Combination Products Workshop: CGMP and PMSR Requirements

GMP by the Sea
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Definition of a Combination Product

A combination of a drug, device and/or biological product:

- “Single entity” – physically/chemically combined:
  - prefilled syringe
  - drug-coated device
  - cells on scaffold
  - drug-biologic conjugate

- Co-packages of devices, drugs and/or biologics
- Cross labeled products
The CGMP Regulation

21 CFR 4

Effective July 22, 2013
Two Options to Demonstrate Compliance

- Fully implement “both” sets of CGMP regulations (211 AND 820) OR
- “Streamlined approach”:  
  - Fully comply with a primary set of requirements (211 OR 820) AND 
  - Comply with specific requirements of the “other” set of regulations that are unique to that type of article and would be lost if not required
210/211 “Base” – Device “Add-on’s”

- 820.20 Management responsibility
- 820.30 Design controls
- 820.50 Purchasing controls
- 820.100 Corrective and preventive action
- 820.170 Installation
- 820.200 Servicing

Design controls will likely be the main gap for most drug/biologic sponsors...
...the above requirements apply to the device constituent part and the combination product as a whole
820 “Base” – Drug “Add-on’s”

- 211.84 Testing and approval or rejection of components, drug product containers, and closures
- 211.103 Calculation of yield
- 211.132 Tamper-evident packaging (for OTC drug products)
- 211.137 Expiration dating
- 211.165 Testing and release for distribution
- 211.166 Stability testing
- 211.167 Special testing requirements
- 211.170 Reserve samples

All can be gaps for device companies, to varying degrees
The PMSR Regulation

21 CFR 4

Effective January 19, 2017
Overall Reporting Scheme Dictated by Application Type

- If the combination product or device constituent part received marketing authorization under a device application, comply with 21 CFR 803 and 806

- If the combination product or drug constituent part received marketing authorization under an NDA or ANDA, comply with 21 CFR 314

- If the combination product or biological product constituent part received marketing authorization under a BLA, comply with 21 CFR 600 and 606
Additional Requirements for Combo Applicants – Devices

- If the combination product was approved under BLA, NDA or ANDA and includes a device constituent part, also submit:
  - 5-day reports (21 CFR 803.3/803.53)
  - Malfunction reports (21 CFR 803.50)
  - Correction and removal reports (21 CFR 806.10)
Additional Requirements for Combo Applicants - Drugs

- If the combination product was approved under a BLA or device application and includes a drug constituent part, also submit:
  - Field alert reports (21 CFR 314.81)
  - 15-day reports (21 CFR 314.80) however the regulation permits reporting within 30 calendar days instead of 15 calendar days if the product was approved/cleared under a device application
Additional Requirements for Combo Applicants - Biologics

- If the combination product was approved under NDA, ANDA or device application and includes a **biological product constituent part**, also submit:
  
  - Biological product deviation reports (21 600.14/606.171)
  
  - 15-day reports (21 CFR 600.80) (with the same 30 calendar day allowance stated above if the product was approved/cleared under a device application)
Compliance Timeframes

- Currently in effect as of January 19, 2017:
  - Existing reporting requirements per application type
- July 19, 2018 (18 months after the effective date) for the “new” requirements:
  - Additional reporting provisions specific to the “additional” constituent part
  - Device events in drug/biologic periodic safety reports
  - Information sharing for constituent part applicants
  - Recordkeeping requirements
Case Study: Legacy Product (Device Issue)

You market a topical drug product administered using an applicator brush that is supplied with the drug. The drug was approved in the 1990’s and at no time during the approval process or since has FDA indicated the product is a combination product nor has the company ever considered this a combination product. The applicator brush is sourced from several suppliers. During your next inspection, the investigator asks you to demonstrate compliance with 21 CFR 4. How do you handle this?
Case Study: Legacy Product (Device Issue)

You market an ophthalmic drug administered as drops from a dropper container. You consider the bottle to be a container closure, but during a routine CGMP inspection, the FDA investigator said that the bottle also has device attributes, since it controls delivery of the drug. You have no design control documentation for the dropper bottle. How do you handle this?
Case Study: Legacy Product (Drug Issue)

You’ve marketed a device for years that you just find out FDA thinks is a combination product because of one of its constituent parts is a drug. Other regulators consider the drug to be a device constituent part and your only supplier for the drug is not in conformance with 21 CFR 211. How do you handle this?
Case Study: Reserve Samples

You are head of quality at a small company about to get PMA approval for a new, first of a kind, drug-device combination product. While implementing the streamlined approach in accordance with 21 CFR 4, you are getting a lot of pushback from the Operations team because of the Reserve Sample requirements of 21 CFR 211.170. Your combination product will sell for over $10,000 a unit and Operations has asked you to consider alternate means to comply with 21 CFR 4 instead of putting several units per lot on reserve. What are your options?
Case Study: Auto-Injector Design Controls

