Guidance for Industry and FDA
Current Good Manufacturing Practice for Combination Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products (OCP)

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Guidance for Industry[1]

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I. INTRODUCTION

This document provides guidance to industry and FDA staff on the applicability of current good manufacturing practice[2] provisions to combination products as defined under 21 CFR 3.2(e). Such provisions apply to the manufacture[3] of combination products to ensure that (1) the product is not adulterated; (2) the product possesses adequate strength, quality, identity, and purity; and (3) the product complies with performance standards as appropriate for the marketed combination product.

This guidance does not address technical manufacturing methods or make recommendations for manufacturers'[4] selection of facilities to manufacture products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by the Office of Combination Products in the Office of the Commissioner in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For purposes of this guidance document, the term *current good manufacturing practice* refers to the current good manufacturing practice regulations for drugs and most biological products under 21 CFR Parts 210 and 211, for certain biological products under 21 CFR Parts 600-680, and the quality system regulations for devices under 21 CFR Part 820.

[3] For purposes of this document, the term *manufacture* refers to the methods to be used in, and the facilities and controls to be used for, the manufacture, processing, packing, or holding of a drug (21 CFR 210.01(a)), and those used for the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use (21 CFR 820.1(a)). In addition, the term *manufacture* refers to the methods and facilities for certain biological products that are considered to supplement, not supercede, the drug provisions, unless the regulations explicitly provide otherwise (21 CFR 210.2(a)).

[4] For purposes of this guidance document, the term "manufacturer" refers to any person who would be required to comply with current good manufacturing practice regulatory requirements for drugs, biological products, devices, or combination products.

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND INFORMATION

A. What is a combination product?

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

1. A product comprising 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;

2. Two or more separate products packaged together in a single package or as a unit comprising drug and device products, device and biological products, or biological and drug products;

3. 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

4. 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.

B. What is a constituent part of a combination product?

For the purposes of this guidance document, a *constituent part of a combination product* is an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product, as defined in section 201 of the Federal Food, Drug, and Cosmetic Act (the Act) or 351(i) of the Public Health Service Act. For example, a device coated or impregnated with a drug has two constituent parts, the device and the drug. For simplicity, the concepts in this guidance are described in the context of a combination product composed of two constituent parts. These concepts are also relevant for combination products with more than two constituent parts.

C. How are combination products regulated?

A combination product is assigned to an Agency center or alternative organizational component that will have primary jurisdiction for its premarket review and regulation. Under section 503(g)(1) of the Act, assignment to a center with primary jurisdiction, or a *lead center*, is based on a determination of the primary mode of action (PMOA) of the combination product.[5] For example, if the PMOA of a device-biological combination product is attributable to the biological product, the Agency component responsible for premarket review of that biological product would have primary jurisdiction for the combination product. The lead center generally has responsibility for oversight of the regulation of the combination product, including the evaluation of current good manufacturing practice.

Section 503(g)(4)(D) of the Act requires FDA to "ensure the consistency and appropriateness of postmarket regulation of like [combination] products." To achieve consistency, FDA will treat like combination products similarly. To ensure appropriateness, FDA plans to require that manufacturers use the applicable current good manufacturing practice regulations for their combination products. In the regulation of a combination product, the application of consistent and appropriate current good manufacturing practice should help to ensure that the combination product is not adulterated under section 501 of the Act and is manufactured in accordance with appropriate regulatory provisions for the combination product and its constituent parts.

III. CURRENT GOOD MANUFACTURING PRACTICE

A. Background

Section 501 of the Act states the circumstances under which a drug or device is deemed adulterated and authorizes FDA to establish current good manufacturing practice to avoid adulteration.[6] Adulteration includes a failure of the drug, biological product, or device to be manufactured in accordance with current good manufacturing practice, regardless of whether the product is actually deficient in some respect.[7] Current good manufacturing practice regulatory provisions are intended to ensure that the drug, biological product, or device is not adulterated; to ensure the product possesses adequate strength, quality, identity, and purity of a drug or biological product; and to ensure compliance with performance standards for a device. The following current good manufacturing practice regulations and other applicable standards are codified for products that may be constituent parts of a combination product:[8]

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[5] A proposed rule defining the primary mode of action of a combination product was published in the May 7, 2004, Federal Register, http://www.fda.gov/oc/combination/default.htm.

