Proposed Rules

Federal Register
Vol. 74, No. 183
Wednesday, September 23, 2009

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF AGRICULTURE

Agricultural Marketing Service

7 CFR Part 970

[Docket No. AO–FV–09–0138; AMS–FV–09–0029; FV09–970–1E]

Leafy Green Vegetables Handled in the United States; Extension of Time for First Session of Hearing on Proposed Marketing Agreement No. 970

AGENCY: Agricultural Marketing Service, USDA.

ACTION: Proposed rule; notice of additional time for public hearing on proposed national marketing agreement for leafy green vegetables.

SUMMARY: This notice announces that the scheduled hearing date for the Monterey, California session of a public hearing to consider a proposed marketing agreement for the handling of leafy green vegetables in the United States may be extended by one day, if deemed necessary by the presiding administrative law judge.

DATES: The Monterey, California session for the public hearing is currently scheduled for September 22 through 24, 2009. This hearing session may be extended by an additional day, September 25, 2009, if deemed necessary. As with the other scheduled sessions, this session would begin at 8:30 a.m. and conclude at 5 p.m., or any other time as determined by the presiding administrative law judge.

ADDRESSES: The hearing location in Monterey is: Hyatt Regency Monterey, 1 Old Golf Course Road, Monterey, California, (831) 372–1234.

FOR FURTHER INFORMATION CONTACT: Antoinette Carter, Marketing Order Administration Branch, Fruit and Vegetable Programs, AMS, USDA, 1400 Independence Avenue, SW., Stop 0237, Washington, DC 20250–0237; *Telephone:* (202) 720–2491, *Fax:* (202) 720–8938, or *e-mail: Antoinette.Carter@ams.usda.gov*; or Melissa Schmaedick, Marketing Order Administration Branch, Fruit and Vegetable Programs, Northwest Marketing Field Office, AMS, USDA, 1220 SW. Third Avenue, Room 385, Portland, OR 97204; *Telephone:* (503) 326–2724, *Fax:* (503) 326–7440, or *e-mail: Melissa.Schmaedick@ams.usda.gov*.

SUPPLEMENTARY INFORMATION:

Prior documents in this proceeding: Notice of Hearing issued August 31, 2009; published September 3, 2009 (74 FR 45565).

Notice is hereby given that the scheduled hearing date for the Monterey, California session of a public hearing to consider a proposed marketing agreement for the handling of leafy green vegetables in the United States may be extended by one day, if deemed necessary by the presiding administrative law judge.

The Department of Agriculture (USDA) previously announced a hearing to consider a proposed marketing agreement for the handling of leafy green produce in the United States. Hearing dates have been scheduled for various locations throughout the United States, including Monterey, California. However, an additional day may be required to receive testimony and evidence in Monterey. This notice announces the addition of September 25, 2009 to the first session, if deemed necessary by the presiding administrative law judge.

Information regarding the hearing and the proposed marketing agreement is contained in the Notice of Hearing, which may be viewed at: *http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480a1c313*.

List of Subjects in 7 CFR Part 970

Marketing agreements, Reporting and recordkeeping requirements, Vegetables.

Authority: U.S.C. 601–674.

Dated: September 18, 2009.

Rayne Pegg,

Administrator, Agricultural Marketing Service.

[FR Doc. E9–22992 Filed 9–21–09; 11:15 am]

BILLING CODE 3410–02–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 4

[Docket No. FDA–2008–D–0409]

Current Good Manufacturing Practice Requirements for Combination Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or agency) proposes to codify the current good manufacturing practice (cGMP) requirements applicable to combination products. This proposed rule is intended to promote the public health by clarifying which cGMP requirements apply when drugs, devices, and biological products are combined to create a combination product. In addition, the proposed rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with cGMP requirements for ''single-entity'' and ''co-packaged'' combination products.

DATES: Submit written or electronic comments on this proposed rule by December 22, 2009. See section IX of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. FDA–2008–D–0409 (formerly Docket No. 2004D–0431), by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-

mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and docket number for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: John Weiner, Office of Combination Products (HFG–3), Food and Drug Administration, 15800 Crabbs Branch Way, suite 200, Rockville, MD 20855, 301–427–1934.

SUPPLEMENTARY INFORMATION:

I. Introduction

As set forth in part 3 (21 CFR Part 3), a combination product is a product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product.[1] Under § 3.2(e), a combination product includes:

1. A product comprised of 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 (single-entity combination products);

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (co-packaged combination 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.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) modified section 503(g) of the act) (21 U.S.C. 353(g)) to require the establishment of an Office (Office of Combination Products (OCP)) within the Office of the Commissioner of FDA. The responsibilities of OCP include ensuring the prompt assignment of combination products to agency components, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law (21 U.S.C. 353(g)(4)).

