Advancing Innovation in Healthcare with Combination Products

FDA Small Business Regulatory Education for Industry (REdI) Annual Conference

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U.S. Food and Drug Administration

What's the Right Path(way) for Your Innovative Combination Product?

Learning Objectives

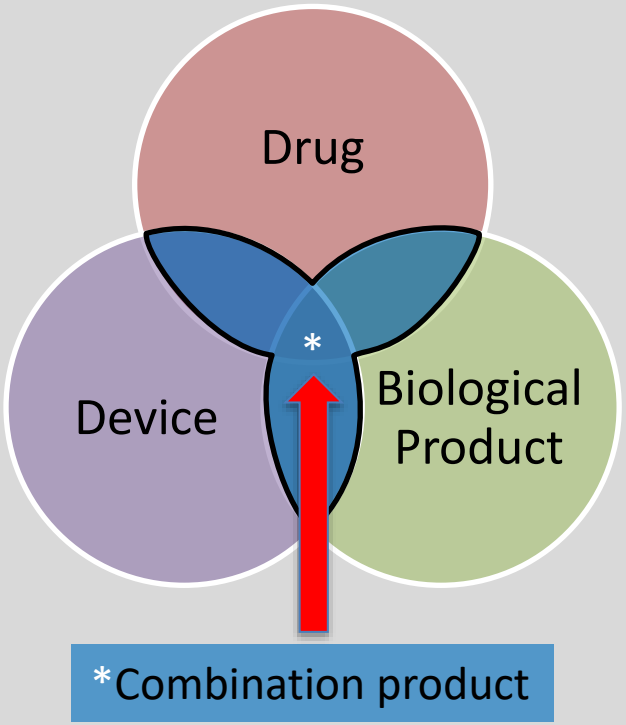
- Provide an overview of FDA review of combination products
- Review Product Jurisdiction Officer (PJO) roles
- Share updates of regulations/guidances that impact combination products
- Identify best practices and regulatory considerations

Overview of FDA Review of Combination Products

What is a Combination Product?

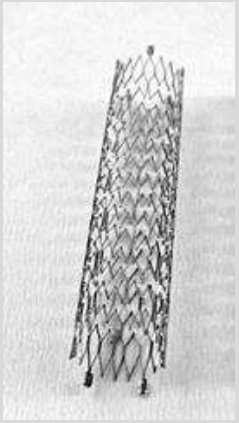
- Composed of 2 or more **DIFFERENT** type of medical products
  - A drug, device or biological product in a combination product is referred to as a "constituent part."

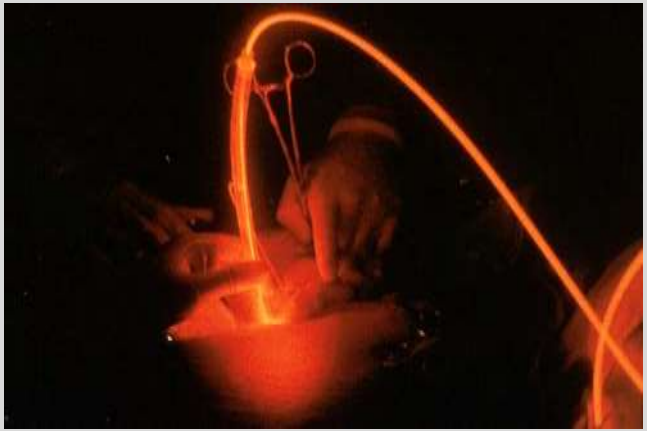
    (21 CFR 4)