[6] See also section 520(f)(1).

[7] See generally sections 501(a)(2)(B) and 501(h).

[8] FDA has also issued a proposed rule for Good Tissue Practices, Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (Federal Register Notice, January 8, 2001,Vol 66, No. 5, p 1507-1559).

- Current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, or drug products (21 CFR Parts 210 and 211).[9] Drug products not subject to these regulations (e.g., bulk drugs or active pharmaceutical ingredients) must still meet the current good manufacturing practice general standard required by the statute.
- Quality system (QS) regulation for devices (21 CFR Part 820).

The biological product regulations, 21 CFR Parts 600-680, may also apply to the manufacture of drugs that are also biological products along with the drug CGMP provisions.[10] They also may apply along with the QS regulations to the manufacture of devices that are also biological products.[11]

There is considerable overlap in the CGMP and QS regulations, and for the most part the overlap is apparent. For example, both establish requirements for management, organization, and personnel; both require documentation and record keeping; and both allow flexibility in application to the manufacture of particular products.[12] FDA considers the CGMP[13] and the QS regulations to be similar, and they are meant to achieve the same goals.

Nonetheless, FDA recognizes that each set of regulations is somewhat different because each is tailored to the characteristics of the types of products for which they were designed (i.e., CGMP for drugs or biological products, QS regulation for devices). Each set of regulations contains certain express/specific requirements that may be only more generally described in the other regulation. Typically, these express/specific requirements are related to the unique characteristics of a drug, device, or biological product. For example:

- Calculating the yield and stability of a drug constituent part: The CGMP regulation has specific requirements for the calculation of yield (21 CFR 211.103) and for ensuring stability of the drug product (21 CFR 211.166). Under the QS regulation, for a combination product with a drug constituent part, yield and stability requirements would be incorporated more generally as part of the design validation provisions (21 CFR

[9] For the purposes of this guidance document, the abbreviation "CGMP" refers only to the drug regulations at 21 CFR Parts 210 and 211, while the phrase "current good manufacturing practice" refers to the various sets of manufacturing practice regulations (see footnote 2).

[10] See 21 CFR 211.1(b) and 21 CFR 210.2(b).

[11] See 21 CFR 820.1(b).

[12] Each set of regulations also allows either a device or a drug manufacturer who is engaging in only some operations that are subject to the requirements in either 21 CFR 820 or 21 CFR 210 and 211 to only comply with the regulations applicable to the operations in which it is engaged. Therefore, a device manufacturer only has to comply with the regulations in 21 CFR 820 that are applicable to the operations in which it is engaged in the manufacture of the device, and a drug manufacturer only has to comply with the regulations in 21 CFR 210 and 211 that are applicable to the operations in which it is engaged in the manufacture of the drug. For example, a drug manufacturer who is only involved in the issuance of labeling of the product, 21 CFR 211.125, may not need to comply with regulations related to receipt and storage of untested components, 21 CFR 211.82.

[13] See FDA Guidance, "Quality System Approach to Pharmaceutical Current Good Manufacturing Practice Regulations," available at http://www.fda.gov/cder/guidance/index.htm for an explanation of how to implement a comprehensive QS model under the CGMPs.

820.30(g)).

- Corrective and preventive action (CAPA): The QS regulation has detailed CAPA requirements (21 CFR 820.100), while CAPA principles are more generally identified in the CGMP regulation as part of Production Record Review (21 CFR 211.192).