Section 501 of the act (21 U.S.C. 351) states circumstances under which drugs and devices (including biological products, which by definition are also drugs or devices, and including human cellular and tissue-based products (HCT/Ps) that are regulated as drugs, devices, and/or biological products) are deemed adulterated.[2] Adulteration includes the failure to manufacture a product in accordance with applicable cGMP requirements, regardless of whether the product appears to meet its final specifications.[3]

The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) even after they are combined. Accordingly, the cGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products. To date, however, the agency has not issued specific regulations clarifying the applicability of the cGMP requirements to combination products. While cGMP regulations are in place that establish requirements for drugs, devices, biological products, and HCT/Ps, there are currently no regulations that clarify and explain the application of these cGMP requirements when these drugs, devices, biological products, and HCT/Ps are constituent parts of a combination product.

FDA believes that the absence of clear cGMP requirements for combination products could result in inconsistent or differing application of the various cGMP requirements applicable to the constituent parts, which could affect product safety and the public health.

In the **Federal Register** of October 4, 2004 (69 FR 59239), the agency announced the availability of a Draft Guidance for Industry and FDA entitled ''Current Good Manufacturing Practice for Combination Products.'' The agency received 15 comments, which were largely supportive of the regulatory approach described in the draft guidance. The agency has carefully reviewed these comments and has addressed many of them in the proposed rule. A common theme that emerged from these comments was the need to develop a clear regulatory framework that takes account of the fact that combination products are made up of drug, device, and biological product constituent parts. At the same time, commenters wanted to ensure that the framework would not demand unnecessary redundancy in the operating systems to meet cGMP requirements (cGMP operating systems).

After careful consideration of the comments, and of how best to ensure that cGMPs for combination products are consistent and appropriate, FDA has determined that rulemaking is warranted. FDA believes that rulemaking will best help ensure the manufacture of safe and effective combination products, by providing a clear and transparent regulatory roadmap for the application of cGMP requirements to these products. The rule is being proposed as part of FDA's ongoing effort to improve the consistency and appropriateness of the regulatory requirements for combination products.

For certain types of combination products, the application of current good manufacturing practice requirements is fairly straightforward. Specifically, the constituent parts of a combination product are each subject only to the cGMP regulations applicable to that type of constituent part (e.g., drug or device) if the combination product consists of constituent parts that are packaged separately and intended for use only with another approved or investigational, individually specified drug, device, or biological product, as defined in

[1] For purposes of part 3 and this proposed rule, a ''biological product'' means a biological product subject to regulation under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). All biological products regulated under the PHS Act meet the definitions of drug or device in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321).

[2] See also 21 U.S.C. 360j(f)(1).

[3] See, generally, 21 U.S.C. 351(a)(2)(B) and (h).

§ 3.2(e)(3) and (e)(4). This is because these constituent parts, while part of a combination product, are separately manufactured and packaged. Accordingly, they remain separate for purposes of applying the cGMP regulations.

Thus, for example, if a combination product were to include a separately manufactured and packaged drug constituent part, the manufacture of that constituent part would be subject to the cGMP regulations for drugs at parts 210 and 211 (21 CFR parts 210 and 211) (drug cGMPs). Similarly, if a combination product were to include a separately manufactured and packaged device constituent part, the manufacture of that constituent part would be subject to the quality system (QS) regulation for devices at part 820 (21 CFR part 820). Likewise, a drug, device, or biological constituent part of a combination product that is separately packaged for investigational use as defined in § 3.2(e)(4) is subject to the cGMP requirements that apply to either an investigational drug, device, or biological product, respectively. For example, an investigational drug that was labeled for use with a separately marketed device would be subject to the cGMP requirements that apply to investigational drugs under section 501(a)(2)(B) of the act and part 211.

Section 4.3 of the proposed rule would identify the cGMP regulations that apply to the constituent parts of a combination product, regardless of whether the product is a combination product under § 3.2(e)(1), (e)(2), (e)(3), or (e)(4). Since each constituent part of a combination product as defined in § 3.2(e)(3) and (e)(4) is subject only to the cGMP requirements that would otherwise apply to that constituent part, the agency sees no need to elaborate upon the practical application of cGMP requirements for these two types of combination products. The proposed rule would expressly address, however, the practical application of cGMP requirements to single-entity and co-packaged combination products as defined at § 3.2(e)(1) and (e)(2).

The proposed rule recognizes that, in most instances, for single-entity and co-packaged combination products, a cGMP operating system that satisfies the cGMP regulations applicable to one constituent part will also satisfy most of the cGMP requirements applicable to the other constituent part. In particular, the agency believes that compliance with either the drug cGMPs or the QS regulation will satisfy most of the cGMP requirements applicable to either a drug or a device constituent part. The agency has reviewed the drug cGMPs and QS regulation and identified those specific provisions from each that a firm would need to satisfy in addition to complying with the other of these two sets of cGMP regulations.

