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Client Alert

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FDA Issues Final Rule on Combination Products cGMPs

On January 22, 2013, FDA issued a final rule on the current Good Manufacturing Practice (cGMP) requirements for combination products.[1] As discussed in the Federal Register preamble, the final rule is intended to establish a framework for companies to use when demonstrating compliance with cGMP requirements. In response to several comments to a 2004 Draft Guidance entitled, "Current Good Manufacturing Practices for Combination Products," FDA published a proposed rule on the topic in September 2009.[2] The Final Rule becomes effective on July 22, 2013 and is now codified at new 21 C.F.R. Part 4. FDA said, in several places, that its intent is not to create new cGMPs, but to clarify how to apply them to combination products. The agency intends to issue further guidance in the future.

The new rule addresses "single-entity" combination products, (e.g., pre-filled syringes) and "co-packaged" combination products (e.g., convenience kits.)[3] This Bulletin summarizes the major points of the new rule and some of FDA's responses to the industry comments that we view as noteworthy.

- A manufacturer can demonstrate compliance with each applicable set of cGMP regulations in its entirety. For instance, a drug-device combination product may demonstrate cGMP compliance by complying with all of the drug cGMPs and the Quality System Regulations (QSRs). Alternatively, a manufacturer can demonstrate compliance with only one set of applicable regulations (e.g., QSRs only) and a limited set of specified provisions of the other applicable regulations (e.g., cGMPs for drugs). For instance, if the product is subject to drug cGMPs and QSRs, these two sets of requirements can be met by demonstrating compliance with the full set of drug cGMPs and only certain QSR provisions listed in the rule (e.g., design controls and servicing). On the other hand, a manufacturer can also demonstrate compliance for this same product by demonstrating compliance with the full set of QSRs and only certain drug cGMPs listed in the rule (e.g., expiration dating and

1 78 Fed. Reg. 4,307 (Jan. 22, 2013).
2 74 Fed. Reg. 48,423 (Sept. 23, 2009). The Draft Guidance is *available* at: **http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm**.
3 "Single-entity" combination products are products with two or more regulated components, e.g., drug/device, biologic/device, that are produced as a single entity. "Co-packaged" combination products are two or more separate products packaged together in a single package, and these products are either drug and devices, devices and biological products, or biological and drug products. 21 C.F.R. § 3.2(e)(1).

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stability testing). However, if the product contains a biological product, or human cell, issue, and cellular and tissue-based product, the manufacturer must comply fully with their respective quality-related regulations.

- The Final Rule notes that a facility manufacturing only one type of constituent part need comply solely with the cGMP requirement applicable to that constituent part (e.g., the QSR if the constitute part is a device). Facilities that manufacture more than one type of constituent part must comply with the cGMP requirements applicable to each type.

Scope of New 21 C.F.R. § 4.1

- An investigational drug for use in a phase I study is not subject to cGMPs. However, the exemption does not apply to an investigational combination product or constituent part of a combination product in phase 2 or 3 studies, or when the drug has been lawfully marketed. See 21 C.F.R. § 210.2(c). Similarly, investigational devices are exempt from QSRs, except for design control requirements. See 21 C.F.R. § 812.30(b)(5)(ii). These exemptions remain in the Final Rule.

- For purposes of the Final Rule, FDA defined "convenience kit" to include only kits that contain products that are legally marketed independently and included in the kit as already packaged for independent marketing and with the same labeling as for independent marketing. That is, products packaged and labeled within their existing marketing authorization. For this type of convenience kit, the agency would expect no additional cGMP requirement, except those applicable to the assembly, packaging, labeling, any sterilization, or further processing of the kit itself. However, if any of the products are repackaged, relabeled, or otherwise modified for the purpose of inclusion in a kit (e.g., a new intended use), FDA does not consider this kit to be a "convenience kit" under the Final Rule and any applicable cGMP requirements will apply to any changes made to the constituent parts, such as design controls.

Compliance with cGMPs for a Co-Packaged or Single-Entity Combination Product – New 21 C.F.R. § 4.4

- FDA acknowledged that not all of the combination product cGMP requirements will apply to a particular product. Similarly, not all requirements will apply at a facility that is performing only some parts of the combination product manufacture. However, the burden is on the company to demonstrate why it is acceptable not to follow a particular requirement, i.e., why not appropriate in the specific case.

> [T]he applicability of some CGMP requirements will vary depending on the circumstances, including what aspect of a product's manufacture takes place at a facility and whether multiple facilities are involved in the manufacture of a combination product. Accordingly, we

do not agree that the rule should be either "product-based" or "facility-based."

- According to the Final Rule, FDA addressed how to comply with cGMPs for a co-packaged or single-entity combination product. See New 21 C.F.R. § 4.4. The agency noted:

> (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 QSRs 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 QSR need be made:
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> (i) Management responsibility
> (ii) Design controls
> (iii) Purchasing controls
> (iv) Corrective and preventive action
> (v) Installation
> (vi) Servicing
>
> (2) If the combination product includes a device constituent part, and the current good manufacturing practice operating system has been shown to comply with the QSR, 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:
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> (i) Testing and approval or rejection of components, drug product containers, and closures
> (ii) Calculation of yield
> (iii) Tamper-evident packaging requirements for over-the-counter human drug products
> (iv) Expiration dating
> (v) Testing and release for distribution
> (vi) Stability testing
> (vii) Special testing requirements
> (viii) Reserve samples

See 21 C.F.R. § 4.4.