and any consulting agency components. The product jurisdiction officer may request a meeting with the sponsor during the review period to discuss the request for designation. If the product jurisdiction officer has not issued a letter of designation within 60 days of the filing date of a request for designation, the sponsor's recommendation of the center with primary jurisdiction, in accordance with §3.7(c)(3), shall become the designated agency component.

(c) Request for reconsideration by sponsor: If the sponsor disagrees with the designation, it may request the product jurisdiction officer to reconsider the decision by filing, within 15 days of receipt of the letter of designation, a written request for reconsideration not exceeding 5 pages. No new information may be included in a request for reconsideration. The product jurisdiction officer shall review and act on the request in writing within 15 days of its receipt.

§3.9 Effect of letter of designation.

(a) The letter of designation constitutes an agency determination that is subject to change only as provided in paragraph (b) of this section.

(b) The product jurisdiction officer may change the designated agency component with the written consent of the sponsor, or without its consent to protect the public health or for other compelling reasons. A sponsor shall be given 30 days written notice of any proposed nonconsensual change in designated agency component. The sponsor may request an additional 30 days to submit written objections, not to exceed 15 pages, to the proposed change, and shall be granted, upon request, a timely meeting with the product jurisdiction officer and appropriate center officials. Within 30 days of receipt of the sponsor's written objections, the product jurisdiction officer shall issue to the sponsor, with copies to appropriate center officials, a written determination setting forth a statement of reasons for the proposed change in designated agency component. A nonconsensual change in the designated agency component requires the concurrence of the Principal Associate Commissioner.

[56 FR 58756, Nov. 21, 1991, as amended at 68 FR 37077, June 23, 2003]

§3.10 Stay of review time.

Any filing with or review by the product jurisdiction officer stays the review clock or other established time periods for agency action for an application for marketing approval or required investigational notice during the pendency of the review by the product jurisdiction officer.

Subpart B [Reserved]

PART 4—REGULATION OF COMBINATION PRODUCTS

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

Subpart B—Postmarketing Safety Reporting for Combination Products

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

EFFECTIVE DATE NOTE: Amendments to the part 4 authority citation were published at

90 FR 51765, June 18, 2024, effective Dec. 18, 2025.

SOURCE: 78 FR 4321, Jan. 22, 2013, unless otherwise noted.

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

§ 4.1 What is the scope of this subpart?

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

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

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

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

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

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

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

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

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

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

[78 FR 4321, Jan. 22, 2013]

EFFECTIVE DATE NOTE: At 89 FR 7522, Feb. 2, 2024, §4.2 was amended, effective Feb. 2, 2026.

§ 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.

EFFECTIVE DATE NOTE: Amendments to § 4.3 were published at 89 FR 51765, June 18, 2024, effective Feb. 2, 2026.

§ 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.

[78 FR 4321, Jan. 22, 2013]

EFFECTIVE DATE NOTE: Amendments to §4.4 were published at 89 FR 7522, Feb. 2, 2024, and at 89 FR 51766, June. 18, 2024, effective Feb. 2, 2026.

Subpart B—Postmarketing Safety Reporting for Combination Products

SOURCE: 81 FR 92624, Dec. 20, 2016, unless otherwise noted.

§ 4.100 What is the scope of this subpart?

(a) This subpart identifies postmarketing safety reporting requirements for combination product applicants and constituent part applicants.

(b) This subpart does not apply to investigational combination products, combination products that have not received marketing authorization, or to persons other than combination product applicants and constituent part applicants.

(c) This subpart supplements and does not supersede other provisions of this chapter, including the provisions in parts 314, 600, 606, 803, and 806 of this chapter, unless a regulation explicitly provides otherwise.

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

Abbreviated new drug application (ANDA) has the same meaning given the term ''abbreviated application'' in §314.3(b) of this chapter.

Agency or we means Food and Drug Administration.

Applicant means, for the purposes of this subpart, a person holding an application under which a combination product or constituent part of a combination product has received marketing authorization (such as approval, licensure, or clearance). For the purposes of this subpart, applicant is used interchangeably with the term ''you.''

Application means, for purposes of this subpart, a BLA, an NDA, an ANDA, or a device application, including all amendments and supplements to them.

Biological product has the meaning given the term in section 351 of the Public Health Service Act (42 U.S.C. 262).

