COMBINATION PRODUCTS

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Regulations

- 78 *Federal Register* (78 FR) 4307, published 1/22/13, effective 7/22/13
  - https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products
- Title 21 *Code of Federal Regulations* (21 CFR) Part 4
  - http://www.ecfr.gov/cgi-bin/text-idx?SID=eb4ea6d0889250e5b0234f4cd9caa865&mc=true&tpl=/ecfrbrowse/Title21/21cfr4_main_02.tpl

Definitions

- Single Entity -- Product comprised of two or more regulated components that are physically, chemically, or otherwise mixed or combined and produced as a single entity
- Co-Packaged -- Two or more separate products packaged together in a single package or unit

Definitions

- Cross-Labeled -- A drug, biological product, or device packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved, individually specified, drug, biological product, or device where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed

Definitions

- Cross-Labeled -- Any investigational drug, biological product, or device packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, biological product, or device where both are required to achieve the intended use, indication, or effect

Mode of Action

- Mode of Action – the means by which a combination product achieves its intended therapeutic effect or action
- Primary Mode of Action – the single mode of action by a combination product which provides the most important therapeutic effect (that which makes the greatest contribution to the overall intended therapeutic effects)

Office of Combination Products

- Established in December 2002
- Assigns Center for primary jurisdiction for review based on primary mode of action of product
- Oversees pre-market reviews done by more than one Center to ensure timeliness and effectiveness

Office of Combination Products

- Ensures consistency and appropriateness of post-market regulation
- Updates agreements, guidance documents, or practices specific to Center assignment
- Submits annual reports to Congress regarding its activities and impact

Combination Products

- Drug/Device
- Drug/Biological
- Device/Biological
- Device/Drug/Biological

Examples

- Drug coated stents
- Photodynamic therapy system
- Convenience kits containing a drug
- Heparin solution in a pre-filled syringe
- Orthopedic implant with growth factors

Not Examples

- Facial moisturizers containing a Sun Protection Factor (SPF)
- Cold medication with Vitamin C
- Drugs in container/closure systems

Good Manufacturing Practice

- Current good manufacturing practice (cGMP) regulations at 21 CFR Part 4, effective July 2013
- Draft guidance dated January 2015
- Constituent part – an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product

GMP Requirement

- Each constituent part remains subject to its applicable GMP regulation while manufactured or marketed separately (prior to combination).
- Products that are produced as a single entity or co-packaged are subject to a cGMP operating system designed to:

GMP Requirement

- Comply with each set of cGMP regulations as they relate to each constituent part included in the combination product, or
- For drug/device combination products, a drug cGMP operating system must include specific portions of the device Quality System regulation (QSR), or
- For drug/device combination products, a device cGMP operating system must include specific portions of the drug cGMP regulation

Drug cGMP Operating Systems	Device QSR Operating Systems
21 CFR 820.20, Management responsibility	21 CFR 211.84, Testing and approval or rejection of components, drug product containers, and closures
21 CFR 820.30, Design controls	21 CFR 211.103, Calculation of yield
21 CFR 820.50, Purchasing controls	21 CFR 211.132, Tamper-evident packaging requirements for over-the-counter human drug products
21 CFR 820.100, Corrective and preventive action	21 CFR 211.137, Expiration dating
21 CFR 820.170, Installation	21 CFR 211.165, Testing and release for distribution
21 CFR 820.200, Servicing	21 CFR 211.166, Stability testing
	21 CFR 211.167, Special testing requirements
	21 CFR 211.170, Reserve samples

GMP Requirement

- For combination products that include a biological product, the cGMP operating system must comply with all manufacturing requirements that would apply to the biological product.
- For combination products that include human cells, tissues, and cellular and tissue-based products (HCT/Ps), the cGMP operating system must comply with all manufacturing requirements that would apply to the HCT/Ps.

Inspection Example

- Manufacturer of sterile, Class II devices including convenience kits with drugs
  - No testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)]
  - Certain indicators of non-conformities are not investigated to determine the cause of the non-conformity [21 CFR 820.100(a)(2)]
  - The reserve sample of drug product does not consist of at least twice the quantity necessary to perform all required tests [21 CFR 211.170(a)]

References

- Office of Combination Products website
  - http://www.fda.gov/CombinationProducts/default.htm
- Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, January 2015
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf
- Frequently Asked Questions About Combination Products
  - http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm