

# Current good manufacturing practice requirements for combination products

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On January 11, 2017, the U.S. Food and Drug Administration (FDA) issued a final guidance document entitled “Current Good Manufacturing Practice Requirements for Combination Products.”<sup>1</sup> This guidance describes and explains the agency’s January 22, 2013 final rule on current good manufacturing practice (CGMP) requirements for combination products (the Final Rule).<sup>2</sup>

Largely adhering to a January 2015 draft guidance that was put out for comment, the final guidance provides:

- A discussion regarding the definition of a “combination product.”
- An overview of the Final Rule.
- A description of the agency’s review of combination product CGMP issues.
- General considerations for CGMP compliance and requirements for combination products.

## Definition of a “combination product”

The guidance provides a straightforward discussion on what constitutes a combination product. In short, combination products are products composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another).<sup>3</sup> The drugs, devices, and biological products are referred to as “constituent parts” of the combination product. As outlined in 21 C.F.R. 3.2(e), combination products include:

- 1) A single-entity combination product—products comprised of two or more regulated components that are combined or mixed and produced as a single entity (such as a prefilled syringe or drug-eluting stent.)
- 2) A co-packaged product—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 (such as a surgical or first aid kit.)
- 3) A cross-labeled combination product—a drug, device, or biological product packaged separately that 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 (as might be the case for a light-emitting device and a light-activated drug.)

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<sup>1</sup> Available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>

<sup>2</sup> 21 C.F.R. Part 4.

<sup>3</sup> 21 C.F.R. Part 3.

- 4) A cross-labeled combination product for investigational use—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.

## Overview of the Final Rule

The guidance expands upon the Final Rule and discusses the ability of combination product manufacturing facilities to adopt a streamlined approach to combination product CGMP compliance in certain situations. This streamlined approach allows manufacturers of single-entity combination products and co-packaged combination products to be in compliance with good manufacturing practices by demonstrating that the manufacturer is in compliance with either the drug CGMP (21 C.F.R. Parts 210 and 211) or the device Quality System (“QS”) requirements (21 C.F.R. Part 820) while also demonstrating compliance with specified provisions from the other of these two sets of good manufacturing practices requirements. Combination products including a biological product require compliance with CGMP requirements specific to biological products in 21 C.F.R. parts 600 through 680, while combination products with Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) require demonstrating compliance with the requirements in 21 C.F.R. Part 1271.

For single-entity combination products and co-packaged combination products, the guidance explains that the Final Rule offers two ways to demonstrate compliance with drug CGMP and device QS requirements:

- Under the first option, the manufacturer can demonstrate compliance with all CGMP requirements applicable to each of the constituent parts included in the combination product (both drug CGMP and device QS requirements.)
- Under the second option, the manufacturer can implement the more streamlined approach described above.

The second option provides a far more convenient and significantly less burdensome approach for manufacturing facilities to establish and maintain quality systems that more closely reflect the needs of the combination product being manufactured, as facilities can largely choose to adhere to either the drug CGMP or the device QS requirements, depending on what is more appropriate for a given facility and then fill gaps with processes from the other requirements. For instance, a facility that manufactures a combination product as well as a drug may choose to follow the drug CGMP requirements and add in the necessary device QS elements, whereas a facility that manufactures a device and a combination product may prefer to follow the device QS requirements and add in the necessary drug CGMP elements under the second option.

When cross-labeled combination products are manufactured at the same facility, a streamlined approach to CGMP for the manufacture of the products can be implemented rather than distinct systems for each cross-labeled product. In contrast, when cross-labeled combination products are manufactured at separate facilities, each facility must comply with the full drug CGMP or device QS obligations applicable to the respective drug, device, or biological product manufactured at each respective facility.

FDA notes the continued importance of documentation in compliance with the Final Rule, and identification in the facility’s documentation of what requirements are being adhered to at a given

facility (including whether or not this streamlined approach is being used). Where an operating system may require changes to come into compliance, manufacturers should document the steps taken to ensure ongoing product safety and effectiveness and be prepared to discuss their approach during an inspection.

### Compliance with CGMP requirements of 21 CFR 4.4(b)

When manufacturers of a combination product that contains a device component choose to follow drug CGMP under the streamlined approach, the manufacturers must also follow certain additional device QS requirements. Likewise, manufacturers of a combination product that contains a drug component who choose to follow device QS under the streamlined approach must also follow certain additional drug CGMP requirements. The next section of the guidance provided descriptions of the device QS and drug CGMP requirements that must be followed by manufacturers complying with the opposite scheme.

Manufacturers of single-entity and co-packaged combination products that contain a device component must comply with the following additional device QS requirements when using the drug CGMP-based streamlined approach, as these device QS processes are not addressed under the drug CGMP requirements:

- Management responsibility (21 CFR 820.20).
- Design controls (21 CFR 820.30).
- Purchasing controls (21 CFR 820.50).
- Corrective and preventive actions (21 CFR 820.100).

The guidance includes extensive discussion of each of these requirements. Of particular interest may be FDA’s discussion of the management responsibility requirements, which have been rephrased from the draft guidance to further emphasize the requirement that executive management “demonstrate an active, ongoing commitment to quality system development and implementation.”