Combination Product Examples

- 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 Assignment/Jurisdiction

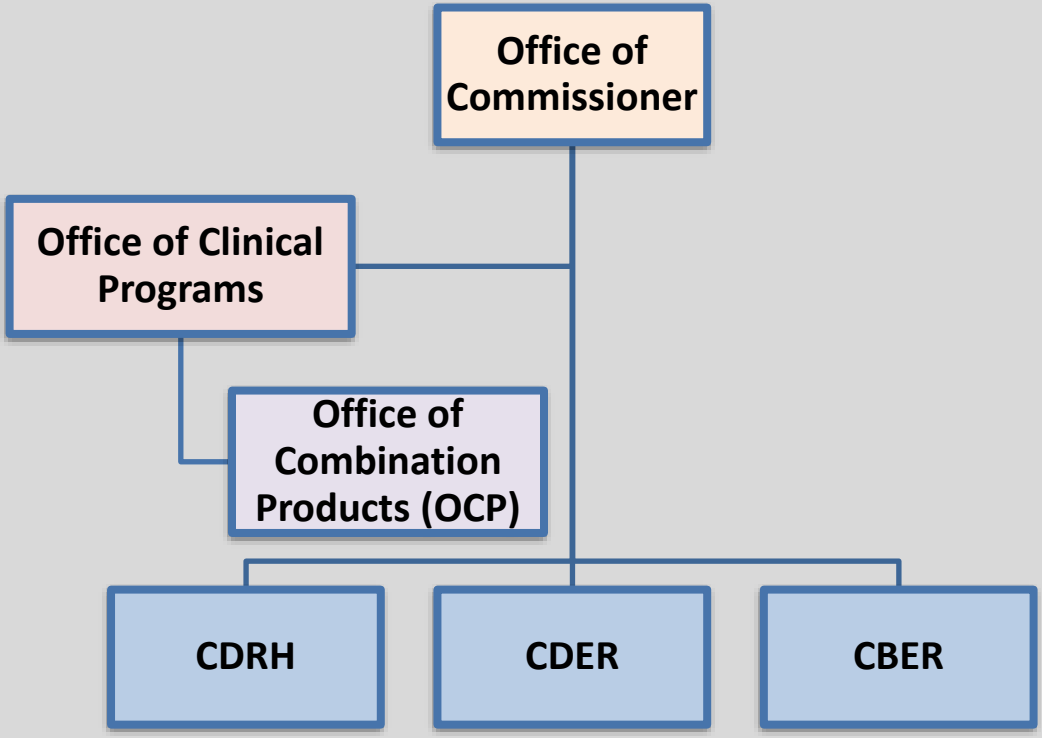
- **Primary mode of action (PMOA)**
  - Single mode of action of a combination product that provides most important therapeutic action of combination product (21 CFR 3.2 (m), 3.4 (a))
  - Assignment Designates “Lead-Center” for review of product
  - Non-Lead Center(s) are often consulted during review process

Combination Product Assignment/Jurisdiction (cont'd)

- **Product assignment algorithm (21 CFR 3.4 (b))**
  - **Tier 1:** Center that regulates products raising similar questions of safety and effectiveness
  - **Tier 2:** Center with most expertise to evaluate most significant safety and effectiveness questions raised by product

Product Jurisdiction Officer (PJO) Roles

PJO Teams



Each Center has a PJO Team:

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

PJO Core Functions

- Classify medical products*
- Assign combination and non-combination products to appropriate Centers*
- Develop, review, and comment on Agency policy, regulations, and guidance documents*
- Ensure consistent regulation of combination products
- Serve as focal point/resource for internal/external stakeholders

*Done in conjunction with OCP and other Centers

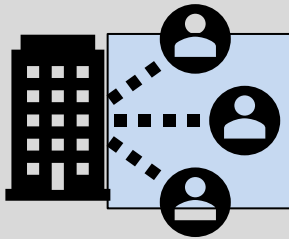
Types of Inquiries

- Classification and jurisdiction
- Regulatory pathway
- Internal consulting between Centers
- Meeting request input
- Adverse event reporting in clinical research submissions (IND IDEs)
- Post-marketing safety reporting
- Current good manufacturing practices (cGMPs)
- Patent and exclusivity

PJO Engagement

- **Contact PJO**
  - If you know (or think you know) the Center or have a current application
- **Contact OCP**
  - If you don’t know appropriate Center
- **Request PJO involvement**
  - If including question(s) as part of a meeting request / pre-submission interaction

Premarket Review of Combination Products



FDA assesses safety and effectiveness of combination product as a whole

Lead Center for combination product

- Serves as Sponsor's primary point of contact
- Uses Lead Center's processes and procedures (such as, meetings, applications)
- Engages expertise in other Centers

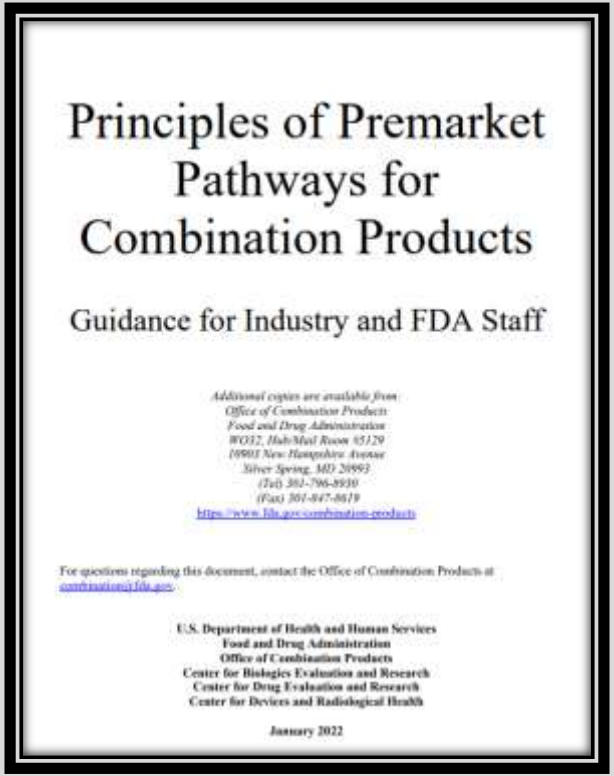
Submission Types		
CDER	**CDRH**	**CBER**
IND NDA BLA ANDA	IDE 510(k) De Novo PMA HDE	IND/IDE BLA PMA 510(K) NDA (rare)

Various Guidances and Regulations Updates

Principles of Premarket Pathways for Combination Products

- Basics of premarket regulation of combination products
- Basics of interacting with FDA
- Considerations of available pathways

Guidance: Principles of Premarket Pathways for Combination Products



Principles of Premarket Pathways for Combination Products

Guidance for Industry and FDA Staff

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room 05129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
https://www.fda.gov/combination-products

For questions regarding this document, contact the Office of Combination Products at combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health

January 2022

CDRH Pathways to Market for Combos

- **510(k)**
  - Predicate must be a combination product
  - Predicate should include same active ingredient as new device
- **De Novo**
  - May include well-understood, previously licensed or approved drug or biological product constituent (not appropriate for new chemical/molecular entity)
- **Premarket Approval (PMA)**

Genus Decision

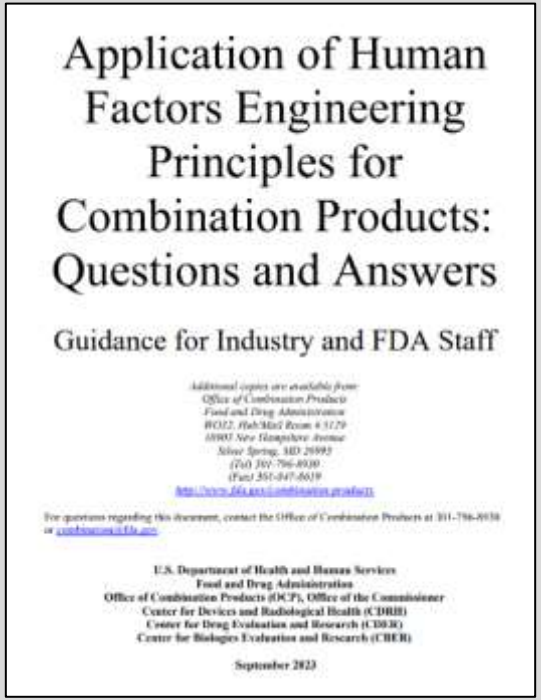
- Barium sulfate contrast imaging agents are used to improve visualization of gastrointestinal tract in radiographic diagnostic studies
- FDA lost discretion to regulate devices as drugs
- Congress later clarified in Section 503 of the FD&C Act that any contrast agent, radioactive drug, or over-the-counter monograph drug shall be deemed to be a drug under section 201(g) and not a device under section 201(h).

