

New US Regulation on CGMPs for Combination Products

US FDA has recently published its long-awaited regulation on current good manufacturing practices (CGMPs) applicable to combination products. The regulation becomes effective on 22 July 2013 and applies to combination products already on the market in addition to newly developed products.

In September 2004, US FDA published draft guidance on CGMPs for combination products¹ that was intended to provide definitive guidance on this issue once it became final. The agency received 15 comments from stakeholders, which reportedly were largely supportive of the approach in the draft guidance; however, the comments also underlined a preference for a clear regulatory framework that would not lead to unnecessary redundancy. After considering the comments and the best ways to ensure a consistent and appropriate approach, the agency decided to pursue rulemaking, which led to a proposed rule on CGMPs for combination products that was published on 23 September 2009. To facilitate the development of comments on the proposed rule, US FDA co-sponsored a workshop in January 2010 on the subject. On 22 January 2013, the final rule was published² along with a preamble that contains a detailed analysis of comments received and US FDA's responses to the comments. Readers are encouraged to review the comments and responses, which provide helpful insight into the agency's interpretation of various aspects of the new regulatory provisions. Readers familiar with the proposed rule will note that the final rule is largely identical to the proposed rule.

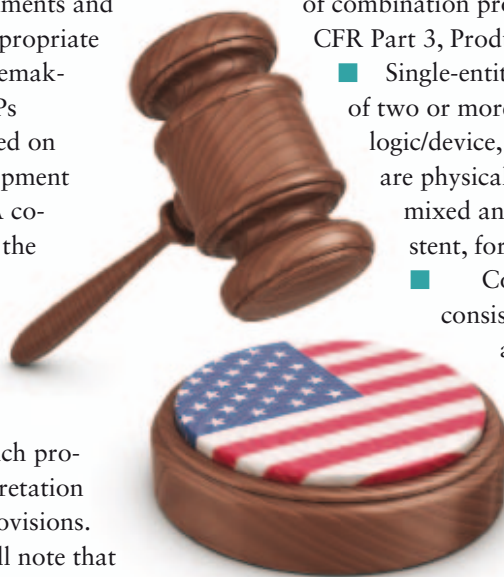
Purpose of the regulation

The purpose of the new regulation is to clarify which CGMP requirements apply when drugs, devices and biological products are combined to create combination products. It is also intended to provide a transparent and streamlined regulatory framework

for firms to use when demonstrating compliance with CGMP requirements for so-called single-entity and co-packaged combination products. In the United States, combination products are considered to be products comprised of two or more types of medical products—namely, a medical device, drug or biologic product.

The new regulation provides options for demonstrating compliance with CGMPs, depending upon which of the three types of combination product is concerned, these being defined in 21 CFR Part 3, Product Jurisdiction:

- Single-entity combination product, which is comprised of two or more regulated components—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 (a drug-eluting stent, for example).
- Co-packaged combination product, which consists of two or more separate products packaged together in a single package or as a unit comprising drug and device products, device and biological products or biological and drug products (such as a syringe packaged with a vial containing a drug).
- Cross-labelled combination product, which is considered to be a drug, device or biological product packaged separately that according to its investigational plan or proposed labelling 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 labelling of the approved product would need to be changed, for



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example, to reflect a change in intended use, dosage, dosage form, strength, or route of administration. A light-emitting device and light-activated drug is one example.

The regulation has the following four sections:

4.1 What is the scope of this subpart?

4.2 How does FDA define key terms and phrases in this subpart?

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

4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

Streamlined approach

Section 4.3 lists the CGMPs that apply to the various constituent parts of a combination product. A constituent part is a drug, device or biological product that is part of a combination product. That is, the drug CGMPs in 21 CFR Parts 210 and 211 apply to a combination product that includes a drug constituent. The device CGMPs in 21 CFR Part 820 apply to a combination product that includes a device constituent. The CGMPs that are among the requirements (including standards) for biological products in 21 CFR Parts 600 through 680 apply to a combination product that includes a biological product constituent. The current good tissue practice requirements, including donor eligibility requirements for human cell, tissue and cellular and tissue-based products (HCT/Ps) in 21 CFR Part 1271, apply to a combination product that includes an HCT/P.

