
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DRAFT GUIDANCE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)**

September 2004

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Guidance for Industry¹
Current Good Manufacturing Practice for Combination Products

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry and FDA staff on the applicability of current good manufacturing practice² provisions to combination products as defined under 21 CFR 3.2(e). Such provisions apply to the manufacture³ 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 manufacturers⁴ 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.

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

II. BACKGROUND INFORMATION

A. What is a combination product?

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

- 41 1. A product comprising two or more regulated components (i.e., drug/device,
42 biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically,
43 or otherwise combined or mixed and produced as a single entity;
- 45 2. Two or more separate products packaged together in a single package or as a unit
46 comprising drug and device products, device and biological products, or biological and
47 drug products;
- 49 3. A drug, device, or biological product packaged separately that according to its
50 investigational plan or proposed labeling is intended for use only with an approved
51 individually specified drug, device, or biological product where both are required to
52 achieve the intended use, indication, or effect and where, upon approval of the proposed
53 product, the labeling of the approved product would need to be changed (e.g., to reflect a
54 change in intended use, dosage form, strength, route of administration, or significant
55 change in dose); or
- 57 4. Any investigational drug, device, or biological product packaged separately that
58 according to its proposed labeling is for use only with another individually specified
59 investigational drug, device, or biological product where both are required to achieve the
60 intended use, indication, or effect.

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

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

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74 **C. How are combination products regulated?**

75

76 A combination product is assigned to an Agency center or alternative organizational component
77 that will have primary jurisdiction for its premarket review and regulation. Under section
78 503(g)(1) of the Act, assignment to a center with primary jurisdiction, or a *lead center*, is based
79 on a determination of the primary mode of action (PMOA) of the combination product.⁵ For
80 example, if the PMOA of a device-biological combination product is attributable to the
81 biological product, the Agency component responsible for premarket review of that biological
82 product would have primary jurisdiction for the combination product. The lead center generally
83 has responsibility for oversight of the regulation of the combination product, including the
84 evaluation of current good manufacturing practice.

85

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

94

95

96 **III. CURRENT GOOD MANUFACTURING PRACTICE**

97

98 **A. Background**

99

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

110

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).

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111 ▪ Current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, or
112 drug products (21 CFR Parts 210 and 211).⁹ Drug products not subject to these
113 regulations (e.g., bulk drugs or active pharmaceutical ingredients) must still meet the
114 current good manufacturing practice general standard required by the statute.

115 ▪ Quality system (QS) regulation for devices (21 CFR Part 820).

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

120
121 There is considerable overlap in the CGMP and QS regulations, and for the most part the overlap
122 is apparent. For example, both establish requirements for management, organization, and
123 personnel; both require documentation and record keeping; and both allow flexibility in
124 application to the manufacture of particular products.¹² FDA considers the CGMP¹³ and the QS
125 regulations to be similar, and they are meant to achieve the same goals.

126
127 Nonetheless, FDA recognizes that each set of regulations is somewhat different because each is
128 tailored to the characteristics of the types of products for which they were designed (i.e., CGMP
129 for drugs or biological products, QS regulation for devices). Each set of regulations contains
130 certain express/specific requirements that may be only more generally described in the other
131 regulation. Typically, these express/specific requirements are related to the unique
132 characteristics of a drug, device, or biological product. For example:

133
134 • Calculating the yield and stability of a drug constituent part: The CGMP regulation has
135 specific requirements for the calculation of yield (21 CFR 211.103) and for ensuring
136 stability of the drug product (21 CFR 211.166). Under the QS regulation, for a
137 combination product with a drug constituent part, yield and stability requirements would
138 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.

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139 820.30(g)).

140

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

144

B. Current Good Manufacturing Practice for Combination Products

145

146
147 FDA has not promulgated current good manufacturing practice regulations specifically for
148 combination products. Until it does so, each constituent part (i.e., the drug, device, or biological
149 product) remains subject only to its governing current good manufacturing practice regulations
150 when marketed separately, see 21 CFR 3.2(e)(3) and (4), and when manufactured separately as
151 constituent parts of a combination that will later be combined, see 21 CFR 3.2(e)(1) and (2). For
152 example, if a drug is marketed that is intended for use only with an approved individually
153 specified device that is also marketed separately, the drug constituent must comply only with 21
154 CFR Parts 210 and 211, and the device constituent must comply only with 21 CFR Part 820.
155 Similarly, during the time of separate manufacture (i.e., before drug and device combination
156 products are produced as a single entity or are co-packaged) 21 CFR Parts 210 and 211 apply
157 only to the drug constituent, and 21 CFR Part 820 applies only to the device constituent.

158

159 However, for combination products that are produced as a single-entity or are co-packaged, see
160 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are
161 applicable during and after joining the constituent parts together. The rest of this section refers
162 only to situations when combination products that are produced as a single entity or are co-
163 packaged as defined in 21 CFR 3.2(e)(1) and (2) are joined together.

