US FDA Current Good Manufacturing Practice Requirements for Combination Products

This summary was prepared by the Rx-360 Monitoring and Reporting Working Group which tracks regulatory, legislative and policy developments relevant to pharmaceutical/medical device supply chain integrity. The summary is not intended to serve as comprehensive and formal interpretation or guidance (and should not replace your own review and analysis of any referenced source documents). If you have questions, please contact Brittany Tobery, Rx-360 Secretariat, at 301-710-9399 or btobery@rx-360.org.
I. Introduction

- Guidance intended to describe and explain final rule on cGMP for combination products 21 CFR part 4, issued on Jan 22, 2013
- Final rule did not establish any new requirements
  - Intended to clarify which cGMP requirements are applicable when drugs, devices, and biological products are combined
  - Establish transparent, streamlined regulatory framework for firms to use to demonstrate compliance with applicable cGMP requirements
II. Background

- The drug CGMP and device QS regulations, as well as the CGMPs for biologics and current good tissue practices for HCT/Ps provide a framework of minimum requirements to help assure product quality.

- The core requirements embedded in these regulations provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
Quality and Current Good Manufacturing Practice

• Establish a strong quality management system
• Use appropriate quality raw materials,
• Establish robust manufacturing and control procedures based on sound design principles
• Detect and investigate product quality deviations.
• Ongoing assessment of systems
• Implement of corrective actions where appropriate.
Combination Product Definition

- A combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another).

- The drugs, devices, and biological products included in combination products are referred to as “constituent parts” of the combination product.
Constituent Parts of Combination Products

• Constituent parts of a combination product retain their regulatory status after they are combined

• Final rule clarifies that cGMP requirements that apply to each of the constituent parts apply to the final combination product

• Final rule applies to all combination products
Combination Product Examples

• A product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity
  – Also called a “single entity” combination product
  – Examples include a prefilled syringe or drug-eluting stent)

• Two or more separate products packaged together in a single package or as a unit
  – Also called a “co-packaged” combination product
  – Examples include a surgical kit or first-aid kit)

• A drug, device, or biological product packaged separately that is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect
  – Upon approval, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose)
  – Also called a “cross-labeled” combination product
  – Examples include a light-emitting device and a light-activated drug
Demonstrating cGMP compliance

• For single-entity and co-packed combination products, two options to demonstrate compliance
  – Develop a system to demonstrate compliance of the combination product with all applicable provisions of both the drug cGMPs and the device QS regulation
  – Streamlined approach
    • Comply with either drug GMPs or device QS along with specified provisions from the other set of GMPs
    • If a biological product is one of the constituent parts, applicable requirements in parts 600 – 680 also need to be incorporated
Streamlined approach – Drug GMPs

- All of the drug CGMPs (21 CFR parts 210 and 211)
- The following provisions from the device QS regulation (21 CFR 820)
  - (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
Streamlined approach – Device QS

- All of the device QS regulation (21 CFR 820)
- The following provisions from the drug CGMPs
  - (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-the-counter (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
Streamlined Approach Considerations

- Manufacturer not required to choose approach based on constituent part that provides the primary mode of action – either is acceptable
- If a facility only manufactures one constituent part of a combination product, only the cGMPs for the constituent part are applicable
- Once two or more constituent parts arrive at the same facility, or when manufacture of constituent parts occurs at the same facility, cGMPs for both constituent parts are applicable for the combination product
Documenting cGMP Approach

• Combination product manufacturers should
  – Identify all documentation needed to demonstrate compliance with part 4
  – Have the documentation accessible for an FDA inspection
  – Have quality system documentation that identifies the cGMP operating system for combination products manufactured at that facility
  – Share this information with investigators at the initiation of the inspection
  – Be prepared to discuss their approach during inspections

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cGMP Coordination Compliance Across Facilities

• Combination product owner retains overall responsibility for the product, even if not directly involved in manufacture

• Facilities that manufacture one type of regulated constituent part only need to comply with applicable cGMPs
  – The cGMP system should consider downstream impact on combination product
  – Access to relevant documentation needs to be provided to the combination product owner
Control of Changes to a Combination Product

• Appropriate consideration should be given for any potential implications for safety and effectiveness of the combination product that may arise because of the proposed change
  • This includes potential impact downstream to either subsequent manufacturing processes and/or product quality
• Notice of change needs to be arranged between combination product owner and suppliers, contractors and consultants
Streamlined cGMP Approach

• Summary descriptions are provided on applicable sections from the drug, device, and biological regulations which are applicable using the streamlined approach, including considerations specific to applying these requirements to combination products
• FDA’s intent is to help familiarize manufacturers who may not be familiar with drug cGMP regulations better understand device QS regulations, and vice versa
• Links to additional FDA guidances are also provided for awareness and education
• Additional details also provided for combination products that include biological products and/or human cells, tissues, and cellular and tissue-based products
Streamlined cGMP approach

**Device QS**
- All of the device QS regulation (21 CFR 820)
- The following provisions from the drug CGMPs
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  - (ii) 21 CFR 211.103 Calculation of yield
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  - (viii) 21 CFR 211.170 Reserve samples

**Drug GMPs**
- All of the drug CGMPs (21 CFR parts 210 and 211)
- The following provisions from the device QS regulation
  - (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
Hypothetical Scenarios

- Three hypothetical scenarios provided to illustrate points from the guidance
  - Prefilled syringe –
    - Focusing on compliance with the device QS regulation if a manufacturer adopts a drug-based streamlined approach
  - Drug-coated mesh –
    - Focusing on complying with device QS regulations after a drug constituent part is combined with a device
  - Drug-eluting stent –
    - Focusing on how to comply with the drug provisions if the manufacturer adopts a device QS regulation based streamlined approach
Thank you

For More Information  info@Rx-360.org