When combination products are manufactured and marketed separately, such as in the case of cross-labelled combination products, the application of CGMPs is straightforward. For example, if such a product consists of a separately manufactured and marketed drug and device, the drug CGMPs would apply to the drug constituent and the device CGMPs would apply to the device. However, determining acceptable compliance with CGMPs for single-entity or co-packaged combination products is less straightforward. Thus, the primary value of the new regulation is in the options that section 4.4 provides for demonstrating compliance with applicable CGMPs for single-entity and co-packaged combination products.

Section 4.4(a) specifies that for single-entity or co-packaged combination products, compliance with all applicable CGMP requirements for the combination product shall be achieved through the design and implementation of a CGMP operating system that complies with the specifics of each set of CGMPs listed in section 4.3 as they apply to each constituent part included in the combination product.

Alternatively, section 4.4(b) provides two additional options that US FDA describes as the streamlined approach. One option is that if the combination product includes a device constituent part and a drug constituent part, and the CGMP operating system has been shown to comply with the drug CGMPs, the



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following provisions of 21 CFR Part 820 must also be shown to have been satisfied:

- Section 820.20, Management responsibility
- Section 820.30, Design controls
- Section 820.50, Purchasing controls
- Section 820.100, Corrective and preventive action
- Section 820.170, Installation
- Section 820.200, Servicing.

The second option is that if the combination product includes a device constituent part and a drug constituent part, and the CGMP operating system has been shown to comply with 21 CFR Part 820, the following provisions of the drug CGMPs must also be shown to have been satisfied:

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

These two options reflect US FDA's view that, in general, 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 addition, section 4.4 requires that biological products, in addition to being shown to comply with either device or drug CGMPs based upon its regulatory category as a device or drug, also must comply with all manufacturing requirements of 21 CFR Parts 600 through 680. This approach also applies to HCT/Ps: that is, if the combination product includes an HCT/P, the CGMP operating system must also be shown to comply with all CGMP requirements identified in 21 CFR Part 1271.

Forthcoming guidance

US FDA states that it is working on companion guidance to the final regulation and intends to publish this during 2013. In responding to stakeholder comments, US FDA has indicated some of the issues that are expected to be included in forthcoming guidance.

For example, some comments asked whether containers and closures would continue to be treated as drug components, to which US FDA responded that the agency will continue to

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regulate drug containers and closures in accordance with the drug CGMPs. Other comments asked whether a prefilled syringe would be considered a combination product, to which US FDA's response was that a syringe is not a mere container/closure, but is a device used to deliver another medical product such as a drug (see 21 CFR 880.5860). Accordingly, a prefilled syringe is a combination product and subject to the new regulation. US FDA also added that it plans to address distinctions between devices and containers/closures in further detail in the guidance.

Some comments argued that reserve sample requirements in section 211.170 should apply only to drug constituent parts of combination products and not to device constituent parts or the entire combination product. US FDA responded that reserve samples are needed to help ensure the postmarket safety and effectiveness of combination products, as they are for drugs and biological products. In addition, US FDA stated that for a single-entity combination product, such as a prefilled syringe or a drug-eluting disc or stent, it would be appropriate to retain samples of the complete product from each lot and, in any event, the samples should include the drug and all device components that come into direct contact with the drug. For co-packaged and cross-labelled combination products, it generally should be sufficient to maintain samples of each lot of the drug or biological product in the immediate container/closure in which it is marketed. Furthermore, US FDA stated that information regarding how to comply with sample retention requirements for combination products will be provided in the guidance.

Ensuring compliance

US FDA states in the preamble to the final rule that manufacturers are already responsible for compliance with the CGMP requirements that apply to each constituent part of their combination products and that the new regulation does not establish any new requirements. Prudent manufacturers will use the new regulation and the information in the preamble to make any necessary modifications to their operating systems to ensure full compliance with CGMP requirements for combination products before the effective date.

References

1. Current Good Manufacturing Practice for Combination Products (Draft Guidance), September 2004, www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm
2. Current Good Manufacturing Practice Requirements for Combination Products Final Rule, *Federal Register*, 8, 14, 22 January 2013, www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

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