performed, the formula used and the data generated for the yield calculation for the phase should be documented. For manufacturers operating under a device QS regulation-based system, documentation of yield calculations may be incorporated into existing part 820 documentation (for example, as part of the device history record, 21 CFR 820.184). These records should include actual yields, percentages of theoretical yields, and the maximum and minimum percentages of theoretical yield beyond which investigation is required for the drug constituent part, 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 combination product manufacturer's purchasing controls for its 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

[83] See 21 CFR 211.103.
[84] See 21 CFR 211.103.

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.

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.

Certain combination products may be exempt from OTC tamper-evident packaging requirements[85] (e.g., toothpaste co-packaged with a toothbrush) or from bearing a statement of tamper-evident features on the package[86] (e.g., aerosol saline nasal spray).

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.[87]

4. Expiration dating (21 CFR 211.137)

21 CFR 211.137 helps ensure 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 (See section IV.B.6).[88] The expiration dating 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 ensured to retain its integrity and, thereby, maintain a sterile barrier). In some cases, the drug constituent part might not have an expiration date because current regulations exempt it from this requirement.[89] Similarly, some device constituent parts may not have expiration dates.

When expiration dating is required, the constituent parts of combination products may have individual expiration dates or an expiration date for the entire combination product may be appropriate. Generally, when constituent parts of a co-packaged combination product can be used independently, expiration dating should be addressed separately for each constituent part. If a single expiration date is listed for a co-packaged combination product, this date should be the earliest expiration date/shortest shelf-life for any constituent part. The expiration date for a combination product may be shorter than the expiration date or shelf life for its constituent

[85] See 21 CFR 211.132(b)(1).
[86] See 21 CFR 211.132(c)(1).
[87] See 21 CFR 211.132(e).
[88] See 21 CFR 211.137(b).
[89] See 21 CFR 211.137.

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. 21 CFR 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. 21 CFR 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.[90]

Accordingly, manufacturers must test each batch of their combination product to determine satisfactory conformance to final written specifications for the drug constituent part.[91] For single-entity combination products, laboratory testing must be performed on every batch of the combination product; for co-packaged combination products, laboratory testing must be performed on every batch of the drug constituent part(s).[92] This testing ensures that all batches meet appropriate specifications for their approval and release.[93] A detailed listing of all the tests performed and the acceptance criteria used should be maintained and be available for inspection.[94]

In some cases, for single-entity combination products, in lieu of using actual units from a finished combination product batch for testing to determine whether the drug constituent part meets final specifications, manufacturers may wish to use samples that are not finished combination products (but that are representative of the finished combination product with respect to the characteristics and attributes being tested). The Agency does not intend to object to such an approach where the manufacturer can establish, including where appropriate through bridging studies and other quantitative means, that any differences in the manufacturing process for the samples and the finished combination product do not affect the drug constituent part. Such approaches should be supported by appropriate justification and data and discussed with the lead Center, and OCP as needed.

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[90] See 21 CFR 211.165(c).
[91] See 21 CFR 211.165(a).
[92] See 21 CFR 211.165(a).
[93] See 21 CFR 211.165(a), (b).
[94] 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 device QS regulation that are not specified in part 4. If a 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 under the other regulation (that it did not choose as the base for its CGMP operating system). For example, if the facility operates under a device QS regulation-based streamlined 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 in-process materials for drug products may facilitate appropriate consideration of the controls for drug constituent parts.

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. For combination products that include a device constituent part, the combination product manufacturer is responsible for ensuring through purchasing controls in accordance with 21 CFR 820.50 that the drug constituent part conforms to specified requirements, including laboratory testing requirements. 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)

21 CFR 211.166 requires a 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.[95]

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 its marketed container closure system, which may be a device constituent part (or component of a device constituent part).[96] For a single-entity combination product, testing must be performed on the drug constituent part as incorporated into the finished combination product.[97]

The Agency does not intend to object to the use of bracketing and matrix approaches for stability studies where the approach has been adequately justified and, where applicable, reviewed by FDA.[98] The Agency also does not intend to object to leveraging stability data for an already marketed combination product during new product development, with adequate justification and, where applicable, review by FDA. In particular, for purposes of establishing an expiration date for a new combination product, such leveraging may be acceptable if the new product represents a modification to the existing marketed combination product that would not impact the stability of the drug constituent part (for example, a change to the catheter length for a