You are developing a new biological product that will be prefilled into an auto-injector. The auto-injector is supplied by another company and was recently approved under an NDA for another drug. Your company already complies with the management controls, CAPA and purchasing controls provisions of 21 CFR 820 but has no experience implementing design controls. Since the auto-injector has been previously approved, can you rely on the design controls already in place for the device to satisfy your 21 CFR 4 requirements?
Case Study: Quality System for Start-up

You have just signed on to develop the quality system for a start-up company whose first product will be a structural bone void filler (device) impregnated with bone morphogenetic protein (biological product). Nothing is in place and you’re free to set up the quality system from the ground up. You’ve heard of the streamlined approach and have decided that it is preferable to fully implementing 21 CFR 820 and 211 and applicable sections of the 21 CFR 600-680. What are the considerations in deciding whether to base the quality system primarily on 21 CFR 820 or 21 CFR 211?
Case Study: Co-Package Requirements

You are developing a co-packaged combination product which includes your drug product in a vial and some simple devices used to withdraw the drug from its vial and deliver the drug to the patient. The devices are already 510(k) cleared and are being used consistent with the cleared intended uses. What are your obligations for compliance with 21 CFR 4 for the co-packaged product?
Case Study: AE Reporting for Drug-Biologic

Your company has approval for a chemotherapy drug conjugated to a monoclonal antibody that is regulated by CDER. The product was approved under a BLA and you are compliant with 21 CFR 600.80 for adverse experience reporting and also compliant with biological product deviation reporting. What additional requirements must you implement when the additional provisions of the combination product PMSR rule go into effect in July 2018?
You have approval for a biological product for which a companion diagnostic (device) is used to determine eligible candidates for the biologic. The diagnostic is made by a device company you have partnered with for this purpose. You learn that a patient was inadvertently treated because the diagnostic failed to detect that this patient was ineligible for treatment with your drug. What are the reporting responsibilities for you and your partner company? What if there was no patient injury as a result of the treatment?
Discussion Questions

▪ How have your experiences with OUS audits/inspections for combination products compared to FDA inspections?

▪ How have your experiences with prior approval inspections differed from routine inspections? Have you been expected to provide information demonstrating compliance with 21 CFR 4 in marketing applications? How has investigator awareness of 21 CFR 4 requirements been evident during inspections?

▪ What kinds of FDA inspection practices can you share for combination products and how do they differ from standalone drugs or devices? Number of investigators participating? Inspections of manufacturers of the “other half” of the product?
Discussion Questions

▪ What is your experience/best practices for establishing compliance with 21 CFR 4 for legacy combination products?

▪ What kinds of changes will companies typically need to make internally to get ready for the new postmarket safety reporting requirements for combination products?

▪ Have any participants decided to fully implement both sets of CGMP requirements (211/820) instead of the streamlined approach? What led to your decision?
Discussion Questions

▪ Have any participants selected a “base” quality system different than how their product is regulated? For example, choosing a 21 CFR 820-based system for a drug/device combination regulated under a NDA? What led to your decision and are there any recommendations or lessons learned?

▪ Can participants share their experiences implementing design controls for combination products regulated as drugs or biologics? What were the lessons learned? How did you merge the drug and device development cycles?

▪ FDA participants: what is your experience with implementation of 21 CFR 4 thus far? Can you share the extent of training for the field investigators, since there seems to be a mix of investigators who are both familiar and unfamiliar with the requirements?
Discussion Questions

- Has anyone received 483’s associated with 21 CFR 4 CGMP requirements? Is FDA citing to 21 CFR 4 or the underlying requirements?

- Has anyone received or become aware of a warning letter specifically including combination product observations? There is no search field for combination product keywords in the warning letter database.

- For drug/biologic companies, which device “add-on” requirements have raised the most challenges?
Discussion Questions

▪ For device companies, which drug/biologic “add-on” requirements have raised the most challenges?

▪ Has anyone implemented the combination product CGMP requirements for a combination product including an HCT/P product? What unique issues have you faced with application of the GTP requirements?

▪ Has anyone experienced issues raised by the sample retention requirements of 211.170 for combination products incorporating devices?
Discussion Questions

▪ Has anyone experienced issues raised by the stability requirements under 211 with respect to the combination product as a whole (assessing device attributes such as functionality, sterility in addition to routine drug issues)?

▪ How have participants considered the distinction between container closures and simple devices that also act as container closures? Should an eye dropper container be considered a medical device?

▪ How have participants considered the applicability of CGMP requirements to the constituent part vs. the combination product as a whole?

▪ How have participants considered the existing exemptions to the CGMP requirements for investigational combination products (21 CFR 211 for Phase 1 studies; 21 CFR 820 except for design controls for all phases)?