Manufacturers of single-entity and co-packaged combination products that contain a drug component must comply with the following additional drug CGMP requirements when using the device QS-based streamlined approach, as these drug CGMP processes are not addressed under the device QS requirements:

- Testing and approval or rejection of drug product components, containers, and closures (21 CFR 211.84).
- Calculation of yield (21 CFR 211.103), tamper-evident packaging requirements for over-the-counter human drug products (21 CFR 211.132).
- Expiration dating (21 CFR 211.137).
- Testing and release for distribution (21 CFR 211.165).
- Stability testing (21 CFR 211.166).
- Special testing requirements (21 CFR 211.167).
- Reserve samples (21 CFR 211.170).

As above, the guidance includes extensive discussion of each of these requirements. Note that the tamper-evident packaging requirements do not necessarily apply to all drug-device combination products; instead, the requirements are limited to “[m]anufacturers of OTC combination products.” Further, FDA added language not present in the draft guidance to note that certain combination products, such as toothpaste co-packaged with a toothbrush, may be exempt from tamper-evident

packaging requirements. Other products, such as certain aerosol saline nasal sprays, may be exempt from the requirement to bear a statement of tamper-evident features on the package. Also of note, FDA added new language on the requirement for testing for release and distribution that noted that for some single-entity combination products, manufacturers may be able to conduct release testing on samples that are not themselves finished combination products, but are representative of finished combination products with respect to the attribute being tested. This approach must be justified with bridging studies to demonstrate that any differences in manufacturing process will not affect the drug constituent part. This section also includes a discussion of when prior stability data may be accepted when a combination product receives a minor change to the device component that is not expected to affect the drug component. Affected manufacturers are encouraged to review the guidance in full.

This section also describes the additional requirements for combination products that include a biological product or an HCT/P. As the guidance document reminds manufacturers, a biological product is also, by definition, a drug or a device. Accordingly, a combination product that includes a biological product must choose to either comply with all of drug CGMP and the selected parts of device QS described above, or all of device QS and the selected parts of drug CGMP described above. In addition, the product must comply with the CGMP requirements for biological products in 21 CFR parts 600 through 680. The guidance notes that many of the requirements of 600 through 680 are applicable only to certain types of biological products, so the combination product need only comply with the requirements applicable to the biological product included in the combination product. An HCT/P that is not regulated solely under section 361 of the PHS Act and Part 1271 is also regulated as a drug, device, or biological product. Such an HCT/P may also be required to comply with drug CGMP, device QS, and the CGMP requirements for biologics in parts 600 through 680, depending on whether the product is regulated as a drug, device, or biological product. These requirements are in addition to the HCT/P requirements, but where the requirements conflict, the guidance states that the more specifically applicable requirements will supersede the more general requirements. The guidance states that due to the complexity of manufacturing requirements for HCT/P products, manufacturers should contact the lead center for their product or Office of Combination products (OCP) with questions on manufacturing compliance.

### Application of requirements to specific types of combination products

The guidance closes by explaining the application of these requirements to three common types of combination products: prefilled syringes, drug-coated mesh, and drug-eluting stents (DES). The guidance presents each situation as a hypothetical scenario and then explains certain common issues in the application of manufacturing requirements to the products. The section is largely unchanged from the draft guidance, although the discussion of compliance with design history file requirements in device QS requirements has been expanded. The scenarios provide examples of the necessary considerations for adopting the streamlined approach.

FDA also provides some clarity regarding convenience kits that contain two or more types of products co-packaged together and makes clear that Part 4 applies to the manufacture of the kit and the kit manufacturer would only need to demonstrate compliance to the CGMP requirements that are associated with activities performed, e.g., assembly, packaging, labeling, sterilization, etc. The guidance goes on to point out that certain changes to the products contained in the kit will affect whether the kit is deemed a convenience kit, such as repackaging, relabeling, or other

modifications from the independent marketed product, as well as labeling changes that modify the intended use of the constituent part. For example, inclusion of a QS-exempt device constituent in a kit with other products, such that the intended use of the device constituent is new, may result in the device QS exemption becoming unavailable to the kit manufacturer. Where there are such changes to the constituent parts, the kit manufacturer will have to demonstrate compliance to the drug CGMP/device QS requirements for the constituent parts as well as for the overall kit. FDA also cautions manufacturers to carefully consider the impact of any sterilization processes on the constituent parts and whether additional processes to account for the effect may be necessary.

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FDA's drug CGMP/device QS requirements have always embraced a certain degree of flexibility to account for the wide variety of products and technologies that are regulated by the agency. The approach outlined in the guidance continues to embody FDA's recognition of the need for flexibility, demonstrate a desire for developing systems and requirements that represent the least burdensome approach, and account for those processes that the agency believes create the necessary controls to protect the public health. As with any implementation, the devil is always in the details, but this framework in particular is logical and benefits from years of experience from both FDA and industry. Further, it allows manufacturers to develop systems and processes that best reflect the combination product they are producing and allows them to leverage their existing systems and experience to the fullest extent. Given the extent of the flexibility and judgment that is permitted, here more than ever, we encourage companies to conduct formal analyses of requirements and develop clear implementation plans that can be shared with FDA on inspection to demonstrate diligence and the reasonableness of the company's plans for demonstrating compliance.

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