Biological product deviation report (BPDR) is a report as described in §§600.14 and 606.171 of this chapter.

Biologics license application (BLA) has the meaning given the term in section 351 of the Public Health Service Act (42 U.S.C. 262) and §601.2 of this chapter.

Combination product has the meaning given the term in §3.2(e) of this chapter.

Combination product applicant means an applicant that holds the application(s) for a combination product.

Constituent part has the meaning given the term in § 4.2.

Constituent part applicant means the applicant for a constituent part of a combination product the constituent parts of which are marketed under applications held by different applicants.

Correction or removal report is a report as described in § 806.10 of this chapter.

De novo classification request is a submission requesting *de novo* classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act.

Device has the meaning given the term in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Device application means a PMA, PDP, premarket notification submission, *de novo* classification request, or HDE.

Drug has the meaning given the term in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act.

Field alert report is a report as described in § 314.81 of this chapter.

Fifteen-day report is a report required to be submitted within 15 days as described in § 314.80 of this chapter or § 600.80 of this chapter, as well as followup reports to such a report.

Five-day report is a report as described in §§ 803.3 and 803.53 of this chapter, as well as supplemental or followup reports to such a report as described in § 803.56 of this chapter.

Humanitarian device exemption (HDE) has the meaning given the term in § 814.3 of this chapter.

Malfunction report is a report as described in § 803.50 of this chapter as well as supplemental or followup reports to such a report as described in § 803.56 of this chapter.

New drug application (NDA) has the meaning given the term ''application'' in § 314.3(b) of this chapter.

Premarket approval application (PMA) has the meaning given the term in § 814.3 of this chapter.

Premarket notification submission is a submission as described in § 807.87 of this chapter.

Product Development Protocol (PDP) is a submission as set forth in section 515(f) of the Federal Food, Drug, and Cosmetic Act.

§ 4.102 What reports must you submit to FDA for your combination product or constituent part?

(a) *In general.* If you are a constituent part applicant, the reporting requirements applicable to you that are identified in this section apply to your constituent part, and if you are a combination product applicant, the reporting requirements applicable to you that are identified in this section apply to your combination product as a whole.

(b) *Reporting requirements applicable to both combination product applicants and constituent part applicants.* If you are a combination product applicant or constituent part applicant, you must comply with the reporting requirements identified in paragraphs (b)(1), (b)(2), or (b)(3) of this section for your product based on its application type. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (c) of this section for the same event that: Includes the information required under the applicable regulations identified in this paragraph, is required to be submitted in the same manner under § 4.104, and meets the deadlines under the applicable regulations identified in this paragraph.

(1) If your combination product or device constituent part received marketing authorization under a device application, you must comply with the requirements for postmarketing safety reporting described in parts 803 and 806 of this chapter with respect to your product.

(2) If your combination product or drug constituent part received marketing authorization under an NDA or ANDA, you must comply with the requirements for postmarketing safety reporting described in part 314 of this chapter with respect to your product.

(3) If your combination product or biological product constituent part received marketing authorization under a BLA, you must comply with the requirements for postmarketing safety reporting described in parts 600 and 606 of this chapter with respect to your product.

(c) *Reporting requirements applicable only to combination product applicants.* If you are a combination product applicant, in addition to compliance with paragraph (a) of this section, you must also comply with the reporting requirements identified under this paragraph as applicable to your product based on its constituent parts. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (b) of this section for the same event that: Includes the information required under the applicable regulations for the report identified in this paragraph; is required to be submitted in the same manner under § 4.104 of this chapter; and, unless otherwise specified in this paragraph, meets the deadlines under the applicable regulations for the report identified in this paragraph.

(1) If your combination product contains a device constituent part, you must submit:

(i) Five-day reports;

(ii) Malfunction reports; and

(iii) Correction or removal reports, and maintain records as described in § 806.20 of this chapter for corrections and removals not required to be reported.

