U.S. FOOD & DRUG ADMINISTRATION

FDA Regulation of Combination Products

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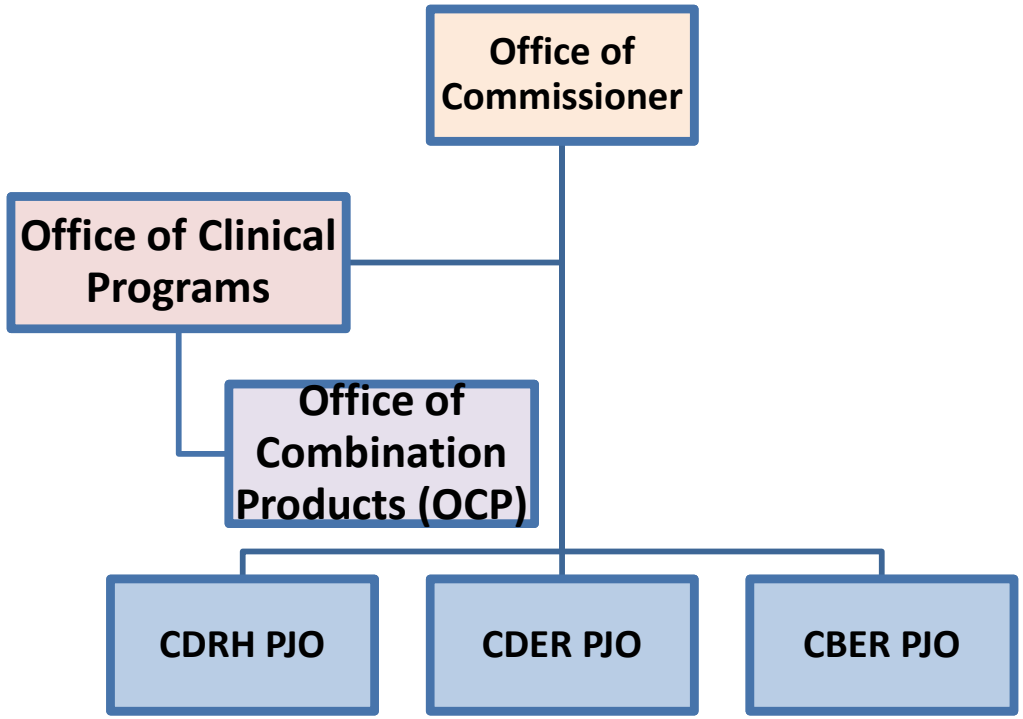
*Disclaimer – The speaker is FDA/CDRH staff who has claimed no interests, financial or otherwise, with commercial supporters, manufacturers, or providers of products that may be presented in this presentation

Agenda

- Roles and Responsibilities
- Classification and Jurisdiction Process
- Center Review Process

The Office of Combination Products (OCP) and Center Product Jursidiction Officers (PJO)

- OCP classifies medical products and assigns an FDA center to have primary jurisdiction
  - Lead the review of Requests for Designation (RFD) and preRFDs
- PJOs are center resources for questions on the classification and jurisdiction (CDRH, CDER, CBER) of medical products
- CDRH PJOs
  - Support review work that involve our staff,
  - Provide Center review of preRFD/RFD submissions to OCP,
  - Engage in cross-Center policy development,
  - Address external inquiries,
  - And more!



Agenda

- Roles and Responsibilities
- **Classification and Jurisdiction Process**
- Center Review Process

Medical Product Statutory Definitions

Drug (FDCA Sec 201(g), in part)	Device (FDCA Sec 201(h), in part)
• Articles • Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals • Intended to affect the structure or any function of the body of man or other animals (other than food)	• An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory • Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals • Intended to affect the structure or any function of the body of man or other animals • And that does not achieve its primary intended purposes by chemical action or by being metabolized • The term "device" does not include software functions excluded pursuant to section 520(o).

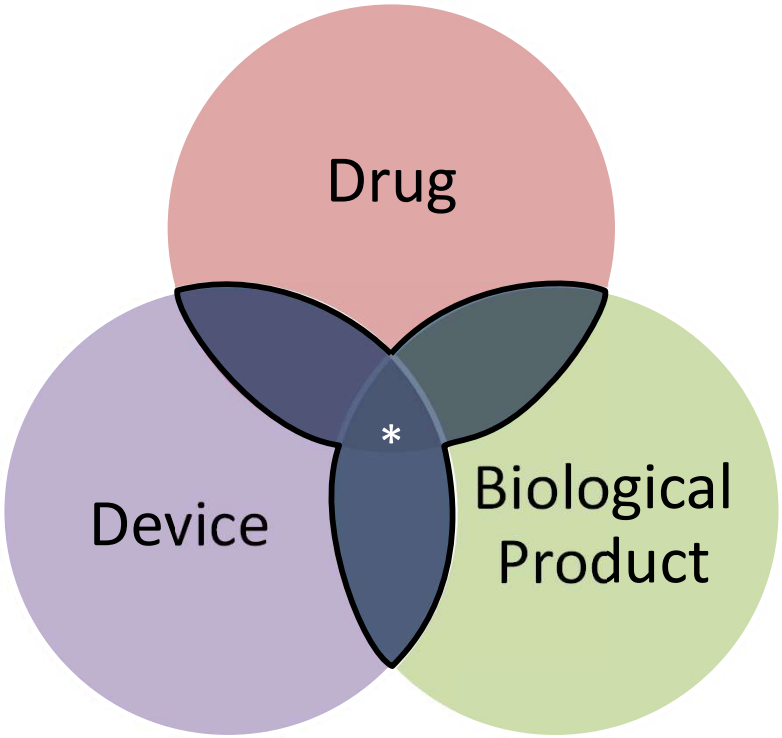
Biological Product

(PHS Act Sec 351(i), in part)

a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings"

What is a Combination Product?

- Composed of 2 or more **DIFFERENT** medical products
  - A drug, device or biological product in a combination product is referred to as a "constituent part." (21 CFR 4.1)
- 21 CFR 3.2(e)
  - Combined physically or chemically into a single entity ("single-entity")
  - Co-packaged / Kit ("co-packaged")
  - Sold separately, but labeled for use together ("cross-labeled)