Accordingly, the proposed rule at § 4.4(b) would offer two options for demonstrating compliance with the cGMP requirements applicable to each of the constituent parts in a co-packaged or single-entity combination product. These options would be either: (1) To demonstrate compliance with the specifics of all cGMP regulations applicable to each of the constituent parts included in the combination product containing, or (2) to demonstrate compliance with the specifics of either the drug cGMPs or the QS regulation, rather than both, when the combination contains both a drug and a device, under certain conditions. These conditions include demonstrating compliance with specified provisions for the other of these two sets of requirements, and with all other cGMP requirements applicable to the constituent parts (i.e., in parts 600 through 680 (21 CFR parts 600 through 680) for biological products or in part 1271 (21 CFR part 1271) for HCT/Ps).

The proposed rule would help ensure that cGMP requirements that apply to single-entity and co-packaged combination products are clear and consistent, regardless of which agency component has lead jurisdiction for the combination product, or which type of application is submitted for marketing authorization. The proposed rule would permit practical streamlining by providing options for demonstrating compliance with cGMP requirements for these types of combination products. This proposed approach would help ensure appropriate implementation of these requirements while avoiding unnecessary redundancy in cGMP operating systems for these products. The proposed rule would also help ensure that the cGMP operating systems for these types of combination products are appropriately tailored both to the specific constituent parts included in the combination product and to the specific manufacturing processes being used.

FDA recognizes that timely, comprehensive guidance and training is important to help ensure consistent and appropriate implementation of any final rule that may issue based upon this proposed rule. FDA intends to issue such guidance to industry on the implementation of the regulatory requirements for use of a streamlined cGMP operating system for single-entity and co-packaged combination products. FDA invites comments on particular areas of guidance that would be most helpful in designing and implementing a cGMP operating system in accordance with the proposed rule.

II. Description of the Proposed Rule

FDA proposes to create 21 CFR part 4, subpart A, to codify the cGMP requirements that apply to combination products.[4]

A. General Principles

A combination product is comprised of constituent parts, i.e., drug(s), device(s), and/or biological product(s) (21 U.S.C. 353(g)(1); see also § 3.2(e)). These drug, device, and/or biological product constituent parts retain their regulatory identity as a drug, device and/or biological product when they are combined to create a combination product. Accordingly, when combined to create a combination product, each of the constituent parts remains subject to its respective cGMP requirements.

Under proposed § 4.3, the cGMP requirements in parts 210 and 211 would apply to combination products that include a drug, and those in part 820 would apply to combination products that include a device. All biological constituent parts of combination products meet the definition for device or drug in the act, and all HCT/Ps included as constituent parts of combination products are regulated as drugs, devices, and/or biological products (see section C below). Accordingly, all constituent parts of a combination product would be subject either to the drug cGMPs or QS regulation. In addition, if a constituent part of a combination product is also a biological product, the cGMP requirements in part 606 for blood and blood components, and among the requirements (standards) for biological products in other sections of parts 600 through 680 would be applicable.[5] Similarly, if a constituent part is also an HCT/P, the current good

[4] As described in the Department of Health and Human Services (DHHS) Unified Agenda, 72 FR 22490 (April 30, 2007), FDA also plans to propose regulations on postmarketing safety reporting for combination products. FDA proposes to codify those requirements in 21 CFR part 4, subpart B.

[5] See §§ 210.1(c), 820.1(a), and 1271.45(a). For the purposes of this proposed rule, FDA uses the term ''current good manufacturing practice requirements'' to include all such requirements found in the standards in parts 600 through 680 that may apply to combination products. See § 211.1(b). FDA notes that many of the requirements in parts 600 through 680 are not considered cGMP requirements and are not covered by this proposed rule. In addition, FDA notes that biological products must comply with all applicable requirements in parts 600 through 680.

tissue practice requirements in part 1271 would be applicable.

B. CGMP Requirements for Single-Entity and Co-Packaged Combination Products

For single-entity and co-packaged combination products, the proposed rule would allow firms to demonstrate compliance with cGMP requirements by implementing and complying with either the drug cGMPs or the QS regulation, rather than both, under certain conditions. These conditions include demonstrating that the cGMP operating system complies with specified provisions from the other of these two sets of regulations. In addition, this operating system would have to be shown to comply with all other cGMP regulations applicable to the constituent parts (i.e., in parts 600 through 680 for biological products or in part 1271 for HCT/Ps).

More specifically, if a single-entity or co-packaged combination product includes both a drug and a device and the cGMP operating system is shown to comply with the drug cGMP regulations at 21 CFR parts 210 and 211, the system would also have to be shown to comply with the following specific provisions of the QS regulation, as described in proposed § 4.4(b)(1):

1. § 820.20. Management responsibility.
2. § 820.30. Design controls.
3. § 820.50. Purchasing controls.
4. § 820.100. Corrective and preventive action.
5. § 820.170. Installation.
6. § 820.200. Servicing.