164

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

175

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

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185
186 Table 1 identifies key provisions of the CGMP and QS regulations that differ in their specificity.
187 FDA recommends manufacturers of combination products that are co-packaged or produced as a
188 single entity carefully consider these provisions during and after joining the constituent parts, to
189 ensure compliance with both the CGMP and QS regulations.
190

191
192 **Table 1: Key Current Good Manufacturing Practice Provisions to Consider During and**
193 **After Joining Together Co-packaged and Single-Entity Combination Products**
194

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.			

195
196
197 In addition, depending on the particular combination product, it may be important to consider
198 other specific requirements to ensure compliance with both the CGMP and QS regulations.
199 Examples include aseptic control assurance for drug and biological product constituent parts
200 unable to withstand terminal sterilization (21 CFR 211.113(b) and § 211.42)); 21 CFR 606 for
201 blood and blood component constituent parts; 21 CFR 211.132 for combination products
202 incorporating drug constituent parts that are sold over-the-counter; and any good tissue practice
203 regulations that may be promulgated.
204

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

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

211
212 If a manufacturer of these types of combination products is concerned about whether application
213 of one set of current good manufacturing practice regulations satisfies the requirements of the
214 other set(s), FDA encourages the manufacturer to discuss with the appropriate Agency personnel
215 when the product is being developed how best to achieve current good manufacturing practice
216 compliance. Further, FDA expects that this guidance will be revised as FDA modifies the
217 existing CGMP/QS regulations.¹⁴

C. Considerations for different types of combination products

218
219
220
221 As described under section I.A, there are four types of combination products. To summarize, the
222 following are considerations by type of combination product:

- 223
224 ■ Combination products with constituent parts that are physically, chemically or otherwise
225 combined or mixed and produced as a single entity (21 CFR 3.2(e)(1)), and combination
226 products with constituent parts that are packaged together (21 CFR 3.2(e)(2)):

227
228 Before combination or co-packaging, the manufacture of each constituent part is subject
229 only to the current good manufacturing practice regulations associated with each
230 constituent part. For example, for a drug-coated device, the drug constituent part would
231 be subject only to the CGMP regulation (or to Section 501(a)(2)(B) of the Act for a bulk
232 drug substance or active pharmaceutical ingredient), while the device constituent part
233 would be subject only to the QS regulation.

234
235 Once the product is combined into a single entity or co-packaged, both sets of regulations
236 apply to the combination. FDA recommends manufacturers follow the guidance
237 described in section III.B above to achieve compliance with all applicable current good
238 manufacturing practice regulations.

- 239
240 ■ Combination products with constituent parts that are separately marketed but intended to
241 be used together (21 CFR 3.2(e)(3) and (e)(4)):

242
243 The manufacture of each constituent part is subject to the current good manufacturing
244 practice regulations associated with each constituent part, and is not subject to both sets
245 of regulations. For example, for a photodynamic therapy system consisting of a laser and
246 a photosensitizing drug that are marketed separately, the laser would be subject to the QS
247 regulation while the photosensitizing drug would be subject to the CGMP regulation.

248

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).

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249 **IV. COMMUNICATION WITH FDA DURING DEVELOPMENT OF A** 250 **COMBINATION PRODUCT**

251 **A. When does FDA recommend discussing CGMP issues with the Agency?** 252

253
254 FDA recommends that manufacturers of combination products discuss with the Agency how
255 current good manufacturing practice regulations apply to their products. Manufacturers are
256 encouraged to seek FDA comment on their implementation of current good manufacturing
257 practice during pre-investigational (pre-IND/IDE) meetings and throughout combination
258 product development.¹⁵ FDA recommends that these discussions include consideration of the
259 risks of the combination product, its technology, and any anticipated postmarket
260 development and post approval changes. FDA recommends that the applicant(s) include all
261 critical manufacturers in these discussions and include information on critical steps that may
262 be conducted at source/contract firms and any special testing.

263
264 FDA staff involved in the discussions about the application of current good manufacturing
265 practice regulations to a combination product may include, but are not limited to, reviewers
266 in the lead and consulting product review divisions (CBER, CDER, and CDRH); the current
267 good manufacturing practice experts in the Offices of Compliance in the lead and consulting
268 centers and the district office; Office of Regulatory Affairs national expert advisors, as
269 appropriate; and the Office of Combination Products.¹⁶ FDA will document its
270 recommendations concerning the manufacturer's proposal in FDA meeting minutes, letters,
271 or other permanent communication records, as appropriate. Also, FDA staff should
272 communicate this information to the appropriate District Office.

273 **B. Where can I get more information?** 274

275
276 The Office of Combination Products is available as a resource to sponsors and review staff
277 throughout the lifecycle (development, premarket review and postmarket regulation) of a
278 combination product. The Office can be reached at (301) 427-1934 or by email at
279 combination@fda.gov. In addition, the Office maintains an updated list of FDA guidance
280 documents that sponsors may find helpful in determining the regulatory provisions for their
281 products. The guidance is available at the Office's Internet Website at
282 <http://www.fda.gov/oc/combination> (for FDA staff, <http://intranet.fda.gov/oc/ocp/index.html>).

283
284 The Office of Regulatory Affairs Website provides detailed information on inspection
285 policies. The Office can be reached at <http://www.fda.gov/ora>. ORA inspectional guidances
286 are located at http://www.fda.gov/ora/inspect_ref/igs/iglist.html.

287

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>