*Combination product

Drug + Device
Device + Biologic
Drug + Biologic
Drug + Device + Biologic

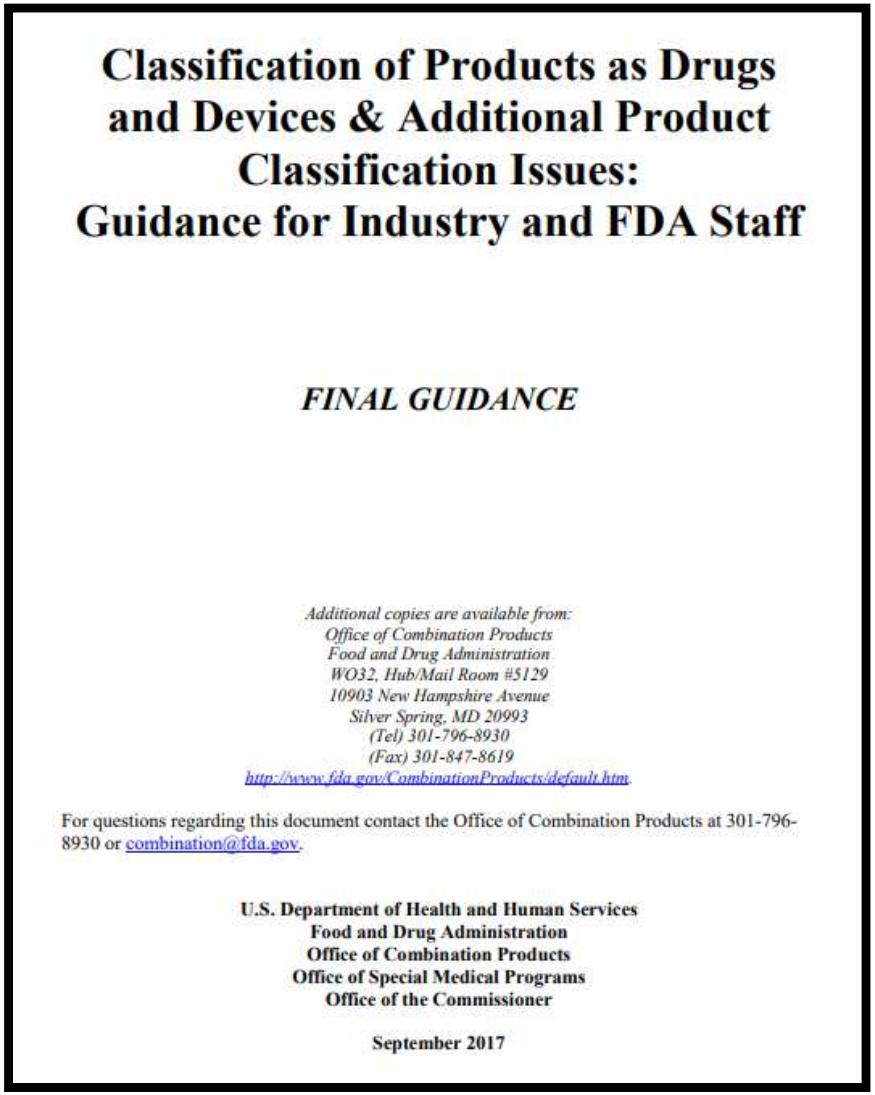
Assignment of Combination Products

(Determining Center with primary jurisdiction)

- **Primary mode of action (PMOA)**
  - PMOA is the single mode of action of a combination product that provides the most important therapeutic action of the combination product (21 CFR 3.2 (m), 3.4 (a))
- **Product assignment algorithm (21 CFR 3.4 (b))**
  - Center that regulates products raising similar questions of safety and effectiveness [TIER 1]
  - Center with most expertise to evaluate the most significant safety and effectiveness questions raised by the product [TIER 2]

Classification of Products as Drugs and Devices & Additional Product Classification Issues ("Classification Guidance")

- Drug vs. Device
- Interpretation of "chemical action", "within or on the body", and "primary intended purposes" in the device statutory definition



Classification of Products as Drugs and Devices & Additional Product Classification Issues: Guidance for Industry and FDA Staff

FINAL GUIDANCE

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/CombinationProducts/default.htm

For questions regarding this document contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Office of Special Medical Programs
Office of the Commissioner

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"Chemical Action"

"which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" (section 201(h) of the FD&C Act)

Product exhibits "chemical action" if it…

"interacts at the molecular level with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) so as to alter that entity's interaction with the body" (page 7 of the Classification Guidance)

Examples

Not "Chemical Action"

- **Topical surgical adhesive to aid in the approximation of skin**
- Cyanoacrylate polymer reacts with ions in water to form long chains
- Chemical reaction not considered "chemical action" because it doesn't mediate a bodily response

"Primary Intended Purposes"

- **Hip implant to stabilize and restore movement**
- Presence of implant initiates foreign body response
- Foreign body response does not achieve the primary intended purpose of restoring movement

"Within or on the Body" Examples

Drug

- **Chlorohexidine skin prep to disinfect skin prior to surgery**
- Chlorohexidine kills microorganisms through chemical action
- The chemical action occurs within or on the body (on the skin)

Device

- **Respirator mask impregnated with chlorohexidine impregnated filter to kill microbes the user may otherwise inhale**
- Chlorohexidine kills microorganisms through chemical action
- The chemical action does not occur within or on the body

Agenda

- Roles and Responsibilities
- Classification and Jurisdiction Process
- **Center Review Process**

RFD and Pre-RFD (Request for Designation)

Guidance for Industry
How to Write a Request for Designation (RFD)

For questions regarding this document, contact:
Office of Combination Products (OCP) at 301-796-8930 or combination@fda.gov

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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How to Prepare a Pre-Request for Designation (Pre-RFD)

Draft Guidance for Industry

This guidance document is being distributed for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Combination Products website at http://www.fda.gov/CombinationProducts/default.htm.

For questions on the content of this guidance, contact the Office of Combination Products at combination@fda.gov

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Office of Combination Products in the Office of the Commissioner

January 2017

Pre-RFD and RFD Submissions

Pre-RFD	RFD
Often helpful for early development products	Well characterized, configured products
Non-binding decision	Binding decision
Interactive process	Non-interactive process after RFD is filed
No page limit	15 page limit
Less information required as compared to RFD	Requirements in 21 CFR 3.7
Pre-RFD response goal is 60 days	RFD letter issued in 60 days

- Determination on classification (i.e., device, drug, biological product, or combination product) and jurisdiction (i.e., assignment of a lead Center)
- Sponsors should submit a preRFD (typically preferred) or RFD before any submission to a Center if there is ambiguity in the classification nor jurisdiction of a medical product
- Not required before proceeding to a Center
- Sponsors may be referred to OCP if information in a submission raises classification or jurisdiction concerns

Contact Info: combination@fda.gov
www.fda.gov/CombinationProducts/default.htm

Principles of Premarket Pathways for Combination Products

Drugs, devices, and biological products retain their discrete regulatory identities

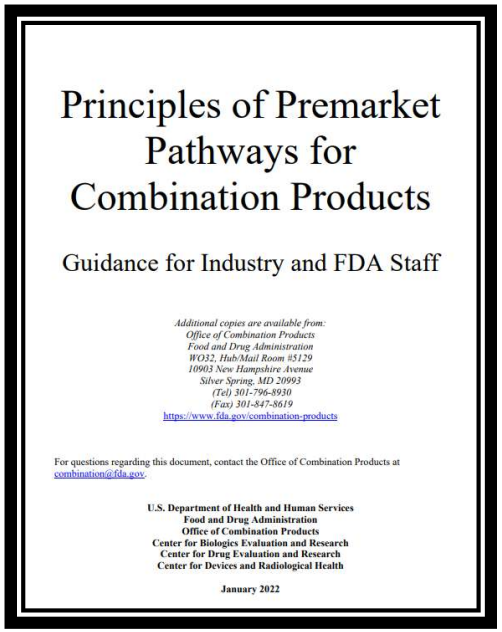
- FDA takes into account the questions and considerations reflected in the statutes and regulations for each constituent part

A distinct category of medical products that can be subject to specialized regulatory requirements

- Review takes into account the differing conditions of use for the drug or device due to the intended use

A single application is generally appropriate for a combination product

The Annex of the guidance includes illustrative examples of pathway availability for combination products



Principles of Premarket Pathways for Combination Products

Guidance for Industry and FDA Staff

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Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health

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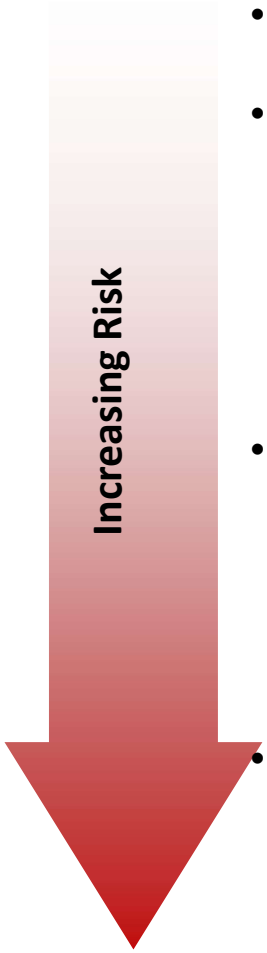
- Basics of premarket regulation of combination products
- Basics of interacting with FDA
- What are combination products and how center assignment is determined?

