Navigating the World of Combination Products

James Bertram, PhD
Assistant Director
Regulations, Policy, and Guidance Staff
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Kristina Lauritsen, PhD
Combination Product Policy Advisor
Office of Executive Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Let the Journey Begin

Who are we?

Kristina Lauritsen

CDER – Combination Product Regulatory Policy and Product Jurisdiction

CDERProductJurisdiction@fda.hhs.gov (preferred)

(301) 796-8936

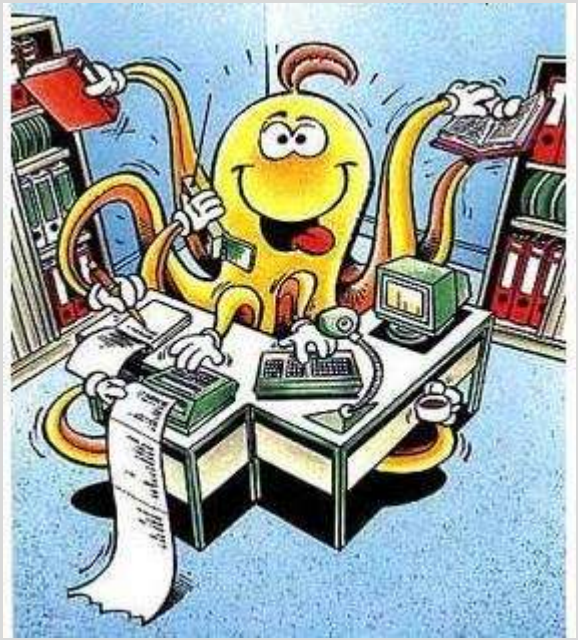
James Bertram

CDRH Product Jurisdiction Officer

CDRHProductJurisdiction@fda.hhs.gov (preferred)

(301) 796-9588

What do we do?