In this instance, if a firm demonstrates compliance with the drug cGMP regulations at parts 210 and 211 and the specific QS regulation provisions listed above, it would also be considered to be in compliance with all other provisions of the QS regulation. The firm would not have to demonstrate compliance with the other provisions of the QS regulation.

If a single-entity or co-packaged combination product includes both a drug and a device and the cGMP operating system is shown to comply with the QS regulation requirements at part 820, the system would also have to be shown to comply with the following specific provisions of the drug cGMP regulations, as described in proposed § 4.4(b)(2):

1. § 211.84. Testing and approval or rejection of components, drug product containers, and closures.
2. § 211.103. Calculation of yield.
3. § 211.132. Tamper-evident packaging for over-the-counter (OTC) human drug products.
4. § 211.137. Expiration dating.
5. § 211.165. Testing and release for distribution.
6. § 211.166. Stability testing.
7. § 211.167. Special testing requirements.
8. § 211.170. Reserve samples.

In this instance, if a firm demonstrates compliance with the QS regulation at part 820 and the specific drug cGMP regulation provisions listed above, it would also be considered to be in compliance with all other provisions of the drug cGMP regulations. The firm would not have to demonstrate compliance with the other provisions of the drug cGMPs.

Furthermore, if the combination product includes a biological product constituent part, in addition to demonstrating compliance with either the drug cGMPs or the device QS regulation, along with the specified provisions of the other of these two sets of regulations if applicable, the cGMP operating system would also have to be shown to comply with all additional cGMP requirements that apply to that constituent part as a biological product (see parts 600 through 680). Similarly, if the combination product includes an HCT/P constituent part, it would also have to be shown to comply with the requirements of part 1271. For those combination products that contain biological products and/or HCT/Ps, the proposed rule would impose no additional burdens and, in many cases, would offer the option of streamlining related to the drug cGMPs and the device QS regulation.

The applicability of the specific provisions identified in proposed § 4.4(b) would, as is the case with all cGMP regulations, depend upon the characteristics of the constituent part and the type of manufacturing activity performed. For example, if a manufacturer makes an OTC combination product that includes a drug constituent part, it would need to comply with the specific tamper-evident packaging requirements of § 211.132. A manufacturer who makes a prescription combination product would not need to comply with that provision. To take another example, if a manufacturer makes a product that has hardware requiring installation and/or servicing, it would need to comply with the installation and/or servicing provisions at §§ 820.170 and 820.200, respectively. Similarly, the scope, specificity, and complexity of the requirements will vary depending on the type of activity performed. For example, the cGMP requirements for firms that repackage articles into certain ''convenience'' kits or package a drug with a disposable delivery device will generally be less demanding than the more extensive requirements associated with the manufacture of some other combination products, such as drug-coated devices.

The streamlined option provides for the potential to incorporate specific requirements from the drug cGMPs into the framework of a QS operating system, and vice versa. These additional, specific requirements should be incorporated where most appropriate into the operating system.

Both the QS and drug cGMP regulations require that procedures be written to assure that the products being manufactured, processed, and held meet cGMP requirements. Accordingly, the written procedures for a streamlined system would have to assure that the firm could demonstrate compliance with the cGMP requirements specified in the proposed rule.

In addition to reducing duplicative documentation that would otherwise be required if multiple sets of cGMP regulations were implemented independently, this approach to documentation of the procedures would help facilitate cGMP inspections, by setting forth how the cGMP requirements for combination products are being met and how this is being demonstrated in accordance with the streamlined approach.

C. Requirements for a Combination Product That Includes an HCT/P

Questions have been raised by stakeholders concerning the application of cGMP requirements to HCT/Ps that are constituent parts of combination products. The HCT/P regulation at part 1271 distinguishes between HCT/Ps regulated solely under section 361 of the PHS Act (42 U.S.C. 264), and those that are regulated as drugs, devices, and biological products under the PHS Act and/or the act. The HCT/P regulation provides, among other things, that an HCT/P that is combined with another article (other than water, crystalloids, or a sterilizing, preserving, or storage agent) does not meet the criteria for regulation solely under section 361 of the PHS Act, but rather would be regulated under the PHS Act and/or the act as a drug, device, and/or biological product. (See §§ 1271.10 and 1271.20). Thus, by operation of the HCT/P regulation, an HCT/P that is a constituent part of a combination product will be regulated as a drug, device, and/or biological product. Further, because all biological product constituent parts meet the definition of drug or device, all HCT/P constituent parts of a combination product regulated as a biological product also meet the definition of drug or device.

Therefore, if a combination product includes an HCT/P constituent part, in addition to whatever other cGMP requirements may apply due to the other constituent parts of the combination product, these cGMP requirements would apply:

- Part 1271;[6]
- Either the drug cGMPs or the QS regulation; and
- If the HCT/P is regulated as a biological product, whichever biological product cGMP requirements apply, as specified in parts 600 through 680.

