Draft Guidance: Current Good Manufacturing Practice Requirements for Combination Products

When finalized, the draft guidance, will represent FDA's current thinking on Current Good Manufacturing Practice Requirements for Combination Products. In the meantime, the draft Guidance provides the pharmaceutical and medical device manufacturers of combination products with insights into what FDA thinks it thinks about its interpretation of 21CFR4. The final rule and draft guidance focus mainly on how to *demonstrate* compliance with predicate quality system rules [i.e., 21CFR820 (QSR), 21CFR210, 211 (GMP), 21CFR 600-680, and 21CFR 1271] as they may apply to a particular combination product. The draft guidance restates much of what FDA has said in the final quality system rule for combination products, so it does not warrant repetition here, although a detailed review of the draft guidance is highly recommended. This analysis will focus on a few points in the draft guidance that provide important insights. *Commentary* is provided and two remaining uncertainties are identified.

- Manufacturers should explain in their applications how their combination product quality systems are structured. A combination product quality system can be structured as streamlined quality system (i.e., a hybrid of applicable predicate rules) or a redundant quality system (i.e., parallel application of applicable predicate rules in their entirety).
    - *Hybrid and parallel quality systems are not official FDA terms for quality system structures.*
- Regardless of the Primary Mode of Action (PMOA) of a combination product a streamlined quality system (i.e., a hybrid quality system) can be based on either a GMP or a QSR platform by adding the required and applicable elements from the other regulation. When conducting inspections, the FDA Center with Primary Jurisdiction for premarket review of a combination product application has the primary responsibility for ensuring compliance with quality system requirements. FDA intends to apply the same inspectional approach regardless of which predicate rule platform the core quality system is based. FDA Centers will coordinate, as appropriate, in the conduct of inspections.
    - *FDA's QSR and GMP inspectional approaches are different. It remains to be seen how FDA will approach combination product inspections. Will the approach be the same regardless of the quality system platform used to establish the quality system?*
- The definition of "manufacture" in 21CFR4.2 includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage of a combination product. An

entity that undertakes any of these activities in the manufacture of a combination product is considered to be a manufacturer.

- The term “constituent part” is used to identify a medical product type (i.e., a drug, device, or biological product) included in a combination product. Under 21CFR210.3, a “component” is defined as “any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.” Components used to manufacture drugs are subject to 21CFR210 and 211 and are thus subject to 21CFR 4. Under 21CFR 820.3(c), the term “component” is defined as “any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.” If a facility only manufactures a device component and not a finished device, and is not otherwise subject to the QSR, it is not subject to the QSR.
- The distinction between a drug container closure system and drug delivery device is made based on whether the article is intended to deliver the drug it contains, or only hold it. If the article only holds the drug, it is only subject to 21CFR210 and 211. If it is intended to both hold and deliver a drug then it is a combination product and also subject 21CFR820.
- Certain stand-alone delivery devices regulated as Class I medical devices, are exempt from many of the requirements of the QSR. When such devices are co-packaged with a drug in a “convenience kit”, such devices may be subject to certain GMP and QSR requirements, such as Design Controls.
    - *No mention is made is made in the draft guidance of the case of single-entity combination products which contain device constituent parts which if stand-alone would be Class I medical devices. It can only be presumed that the same approach would follow in such cases, although this remains to be stated by FDA.*
- Term “where appropriate” and similar language is used in predicate rules to acknowledge that compliance with certain requirements may not be necessary, under certain circumstances. Manufacturers should be prepared to provide justifications for not complying with these requirements.
    - *It is not stated where such justifications might be presented but at a minimum they should be documented and available during inspections.*
- When changes or modifications to the combination product or to its manufacturing process occur, if the changes affect material(s)or specifications, the intended outcome of change can be verified through measurement and testing and may not need to be validated. When changes impact intended use or user needs, these may require validation.

- The manufacturer of a finished combination product is responsible for assuring that the manufacturing activities occurring at any facility involved in the manufacture of a combination product, including those operated by third parties, is in compliance with combination product quality system requirements. Each manufacturing facility must be in full compliance with requirements applicable to each manufacturing process that occurs at that facility. Quality agreements may specify expectations as to which facility will perform activities and develop and maintain documentation needed to demonstrate compliance with which CGMP requirements. Such agreements may also detail what measures a facility will take to ensure compliance with CGMP requirements and any other relevant duties established by the manufacturer of the finished combination product, for that facility. Each manufacturing facility involved in the manufacture of a combination product should have documentation specifying its respective responsibilities. The manufacturer of the finished combination product should have access to the documentation.
- CAPA concerns the entire quality system as a whole. Finished combination product manufacturers may need to establish a CAPA system that is shared between facilities, or alternatively facility-specific CAPA systems may need to be linked.
- Manufacturers of finished combination products should have assurances that manufacturers involved in the design of the combination product (e.g., specification developers) maintain an adequate design control systems. It is appropriate to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls.
    - *This is the only (draft) guidance provided that bears on the Retrospective Design History File (see below).*
- For single-entity combination products, manufacturers should maintain reserve samples of the active ingredient and of the drug product within its container/closure, which in some cases may be the entire device constituent part of a combination product. In others, it may be a part of the device, or distinct from the device constituent part. For a drug-eluting stent or disc, or a prefilled syringe reserve samples should be kept of the entire combination product. If the combination product consists of an injector system (device constituent part) into which the user inserts cartridges containing the drug, reserve samples of the filled cartridge alone would suffice to comply with drug product sample retention duties. However, a complete injector system may be needed to conduct performance testing.

Two Remaining Important Uncertainties:

- *An important un-addressed issue is the retrospective construction of a Design History File (i.e., a "Retrospective, or Retroactive Design History File" for those combination products that were developed and marketed between 1996 when the 21CFR820 took effect and 2013 when the 21CFR4 took effect (i.e., Legacy Combination Products). While FDA has stated publicly that compliance with Design Controls will be expected for legacy products, no details have been provided as to how compliance can or should be be achieved.*
- *No (draft) guidance is provided on FDA's expectations on the application of Design Controls to the drug constituent part of a combination product. It can only be assumed that compliance with Design control requirements is expected where the drug and device constituent parts of a combination product interact.*