[95] For further information on stability testing considerations, see, for example, the Guidance for Industry on *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).
[96] See 21 CFR 211.166(a)(4).
[97] See 21 CFR 4.3, 4.4, and 211.166. In addition, while stability testing requirements under 21 CFR 211.166 do not apply to device constituent parts of a co-packaged combination product, under design control requirements, testing must be performed to demonstrate that device functionality (i.e., mechanical performance of the device constituent part) is maintained until the specified expiration date for the combination product. See 21 CFR 820.30.
[98] For further information on bracketing and matrixing considerations, see, for example, the Guidance for Industry on *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* (January 2003).

drug-coated balloon, where the balloon component remains unchanged) and is not otherwise material to the expiration date.[99]

If a new product has minor differences that present a low risk of affecting the stability of the drug (for example, a different size of a drug-coated balloon that is bracketed within the balloon size matrix previously used to establish the expiration date, and without other changes relevant to stability, for example, in the coating application process),[100] the Agency does not intend to object, in appropriate cases, to: i) the use of previously generated stability data for the existing product (or family of products) to support reduced stability data requirements for the new product (for example, generation of only short-term accelerated data) or ii) to incorporating the product into the ongoing stability program for the existing marketed product(s), provided that stability data trends and stability history for the existing product or product family are sufficiently robust for this purpose. Applicants should contact the lead center for their product, or OCP as needed, regarding such approaches.[101]

The need for new stability studies should be evaluated when there are changes to any constituent part of a combination product. For example, changes to the manufacturing process, including changes based on the size or shape of the device constituent part that holds the drug or that is coated with the drug, or changes in material of construction of such a device constituent part, may impact drug stability.

Manufacturers are responsible for establishing and managing the stability program. If a combination product manufacturer purchases a drug product from another manufacturer for inclusion in its co-packaged combination product, the combination product manufacturer is responsible for ensuring the stability of the drug product as marketed in the co-packaged product through appropriate mechanisms, such as by implementing purchasing controls to ensure the adequacy of the drug product manufacturer's stability testing or by conducting additional stability testing (see 21 CFR 820.50). Documentation of such oversight should be included in the CGMP records.

If a drug constituent part of a co-packaged combination product has an expiration date, the combination product manufacturer may be able to rely on that labeled expiration date in lieu of conducting new stability studies, if it can be documented that any additional manufacturing operations conducted on the co-packaged product would not be expected to impact the constituent part, including its container-closure system.

[99] Note that shelf life testing to evaluate the impact of the modification to the device constituent part may still be appropriate.

[100] This might also be the case for a family of products that vary in shape from one another, provided, again, that these variations pose a low risk.

[101] Note that shelf life testing to evaluate the impact of a modification on the device constituent part may still be appropriate.

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 the three categories described above. 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.[102] 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.

For purposes of conducting pyrogen and endotoxin testing, it may be permissible in some circumstances to define a "batch" based on the finished drug product rather than the finished combination product. For example, it may be acceptable to define a batch as a subcomponent of the combination product that incorporates the drug constituent part. However, the viability of such an approach would depend on many factors including: appropriate upstream controls to reduce/limit pyrogens and endotoxins; the chemical or materials-mediated pyrogenicity of the constituent parts, and the risks of pyrogen and endotoxin introduction to the combination product by manufacturing operations that occur after the step at which the batch is defined. For instance, for some products, it may be possible to test material for endotoxin during an in-process manufacturing step and there may be no need to test for endotoxins in the single entity combination product.

21 CFR 211.167(c) would apply both 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-

[102] The requirements related to sterility and non-pyrogenicity of the empty syringe would be addressed through compliance with other provisions (for example, process controls requirements under 21 CFR 211 or 21 CFR 820, design controls requirements under 21 CFR 820.30, and purchasing controls requirements under 21 CFR 820.50). For additional information on pyrogen and endotoxin testing, see the Guidance for Industry on *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012)).

eluting disc or stent would be subject to 21 CFR 211.167(c).

As with drugs and devices, parametric release may be acceptable for some combination products when supported by appropriate data. Such approaches should be discussed with the lead Center, or OCP as needed, prior to implementation and included in premarket submissions.[103]

8. Reserve samples (21 CFR 211.170)

Reserve samples are needed to help ensure the safety and effectiveness of combination products in distribution, 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 for the drug constituent parts of combination products.

Under 21 CFR 211.170, reserve samples must be kept that are representative of both:

- each lot of the active ingredient (21 CFR 211.170(a)), and
- each lot or batch of the drug product (21 CFR 211.170(b)).