As indicated in section II.B of this document, a firm could choose the streamlining option in proposed § 4.4(b), as applicable, with respect to the drug and device cGMP requirements for combination products containing HCT/Ps.

D. What Requirements Apply to the Constituent Parts of a Combination Product Before They Are Combined, or Packaged Together?

FDA recognizes that the manufacture of a single-entity or co-packaged combination product is a complex process. The firm or firms participating in the production process may manufacture, receive, store, or otherwise handle the constituent parts of the combination product at various facilities, including the facility at which the constituent parts are combined to make the single-entity or co-packaged combination product. The fact that many firms and/or facilities may be involved raises questions about whether and when the proposed streamlined approach to cGMP operating systems could be used. Proposed § 4.4(c) would make clear that when manufacturing of a constituent part does not occur at the same facility as another type of constituent part, the operating system must be shown to comply with all of the cGMP regulations applicable to that constituent part. Proposed § 4.4(d) would provide that when two or more types of constituent parts are in the same facility, the streamlined approach may be used. However, proposed § 4.4(d) also clarifies that whenever manufacture of a constituent part occurs at a separate facility from all other types of constituent parts, the manufacture of that part must occur under the regulations applicable to that part.

Following are some examples to illustrate the situations in which the proposed streamlined approach could or could not be used.

Example 1: *Drug and device constituent parts are manufactured at two different facilities. Then a third facility combines the constituent parts into a single-entity or co-packaged combination product.* Before the constituent parts of a single-entity or co-packaged combination product are in the same facility for incorporation into the combination product, the manufacturing processes for the constituent parts at their separate facilities are distinct. Accordingly, under proposed § 4.4(c), each of these separate facilities must maintain a separate cGMP operating system and demonstrate compliance with the cGMP regulations applicable to that type of constituent part (for example, drug cGMPs if the constituent part is a drug). Once the constituent parts are brought to the third facility, the streamlined approach could be used.

Example 2: *The constituent parts are manufactured in the same facility, and are then sent to another facility to be combined into a single-entity or co-packaged combination product.*

The streamlined approach could be used for the manufacture in both facilities. Proposed § 4.4(d) addresses this situation.

Example 3: *Facility 1 manufactures a drug constituent part. Facility 2 manufactures a device constituent part. The drug constituent part is shipped to facility 2. Then both the drug constituent part and the device constituent part are shipped from facility 2 to facility 3. Facility 3 combines the constituent parts into a single-entity or co-packaged combination product.*

In this situation, manufacture of the drug constituent part at facility 1 must be shown to comply with the drug cGMP regulations. Manufacture of the device at facility 2 must be shown to comply with the device QS regulation. Proposed § 4.4(c) would make this clear.

For the drug constituent part while it is at facility 2, the streamlined approach could be used. That is, the QS operating system at facility 2 could be supplemented by the applicable, additional drug cGMP provisions specified in proposed § 4.4(b). Proposed § 4.4(d) addresses this situation. Facility 3 could use the streamlined approach by demonstrating compliance with either the drug cGMPs or the QS regulation as the cGMP operating system, supplemented by the particular provisions from the other (drug or device) regulations specified in proposed § 4.4(b). Proposed § 4.4(d) also addresses this situation.

E. Inspection and Enforcement

For purposes of enforcing the act, section 704 of the act provides that FDA can enter any factory, warehouse, or establishment in which drugs and devices are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, to enter any vehicle being used to transport or hold drugs or devices in interstate commerce, and to inspect such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. This inspection extends to all records and all things bearing on whether the drugs or devices are adulterated.

In the case of combination products, if a firm chooses to use the streamlined approach outlined in the proposed rule at § 4.4(b) by implementing the drug cGMPs supplemented by compliance with the provisions of the QS regulation specified in proposed § 4.4(b)(1), the FDA inspection would focus on compliance with the drug cGMPs and the specified QS provisions. If the firm complies with the drug cGMPs and the specified QS provisions, the firm would be considered to be in compliance with the other provisions of the QS regulation. Likewise, if the operating system satisfies the QS regulation and the drug cGMP provisions proposed at § 4.4(b)(2) are also satisfied, a firm would be considered to be in compliance with all other drug cGMP provisions.

III. Legal Authority

The agency derives its authority to issue the regulations in proposed 21 CFR part 4, subpart A, from 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, and 394, Federal Food, Drug, and Cosmetic Act, and 42 U.S.C. 216, 262, 263a, 264, and 271, Public Health Service Act. Most importantly, the provisions at sections 501(a)(2)(B) and 501(h) of the act (21 U.S.C. 351(a)(2)(B) and 351(h)) require drugs and devices to be manufactured in accordance with cGMPs. Section 520(f) of the act (21 U.S.C. 360j(f)) specifically authorizes the issuance of cGMP regulations for devices.