B. Current Good Manufacturing Practice for Combination Products

FDA has not promulgated current good manufacturing practice regulations specifically for combination products. Until it does so, each constituent part (i.e., the drug, device, or biological product) remains subject only to its governing current good manufacturing practice regulations when marketed separately, see 21 CFR 3.2(e)(3) and (4), and when manufactured separately as constituent parts of a combination that will later be combined, see 21 CFR 3.2(e)(1) and (2). For example, if a drug is marketed that is intended for use only with an approved individually specified device that is also marketed separately, the drug constituent must comply only with 21 CFR Parts 210 and 211, and the device constituent must comply only with 21 CFR Part 820. Similarly, during the time of separate manufacture (i.e., before drug and device combination products are produced as a single entity or are co-packaged) 21 CFR Parts 210 and 211 apply only to the drug constituent, and 21 CFR Part 820 applies only to the device constituent.

However, for combination products that are produced as a single-entity or are co-packaged, see 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together. The rest of this section refers only to situations when combination products that are produced as a single entity or are co-packaged as defined in 21 CFR 3.2(e)(1) and (2) are joined together.

FDA recognizes that many manufacturing facilities operate under one type of current good manufacturing practice system (i.e., either that described by the QS or CGMP regulation). As noted above, FDA recognizes that there is considerable overlap between the QS and CGMP regulations. It should generally not be necessary for manufacturers who make combination products that are produced as a single entity or are co-packaged to maintain two separate manufacturing systems to ensure compliance with both sets of regulations during and after joining the constituents together. FDA believes that compliance with both sets of regulations during and after joining these types of combination products can generally be achieved by using either the CGMP or QS regulations, e.g., by using the current good manufacturing practice system already operating at a manufacturing facility, as described below.

During and after joining these types of combination products together, FDA believes that compliance with both sets of regulations can generally be achieved by following one set because under a more general requirement in one set of regulations, it will be possible to develop and implement a practice that complies with a more specific requirement in the other set of regulations. To ensure consistent and appropriate current good manufacturing practice, FDA recommends that manufacturers of these types of combination products assess how best to comply with both sets of regulations, during and after joining the constituent parts together, by carefully considering the requirements of the CGMP and QS regulations in relation to the constituent parts, and the combination product(s) they manufacture.

Table 1 identifies key provisions of the CGMP and QS regulations that differ in their specificity. FDA recommends manufacturers of combination products that are co-packaged or produced as a single entity carefully consider these provisions during and after joining the constituent parts, to ensure compliance with both the CGMP and QS regulations.

Table 1: Key Current Good Manufacturing Practice Provisions to Consider During and After Joining Together Co-packaged and Single-Entity Combination Products

If the Operating Manufacturing Control System is Part 820 (QS Regulation)		**If the Operating Manufacturing Control System is Part 210/211 (CGMP Regulation)**	
Carefully Consider These Specific CGMP Requirements	**Title**	**Carefully Consider These Specific QS Requirements**	**Title**
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§ 820.30	Design controls
§ 211.103	Calculation of yield	§ 820.50	Purchasing controls
§ 211.137	Expiration dating	§ 820.100	Corrective and preventative actions
§ 211.165	Testing and release for distribution		
§ 211.166	Stability testing		
§ 211.167	Special testing requirements		
§ 211.170	Reserve samples		
* Including all subsections, as appropriate.			

In addition, depending on the particular combination product, it may be important to consider other specific requirements to ensure compliance with both the CGMP and QS regulations. Examples include aseptic control assurance for drug and biological product constituent parts unable to withstand terminal sterilization (21 CFR 211.113(b) and § 211.42)); 21 CFR 606 for blood and blood component constituent parts; 21 CFR 211.132 for combination products incorporating drug constituent parts that are sold over-the-counter; and any good tissue practice regulations that may be promulgated.

FDA recommends that manufacturers of these types of combination products present information to the Agency when the product is being developed (e.g., during Agency meetings or during inspections) about how they intend to achieve compliance with each set of regulations during and after joining the products together, in particular by showing how they achieve compliance with

the provisions identified in Table 1 above, as well as any other provisions applicable to the combination product being manufactured.