All reserve samples must consist of at least twice the quantity necessary to perform all required tests, except those for sterility and pyrogenicity.[104] 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.[105]

Accordingly, single-entity and co-packaged combination product manufacturers alike must keep reserve samples of each lot of the active ingredient, if any, that they receive, in whatever form it arrives at their facility (e.g., as bulk active pharmaceutical ingredient or incorporated into an in-process material).

For co-packaged combination products, the requirement to keep reserve samples of drug products can be met by maintaining samples of the drug constituent part in its immediate container-closure system, without the need to retain any samples of the device or portions of it.[106] For single-entity combination products, the drug product reserve samples should be of the drug constituent part in or upon the device constituent part or components thereof that come into contact with the drug product as packaged for distribution.

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[103] See, for example, Guidance for Industry *Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes* (February 2010) .

[104] 21 CFR 211.170. Stability is not required to be assessed on every drug batch. See 21 CFR 211.166(b). Drug product reserve samples must be visually examined at least once a year while in storage as an ongoing check on the quality of the material in distribution, unless a visual examination would affect the integrity of the reserve sample. 21 CFR 211.170(b).

[105] 21 CFR 211.170(b).

[106] See 21 CFR 211.170(b).

Manufacturers must examine drug product samples for deterioration, investigate evidence of deterioration, and record and maintain the results of such examination.[107] 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.[108] 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.[109] Accordingly, manufacturers should retain samples from each lot of bulk drug substance for 1 year after the expiration date of the last lot of the combination product that uses that lot of the active ingredient.

Combination product manufacturers may choose to have their reserve samples of the API, drug/biologic constituent part, or finished combination product at a location other than the combination product manufacturing facility. In these cases, the combination product manufacturer should have appropriate controls in place to ensure that requirements under 21 CFR 211.170 continue to be met. Such controls could include agreements with the facilities holding the reserve samples to ensure appropriate storage conditions, access to the samples by the combination product manufacturer, ability to analyze the reserve samples, if needed, and maintenance of adequate numbers of samples for each lot.

For combination products, it is generally sufficient to maintain the appropriate number of reserve samples from each lot of the active ingredient and from each lot or batch of the drug constituent part in the immediate container/closure in which it is marketed. For single-entity combination products, the device constituent part may be the drug's container/closure or a part of it, or the container/closure may be distinct from the device constituent part. For a drug-eluting stent or disc, or a prefilled syringe, for example, reserve samples should generally 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 a prefilled cartridge containing the drug, reserve samples of the prefilled cartridge alone would generally suffice to comply with the drug product sample retention requirements. An injector may need to be available, however, to enable testing of reserve samples.

Manufacturers that want to retain and store reserve samples that are representative of, but not identical to, a finished drug constituent part or combination product, as appropriate, should include adequate justification and data to support that:

- Any differences in the manufacturing process for the reserve sample and the finished combination product do not affect the drug constituent part (see discussion in IV.B.5 above);
- The immediate container/closure has essentially the same characteristics as the immediate container/closure for the drug as packaged in the combination product for distribution (if the actual immediate container closure is not being used), and
- The proposed representative samples are suitable for all required testing of the drug constituent part for which those reserve samples are being kept.

[107] See 21 CFR 211.170(b).
[108] See 21 CFR 211.170(b).
[109] See 21 CFR 211.170(a).

It may be possible to keep properly defined and validated surrogates for some testing while retaining complete samples of the combination product for other tests as an alternative to retaining complete samples for all testing. Bracketing and matrixing approaches also may be acceptable, as may use of samples from representative lots of a larger batch (for example, representative samples of each size from within a broadly defined batch that includes multiple sizes from the same family of coated combination products).[110]

Manufacturers considering use of novel approaches to comply with reserve sampling requirements are advised to discuss them with the lead center for their combination product, or OCP, as needed.

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

In addition to complying with drug CGMP and device QS regulation requirements as applicable in accordance with part 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 regulated under section 351 of the PHS Act is also, by definition, a drug or a device. Accordingly, in addition to the requirements in parts 600 through 680, a biological product is always either subject to the drug CGMPs or subject to the device QS regulation, regardless of whether the biological product is a constituent part of a combination product. The CGMP requirements for biological products in parts 600 through 680 augment the drug CGMPs and device QS regulation to ensure adequate consideration of issues for biological products. The CGMP requirements for biological products in 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 parts 600 through 680 must be satisfied if a combination product includes a biological product constituent part. However, 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 considerations specific to the particular biological product.