Section 501 of the act (21 U.S.C. 351) states that a drug or device is deemed adulterated if it is not manufactured in accordance with cGMPs. This provision also applies to biological products that are constituent parts of combination products because these products meet the definition of drug or device under section 201 of the act (21 U.S.C. 321). This provision also applies to HCT/Ps that are constituent parts of combination products because the HCT/P regulation

[6] See §§ 210.1(c), 210.2, 211.1(b), 820.1(a), and 1271.1(b)(2).

provides, among other things, that an HCT/P that is combined with another article (other than water, crystalloids, or a sterilizing, preserving, or storage agent) is regulated under the PHS Act and/or the act as a drug, device, and/or biological product (see §§ 1271.10 and 1271.20). In addition, section 351 of the PHS Act (42 U.S.C. 262) authorizes FDA to issue manufacturing standards for biological products. Section 361 of the PHS Act (42 U.S.C. 264) authorizes the issuance of regulations to prevent the introduction, transmission, or spread of communicable diseases.

Under applicable statutory provisions, the following cGMP regulations were previously issued for drugs, devices, and biological products that may be included as constituent parts of combination products:

- Drug cGMP regulations for finished pharmaceuticals or drug products set forth at parts 210 and 211).

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.

- QS regulation for devices set forth at part 820.
- cGMP regulations specific to certain types of biological products and/or HCT/Ps set forth at parts 600 through 680 and 1271.

There is considerable overlap in the drug cGMPs and QS regulation, 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 their application to the manufacture of a particular product. FDA considers the drug cGMPs and the QS regulation to be similar, and they are meant to achieve the same general goals.

Nevertheless, these two sets of regulations differ somewhat because each is tailored to the characteristics of the types of products for which it was designed. For instance, each set of regulations contains certain specific requirements for various cGMP concepts that are only more generally addressed in the other regulation. For example, the QS regulation has detailed corrective and preventive action (CAPA) requirements (§ 820.100) while CAPA principles are more generally addressed in the cGMP regulation as part of Production Record Review (§ 211.192).

The cGMP requirements specific to each constituent part of a combination product also apply to the combination product itself because, by definition, combination products consist of drugs, devices, and/or biological products. These articles do not lose their discrete regulatory identity when they become constituent parts of a combination product. Therefore, all combination products are subject to at least two sets of cGMP requirements. For example, in the case of a drug-device combination product, the QS regulation in part 820 and the drug cGMP regulations in parts 210 and 211 would apply to the combination product. This proposed rule is intended to clarify the applicability of these requirements to combination products and to provide a streamlined option for practical implementation for co-packaged and single-entity combination products.

Because the drug and device cGMP requirements are so similar, when using this streamlined approach, demonstrating compliance with the requirements of one set of regulations (e.g., drug cGMPs), along with demonstrating compliance with the requirements of the specified provisions from the other set (e.g., QS regulation), would be considered to be demonstrating compliance with all requirements from the other set (e.g., QS regulation).

Although combination products retain the regulatory identities of their constituent parts, the act also recognizes combination products as a category of products that are distinct from products that are solely drugs, devices, or biological products. For example, section 503(g)(4)(A) of the act (21 U.S.C. 353(g)(4)(A)) requires OCP to ''designate'' a product as a combination product as well as to ensure ''consistent and appropriate postmarket regulation of like products subject to the same statutory requirements.'' Further, section 563 of the act, (21 U.S.C. 360bbb–2(a)), governs the ''classification'' of products as ''drug, biological product, device, or a *combination product* subject to section 503(g)'' (emphasis added). In this respect, the act identifies a combination product as a distinct type of product that could be subject to specialized regulatory controls.

Under the preceding authorities and section 701(a) of the act (21 U.S.C. 371), which authorizes FDA to issue regulations for the efficient enforcement of the act, FDA has the authority to issue regulations clarifying the applicability of cGMP requirements to combination products. The agency is also authorized under these authorities to issue regulations specifying how compliance with cGMP requirements for combination products may be demonstrated.

IV. Environmental Impact

FDA has determined under 21 CFR 25.30(a), 25.30(h), 25.30(j), 25.31(a), (c), (h), and (j), and 25.34(a) and (d) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1995

We note that the information collected under the underlying cGMP regulations for drugs, devices, and biological products, including HCT/Ps, found at parts 211, 820, 600 through 680, and 1271 have already been approved and are in effect. The currently approved burden estimates are available in the following links. The provisions of part 211 are approved under OMB control number 0910–0139, which expires November 30, 2011 (*http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200809-0910-008*). The provisions of part 820 are approved under OMB control number 0910–0073, which expires on November 30, 2010 (*http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200709-0910-006*). The provisions of parts 606, 640, and 660 are approved under OMB control number 0910–0116, which expires February 29, 2012 (*http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200811-0910-006*). The provisions of part 610 are approved under OMB control number 0910–0116, which expires February 29, 2012, (link already provided in this paragraph) and OMB control number 0910–0338, which expires on June 10, 2010 (also for part 680) (*http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200703-0910-017*). The provisions of part 1271, subparts C and D, are approved under OMB control number 0910–0543, which expires on May 31, 2010 (*http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200705-0910-001*). To obtain more detailed, itemized estimates of the burden associated with particular regulatory provisions, please click on the link called ''View Supporting Statement and Other Documents'' from any of the Reginfo.gov links provided in this paragraph. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

