KING & SPALDING

Client Alert

FDA & Life Sciences Practice Group

January 31, 2012

FDA Issues Final Rule Regarding CGMPs for Combination Products

On Tuesday, January 22, 2013, the United States Food and Drug Administration (FDA or "the Agency") published a final rule regarding Current Good Manufacturing Practice Requirements for Combination Products. 78 Fed. Reg. 4307 (Jan. 22, 2013). FDA intends to clarify which current good manufacturing practice (CGMP) requirements apply to combination products, that is, products that combine drugs, medical devices, biological products, and/or human cell and tissue products (HCT/Ps). The final rule provides guidelines for the creation of a streamlined CGMP operating system for facilities that manufacture single-entity or co-packaged combination products. The final rule will become effective on July 22, 2013.

History of the Rule

FDA first attempted to address the CGMP requirements for combination products via a draft guidance document entitled "Current Good Manufacturing Practices for Combination Products" in October 2004. After receiving comments on the draft guidance, the Agency determined that the issue was best addressed through rulemaking and issued a proposed rule on September 23, 2009. In addition, FDA co-sponsored a stakeholder workshop in January 2010 to identify areas for potential comment on the proposed rule. FDA received 25 sets of comments from industry, trade associations, and individuals about the proposed rule and considered them when drafting the final rule.

Overview of the Final Rule

The content of the final rule is essentially unchanged from the proposed rule. The final rule is applicable to combination products that are described in 21 C.F.R. § 3.2(e). Under that existing regulation, there are three types of combination products; the final rule applies to all three types:

(1) **single-entity combination products** that are comprised of two or more types of constituent parts (*i.e.*, drugs, devices, biologics, or HCT/Ps) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

For more information, contact:

Mark S. Brown
+1 202 626 5443
mbrown@kslaw.com

Pamela F. Forrest
+1 202 661 7888
pforrest@kslaw.com

Elaine H. Tseng
+1 415 318 1240
etseng@kslaw.com

Jessica M. Ringel
+1 202 626 9259
jringel@kslaw.com

King & Spalding
Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500
Fax: +1 202 626 3737

San Francisco
101 Second Street
Suite 2300
San Francisco, CA 94105
Tel: +1 415 318 1200
Fax: +1 415 318 1300

www.kslaw.com

(2) **co-packaged combination products** that contain two or more types of constituent parts that are packaged in a single package or as a unit; and
(3) **cross-labeled combination products** that are (i) packaged separately; (ii) consist of more than one type of constituent part, both of which are required to achieve the intended use, indication, or effect, and (iii) that are required to be labeled for use with each other to achieve the intended use, indication, or effect.

Section 4.3 of the final rule lists the regulatory CGMP provisions that apply to each type of combination product. First, combination products that contain a drug constituent part must be manufactured in accordance with 21 C.F.R. Parts 210 and 211. Second, combination products that contain a device constituent part must be manufactured in accordance with the Quality System regulation (QSR) in 21 C.F.R. Part 820. Third, combination products that contain a biological product as a constituent part must be manufactured under the CGMP requirements and standards that are contained in 21 C.F.R. Parts 600 through 680. Fourth, combination products that contain HCT/Ps must be produced in accordance with the current good tissue practice requirements that are contained in 21 C.F.R. Part 1271, including donor eligibility requirements.

Section 4.4 of the final rule explains how manufacturers can comply with the CGMPs applicable to co-packaged or single entity combination products. There are two options: (1) comply with all aspects of the CGMPs that are required for each constituent part of the combination product; or (2) follow what FDA refers to as a streamlined approach.