[110] FDA notes that approaches that depend upon retaining samples against more broadly defined batches may increase the number of distributed products implicated when corrective actions are necessary to address postmarket issues.

In short, the specific requirements in 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 or OCP, as needed, for assistance.

2. Complying with CGMPs for HCT/Ps

An HCT/P that is not regulated solely under section 361 of the PHS Act and Part 1271 is also regulated as a drug, device, or biological product. [111] The drug CGMPs, device QS regulation, and the requirements in parts 600 through 680 may apply to an HCT/P depending on whether the product is regulated as a drug, device, or biological product.[112] CGMPs and the CGTPs for HCT/Ps supplement one another and do not supersede each other unless the regulation specifically provides otherwise. In the event that a regulation in part 1271 is in conflict with a requirement in parts 210, 211, 600 through 680, or 820, the regulations more specifically applicable to the product in question will supersede the more general.[113]

The CGTPs, including donor eligibility 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. Accordingly, the current CGTPs apply to combination products that include an HCT/P. However, requirements under some sections of part 1271 overlap with the requirements under the drug CGMPs and the device QS regulation. These overlaps are addressed 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*).

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[111] 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 part 1271 and those that are also regulated as drugs, devices, and/or biological products. Section 1271.10 provides that an HCT/P is regulated solely under section 361 of the PHS Act if it meets all of the following criteria: (1) it is minimally manipulated; (2) it is in intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent; (3) manufacturer of the HCT/P does not involve the combination of the cells or tissues with another article (other than water, crystalloids, or a sterilizing, preserving, or storage agent) provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and (4) Either: (i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use, is for allogeneic use in a first-degree or second-degree blood relative; or is for reproductive use. 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.

[112] See 78 FR 4317.

[113] 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).

21 CFR 1271.150(d) explains 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 parts 210, 211, and 820, supplement one another. As a consequence, compliance with certain provisions of part 211 or 820 may also constitute partial or complete compliance with certain provisions of part 1271. However, for certain issues, the CGTP requirements would require additional manufacturing practices. The adjustments that might need to be made to an existing CGMP operating system to be fully compliant with the 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 under 21 CFR 211, a device manufacturing system under part 820, or a combination product manufacturing system that demonstrates compliance with 21 CFR 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. Accordingly, the Agency encourage manufacturers to contact the lead center for their product or OCP, as needed, with 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 device QS regulation, each example is used to focus on particular 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 device QS regulation provisions specified in 21 CFR 4.4(b)(1) if a manufacturer adopts a drug CGMP-based streamlined approach for its CGMP operating system.

- Section B, a drug-coated mesh example, focuses on considerations for complying with certain device QS regulations after a drug constituent part is combined with a device.

- 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 device QS regulation-based streamlined approach for its CGMP operating system.

This discussion is intended to highlight only certain issues that a combination product might raise relating to the CGMP provisions specified in 21 CFR 4.4(b), and considerations for addressing these issues. The discussion may be helpful to inform understanding of the CGMP provisions that are addressed here not only in regard to the types of combination products in the scenarios, but for other types of combination products as well. However, this discussion is not intended to reflect a complete analysis of the CGMP issues that need to be addressed for the types of products discussed in the scenarios or other types of combination 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 or 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.[114] Manufacturer A already has marketing approval for the drug product and intends to apply for marketing approval for the prefilled syringe presentation. No changes to the drug formulation 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.[115] To do so, Manufacturer A opts to establish a CGMP operating system using the drug CGMP-based streamlined 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 device QS regulation specified in 21 CFR 4.4(b)(1).

2. Compliance with device QS regulation requirements

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

a) 21 CFR 820.20, Management Responsibility

While section 501 of the FD&C Act (21 U.S.C. 351) and 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). [116]

[114] The design control considerations for a prefilled syringe with a biological product are largely similar to those covered in the example, although some additional issues may be more common such as the interaction of the biological product with the syringe materials and the effect of product viscosity on delivery.
[115] See 21 CFR part 4.
[116] See 21 CFR 4.4(b)(1).