We do not believe that this proposal would constitute an additional paperwork burden because firms must currently comply with the cGMP regulations addressed by this proposed

rule: In fact, our intent is to minimize burden on respondents by providing a more streamlined approach. Therefore, burden associated with complying with these cGMP regulations represents the maximum burden for compliance with this proposed rule. We invite comment on how many firms might avail themselves of the streamlined approach presented in this proposed rule for co-packaged and single-entity combination products and on what the reduction in paperwork burden would be.

VI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' The sole statutory provision giving preemptive effect to the proposed rule is section 751 of the act (21 U.S.C. 379r), which would apply only with respect to OTC drug components of combination.[7]

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule explains how requirements that are currently in effect apply to combination products, the agency does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities. FDA requests comment on this issue.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $130 million, using the most current (2007) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. The Rationale Behind the Proposed Rule

The proposed rule has two related purposes. The first is to clarify the cGMP requirements that apply to combination products, and the second is to help ensure the consistent and appropriate application and enforcement of these requirements. Constituent parts and manufacturing practices vary among combination products; different cGMP requirements apply depending upon the constituent parts in the combination product and what manufacturing practices are used. Second, the proposed rule attempts to streamline the practical implementation of cGMP requirements for co-packaged and single-entity combination products.

C. Impact of Proposed Rule

FDA estimates that approximately 300 manufacturers of combination products will be affected by the proposed rule. These manufacturers of combination products should benefit from the greater clarity provided regarding which regulatory provisions apply to their products. For both existing and future products, the streamlined approach set forth in the proposed rule would help ensure that cGMPs for co-packaged and single-entity combination products are consistent and appropriate, without duplicative or otherwise unnecessary aspects. This codification of cGMP requirements for combination products would also help ensure predictability and consistency in the application and enforcement of these regulatory requirements with regard to all combination products across FDA.

Firms must already comply with the cGMP regulations for drugs, devices, and biological products, including HCT/Ps, found at parts 211, 820, 600 through 680, and 1271, that are applicable to the constituent parts of their combination products. The cost of this proposed rule would be the incremental costs to modify or streamline existing SOPs. We do not know how many firms may choose to use the proposed streamlined approach for single-entity and co-packaged combination products, or for how many products; nor do we know how many firms are already using such an approach in light of the draft guidance.

Some firms may incur one-time incremental costs assessing compliance with the proposed rule and perhaps altering some standard operating procedures. Because this proposed rule codifies agency practice that is described in current guidance documents and because no new cGMP requirements are proposed, we believe the time required would be small and estimate it to be about 25 hours per product. This estimate is based on numbers we have used in previous rules with similar requirements. The amount of these compliance assessment costs for an individual firm, and the impact of any such costs, will depend on the number and nature of the products the firm produces and how the firm has applied current regulations. Nonetheless, because the time required would be limited, the agency believes the impact will not be significant on entities considered small based on the Small Business Administration's definition of a small entity (500 employees for device and biological product firms and 750 employees for drug firms). The agency requests comment on the incremental burden estimate associated with this rule.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposed rule. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

[7] The proposed rule seeks to clarify which cGMP requirements apply when drugs, devices, and biological products are used to create combination products. The agency notes that there are no express preemption provisions of the act applicable to prescription drugs or biological products. Section 521 of the act (21 U.S.C. 360k) contains an express preemption provision that applies to devices; nonetheless, the Supreme Court concluded in *Medtronic, Inc.* v. *Lohr*, 581 U.S. 470, 500–01 (1996), that requirements not applicable to a particular device (such as the device good manufacturing practice requirements at issue in this proposed rule) do not preempt State law under section 521 of the act.

IX. Proposed Effective Date

The agency is proposing that any final rule that may issue based upon this proposed rule become effective 180 days after its date of publication in the **Federal Register**.

List of Subjects in 21 CFR Part 4

Combination products, Biological products, Devices, Drugs, and Human cell, Tissue, and cellular and tissue-based products, Regulation of combination products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 4 be added to read as follows:

PART 4—REGULATION OF COMBINATION PRODUCTS

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

Subpart B [Reserved]

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.

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 product.

§ 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.

Act means the Federal Food, Drug, and Cosmetic Act.

Agency means the Food and Drug Administration.

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 § 4.2.

