Extended Abstract

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Pharmacology 2019 - FDA cGMP requirements for combination products – considerations for drug manufacturers - Viky Verna - University of Florida

Viky Verna
University of Florida, USA

Abstract

As set forth partially 3 (21 CFR part 3), a mixture product may be a product composed of two or more differing types of medical products (i.e., a mixture of a drug, device, and/or biological product with one another).5 The drugs, devices, and biological products included in combination products are mentioned as “constituent parts” of the mixture product.

In 2013 final rule codified at 21 CFR Part 4 was promulgated to establish the FDA’s cGMP requirements for combination products (CP). This regulation gave rise to the concept of “streamlined approach” adoption to bring a CP company’s quality management system (QMS) to full compliance. For example, this approach allows a drug manufacturer who is already compliant with drug cGMPs (i.e. 21 CFR 210-211) to update and complement its QMS with additional subsystems (applicable 21 CFR 820) to achieve and maintain compliance with 21 CFR Part 4. Accordingly, this presentation covers the most important factors pharmaceutical companies should consider in relation to cGMP, “streamlined approach” implementation, when embarking in the CP realm.

The constituent parts of a mixture product retain their regulatory status (as a drug or device, for example) after they are combined. The final rule clarifies that the CGMP requirements that apply to every of the constituent parts apply to the mixture product they constitute. This guidance refers to a “CGMP OS ” to mean the operating system within an institution that's designed and implemented to deal with and meet the present good manufacturing practice requirements applicable to the manufacture of a mixture product.

The final rule on CGMP requirements for combination products applies to all or any combination products. The CGMP requirements for constituent parts of cross-labeled combination products that are entirely manufactured at separate facilities are an equivalent as those that would apply if these constituent parts weren't a part of a mixture product (e.g., for a drug/device combination product, only parts 210 and 211 (21 CFR parts 210 and 211) would apply to the manufacture of the drug constituent part(s) of the cross-labeled combination product, and only part 820 (21 CFR part 820) would apply to the device constituent part(s)). With regard to cross-labeled combination products, part 4 was intended to clarify only that the CGMP obligations applicable to the drugs, devices, or biological products also apply to those sorts of articles once they are constituent parts of cross-labeled combination products.

Because constituent parts of cross-labeled combination products need only suits the requirements otherwise applicable thereto sort of product (e.g, part 211 for a drug constituent part or part 820 for a tool constituent part), the “streamlined approach” (discussed below) is generally not relevant or applicable to them. However, to the extent that the constituent parts of a cross-labeled combination product are manufactured at an equivalent facility, the manufacturing process would be like when the manufacture of the constituent parts of a co-packaged combination product occurs at the same facility. Accordingly, for cross-labeled combination products when manufactured at an equivalent facility, the Agency doesn't shall object to the utilization of a streamlined CGMP OS for the manufacture of the mixture product rather than distinct systems for the manufacture of every constituent part that's occurring at that facility. We believe this approach is consistent with the principles of part 4.

For single-entity combination products and co-packaged combination products, part 4 identifies two ways to demonstrate compliance with CGMP requirements. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to every of the constituent parts included in the combination product.6 Under the second option, manufacturers implement a streamlined approach for combination products that include both a drug and a tool by demonstrating compliance with either the drug CGMPs (21 CFR parts 210 and 211) or the device Quality System (QS) regulation (21 CFR part 820) and also demonstrating compliance with specified provisions from the opposite of those two sets of CGMP requirements.7, 8 In addition, for a mixture product that has a biological product, the manufacturer must demonstrate compliance with the CGMP requirements specific to biological products in parts 600 through 680 (21 CFR parts 600 through 680). For a combination product that includes any HCT/P, the manufacturer must demonstrate compliance with the regulations in part 1271 (21 CFR part 1271)—including the present good tissue practice (CGTP) requirements and donor eligibility requirements.

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• The drug CGMPs and therefore the following provisions from the device QS regulation in accordance with 21 CFR 4.4(b)(1) (drug CGMP-based streamlined approach):

(i) 21 CFR 820.20 Management responsibility

(ii) 21 CFR 820.30 Design controls

(iii) 21 CFR 820.50 Purchasing controls

(iv) 21 CFR 820.100 Corrective and preventive action

(v) 21 CFR 820.170 Installation

(vi) 21 CFR 820.200 Servicing

OR

• The device QS regulation and therefore the following provisions from the drug CGMPs in accordance with 21 CFR 4.4(b)(2) (device QS regulation-based streamlined approach):

(i) 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures

(ii) 21 CFR 211.103 Calculation of yield

(iii) 21 CFR 211.132 Tamper-evident packaging requirements for over-thecounter (OTC) human drug products

(iv) 21 CFR 211.137 Expiration dating

(v) 21 CFR 211.165 Testing and release for distribution

(vi) 21 CFR 211.166 Stability testing

(vii) 21 CFR 211.167 Special testing requirements

(viii) 21 CFR 211.170 Reserve samples

A manufacturer may prefer one approach over the opposite based, for instance, on the small print of the manufacturing process used at the power or in light of other manufacturing activities undertaken at the facility. The manufacturer is not required to choose a streamlined approach based on the CGMP regulations for the constituent part that gives the first mode of action (PMOA) of the combination product (see II.D below). For example, if the drug constituent part of a drug-device combination product provides the product's PMOA, the manufacturer of that combination product may choose to adopt either the device QS regulation-based or drug CGMP based streamlined approach, or choose to develop a CGMP operating system that wholly complies with the specifics of applicable provisions of both the drug CGMPs and therefore the device QS regulation. 21 CFR 4.4(c) provides that if a facility manufactures only one type of constituent part (e.g., a drug or device constituent part) of a co-packaged or single-entity combination product, that facility is subject only to the CGMP regulations applicable to that constituent part (i.e., part 211 for a drug or part 820 for a tool , also as those under parts 600 through 680 for a biological product and part 1271 for an HCT/P). 21 CFR 4.4(d) provides that when two or more types of constituent parts to be included during a single-entity or co-packaged combination product have arrived at the same facility, or the manufacture of these constituent parts is occurring at the same facility, that facility must suits all CGMP requirements described partially 4 Contains Nonbinding Recommendations applicable to the manufacturing activities at that facility, and a streamlined approach under 21 CFR 4.4(b) could also be wont to demonstrate compliance with these requirements. Similarly, if a facility manufactures a drug or device that is not a constituent part of a combination product and also manufactures a mixture product, the CGMP requirements for the independently marketed drug or device don't change (compliance with parts 210/211 or part 820, respectively). Accordingly, if a facility manufactures an independently marketed device 820, respectively). Accordingly, if a facility manufactures an independently marketed device.

Biography:

As a Senior Consultant and Vice-President at confinis, Mr. Viky Verna currently assists medical device and pharmaceutical companies with regulatory affairs challenges. His qualifications are firstly supported by his education; specifically, a BS and a MS in Biomedical Engineering from the University of Miami, a MS in Pharmacy and a Drug Regulatory Affairs Certificate from the University of Florida, and a Global Regulatory Affairs Certification (RAC) from Regulatory Affairs Professional Society (RAPS). Mr. Verna's experience with Combination Products started at the US Food and Drug Administration (FDA) as in investigator. Later, at the Center for Devices and Radiological Health (CDRH) of the FDA, Mr. Verna held several positions including (Acting) Branch Chief of the Respiratory, ENT, General Hospital, and Ophthalmic (REGO) devices branch which handles the compliance activities of combination products among others, including drug delivery systems. During his time at CDRH.

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