Manufacturer A should, for example, review its existing CGMP operating system to assess whether changes are needed to comply with this provision. As part of this review, 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 that both the policy and oversight are adequate. The oversight procedures should include 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 the CGMP operating system for this product at the facility.

b) 21 CFR 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 owner 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 having overall responsibility 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 documentation from the design controls Manufacturer B uses for its finished syringes.[117] Because no changes are to be made to the drug other than being put into the syringe, the drug comes into the design control process as an input to the design of the syringe to ensure that the syringe's design reflects adequate consideration of the drug's characteristics, as indicated below.

An appropriate first step for Manufacturer A would be to review Manufacturer B's design control data to determine what new questions are raised by the use of the syringe with the drug, and to assess what additional design control activities may be needed as a consequence. It may be the case, for example, that Manufacturer A can demonstrate that the only new design questions that are raised concern the performance of the syringe as a container/closure to store the drug and the extent to which the contact between the syringe and the drug may affect its performance as a delivery system. Regardless, Manufacturer A must ensure that all design considerations for the combination product are addressed in accordance with 21 CFR 820.30.

[117] If the supplier of the device components did not have design control information, Manufacturer A would likely need to undertake more extensive design control activities for the syringe. For example, Manufacturer A would need to perform device-specific verification testing to confirm that the syringe meets necessary specifications for plunger force or other parameters if the syringe component supplier has not conducted such testing suitable to enable leveraging.

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.

Design Input/User Needs	*Design Output*
Required minimum/maximum dose delivery for drug	Drawing/specification for syringe dimensions, markings, etc.
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, etc.
Expected use condition (e.g., expected user experience/education level)	Content and reading level for the prefilled syringe's labeling
Maximum and minimum allowable temperature for prefilled syringe	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, labeling for acceptable storage conditions
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

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.[118] 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; [119] 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 DHF 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).

[118] See 21 CFR 820.30(f) and (g).

[119] For additional information on biocompatibility, see *Guidance for Industry and FDA Staff: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"* (June 2016).
See also, USP Chapter <87> *Biological Reactivity, In Vitro* and USP <88> *Biological Reactivity Tests, In Vivo*.

iii. Risk Analysis

Manufacturer A should identify risks associated with the prefilled syringe design, its manufacturing processes, and intended uses, and also reduce or mitigate any unacceptable risk(s).[120] The table below lists some potential risks associated with prefilled syringes and potential mitigations for these risks.

Risk	*Mitigation*
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 of syringe construction	Purchasing controls (including receiving acceptance activities for components received from 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(s)

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.[121] 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 a material used in the syringe that comes into contact with the drug, Manufacturer A should conduct verification activities to ensure that no degradation of performance characteristics will occur before the expiration date for the combination product as a result of the change of materials.[122] Likewise, any change to the formulation of the drug should include design control activities such as verification to confirm that the new formulation does not degrade performance of the syringe. All of this information would need to become a part of the DHF.[123]

v. Design history file

The DHF may include references or point to information residing elsewhere so long as the reference or pointer is precise enough to allow the necessary information to be readily

[120] See 21 CFR 820.30(g).
[121] See 21 CFR 820.30(i).
[122] Changes to materials that contact the drug may raise drug CGMP considerations, for example, under stability testing and expiration dating requirements (21 CFR 211.137 and 21 CFR 211.167). When possible, manufacturers may leverage data collected in meeting these 21 CFR 211 requirements when determining what verification activities are required under 21 CFR 820.30.
[123] See 21 CFR 820.30(j).

accessed as needed, including for inspections. For example, elements of the syringe component manufacturer's design documentation may be relied upon to support the combination product DHF. Such information on the syringe may reside at Manufacturer B's (syringe component manufacturer) facility, so long as the necessary documentation can be accessed in a reasonable time during inspection of Manufacturer A. Manufacturer A should ensure access to such documentation through supplier agreements with Manufacturer B under its purchasing controls (21 CFR 820.50). Documentation of development of the drug product that preceded the design effort to incorporate the drug product into a prefilled syringe may be referenced in the DHF and become an input to the combination product design effort (though such drug-only development is not itself subject to design controls).

c) 21 CFR 820.50, Purchasing Controls

Manufacturer A is required to control its purchasing activities, including for the syringe components, in accordance with 21 CFR 820.50.[124] 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 to this material prior to implementation of the change. Similarly, if Manufacturer A uses an outside facility for terminal sterilization of the prefilled syringe, Manufacturer A must also have appropriate controls over that sterilization service provider.[125]

d) 21 CFR 820.100, Corrective and Preventive Actions

Manufacturer A is required to establish and maintain CAPA procedures for the combination product. Following are two examples of issues that might arise and exemplary steps for addressing them:

Example 1: Manufacturer A has implemented in-process manufacturing verification procedures to confirm that the syringe is being filled with the correct amount of the drug, and the data from this verification are analyzed for potential nonconformities. Manufacturer A notes an increase in nonconformities relating to the volume of drug being put 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. Manufacturer A updates the maintenance procedures and performs verification/validation testing to confirm that the changes correct the problem and do not cause new ones.