Genus Medical Technologies LLC v. United States Food and Drug Administration, No 20-5026 (D.C. Cir. 2021)

FD&C Act = Federal Food Drug and Cosmetic Act

Human Factors Engineering (HFE)

- Not meant to replace CDRH or CDER HF guidance
- Clarifies how unique aspects of a combination product influence considerations within HFE process
- Key goal of applying HFE principles during development is to ensure that the user interface supports the safety and effectiveness of the combination product as a whole
- Should consider use-related risks associated with combination product as a whole
- User interface for combination product includes all points of interaction between combination product and user(s)


Application of Human Factors Engineering Principles for Combination Products: Questions and Answers

Guidance for Industry and FDA Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP), Office of the Commissioner
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023

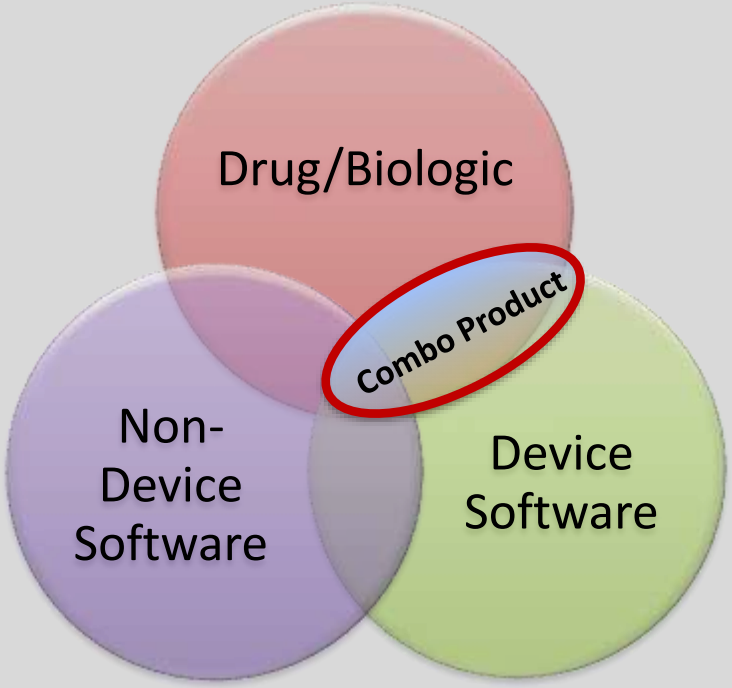
[Guidance: Application of Human Factors Engineering Principles for Combination Products: Questions and Answers]

Digital Health (DH) Products

- DH Product + Drug/Biologic = Combination Product? (*configuration and intended use matter*)

***The term "device" does not include software functions excluded pursuant to section 520(o). (FDCA* Sec 201(h))**

FDA Digital Health Guidance Documents:
- General Wellness
- Mobile Medical Apps
- Clinical Decision Support (CDS)
- Multiple Functions



21 CFR 3.2(e)
- Physically or chemically into a single entity
- Co-packaged / Kit
- Sold separately, but labeled for use together ("cross-labeled")

Proposed Regulation of Wound Dressings

- **Wound dressings and liquid wound washes containing antimicrobial and/or other chemicals**
  - Unclassified, preamendments devices
  - Indicated for “wound management”
- **Diverse and complex device design**
  - solid wound dressings
  - wound dressings formulated as a gel, cream, or ointment
  - liquid wound washes
- **Clarify intended use**
  - Cover/protect wound, maintain moisture, mechanically irrigate

Summary of Proposed Rule

- Develops a risk-based antimicrobial resistance (AMR) framework to support proposed split classification

Summary of Proposed Rule

1. **Class III**: Wound dressings and liquid wound washes containing "medically important" antimicrobials with a high level of AMR concern *(subject to PMA)*
   - Defines medically important antimicrobials as those used to treat or prevent infections in human patients.
   - Consistent with Agency's prior use of this term for CVM guidance. "Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2024-2028: Key Phase 3 and Key Phase 4 Actions," September 2023.
   - World Health Organization's (WHO) 2018 publication "Critically Important Antimicrobials for Human Medicine: 6th Edition" used as reference in the proposed rule for identification of medical importance.

