



September 28, 2009

**FDA Publishes Proposed Rule for
Current Good Manufacturing Practice Requirements for
Combination Products**

*Agency intends to clarify which cGMP requirements apply
and seeks comment by December 22, 2009*

For more information, contact:

Christina M. Markus
(202) 626-2926
cmarkus@kslaw.com

Elaine H. Tseng
(415) 318-1420
etseng@kslaw.com

Douglas B. Poucher
(202) 422-7466
dpoucher@kslaw.com

Jessica M. Ringel
(202) 626-9259
jringel@kslaw.com

**King & Spalding
Washington, D.C.**
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4706
Tel: (202) 737-0500
Fax: (202) 626-3737

San Francisco
Four Embarcadero Center
Suite 3500
San Francisco, CA 94111
Tel: (415) 318-1200
Fax: (415) 318-1300

www.kslaw.com

On September 23, 2009, the Food and Drug Administration (FDA) published a proposed rule regarding the application of current Good Manufacturing Practice (cGMP) requirements to the manufacture of combination products.¹ The proposed rule was issued in response to comments received regarding the FDA's October 4, 2004 Draft Guidance entitled "Current Good Manufacturing Practice for Combination Products." Through the proposed rule, FDA intends to clarify which cGMP requirements apply when drugs, devices, and biological products are combined to create a single-entity or co-packaged combination product. The proposed rule would be codified in Title 21 of the Code of Federal Regulations (CFR), Part 4, "Current Good Manufacturing Practice Requirements for Combination Products." FDA is accepting comments on the proposed rule and on a related guidance it intends to develop after the rule is finalized to facilitate implementation. Comments must be submitted by **December 22, 2009**.

Combination products are products comprised of any combination of drugs, devices, and biological products, including human cellular and tissue-based products (HCT/Ps). Combination products can be of three types: single-entity; co-packaged; or a product that is intended for use only with a separately-packaged and individually specified second product. FDA had not previously promulgated any regulations regarding the cGMPs applicable to combination products, although it published the above-referenced Draft Guidance in 2004 and has also addressed combination product cGMP compliance through Warning Letter issuance. Comments to the Draft Guidance voiced the need for a clear regulatory framework that adequately considers the nature of combination products and that would not demand unnecessary redundancy in meeting cGMP requirements.



FDA & Life Sciences Practice Group

Separately-Packaged Combination Products. In the proposed rule, FDA notes that the application of cGMPs to separately-packaged combination products is fairly straightforward and that each constituent product must be manufactured in accordance with the cGMP regulations applicable to the constituent. Accordingly, the new regulations do not address separately-packaged combination products.

Single-Entity and Co-Packaged Combination Products. For single-entity and co-packaged combination products, the Agency provides two options for ensuring compliance with all applicable cGMP regulations:

1. Compliance with all cGMP regulations applicable to each of the constituent parts (drug, device, biologic, and/or HCT/Ps) included in the combination; **or**
2. As a “streamlined” approach, when the combination contains both a drug constituent and a device constituent that are manufactured at the same facility, compliance with **either** the drug cGMPs or the device Quality System (QS) regulations **and** compliance with specific requirements from the set of regulations that is not selected. If a drug-device combination includes a biological or HCT/P constituent part, in addition to demonstrating compliance with either the drug cGMPs or the device QS regulation and the specified provisions of the other regulations, the operating system must comply with all cGMP requirements that apply to biological products or HCT/Ps, as applicable. In particular, FDA’s proposal would require compliance with the following for companies who elect to adopt the “streamlined approach”:
 - **Drug-Device Combination:** all drug cGMPs and certain device QS regulations (specifically, 21 CFR 820.20 (management responsibility), 820.30 (design controls), 820.50 (purchasing controls), 820.100 (corrective and preventive action), 820.170 (installation), and 820.200 (servicing)); **or** all device QS regulations and certain drug cGMPs (specifically, 21 CFR 211.84 (testing and approval or rejection of components, drug product containers, and closures), 211.103 (calculation of yield), 211.132 (tamper-evident packaging requirements for over-the-counter human drug products), 211.137 (expiration dating), 211.165 (testing and release for distribution), 211.166 (stability testing), 211.167 (special testing requirements), and 211.170 (reserve samples)).
 - **Drug-Biologic Combination:** all drug cGMPs and all applicable biologic cGMPs (see 21 CFR Parts 600 through 680).
 - **Device-Biologic Combination:** all device QS regulations and all applicable biologic cGMPs (see 21 CFR Parts 600 through 680).
 - **Drug-Device-Biologic Combination:** all drug cGMPs, specified device QS regulations, and all applicable biologic cGMPs **or** all device QS regulations, specified drug cGMPs, and all applicable biologic cGMPs.
 - **HCT/P Combinations:** all drug or device cGMPs (depending on how the HCT/P constituent is regulated), 21 CFR Part 1271, applicable biologic cGMPs (if the HCT/P is regulated as a biological product), and other cGMPs or QS regulations as applicable



FDA & Life Sciences Practice Group

under the proposed rule with respect to the non-HCT/P constituent(s) of the combination product.

Constituents Manufactured at Separate Facilities. If the manufacturing of one or more constituents occurs at a facility separate from the other type(s) of constituent(s), then each separately-manufactured constituent must be produced in accordance with the cGMPs for that type of constituent part and the combination approach described above cannot be used.

Differences from Draft Guidance. The proposed rule generally adheres to the recommendations set forth in FDA's 2004 Draft Guidance but includes a few differences. For example, the distinction drawn in the proposed rule between whether constituents of a combination product are manufactured in the same or separate facilities for purposes of determining which cGMP requirements apply, differs from the Draft Guidance, which applied cGMP requirements based in part on whether constituent parts of a combination product had or had not yet been combined. Also, in the Draft Guidance, FDA did not call out 21 CFR 820.20 (management responsibility) as a distinction between the QS and drug cGMP regulations for purposes of combination product cGMP compliance. The proposed rule identifies 820.20 as one of the QS regulations with which manufacturers of single-entity or co-packaged combination products must additionally comply if they elect to adopt the "streamlined" approach of general compliance with drug cGMPs. The proposed rule does not retain provisions from the Draft Guidance that specified 21 CFR 211.113(b) and 211.42 (in the context of aseptic processing) as additional provisions applicable in certain instances to combination product manufacturers that generally follow the QS regulations. Additionally, as noted above, the proposed rule would require compliance with certain specified regulations in 21 CFR Parts 211 or 820 for affected combination product manufacturers that generally comply with one, but not both, of these cGMP requirements. However, unlike the Draft Guidance (and drug cGMP and QS regulations), the combination product cGMP regulations proposed to be codified at 21 CFR Part 4 do not explicitly acknowledge that compliance with specific provisions of 21 CFR Parts 211 and 820 is required only to the extent the provisions are applicable to the product or operations a company performs.

Please contact us if you have questions concerning FDA's proposed rule or other issues regarding the regulation of combination products, or if we can assist with the monitoring, analysis, or preparation of comments regarding this proposed rule.

King & Spalding is an international law firm with more than 800 lawyers in Abu Dhabi, Atlanta, Austin, Charlotte, Dubai, Frankfurt, Houston, London, New York, Paris, Riyadh (affiliated office), San Francisco, Silicon Valley and Washington, D.C. The firm represents half of the Fortune 100 and, according to a Corporate Counsel survey in August 2009, ranks fifth in its total number of representations of those companies. For additional information, visit www.kslaw.com.

This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice

¹ 74 Fed. Reg. 48423 (Sept. 23, 2009), Docket No. FDA-2008-D-0409.