If a manufacturer of these types of combination products is concerned about whether application of one set of current good manufacturing practice regulations satisfies the requirements of the other set(s), FDA encourages the manufacturer to discuss with the appropriate Agency personnel when the product is being developed how best to achieve current good manufacturing practice compliance. Further, FDA expects that this guidance will be revised as FDA modifies the existing CGMP/QS regulations.[14]

C. Considerations for different types of combination products

As described under section I.A, there are four types of combination products. To summarize, the following are considerations by type of combination product:

- Combination products with constituent parts that are physically, chemically or otherwise combined or mixed and produced as a single entity (21 CFR 3.2(e)(1)), and combination products with constituent parts that are packaged together (21 CFR 3.2(e)(2)):

  Before combination or co-packaging, the manufacture of each constituent part is subject only to the current good manufacturing practice regulations associated with each constituent part. For example, for a drug-coated device, the drug constituent part would be subject only to the CGMP regulation (or to Section 501(a)(2)(B) of the Act for a bulk drug substance or active pharmaceutical ingredient), while the device constituent part would be subject only to the QS regulation.

  Once the product is combined into a single entity or co-packaged, both sets of regulations apply to the combination. FDA recommends manufacturers follow the guidance described in section III.B above to achieve compliance with all applicable current good manufacturing practice regulations.

- Combination products with constituent parts that are separately marketed but intended to be used together (21 CFR 3.2(e)(3) and (e)(4)):

  The manufacture of each constituent part is subject to the current good manufacturing practice regulations associated with each constituent part, and is not subject to both sets of regulations. For example, for a photodynamic therapy system consisting of a laser and a photosensitizing drug that are marketed separately, the laser would be subject to the QS regulation while the photosensitizing drug would be subject to the CGMP regulation.

[14] FDA Pharmaceutical GMPs for the 21st Century: A Risk Based Approach, 2nd progress report and implementation plan, (http://www.fda.gov/cder/gmp/2ndProgressRept_Plan.htm).

IV. COMMUNICATION WITH FDA DURING DEVELOPMENT OF A COMBINATION PRODUCT

A. When does FDA recommend discussing CGMP issues with the Agency?

FDA recommends that manufacturers of combination products discuss with the Agency how current good manufacturing practice regulations apply to their products. Manufacturers are encouraged to seek FDA comment on their implementation of current good manufacturing practice during pre-investigational (pre-IND/IDE) meetings and throughout combination product development.[15] FDA recommends that these discussions include consideration of the risks of the combination product, its technology, and any anticipated postmarket development and post approval changes. FDA recommends that the applicant(s) include all critical manufacturers in these discussions and include information on critical steps that may be conducted at source/contract firms and any special testing.

FDA staff involved in the discussions about the application of current good manufacturing practice regulations to a combination product may include, but are not limited to, reviewers in the lead and consulting product review divisions (CBER, CDER, and CDRH); the current good manufacturing practice experts in the Offices of Compliance in the lead and consulting centers and the district office; Office of Regulatory Affairs national expert advisors, as appropriate; and the Office of Combination Products.[16] FDA will document its recommendations concerning the manufacturer's proposal in FDA meeting minutes, letters, or other permanent communication records, as appropriate. Also, FDA staff should communicate this information to the appropriate District Office.

B. Where can I get more information?

The Office of Combination Products is available as a resource to sponsors and review staff throughout the lifecycle (development, premarket review and postmarket regulation) of a combination product. The Office can be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated list of FDA guidance documents that sponsors may find helpful in determining the regulatory provisions for their products. The guidance is available at the Office's Internet Website at http://www.fda.gov/oc/combination (for FDA staff, http://intranet.fda.gov/oc/ocp/index.html).

The Office of Regulatory Affairs Website provides detailed information on inspection policies. The Office can be reached at http://www.fda.gov/ora. ORA inspectional guidances are located at http://www.fda.gov/ora/inspect_ref/igs/iglist.html.

[15] FDA recommends that manufacturers follow the lead Center's existing guidances or practices for requesting formal meetings with the lead center.

[16] FDA staff should follow the procedures outlined for the intercenter consultative/collaborative review process, http://www.fda.gov/oc/combination/consultative.html