Published on *The National Law Review* https://natlawreview.com

FDA Issues Draft Guidance on Combination Product Manufacturing

Article By:

Julia F. Post

Two years after issuing a final rule on ***current good manufacturing practice (cGMP)*** requirements for combination products, FDA has announced the availability of draft guidance that explains the final rule and further clarifies how manufacturers can comply with cGMP requirements. Following the rule's issuance, industry requested additional guidance from FDA about the rule's implementation, and FDA promised to provide such guidance. FDA has now made good on that promise.

The draft guidance reviews the definition of a combination product and reiterates that the final rule on cGMP requirements applies to all combination products. Accordingly, the final rule applies to: (1) a "single entity" combination product, meaning a product comprised of two or more regulated components, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (e.g., a prefilled syringe); (2) a "co-packaged" combination product, meaning two or more separate products that are packaged together as a unit and comprise drug and device, device and biological, or biological and drug products (e.g., a surgical kit); and (3) a "cross-labeled" combination product, meaning a drug, device, or biological product that is intended for use only with another separate drug, device, or biological product, where both are required to achieve the intended use, indication, or effect (e.g., a light-emitting device and a light-activated drug).

Manufacturers of drug-device single entity or co-packaged combination products can demonstrate compliance with the cGMP requirements in two ways. First, manufacturers can demonstrate compliance with all cGMP regulations and Quality System Regulations (QSR) applicable to each of the constituent parts of the combination product. Alternatively, a manufacturer can demonstrate compliance via a streamlined approach, either by demonstrating compliance with the drug cGMPs and a subset of device QSRs (a cGMP-based streamlining approach) or by demonstrating compliance with device QSRs and a subset of drug cGMPs (a QS regulation-based streamlining approach). The guidance emphasizes that, should a manufacturer prefer the streamlined procedure, the manufacturer is not obligated to implement the streamlined approach for the constituent part that provides the primary mode of action (PMOA) of the combination product. For example, even if the drug constituent part of the drug-device combination product provides the PMOA, the manufacturer is still free to implement the QS-regulation based streamlining approach. The draft guidance also states that FDA intends to apply the same policies when inspecting combination products, regardless of the manufacturer's compliance approach, but urges manufacturers to clearly identify in their premarket submissions and indicate at the beginning of an inspection if they are operating under a streamlined

procedure (and if so, which one).

The draft guidance further clarifies the definitions of some of the key terms in the final rule, such as the distinction between drug containers and closures as compared to delivery devices. According to the guidance, “[t]he essential distinction is whether the article is designed to deliver the drug it contains or merely hold it[,]” with the latter defining a drug container or closure. The guidance explains that a “container closure system” is all of the packaging components that hold and protect the drug, and that examples of packaging components include containers, vials, and stoppers, among others. By contrast, a device such as a piston syringe is a delivery device that, if filled with a drug, constitutes a combination product subject to both cGMPs and QSRs. Additionally, the draft guidance dives into the meaning of “convenience kits,” which was addressed in the preamble to the final rule. The draft guidance reiterates that the cGMP requirements applicable to kits (which can constitute co-packaged combination products) will depend on the kit’s contents. Specifically, if a kit includes any products that are repackaged, relabeled, or otherwise modified so that they may be included in the kit, these manufacturing steps would be subject to cGMP requirements.

Perhaps most illuminating in the draft guidance is the use of examples and hypothetical scenarios to further clarify how manufacturers can comply with the cGMP regulations set forth in the final rule. The draft guidance addresses what cGMP responsibilities apply to specific manufacturers and illustrates steps sponsors can take to coordinate cGMP compliance across facilities. In addition, the draft guidance provides examples of how manufacturers can comply with the subset of QSRs required under the cGMP-based streamlining approach (which is instructive for drug and biological product manufacturers who may lack familiarity with these regulations), as well as the subset of cGMPs required under the QS regulation-based streamlining approach (which is instructive for device manufacturers who may lack familiarity with these regulations). Finally, the draft guidance applies the cGMP requirements to three hypothetical scenarios—a pre-filled syringe, a drug-coated mesh, and a drug-eluting stent—to clarify application of the streamlined approach to combination products. These hypothetical examples are intended to be illustrative, and the draft guidance encourages manufacturers to contact their lead center or the Office of Combination Products to discuss questions relating to specific products.

Concurrent with the publication of the draft guidance, FDA withdrew the September 2004 draft guidance for industry and FDA staff entitled “Current Good Manufacturing Practice for Combination Products.” Comments regarding the newly-issued draft guidance are due to FDA by March 30, 2015.

National Law Review, Volume V, Number 40