

# FDA Issues Its Final Rule for Combination Product Quality Systems

**By Michael Gross**

This article is part of a series on the regulation of combination products in the US.<sup>1-10</sup> On 22 January 2013, the US Food and Drug Administration (FDA) published the long-anticipated final rule, *Current Good Manufacturing Practice Requirements for Combination Products*<sup>11</sup> to clarify regulatory requirements for quality systems used to design, develop and manufacture combination products, and to help ensure consistent and appropriate application and enforcement of these requirements. The final rule is codified as 21 CFR 4. It applies to marketed combination products and many products in development. Developers and manufacturers of combination products and their constituent parts have 180 days to comply with the final rule. FDA intends to apply a risk-based approach to combination product facility inspections and has stated it will offer manufacturers a reasonable opportunity to correct quality system deficiencies before taking compliance or enforcement actions.

The final rule preamble points out that the *Food, Drug, and Cosmetic Act* recognizes combination products as a category of medical products distinct from drugs, biologic products and medical devices, which are the constituent parts of combination products. The final rule is largely unchanged from its initial publication as a proposed rule<sup>12</sup> on 23 September 2009. FDA intends to publish a companion guidance document describing how to comply with the final rule, including the structuring of streamlined quality systems (*vide infra*), and how the final rule applies to legacy products. FDA's Office of Combination Products is seeking industry input on issues to be addressed in this guidance.

FDA uses a "legal" style when publishing new regulations. For the purpose of this analysis and to avoid confusion, the regulatory language of the final rule is simplified and certain alternative terms are used. The following terms and acronyms will be used throughout this analysis. The current Good Manufacturing Practice (CGMP) for combination products regulation will be referred to as the combination products quality system regulation, or the final rule. The quality system regulation that applies to drugs and biologics (21

CFR 210, 211) is referred to as CGMP. The quality system regulation that applies to medical devices (21 CFR 820) is referred to as the QSR. The CGMP and QSR regulations are also referred to as predicate rules. The term constituent part refers to the drugs, biologics and medical devices that, when combined, form combination products. This term is not synonymous with component.

### Summary of the Final Rule

The final rule states that CGMP regulations for drugs and biologic products apply to combination products that include a drug or biologic constituent part. CGMP regulations for medical devices, or the QSR, apply to combination products that include a device constituent part. Additional regulatory requirements and standards apply if certain biological products described in 21 CFR 600–680 are incorporated as constituent parts in combination products. And Current Good Tissue Practice requirements, including donor eligibility requirements, for human and cellular and tissue-based products (HCT/Ps) described in 21 CFR 1271 apply to combination products that incorporate an HCT/P.

An article that, in the absence of the final rule, would be considered a device component, which is not subject to the QSR, does not become subject to the QSR as the result of the final rule. Drug manufacturing components are subject to CGMP requirements and continue to fall under the final rule.

For single-entity or co-packaged combination products, compliance with the combination product quality system is achieved by using a quality system demonstrated to comply with predicate rules applicable to combination product's constituent parts. There are two options for demonstrating compliance with applicable quality system requirements for a single-entity or a co-packaged or combination product containing both a drug or biologic and a medical device. A company may demonstrate compliance with the specifics of all quality system regulations applicable to each constituent part or, under certain conditions, it may demonstrate compliance with the specifics of either of the predicate rules rather than both. Under the latter circumstance, in order to demonstrate full compliance with both regulations, a manufacturer basing its quality system on a CGMP platform also may be required to demonstrate compliance with specified provisions of the QSR, thus creating a streamlined (i.e., hybrid) quality system. These specified provisions are:

- management responsibility (21 CFR 820.20)
- design controls (21 CFR 820.30)
- purchasing controls (21 CFR 820.50)
- corrective and preventive action (21 CFR 820.100)
- installation (21 CFR 820.170)
- servicing (21 CFR 820.200)

Should a combination product manufacturer choose to base its quality system operations on the QSR platform, the manufacturer also must demonstrate, as applicable, compliance with specified provisions of the CGMP regulation, again forming a streamlined quality system. These specific provisions are:

- testing and approval or rejection of components, drug product containers and closures (21 CFR 211.84)
- calculation of yield (21 CFR 211.103)
- tamper-evident packaging requirements for over the-counter (OTC) 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)

Additionally, for combination products that incorporate certain types of biological products, compliance with the requirements of 21 CFR 600–680 also must be demonstrated. For a combination product that incorporates HCT/Ps, compliance with the requirements of 21 CFR 1271 must be demonstrated.

When two or more types of constituent parts to be included in a single-entity or co-packaged combination product are held at the same facility, or when the manufacture of a combination product proceeds at the same facility while utilizing these constituent parts, compliance with all applicable quality system requirements must be demonstrated.

For the development or manufacture of a particular combination product, when a conflict occurs between individual predicate rule requirements, the final rule directs that the regulations most specifically applicable to the constituent part at issue take precedence over the more general requirement.

## Discussion

For combination products containing drug, biologic or device constituent parts, the final rule neither creates new requirements nor modifies existing requirements. It clarifies how to apply these requirements to the development and manufacture of combination products. Entities that engage only in certain regulated operations are subject only to those portions of the predicate rules that apply to those operations.

The final rule preamble mainly addresses single-entity and co-packaged (i.e., kit) combination products. It clarifies that certain container closure systems that also serve as drug delivery devices (e.g., a prefilled syringe) may be considered drug manufacturing components but are still constituent parts of combination products and subject to the final rule. Therefore, if a facility manufactures a finished prefilled syringe from drug and device components, it must comply with both QSR and CGMP regulations.

