

PART 4 REGULATION OF COMBINATION PRODUCTS

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Subpart A--Current Good Manufacturing Practice Requirements for Combination Products

Sec. 4.1 What is the scope of this subpart?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- (a) The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part;
- (b) The current good manufacturing practice requirements in part 820 of this chapter apply to a combination product that includes a device constituent part;
- (c) The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to which those requirements would apply if that constituent part were not part of a combination product; and
- (d) The current good tissue practice requirements including donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P.

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

- (a) Under this subpart, for single entity or co-packaged combination products, compliance with all applicable current good manufacturing practice requirements for the combination product shall be achieved through the design and implementation of a current good manufacturing practice operating system that is demonstrated to comply with:
 - (1) The specifics of each set of current good manufacturing practice regulations listed under 4.3 as they apply to each constituent part included in the combination product; or
 - (2) Paragraph (b) of this section.
- (b) If you elect to establish a current good manufacturing practice operating system in accordance with paragraph (b) of this section, the following requirements apply:
 - (1) If the combination product includes a device constituent part and

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

- (i) Section 820.20 of this chapter. Management responsibility.
- (ii) Section 820.30 of this chapter. Design controls.
- (iii) Section 820.50 of this chapter. Purchasing controls.
- (iv) Section 820.100 of this chapter. Corrective and preventive action.
- (v) Section 820.170 of this chapter. Installation.
- (vi) Section 820.200 of this chapter. Servicing.

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

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

(3) In addition to being shown to comply with the other applicable manufacturing requirements listed under 4.3, if the combination product includes a biological product constituent part, the current good manufacturing practice operating system must also be shown to implement and comply with all manufacturing requirements identified under 4.3(c)

that would apply to that biological product if that constituent part were not part of a combination product.

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

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

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

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

Subpart B [Reserved]

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