FDA offers the streamlined approach because it recognizes that there is significant overlap between some aspects of the CGMP regulations for drugs and devices. Under the streamlined approach, the manufacturer of a co-packaged or single entity drug/device combination product can choose to comply with the complete set of CGMPs applicable to one of the constituent parts of the combination product and then additionally comply with select aspects of the CGMP requirements for the other type of constituent part. The additional requirements are prescribed by FDA in section 4.4(b) of the final rule. For example, if a manufacturer makes a single entity combination product that combines a drug and a device (such as a drug eluting stent), the manufacturer may choose to comply with either the complete drug CGMP provisions or the QSR. If the manufacturer elects to follow the complete drug CGMPs, then the firm must additionally comply with six specified aspects of the QSR that are not covered by the drug CGMPs, including design controls, purchasing controls, installation and servicing. *See* 21 C.F.R. § 4.4(b)(1) for the complete list of additional QSR requirements. On the other hand, the manufacturer could choose to follow all of the requirements of the QSR, along with eight provisions that are unique to the drug CGMPs, including calculation of yield, expiration dating, stability testing, and reserve samples. *See* 21 C.F.R. § 4.4(b)(2) for the complete list of additional drug CGMP requirements. This streamlined approach also applies to facilities at which two or more types of constituent parts arrive for further manufacturing.

Impact of the Final Rule

FDA repeatedly states in the preamble to the final rule that the rule does not change the underlying CGMP requirements nor does it add additional requirements. Rather, the CGMP requirements that would apply to each of the constituent parts if they were produced and marketed as independent products continue to apply when the parts are

combined to make a combination product. The rule is intended to clarify how to apply multiple sets of CGMP requirements to a combination product and to streamline the process.

FDA makes clear in the preamble to the final rule that the rule does not apply CGMP requirements to constituent parts that would not otherwise be subject to CGMPs. For example, the constituent parts of investigational products that are exempt from some or all CGMP requirements remain exempt from the CGMP requirements when combined in an investigational combination product. In addition, if aspects of the existing CGMP regulations do not apply to certain constituent parts of a combination product, those elements also do not apply to the total combination product. FDA provides two examples: (1) only combination products that contain an over-the-counter drug must comply with the tamper-evident packaging requirements drug CGMPs and (2) only combination products that contain a device constituent part that must be installed or serviced must comply with the installation and servicing requirements of the QSR.

When constituent parts of a cross-labeled combination product are manufactured at separate facilities, manufacturers of each constituent part will not be impacted by the final rule. These manufacturers should continue operating under the CGMPs that are required for the type of product they are producing. For example, if a drug and a device are intended to be used together but are packaged and sold separately and are manufactured at separate facilities, then the facility that manufactures the drug constituent part would do so under the drug CGMPs contained in 21 C.F.R. Parts 210 and 211 and the facility that manufactures the device constituent part would follow the QSR.

In addition, if a facility manufactures only one type of constituent part, then the facility only needs to follow the CGMP requirements for that type of product, even if the part is ultimately included in a co-packaged or single entity combination product. These manufacturers should also not experience a change from the way they are currently operating as a result of the final rule. For example, if a contract manufacturer produces a syringe that will be later filled at a separate facility with a drug product and sold as a single-entity combination product, the contract manufacturer of the syringe must only comply with the QSR.

When constituent parts of a combination product are manufactured at multiple facilities, each facility is only responsible for manufacturing under the CGMP requirements that apply to the type(s) of constituent part(s) manufactured at that facility. The holder of the application or clearance for the final combination product, on the other hand, is responsible for ensuring compliance with all CGMP requirements applicable to the combination product across all facilities.

Guidance Forthcoming

In the preamble to the final rule, FDA states that it will address a number of issues in a forthcoming guidance document regarding manufacturing requirements for combination products. FDA states that the guidance will contain examples of how to apply the various CGMP requirements to combination products. The guidance will also provide advice on specific CGMP requirements as applicable to combination products, including design controls, corrective and preventive actions, reserve samples, batch release testing, stability testing, and expiration dating. The Agency does not provide a timeline for the issuance of the guidance.

* * * *

King & Spalding will continue to monitor FDA's activity regarding combination products and manufacturing issues in general. If you would like assistance in reviewing or revising your quality system to ensure compliance with applicable CGMP requirements for combination products, please let us know.