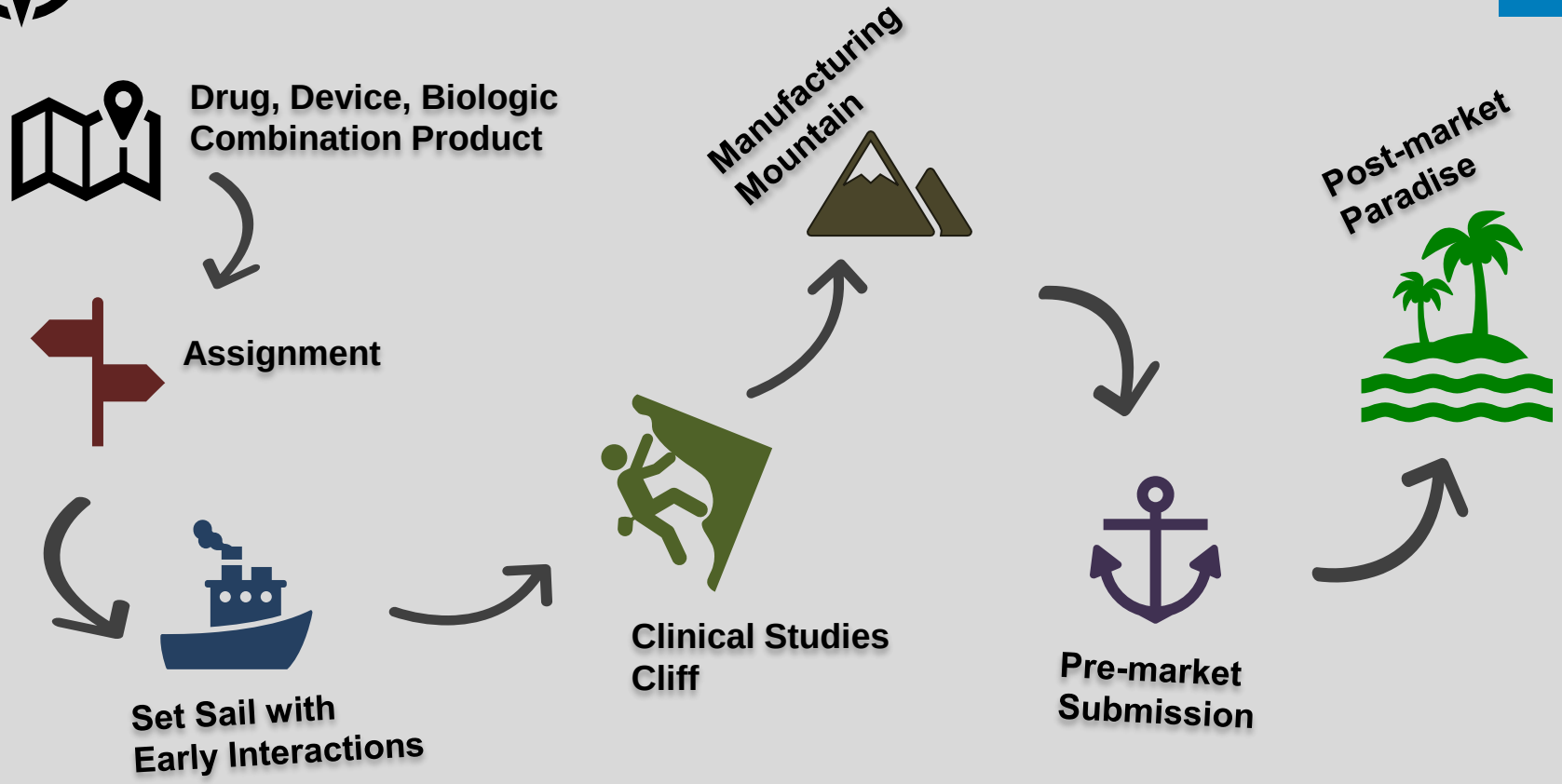


- Center focal point for any combination product questions or issues
- Center liaisons to the Office of Combination Products (OCP)
- Provide recommendations to OCP re: classification and assignment of combination and single-entity products
- Represent their Center on combination product and jurisdiction policies

What do we do?

- Work with OCP to develop guidance documents and regulations that affect their Center
- Represent Center-level position in inter-center working groups
- Help sponsors clarify regulatory pathway for products assigned to their Center
- Respond to internal and external inquiries

Journey Overview



Learning Objectives

- Identify what is and isn't a combination product
- Describe the Agency's assignment of combination products
- Compare/contrast the regulatory paradigms for CDER/CDRH
- Recognize review considerations for combination products
- Understand best practices for combination products and navigating the FDA

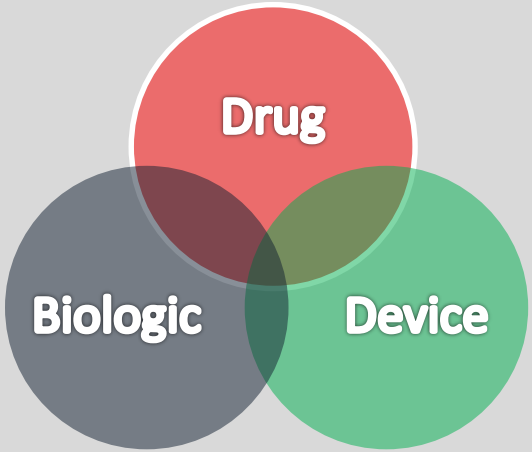
Let the Journey Begin

Drug, Device, Biologic Combination Product

What is a Combination Product?

Combinations of 2 or more <u>DIFFERENT</u> products:

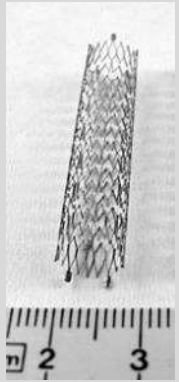
- Drug + Device
- Device + Biologic
- Drug + Biologic
- Drug + Device + Biologic



Device – FDCA 201(h), Drug – FDCA 201(g), Biologic – PHSA 351

Types of Combination Products

- 21 CFR 3.2(e)
  - Physically or chemically into a single entity
  - Co-packaged / Kit
  - Sold separately, but labeled for use together
- Examples
  - Drug-eluting stent
  - Kit w/bandages and antibiotic ointment
  - Photodynamic therapy



NOT Combination Products

- Drug-Drug
- Device-Device
- Biologic-Biologic
- Food + Drug/Device/Biologic
- Cosmetic + Drug/Device/Biologic