The final rule preamble also addresses convenience kits, which are combination products that only include two or more types of medical products that are legally and independently marketed and subsequently co-packaged for marketing with the same labeling as that used for independent marketing. For these convenience kits, generally no additional CGMP requirements apply, except those applicable to the assembly, packaging, labeling, sterilization or further processing of the kit itself. However, if any other medical products are included in such a kit, which are repackaged, relabeled or otherwise modified for purposes of inclusion in the kit, then the kit is no longer considered a convenience kit according to the final rule. Under these circumstances, all of the quality system requirements applicable under the final rule apply to the kit, including design controls intended to ensure that the device constituent part of the kit satisfies the intended use for which it has been included.

The preamble also briefly discusses how the final rule applies to cross-labeled combination products. Because the constituent parts of a cross-labeled combination product are manufactured and marketed separately, they remain separate for purposes of applying the predicate rules. The constituent parts of a cross-labeled combination product still must be manufactured in accordance with the quality system requirements that would apply if they were not part of a combination product.

The final rule preamble discusses how combination product manufacturers are required to demonstrate compliance with the predicate rules as they apply to a particular combination product. Demonstrating compliance includes establishing and maintaining written procedures and records that document and verify the utilization of applicable quality system requirements described in the respective predicate rules.

Under CGMP requirements for combination products, each constituent part of a combination product, when manufactured and marketed separately, is subject only to the individually applicable predicate quality system regulations pertaining to that constituent part type. The constituent parts of single-entity and co-packaged combination products retain their drug, biologic or device regulatory status before and after they are combined. Thus, a facility where a single type of constituent part is manufactured must demonstrate compliance with the quality system requirements applicable to that constituent part type. Quality system requirements that apply to the individual constituent parts of a combination product continue to apply even after the parts are combined to form of a single-entity or co-packaged combination product.

The design control requirements of the QSR apply when a device constituent part is incorporated into a combination product. The QSR requires device manufacturers to establish and maintain procedures that ensure design requirements are appropriately established, and that intended use and user needs are considered and satisfied. In

utilizing design controls, manufacturers may rely on existing information for the constituent parts. Should a combination product developer wish to use an existing or off-the-shelf product as a constituent part of a combination product, design controls must ensure the existing product meets appropriate and prospectively established design requirements that ensure the combination product will be safe and effective. This may result in modification of the existing product for its use as part of the combination product.

Regardless, if the manufacturer of a device-containing combination product chooses to establish its quality system on a CGMP or QSR platform, the design history file requirements of design controls must be satisfied. The manufacturer must address all design issues resulting from the combination of constituent parts and demonstrate that the combination product was developed in accordance with a prospectively established design plan. In a webinar<sup>13</sup> following publication of the final rule, a representative from FDA's Office of Combination Products stated that design controls apply not only to the device constituent part of a combination product but also to the overall combination product, possibly including certain aspects of the drug constituent part. For example, for a co-packaged combination product, the compatibility of the constituent parts should be assessed using design controls, in particular if the drug constituent part is optimized for use in combination with a particular device.

According to the final rule, a device constituent part of a combination product is a finished device and a drug constituent part of a combination product is a drug product. Specification developers and contract manufacturers are considered manufacturers subject to the final rule if they manufacture combination products or combination product constituent parts. However, manufacturers of a device component (e.g., a syringe plunger stopper or barrel) are not considered a manufacturer of a device under the QSR and are therefore not subject to the final rule, even if that component will be incorporated into a combination product or constituent part of a combination product at another facility.

Manufacturers are responsible for ensuring compliance with all quality system regulations applicable to development and manufacturing operations conducted at their facilities. Where multiple facilities are responsible for various aspects of the manufacturing process, the holder of the marketing authorization for the combination product is responsible for ensuring overall compliance with final rule requirements that are applicable to the entire manufacturing process across all facilities.

During any period in which a facility manufactures only one type of constituent part of a single-entity or co-packaged combination product, the facility must comply with all quality system regulations applicable to that type of constituent part, which in some cases may arise from more than one predicate rule. Manufacturing facilities that perform operations for more than one type of combination product constituent part must comply with the quality system regulations applicable to each type of constituent part manufactured at that facility.

For investigational combination products being developed under an Investigational New Drug (IND) application or Investigational Device Exemption (IDE), in certain circumstances, FDA allows such products to be exempt from certain quality system requirements. Combination products containing a drug or biological product, which are in Phase 2 or Phase 3 clinical studies, are subject to the final rule. Investigational medical devices are exempt from all requirements of the QSR requirements, except design controls.

The final rule does not change any quality system requirements described in predicate rules for constituent parts (i.e., drug, biologic, device) described in master files (e.g., Drug Master Files and Master Files for Devices). Under the final rule, if the manufacture of an article described in a master file is subject to CGMP or QSR requirements, these requirements must still be met. If the manufacture of such an article is exempt from certain predicate rule requirements, it may still be subject to other predicate rule requirements (e.g., QSR purchasing controls in the case of device constituent parts).

## Conclusion

Manufacturers of combination products and combination product constituent parts have six months from the date of publication of the final rule to implement changes to their quality systems that are required to demonstrate full compliance, for all affected manufacturing facilities, with the requirements of the final rule. Prudent combination product

manufacturers will assess the impact of the final rule on their manufacturing and quality operations and those of their suppliers and contractors.

Risk-based gap assessments should include a review of purchasing agreements and SOPs, and the conduct of internal and external audits. Additional SOPs and training programs may be needed. Implementing these measures will take time and planning.

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