(2) If your combination product contains a drug constituent part, you must submit:

(i) Field alert reports; and

(ii) Fifteen-day reports as described in § 314.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(3) If your combination product contains a biological product constituent part, you must submit:

(i) Biological product deviation reports; and

(ii) Fifteen-day reports as described in § 600.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(d) *Other reporting requirements for combination product applicants.* (1) If you are the combination product applicant for a combination product that contains a device constituent part and that received marketing authorization under an NDA, ANDA, or BLA, in addition to the information otherwise required in the periodic safety reports you submit under § 314.80 or § 600.80 of this chapter, your periodic safety reports must also include a summary and analysis of the reports identified in paragraphs (c)(1)(i) and (ii) of this section that were submitted during the report interval.

(2) If you are the combination product applicant for a combination product that received marketing authorization under a device application, in addition to the reports required under paragraphs (b) and (c) of this section, you must submit reports regarding postmarketing safety events if notified by the Agency in writing that the Agency requires additional information. We will specify what safety information is needed and will require such information if we determine that protection of the public health requires additional or clarifying safety information for the combination product. In any request under this section, we will state the reason or purpose for the safety information request, specify the due date for submitting the information, and clearly identify the reported event(s) related to our request.

§ 4.103 What information must you share with other constituent part applicants for the combination product?

(a) When you receive information regarding an event that involves a death or serious injury as described in § 803.3 of this chapter, or an adverse experience as described in § 314.80(a) of this chapter or § 600.80(a) of this chapter, associated with the use of the combination product, you must provide the information to the other constituent part applicant(s) for the combination product no later than 5 calendar days of your receipt of the information.

(b) With regard to information you must provide to the other constituent part applicant(s) for the combination product, you must maintain records that include:

(1) A copy of the information you provided,

(2) The date the information was received by you,

(3) The date the information was provided to the other constituent part applicant(s), and

(4) The name and address of the other constituent part applicant(s) to whom you provided the information.

§ 4.104 How and where must you submit postmarketing safety reports for your combination product or constituent part?

(a) If you are a constituent part applicant, you must submit postmarketing safety reports in accordance with the regulations identified in § 4.102(b) that are applicable to your product based on its application type.

(b) If you are a combination product applicant, you must submit postmarketing safety reports required under § 4.102 in the manner specified in the regulation applicable to the type of report, with the following exceptions:

(1) You must submit the postmarketing safety reports identified in § 4.102(c)(1)(i) and (ii) in accordance with § 314.80(g) of this chapter if your combination product received marketing authorization under an NDA or ANDA or in accordance with § 600.80(h) of this chapter if your combination product received marketing authorization under a BLA.

(2) You must submit the postmarketing safety reports identified in § 4.102(c)(2)(ii) and (c)(3)(ii) in accordance with § 803.12(a) of this chapter if your combination product received marketing authorization under a device application.

§ 4.105 What are the postmarketing safety reporting recordkeeping requirements for your combination product or constituent part?

(a) If you are a constituent part applicant:

(1) You must maintain records in accordance with the recordkeeping requirements in the applicable regulation(s) described in § 4.102(b).

(2) You must maintain records required under § 4.103(b) for the longest time period required for records under the postmarketing safety reporting regulations applicable to your product under § 4.102(b).

(b) If you are a combination product applicant, you must maintain records in accordance with the longest time period required for records under the regulations applicable to your product under § 4.102.

PART 5—ORGANIZATION

Subparts A–L [Reserved]

Subpart M—Organization

Sec.

AUTHORITY: 5 U.S.C. 552; 21 U.S.C. 301–397.

SOURCE: 77 FR 15962, Mar. 19, 2012, unless otherwise noted.

Subparts A–L [Reserved]

Subpart M—Organization

§ 5.1100 Headquarters.

Office of the Commissioner.[1]
Office of the Chief Counsel.
Office of the Executive Secretariat.
  Freedom of Information Staff.
  Dockets Management Staff.
Office of the Chief Scientist.[1]
Office of Counter-Terrorism and Emerging Threats.
Office of Scientific Integrity.
Office of Regulatory Science and Innovation.
  Division of Science Innovation and Critical Path.
  Division of Scientific Computing and Medical Information.
Office of Scientific Professional Development.
Office of Health Informatics.
Office of Women's Health.
Office of External Affairs.
  Office of Media Affairs.
  Office of Communications.
  Office of Health and Constituent Affairs.
Office of Minority Health.
National Center for Toxicological Research.[2]
  Office of the Center Director.
  Office of Management.
  Office of Research.
  Division of Biochemical Toxicology.
  Division of Genetic and Molecular Toxicology.

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