Assignment

Drug, Device, Biologic
Combination Product

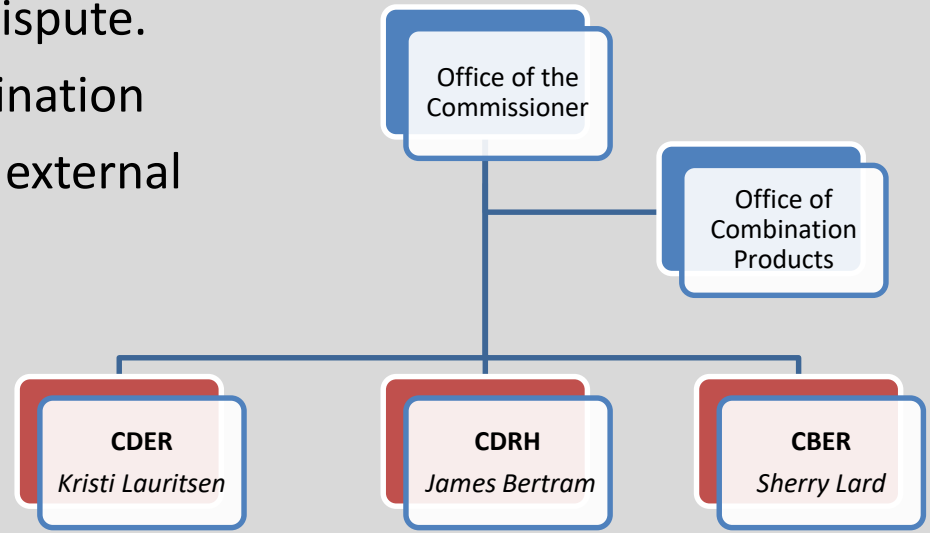
Assignment

Now where do I turn?

1. What am I? (product classification)
2. Where do I go? (product assignment)
3. What do I do when I get there? (regulatory pathway)

Office of Combination Products (OCP)

- Authority to assign an FDA center to have primary jurisdiction for review of both combination and single entity (i.e., non-combination) products where jurisdiction is unclear or in dispute.
- Agency focal point for combination product issues for internal / external stakeholders
- Broad oversight responsibilities covering the regulatory life cycle of combination products



Easy to Remember…

- Non-combinations are assigned based on their classification:
  - Drug (FDCA 201(g)) - ***CDER***
  - Device (FDCA 201(h)) - ***CDRH***
  - Biological Product (PHSA 351(a)) – ***CBER*** or ***CDER***
- Exceptions:
  - Devices that create a biologic at the point of care (devices regulated by CBER)
  - Therapeutic proteins, antibodies (biological products regulated by CDER)

But what about a Combination Product ???

Recall the Statute (FDCA 503(g))…

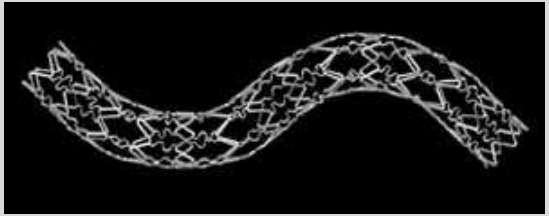
Combination products are assigned based on the primary mode of action (PMOA). If the Secretary determines that the primary mode of action is that of ---

(A) a drug (other than a biological product), the agency center charged with premarket review of drugs shall have primary jurisdiction, --- ***CDER***

(B) a device, the agency center charged with premarket review of devices shall have primary jurisdiction, --- ***CDRH***

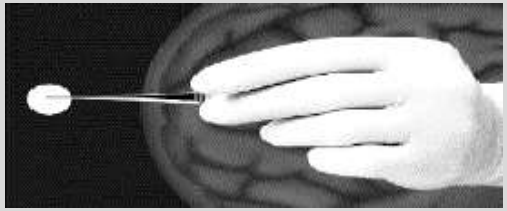
(C) a biological product, the agency center charged with premarket review of biological products shall have primary jurisdiction. --- ***CBER or CDER***

PMOA Examples



Drug Eluting Stent

- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Assigned to **CDRH**



Drug Eluting Disk

- PMOA – chemo for brain tumor (drug)
- Secondary MOA – local delivery of drug by the device
- Assigned to **CDER**

But…PMOA may be hard to identify

- Early development (just don't know)
- Two (or more) completely different modes of action, and neither is subordinate to the other

What happens next?