A Risk-Based Approach



- 510(k) exempt - Typically Class I
  - no premarket submission, general controls only
- 510(k) submission – Typically Class II, can be Class I
  - Allows medical devices with established risk profiles and mitigation methods, to come to market by demonstrating substantial equivalence to a predicate device already on the market
  - Evaluates comparative safety and effectiveness via substantial equivalence; not stand-alone (unlike PMA, NDA, or BLA)
  - **For Combos:** The predicate must be a combination product
- De novo submission – Typically Class II
  - Submission type for low to moderate risk devices that do not have a legally marketed predicate device
  - Creates new regulation, develops special controls
  - **For Combos: 21st Century CURES Act**
  - **For Combos:** May include well understood, previously licensed or approved drug or biological product constituent
- Premarket Approval (PMA) submission - Typically Class III
  - Highest risk devices
  - Demonstrate full safety and effectiveness/standalone data

Classification determines extent of regulatory control (Risk Based)

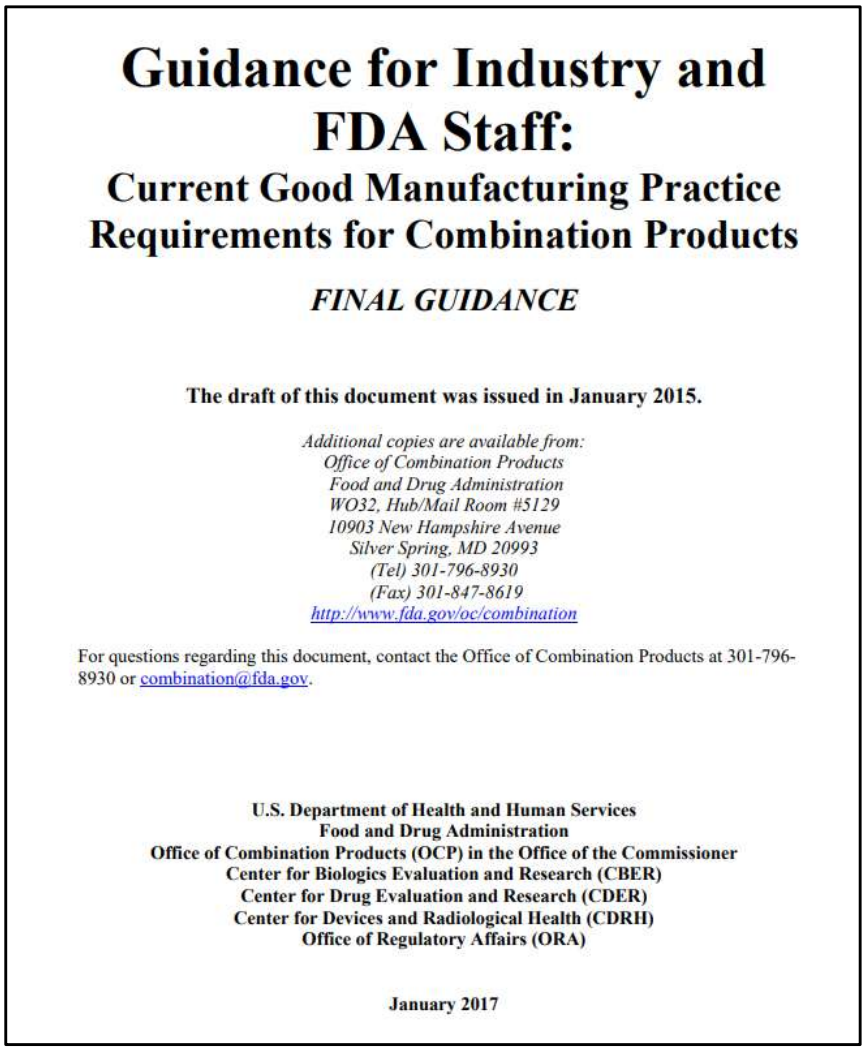
Class I
General Controls

Class II
General controls
Special controls
Premarket Notification

Class III
General controls
Premarket approval (PMA)