Summary of Proposed Rule

2. **<u>Class II</u>**: Wound dressings and liquid wound washes containing non-medically important antimicrobials and/or other chemicals *(subject to special controls and 510(k) requirements)*

Considerations and Best Practices

General Considerations during Review

- Presence of drug/biologic can impact regulatory pathway in CDRH
- Labeling consistency questions
  - Labeling inconsistencies may impact ability to clear or approve a device
- Only one investigational application for a combination product
  - If either the drug and/or device is being used consistent with how already approved/cleared?
  - Not a combination product (e.g., IDE or IND studying device or drug respectively
- Authorization to reference drug (DMF) or device (MAF) master files
  - Permit the submission of proprietary information so that parties other than the owners of that information may rely on it

Best Practices for Combination Product Development

- Determine jurisdiction of product at beginning
- Initiate early discussions with cross-Center review team
- Have a concrete and good business relationship with manufacturer of other constituent part(s)
- Complete a risk-based evaluation of combination product as a whole
- Become familiar with applicable guidances and standards
- Understand regulatory requirements for both constituent parts
- Understand data requirements for approval, anticipate hurdles and leverage information

Engaging with FDA

- **Send a pre-submission early in development process**
  - Receive feedback on your proposed testing strategy
  - May request inclusion of product jurisdiction officers

Engaging with FDA

- **Pre-submission meeting packages**
  - Should include information outlined in below guidance
  - Provide relevant background information and specific questions
  - Include and consider information on the drug/biological product constituent part for conditions of use specified including interactions with device

Guidance: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
Guidance: Requesting FDA Feedback on Combination Products

Engaging with FDA

- **If jurisdiction is unclear, consider**
  - Submitting a pre-RFD or RFD
  - Contacting the Office of Combination Products

Knowledge Check

How are combination products combined?

A. Physically or chemically into a single entity

B. Co-packaged

C. Cross-labeled

D. All of the Above

Knowledge Check

Which of these forms a combination product?

A. Drug + Cosmetic

B. Drug + Device

C. Biologic + Food

D. All of the above

Resources

Slide Number	Cited Resource	URL
16	Guidance: Principles of Premarket Pathways for Combination Products	www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products
18	Genus Medical Technologies LLC v. United States Food and Drug Administration, No 20-5026 (D.C. Cir. 2021)	law.justia.com/cases/federal/appellate-courts/cadc/20-5026/20-5026-2021-04-16.html
19	Guidance: Application of Human Factors Engineering Principles for Combination Products: Questions and Answers	www.fda.gov/regulatory-information/search-fda-guidance-documents/application-human-factors-engineering-principles-combination-products-questions-and-answers
23	Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2024-2028: Key Phase 3 and Key Phase 4 Actions	www.fda.gov/media/172347/download?attachment

Resources

Slide Number	Cited Resource	URL
23	Critically Important Antimicrobials for Human Medicine: 6th Edition	www.who.int/publications/i/item/9789241515528
29	Guidance: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program	www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
29	Guidance: Requesting FDA Feedback on Combination Products	www.fda.gov/regulatory-information/search-fda-guidance-documents/requesting-fda-feedback-combination-products
30	Pre-RFD or RFD	www.fda.gov/combination-products/rfd-process
30	Office of Combination Products	combination@fda.gov

Other Resources

Resource	URL
Combination Products (FDA Main Page)	www.fda.gov/combination-products
Frequently Asked Questions About Combination Products	www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products
21 CFR 3 – Product Jurisdiction	www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-3
FDA Guidance: Classification of Products as Drugs and Devices and Additional Product Classification Issues	www.fda.gov/regulatory-information/search-fda-guidance-documents/classification-products-drugs-and-devices-and-additional-product-classification-issues
FDA Guidance: How to Prepare a Pre-Request for Designation (Pre-RFD)	www.fda.gov/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd
FDA Guidance: How to Write a Request for Designation (RFD)	www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd

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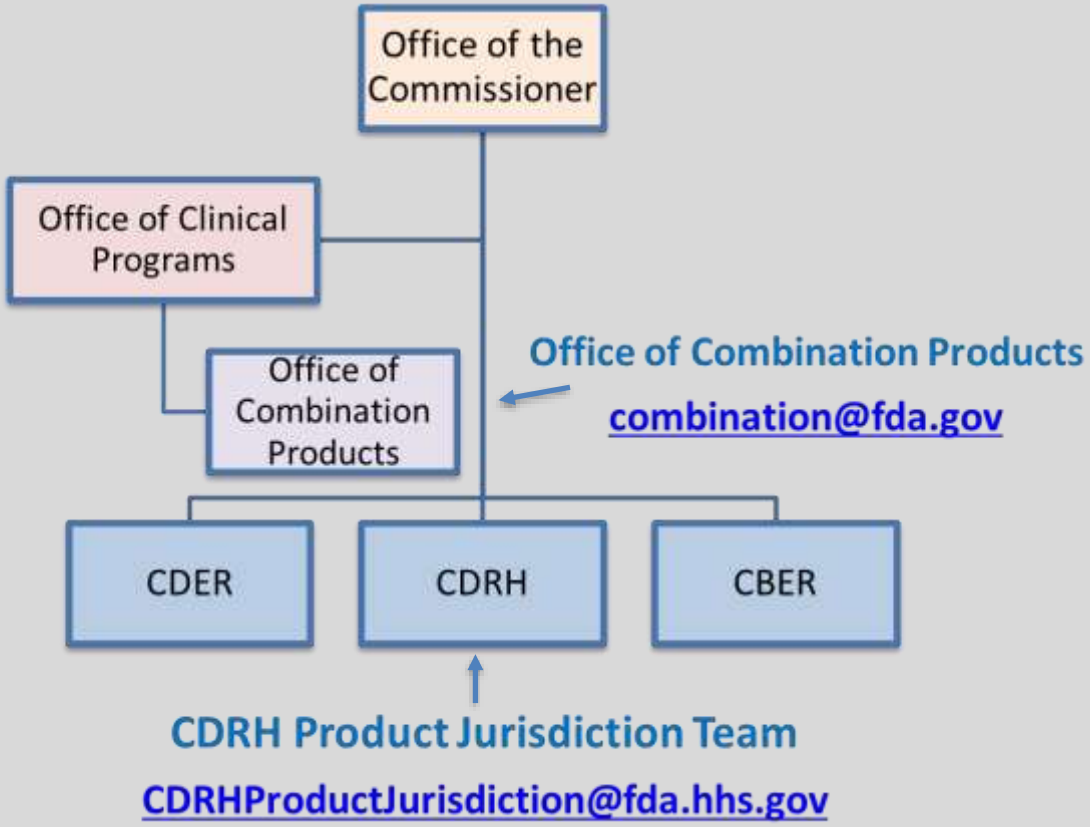
FDA Guidance: Principles of Premarket Pathways for Combination Products	www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products
FDA Guidance: Current Good Manufacturing Practice Requirements for Combination Products	www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products
FDA Guidance: General Wellness: Policy for Low Risk Devices	www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices
FDA Guidance: Policy for Device Software Functions and Mobile Medical Applications	www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications
FDA Guidance: Clinical Decision Support Software	www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software
FDA Guidance: Multiple Function Device Products: Policy and Considerations	www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-function-device-products-policy-and-considerations

Questions? Contact Us!



Summary

- Medical product classification is based on statutory definitions (FDCA and PHS)
- FDA has regulations for the combo product definition (21 CFR 3.2e) and combination product assignment algorithm (21 CFR 3.4)
- Understanding FDA's resources available on combination products is valuable
- Following FDA's recommendations and best practices will facilitate efficient communication with the FDA Review team

Questions

Your Call to Action

- Engage with FDA early in your development process to establish jurisdiction / classification
- Include sufficient information in your submission for FDA to determine role of all constituent parts
- Review all applicable guidance documents
- Leverage available / existing data for constituent parts, while taking into consideration the product as a whole (e.g., synergistic effects)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