Assignment Algorithm

If unable to determine PMOA with reasonable certainty, OCP will then consider…

- **FIRST: Consistency**
  - Assign product to Center that regulates other combination products that present similar questions of safety and effectiveness

- **SECOND: Safety and Effectiveness**
  - When FIRST does ***not*** apply, assign product to Center with most expertise related to most significant safety and effectiveness questions

(21 CFR 3.4)

Algorithm Assignment example

Contact lens coated with glaucoma drug

- Device MOA: Lens corrects vision
- Drug MOA: Drug treats glaucoma
- Device and drug have independent modes of action
  - Tier 1 – no prior assignments of a contact lens + glaucoma drug
  - Tier 2 – the most significant safety and effectiveness questions relate to the clinical performance and characterization of the drug, while the questions related to the vision-correcting lens are considered more routine
  - Product is assigned to **CDER**

How do I get a Classification / Jurisdiction Assignment?

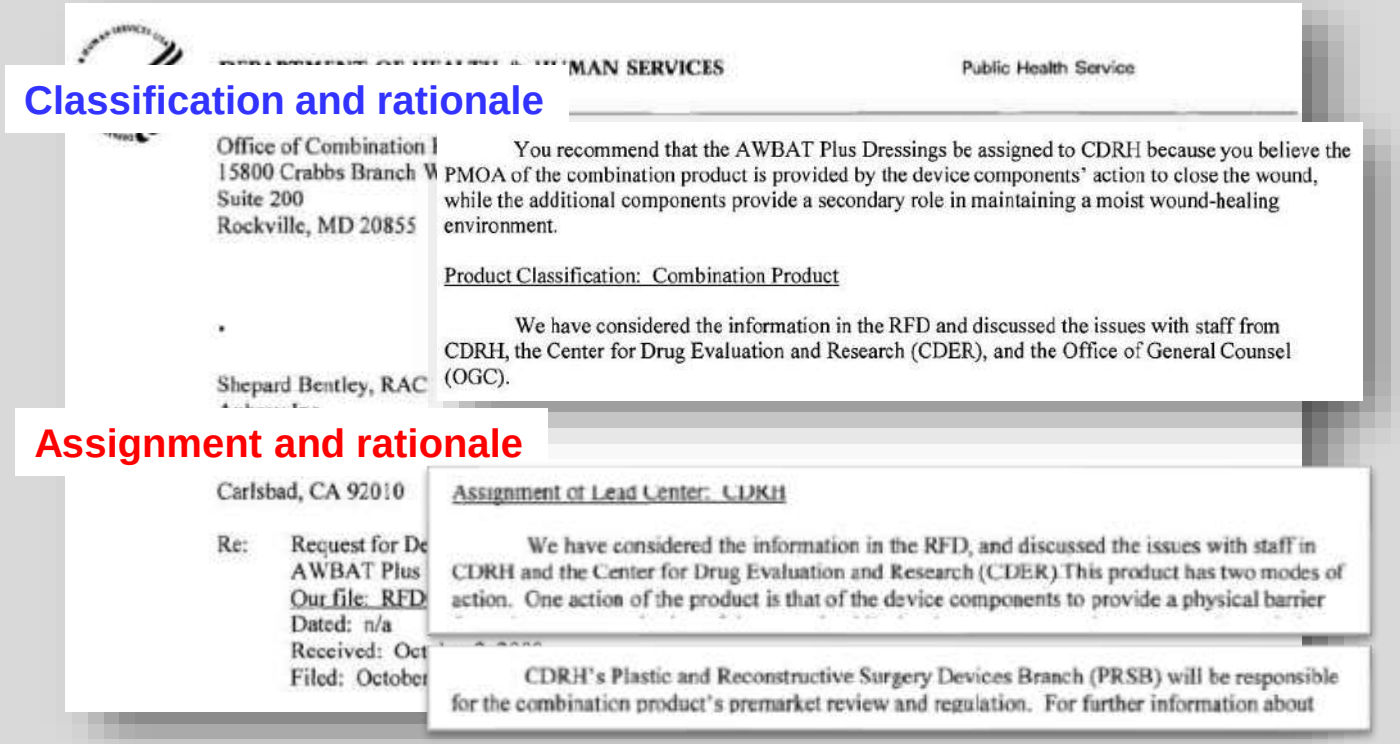
- **Informal advice:**
  - Email: combination@fda.gov
  - Simple issues, uncertainty, process concerns
  - Determine whether a preRFD/RFD is needed
- **Pre-RFD (pre-Request for Designation)**
  - Final Guidance (Feb 2018)
  - Most common option
- **RFD (Request for Designation)**
  - Formal, binding determination – **60** days
  - Complex issues or dispute / uncertainty
  - Requirements in 21 CFR 3.7

When to submit a preRFD/RFD?