Current Good Manufacturing Practice (CGMP) for Combination Products

- Guidance explains **final rule** on current good manufacturing (CGMP) requirements for combination products that FDA issued on January 22, 2013
- Two options for compliance with Part 4:
  - Compliance with all CGMP regulations of each constituent part
  - "Streamlined approach" (21 CFR 4.4(b))



Guidance for Industry and FDA Staff:

Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

The draft of this document was issued in January 2015.

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Office of Regulatory Affairs (ORA)

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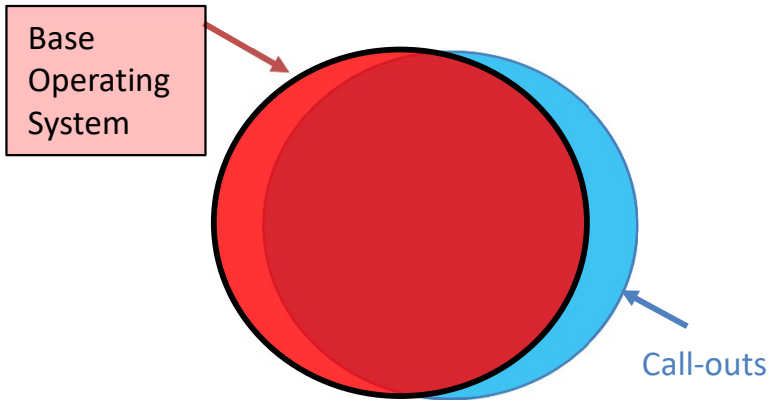
Combination Product CGMPs

- Combination Product CGMP Rule (21 CFR part 4, Subpart A) allows for "streamlined" approach for manufacturers*:
  - Device QS regulation-based streamlined approach:
    Compliance with 21 CFR 820 Device Quality System (QS) Regulation
    PLUS
    21 CFR 211 Drug CGMPs call-outs
  - Drug CGMP-based streamlined approach:
    Compliance with 21 CFR 211 Drug CGMPs
    PLUS
    21 CFR 820 Device QS Regulation call-outs



- If biological product constituent part, also comply with 21 CFR 600-680. If product includes HCT/P, also comply with 21 CFR 1271.

* "Manufacturer" includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage

CGMP Cont.: "Streamlined Approach"

Drug CGMP Based System

Section 4.4(b)(1). Compliance with the drug CGMPs per § 4.4(a)(2), and also compliance with:

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

Device QS Based System

Section 4.4(b)(2). Compliance with the QS regulation per § 4.4(a)(2), and also compliance with:

- § 211.84. Testing and approval or rejection of components, drug product containers, and closures.
- § 211.103. Calculation of yield.
- § 211.132. Tamper-evident packaging requirements for over the-counter (OTC) human 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.

Contact Information

- CDRH Product Jurisdiction Team: CDRHProductJurisdiction@fda.hhs.gov
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- CDER Product Jurisdiction Team: CDERProductJurisdiction@fda.hhs.gov
- CBER Product Jurisdiction Team: CBERProductJurisdiction@fda.hhs.gov
- OCP: combination@fda.gov

Resources

- Combination Product FAQs: https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products
- Guidance Documents:
  - Classification of Products as Drugs and Devices and Additional Product Classification Issues (https://www.fda.gov/media/80384/download)
  - How to Prepare a Pre-Request for Designation (Pre-RFD) (https://www.fda.gov/media/102706/download)
  - How to Write a Request for Designation (RFD) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd)
  - Principles of Premarket Pathways For Combination Products Guidance (https://www.fda.gov/media/119958/download)
  - Current Good Manufacturing Practice for Combination Products (https://www.fda.gov/media/90425/download)


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