Example 2: Manufacturer A begins receiving an increased number of customer complaints related to holes or other damage to the syringe's 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.

[124] 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.
[125] See 21 CFR 820.50.

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) 21 CFR 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 a drug to treat infection at the site of the product's implantation. Manufacturer B has an approval to market a drug for local administration to 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). Therefore, Manufacturer A is subject both to the drug CGMPs and the device QS regulation for this combination product. Accordingly, Manufacturer A must ensure that its CGMP operating system complies with both the device QS regulation and drug CGMPs, in accordance with one of the approaches permitted under 21 CFR 4.4. Because Manufacturer A is already marketing the uncoated mesh, it has an existing device QS regulation-based operating system, and chooses to operate under a device QS regulation-based streamlined approach for the combination product. This discussion focuses on design control and purchasing control considerations arising from inclusion of the drug constituent part in the combination product.

a) 21 CFR 820.30, Design Controls

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 treatment 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 the required dose is provided when the drug elutes from the mesh.[126] In addition, risk analysis must be conducted to identify any risks associated with the design, manufacturing, and use of the mesh.[127] Mitigation measures should then be identified and performed to address any identified risks. Design reviews should cover these and other related design considerations for the product, and personnel with expertise in both the drug- and device-specific issues (as well as an individual independent from the design stage being reviewed) should be included in these reviews. The transfer of the product design into production specifications should address all important aspects of the drug constituent part for use in the combination product.[128]

i. Design inputs and outputs

The table below includes illustrative examples of design inputs, including user needs, and corresponding design outputs relating to the inclusion of the drug constituent part.

Design Input/User Needs	*Design Output*
Required delivery dose and delivery rate for the drug	Drug formulation and concentration, coating thickness, uniformity of coating, manufacturing process requirements, allowable storage conditions
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 formulation drug-contacting materials and packaging, shelf-life labeling
No degradation of the surgical mesh over the expected shelf-life	Specifications for mesh material, drug formulation and packaging, 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 treat infections. Manufacturer A must develop adequate clinical data (design validation) to ensure that the drug, when combined with the mesh, is effective in treating infection and does not raise safety concerns.[129] Design outputs from this study would include the drug concentration in the coating formulation (to be specified in purchasing controls over Manufacturer B)

[126] See 21 CFR 820.30(d), (f), and (g).
[127] See 21 CFR 820.30(g).
[128] See 21 CFR 820.30(h).
[129] See 21 CFR 820.30(g).

and the coating thickness (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 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.[130] The results would be used to define and develop design outputs for the combination product, including in-process acceptance testing criteria during manufacturing, appropriate product specifications for the drug coated mesh, and instructions for use.

- Another input to the design process is that the product have a shelf-life consistent with the stability of the drug formulation and the mesh. Manufacturer A would perform design verification testing such as bench testing after 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, as well as stability studies[131] 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 for 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.

Risk	*Mitigation*
Drug concentration in coating not sufficient to treat infection (e.g., due to insufficient drug coating per surface area of the mesh or non-uniformity of coating), inappropriate delivery rate	Clinical testing of the combination product, in-process acceptance testing, manufacturing process validation
Mesh erodes or drug degrades during use or storage	Design verification testing (bench), clinical testing, labeling (instructions for use, expiration dating), purchasing controls over drug supplier, specifications and other process controls

iv. Design history file

All of the design control activities required by 21 CFR 820.30 (summarized in IV.A.2 above) must be addressed in the DHF for the drug-coated mesh. The information developed as a

[130] See 21 CFR 820.30(f).
[131] See the Guidance for Industry on *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

result of design control activities will be assessed as part of premarket review of this combination product (e.g., the suitability of the drug formulation and the compatibility of the mesh with the drug). Accordingly, much of the information included in the DHF would be submitted as part of the premarket review process. Manufacturer A may opt to incorporate such information into the DHF by cross-reference to such premarket documentation. Whatever approach Manufacturer A selects must ensure that all required design history information is readily available to FDA for review.