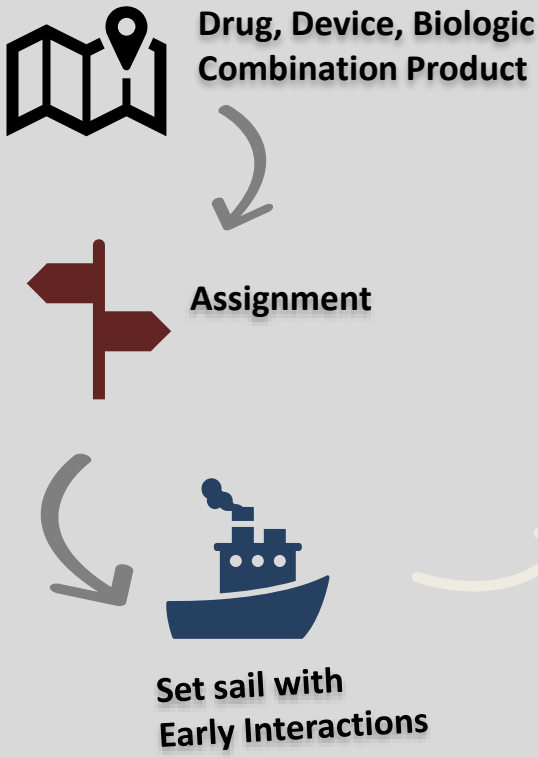
- Start with an informal email inquiry
  - OCP mailbox:
    - combination@fda.gov
  - Center Jurisdiction mailbox:
    - CDERProductJurisdiction@fda.hhs.gov
    - CDRHProductJurisdiction@fda.hhs.gov
- Submit an RFD or pre-RFD **BEFORE** any submission
  (i.e., presubmission / pre-IND, marketing submission)

Why?
FDA may stay review clock while a determination is being made (21 CFR 3.10)

RFD Decision Letter



Early Interactions



CDRH - Early Interaction / Feedback

Q-Submission Type	Meeting	Timeframe for Meeting/Teleconference/Feedback (from receipt of submission)
Pre-Submission	Upon request	70 days (or 5 days prior to meeting) Meeting – Typically 60-75 days
Informational Meeting	Yes	90 days
Study Risk Determination	No	90 days
Agreement Meeting	Yes	Scheduled within 30 days of request
Determination Meeting	Yes	Feedback provided within 30 days after meeting
Submission Issue Request	Upon request	21 days (<60 days) / 70 days (>60 days)
Day 100 Meeting	Yes	100 days (from receipt of PMA)

CDER - Early Interaction / Feedback

	Request	Topic Examples
PDUFA (IND, NDA, 351(a) BLA)	Type A (30 days)	Stalled development
	Type B (60 days)	preIND, end of Phase (1)/2/3, preNDA/BLA
	Type C (75 days)	Any other meeting
BsUFA (351(k) IND or BLA)	Initial Advisory (75 days)	Initial assessment regarding licensure
	BPD Type 1 (30 days)	Stalled development
	BPD Type 2 (90 days)	specific issues related to CMC, study design, etc.
	BPD Type 3 (120 days)	In-depth data review and advice
	BPD Type 4 (60 days)	Format and content of an application or supplement.
GDUFA (ANDA)	Controlled Correspondence (60/120 days)	Information on a specific element of generic development
	Product Development (120 days)	Specific scientific issues/questions prior to submitting ANDA
	Pre-submission (120 days)	Format and content of the ANDA to be submitted
	Mid-Review-Cycle (~30 days)	Specific issues/deficiencies identified during review

Clinical Studies

Drug, Device, Biologic
Combination Product

Assignment

Set sail with
Early Interactions

Clinical Studies
Cliff

CDRH - Clinical Trials

Investigational Device Exemption (IDE)