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

Constituent part is a drug, device, or biological product, including an HCT/P, that is part of a combination product as defined in § 3.2(e) of this chapter.

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.

FDA means the Food and Drug Administration.

HCT/Ps refers to human cell, tissue, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter.

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, a drug, or an HCT/P, as these terms are defined under this § 4.2.

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

If you manufacture a combination product, the current good manufacturing practice 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 in part 606 of this chapter for blood and blood components and among the requirements (standards) for biological products in other sections of 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 and donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P constituent part to which those requirements would apply if that constituent part were not part of a combination product.

§ 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) § 820.20 of this chapter. Management responsibility.

(ii) § 820.30 of this chapter. Design controls.

(iii) § 820.50 of this chapter. Purchasing controls.

(iv) § 820.100 of this chapter. Corrective and preventive action.

(v) § 820.170 of this chapter. Installation.

(vi) § 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) § 211.84 of this chapter. Testing and approval or rejection of components, drug product containers, and closures.

(ii) § 211.103 of this chapter. Calculation of yield.

(iii) § 211.132 of this chapter. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(iv) § 211.137 of this chapter. Expiration dating.

(v) § 211.165 of this chapter. Testing and release for distribution.

(vi) § 211.166. of this chapter. Stability testing.

(vii) § 211.167 of this chapter. Special testing requirements.

(viii) § 211.170 of this chapter. Reserve samples.

(3) 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 a biological product constituent part, the current good manufacturing practice operation system must also be shown to implement and comply with all current good manufacturing practice 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 operation system must also be shown to implement and comply with all current good manufacturing practice requirements identified under § 4.3(d) that would apply to that HCT/P constituent part if that constituent part 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 type(s) of 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 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 § 4.4(b) may begin, except with respect to any constituent part that remains or becomes subject to § 4.4(c).

(e) The current good manufacturing practice requirements set forth in this subpart and in parts 210, 211, 600 through 680, 820, and 1271 of this chapter, 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]

Dated: September 17, 2009.

David Horowitz,

Assistant Commissioner for Policy.

[FR Doc. E9–22850 Filed 9–22–09; 8:45 am]

BILLING CODE 4160–01–S

EQUAL EMPLOYMENT OPPORTUNITY COMMISSION

29 CFR Part 1630

RIN 3046–AA85

Regulations To Implement the Equal Employment Provisions of the Americans With Disabilities Act, as Amended

AGENCY: Equal Employment Opportunity Commission (EEOC).

ACTION: Notice of proposed rulemaking.

SUMMARY: The Equal Employment Opportunity Commission (the Commission or EEOC) proposes to revise its Americans with Disabilities Act (ADA) regulations and accompanying interpretive guidance in order to implement the ADA Amendments Act of 2008. The Commission is responsible for enforcement of title I of the ADA, as amended, which prohibits employment discrimination on the basis of disability. Pursuant to the ADA Amendments Act of 2008, EEOC is expressly granted the authority to amend these regulations, and is expected to do so, in order to conform certain provisions contained in the regulations to the Amendments Act.

DATES: Written comments on this rulemaking must be submitted on or before November 23, 2009.

ADDRESSES: Written comments should be submitted to Stephen Llewellyn, Executive Officer, Executive Secretariat, Equal Employment Opportunity Commission, 131 M Street, NE., Suite 4NW08R, Room 6NE03F, Washington, DC 20507. As a convenience to commenters, the Executive Secretariat will accept comments transmitted by facsimile (''FAX'') machine. The telephone number of the FAX receiver is (202) 663–4114. (This is not a toll-free number.) Only comments of six or fewer pages will be accepted via FAX transmittal to ensure access to the equipment. Receipt of FAX transmittals will not be acknowledged, except that the sender may request confirmation of receipt by calling the Executive Secretariat staff at (202) 663–4070 (voice) or (202) 663–4074 (TTY). (These are not toll-free telephone numbers.) You may also submit comments and attachments electronically at *http://www.regulations.gov*, which is the Federal eRulemaking Portal. Follow the instructions online for submitting comments. Copies of comments submitted by the public will be available for review at the Commission's library, 131 M Street, NE., Suite 4NW08R, Washington, DC 20507, between the hours of 9:30 a.m. and 5 p.m. or can be reviewed at *http://www.regulations.gov*.

FOR FURTHER INFORMATION CONTACT: Christopher Kuczynski, Assistant Legal Counsel, or Jeanne Goldberg, Senior Attorney Advisor, Office of Legal Counsel, U.S. Equal Employment Opportunity Commission at (202) 663–4638 (voice) or (202) 663–7026 (TTY). These are not toll-free-telephone numbers. This document is also available in the following formats: large print, Braille, audio tape, and electronic file on computer disk. Requests for this document in an alternative format should be made to the Office of Communications and Legislative Affairs at (202) 663–4191 (voice) or (202) 663–