The DHF 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 independently marketed. These existing data that supported approval of the drug would be available as a reference for the combination product DHF to enable development of design inputs for the drug constituent part and the combination product as a whole, and thus facilitate its development process.

b) 21 CFR 820.50, Purchasing Controls

Manufacturer A already has established procedures for controlling purchasing/supplier activities pursuant to 21 CFR 820.50. Under this provision, Manufacturer A must ensure that appropriate purchasing controls for Manufacturer B are established and maintained. In particular, based on 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.[132]

Purchasing controls (and acceptance activities under 21 CFR 211.84) with respect to the drug constituent part 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 Manufacturer B's implementation of the changes. The notifications should address issues including changes in the drug specification, its components, composition of drug coating materials, or the drug manufacturing process or facility. 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 the purity and stability of the drug is maintained, pursuant to the requirements of 21 CFR 820.30(i).

C. Drug Eluting Stent (DES)

1. Scenario Description

In this scenario, Manufacturer A is the owner for a drug-eluting stent (DES) composed of a stent coated with a drug. Manufacturer B manufactures the active pharmaceutical ingredient

[132] See 21 CFR 820.50(a)(2).

(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 primary 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 device QS regulation and has elected to establish a device QS regulation-based streamlined approach for the DES in accordance with 21 CFR 4.4(b)(2). While Manufacturer A must ensure that this operating system complies with the device 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).

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

Manufacturer A has controls in place to evaluate suppliers, contractors, and consultants based on their ability to meet quality and other specified requirements and to control incoming materials in accordance with 21 CFR 820.50 and 21 CFR 820.80. 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.

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 primary packaging materials, in conformance with 21 CFR 820.50(a)(1). In addition, under its CGMP operating system for the facility, Manufacturer A has controls to identify the acceptance status of manufactured products. Manufacturer A's responsibilities under 21 CFR 211.84 relate to these various obligations and controls arising from the device QS regulation.

In accordance with 21 CFR 211.84, the bulk drug substance, polymer, and primary packaging materials supplied by manufacturers B, C, and D must be sampled, tested, or examined, as appropriate, by Manufacturer A to determine whether they should be approved or rejected for use. The primary packaging materials should be visually inspected to ensure that the correct, specified materials are received from Manufacturer D. Each lot of bulk drug substance and polymer must be tested to verify conformity with written specifications for purity, quality, and strength.[133] Due to the nature and intended use of sterile drug eluting stents, testing must include microbiological testing of the bulk drug substance and polymer.

[133] See 21 CFR 211.84(d)(2).

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 that 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 the following conditions are met.[134]

Manufacturer A is still responsible for the performance of at least one specific identity test upon receipt of each lot of the bulk drug substance, even when a report of analysis accompanies the lot.[135] 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.[136] The supplier can be evaluated through initial purchasing controls and subsequently at suitable intervals. A similar analysis would apply if Manufacturer C were to conduct conformity testing for the polymer it supplies to Manufacturer A. Incoming examination or testing by Manufacturer A and receipt of any reports of analysis must occur prior to use of the material in the manufacture of the DES.

b) 21 CFR 211.103, Calculation of yield

Calculation of yield should be conducted during all appropriate steps in the manufacturing process prior to and after application of the coating to the stent, including the formulation of the coating.[137] Manufacturer A is responsible for the calculation of yield at appropriate phases of manufacture at its facility, including application of the coating to the DES, and the packaging of the DES. The formula used and the data generated for the calculation should be maintained in Manufacturer A's batch production and control 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 for the finished packaged DES and should also take into account other shelf-life considerations as required under

[134] See 21 CFR 211.84(d)(2).
[135] 21 CFR 211.84(d)(2).
[136] See 21 CFR 211.84(d)(2).
[137] Drug-coated stents that are rejected due only to defects in the device constituent part (stent) will result in corresponding loss of drug constituent part from the batch/lot. This loss should be captured as part of the yield calculations for the drug constituent part and investigation of the cause of that loss should identify the manufacturing problem that is leading to these device constituent part nonconformities.

design control. These considerations include the functionality of the stent and polymer and the integrity of the coating and the packaging.[138]

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 the final written specifications for the product.[139] 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 prepared and documented in standard operating procedures. A general list of tests for drug-eluting stents is provided below:

