Combination Products: Learning about and from the CGMP Rule

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Overview

- Background
- CGMP rule
- Take away

Legal construct

- Constituent parts retain legal status as drugs, devices, biologics

- Combination products a distinct product category (not a drug, device, or biologic)

- Regulatory requirements for combination products arise from authorities for drugs, devices and biologics, as well as combination products

Regulatory approach & policy goals

- Premarket
  - Apply consistent standards to assess comparable safety and effectiveness questions
  - Use comparable regulatory pathways

- Postmarket
  - Require compliance with regulatory requirements for each constituent part while avoiding redundancy
  - Ensure consistent compliance/inspectional standards

Regulatory approach cont'd

- Coordination and training
  – Enable sound, consistent regulation

- Transparency/outreach
  – Identify and address key issues

Final rule on CGMPs

- Final rule on current good manufacturing requirements for combination products (21 CFR part 4) (www.federalregister.gov/ articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products)
  - Published January 22, 2013
  - Effective July 22, 2013
- Addresses application of CGMPs for drugs, devices, biologics, and HCT/Ps to combination products
- What does it say?
- What does it tell us about FDA's regulatory approach for combination products?

CGMP rule continued

- Must comply with CGMPs for all constituent parts

- For constituent parts of cross-labeled combination products, comply with the CGMPs applicable to that type of article (drug, device, or biologic)

- For single-entity and co-packaged combination products, a “streamlined” approach for demonstrating compliance with drug and device CGMPs, based on similarities of these regulations

CGMP rule continued

Streamlined approach cont'd:

- Demonstrate compliance with drug or device CGMPs and specified provisions from the other.

- Must also demonstrate compliance with biologics CGMPs and current good tissue practices for human cells, tissues, and cellular and tissue-based products (HCT/Ps), as applicable.

Specified QSR requirements

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

Specified drug CGMP requirements

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

Response to comments

Frequently raised issues addressed by the rule include . . .

Scope of CGMP requirements

Q: Does the rule create any new CGMP requirements?

A: No, this rule merely clarifies how to comply with existing CGMP requirements and offers a mechanism to streamline compliance.

Q: Do facilities that are not otherwise subject to CGMPs become subject to them because of this rule?

A: No, this rule does not change to whom CGMP requirements apply.

Response to comments cont'd

"Device" v. "container closure system"

Q: Should delivery devices be treated as mere container closures or as prefilled devices?

A: Prefilled devices, so all manufacturing considerations can be appropriately addressed.

Design controls

Q: Do design controls apply to the combination product or just device constituent part(s)?

A: The combination product, to ensure appropriate selection of the constituent parts and appropriate evaluation of their interactions and interrelationships.

Response to comments cont'd

Product testing

Q: Can the product testing and release requirements called out from the drug CGMPs be applicable throughout the manufacturing process for the combination product?

A: Yes, as appropriate to confirm the product meets its specifications and performs properly.

Reserve samples

Q: Do reserve samples need to be kept of the combination product or only the drug constituent part?

A: Reserve samples should include the drug constituent part and the device constituent part/portion(s) of it that come into direct contact with the drug.

Next Steps

- FDA completing draft companion guidance
  - In clearance
  - Agency priority for this year
- Feedback welcome
- Contact product coordinators, ORA, OCP as needed for your product/facility

Take Away

- Requirements for each constituent part
  - Constituent part v combination product
- Clarifying and streamlining duties
  - Addressing the substance
- Recent/upcoming actions
  - PSR Rule; UDI, IND/IDE

Take Away continued

- Considerations
  - Postmarket v premarket
  - Statutory v regulatory
  - Article v application type

- Outreach
  - Transparency and collaboration

Further Information

OCP webpage:
http://www.fda.gov/CombinationProducts/default.htm

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