21 Code of Federal Regulations applicable to Combination Products:

Parts 4, 11, 210, 211 and 820

21 CFR Part 4
Regulation of Combination Products

21 CFR Part 210
Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General

21 CFR Part 211
Current Good Manufacturing Practice for Finished Pharmaceuticals

21 CFR Part 820
Quality System Regulation (Medical Devices)

21 CFR Part 11
Electronic Records; Electronic Signatures

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Subpart A - Current Good Manufacturing Practice Requirements for Combination Products

§ 4.1 What is the scope of this subpart?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(c) The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to

practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.
[43 FR 45076, Sept. 29, 1978, as amended at 69 FR 29828, May 25, 2004]

§210.2 Applicability of current good manufacturing practice regulations

(a) The regulations in this part and in Parts 211, 225, and 226 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.
(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211, 225, and 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.
(c) An investigational drug for use in a phase 1 study, as described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

[43 FR 45076, Sept, 29, 1978, as amended at 73 FR 40463, July 15, 2008, 74 FR 65431, Dec. 12 2011]

§210.3 Definitions

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211, 225, and 226 of this chapter.
(b) The following definitions of terms apply to this part and to Parts 211, 225, and 226 of this chapter.
(1) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).
(2) *Batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.
(4) *Drug product* means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
5) *Fiber* means any particulate contaminant with a length at least three times greater than its width.
(6) *Non-fiber-releasing filter* means any filter which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered.
(7) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
(8) *Inactive ingredient* means any component other than an "active ingredient."