- Appearance
- Identification
- Assay
- Impurities and Degradation Products
- Content Uniformity
- Drug Release Rate (immediate and/or extended release rates)
- Package Integrity and Sterility Assurance
- 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.[140]

g) 21 CFR 211.167, Special testing requirements

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

[138] See 21 CFR 211.137(a) and (b).
[139] See 21 CFR 211.165(a).
[140] If Manufacturer A decides to develop a family of drug-eluting stents over time, differing from one another in the size of the stent, the Agency does not intend to object to the manufacturer's leveraging previously generated stability data for the existing versions to establish expiration dating for later versions, or newer products being incorporated into the ongoing stability program for the existing marketed drug-eluting stents, so long as the manufacturer can provide adequate justification and such approaches have been reviewed by FDA, where applicable.

h) 21 CFR 211.170, Reserve samples

Manufacturer A must maintain reserve samples representative of each lot of the active ingredient used in the combination product and of each lot or batch of the finished, packaged DES.[141] Reserve samples must consist of at least twice the quantity necessary to perform all tests required for the active ingredient and the finished DES, excluding sterility and pyrogen testing.[142] The reserve samples must be kept for the time periods required by 21 CFR 211.170. The samples of the active ingredient must be kept for 1 year past the expiration date of the last lot of finished drug-eluting stents to use that lot of the active ingredient.[143] The samples for each lot or batch of the finished DES must be kept for 1 year after the expiration date for the combination product.[144] If Manufacturer A maintains reserve samples in a third-party storage facility, Manufacturer A should ensure, via purchasing controls (21 CFR 820.50), that the facility can meet applicable CGMP requirements.[145]

VI. Contact Us

If you have questions regarding compliance with CGMP requirements for combination products after reviewing this guidance and the materials 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. You may follow existing processes for your lead center when requesting feedback on combination product issues (e.g., meeting requests to CBER/CDER,[146] pre-submissions to CDRH[147]).

1. CBER

Mail: Office of Communication, Outreach and Development (OCOD)
10903 New Hampshire Avenue
Building 71, Room 3128
Silver Spring, MD 20993
Phone: 1-800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov

[141] See 21 CFR 211.170(a) and (b).
[142] See 21 CFR 211.170(a) and (b).
[143] See 21 CFR 211.170(a)(1).
[144] See 21 CFR 211.170(b)(1).
[145] 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). When finalized, this guidance will represent FDA's current thinking on this topic.
[146] See *Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants* (May 2009).
[147] See *Guidance for Industry and FDA Staff: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* (February 2014).

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

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

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

VII. Glossary

Note: this glossary is for use exclusively with this guidance document. Definitions that have been taken from federal regulations include the relevant citation.

Constituent part: A drug, device, or biological product that is part of a combination product. (21 CFR 4.2)

Co-packaged combination product: 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. (21 CFR 3.2(e)(2))

Cross-labeled combination product: (i) 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; or (ii) 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. (21 CFR 3.2(e)(3) and 21 CFR 3.2(e)(4))

Device QS regulation-based streamlined approach: A CGMP operating system that is intended to demonstrate compliance with all of the provisions of the device QS regulation and the following provisions from the drug CGMPs in accordance with 21 CFR 4.4(b)(2):

(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

Drug CGMPs: The current good manufacturing practice regulations set forth in 21 CFR 210 and 21 CFR part 211. (21 CFR 4.2)

Drug CGMP-based streamlined approach: A CGMP operating system that is intended to demonstrate compliance with all of the provisions from the drug CGMPs and the following provisions from the device QS regulation in accordance with 21 CFR 4.4(b)(1):

(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

Lead center: The FDA center (CBER, CDER, or CDRH) that has primary jurisdiction for premarket review and regulation of a combination product.

Manufacture: Includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage. (21 CFR 4.2)

CGMP operating system: The operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements for a combination product. (21 CFR 4.2)

Owner: For purposes of this guidance, the entity that holds the marketing authorization for a combination product (regardless of whether that entity is directly engaged in the manufacture of the product).

Device QS regulation: The quality system regulation in 21 CFR part 820. (21 CFR 4.2)

Single-entity combination product: 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. (21 CFR 3.2(e)(1))

Streamlined approach: Either of the two approaches permitted under 21 CFR part 4, which allows combination product manufacturers to demonstrate compliance with both the drug CGMPs and device QS regulation by designing and implementing a CGMP operating system that demonstrates compliance with part 211 or part 820 in its entirety plus specified provisions of the other set of regulations.

VIII. References

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