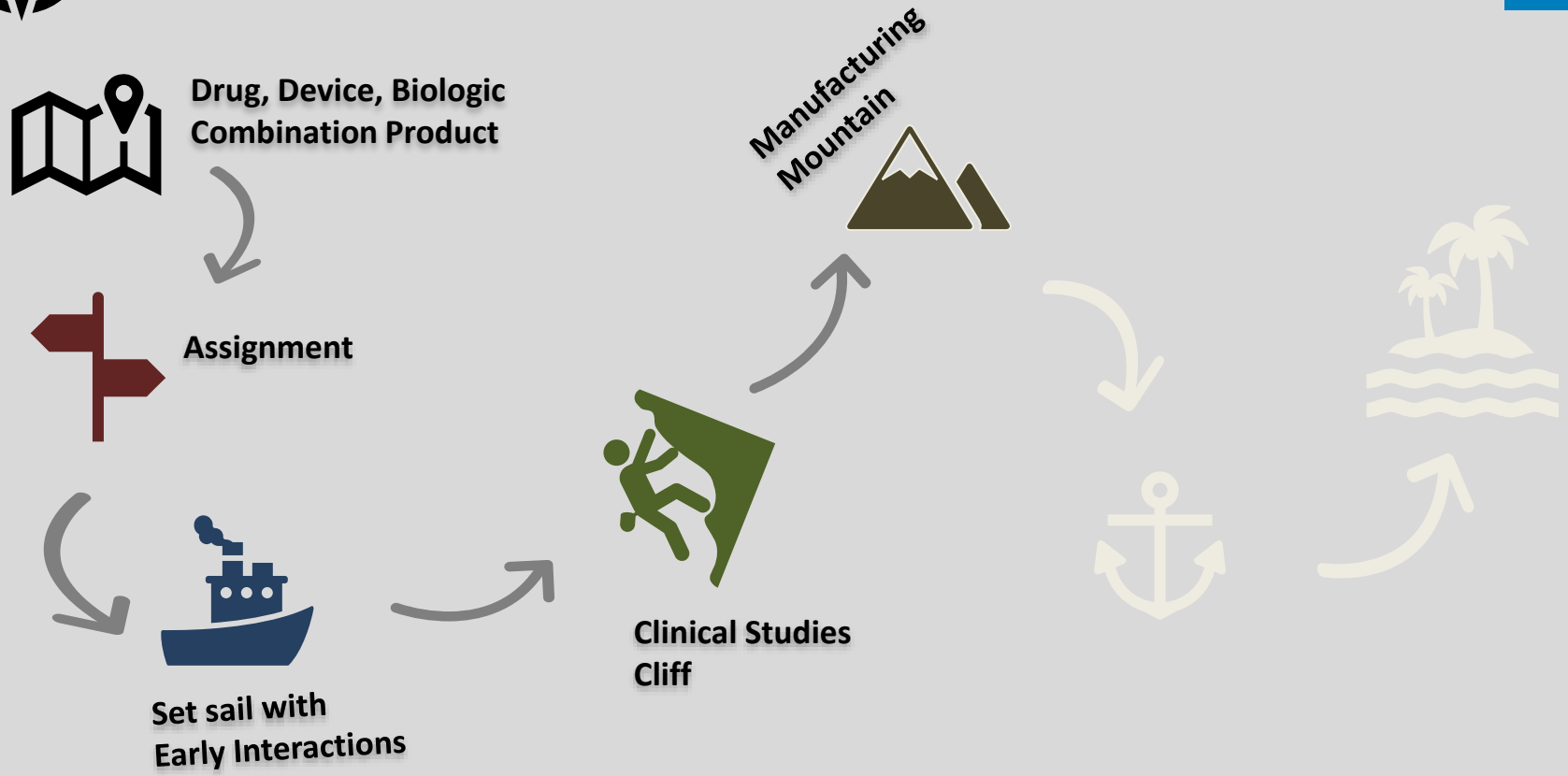
- 21 CFR 812 - Procedures for conducting IDE
- Often conducted in support of a PMA application and sometimes for De Novo request and 510(k)s
- Feasibility Study
  - Early and Traditional feasibility studies
  - Capture preliminary safety and effectiveness (S&E) / Not statistically powered / Inform pivotal study design
- Pivotal Study
  - Powered accordingly to collect S&E evidence
- Early/Expanded Access
  - e.g., compassionate use, emergency use, continued access

CDER - Clinical Trials

Investigational New Drug (IND) application

- Use for both investigational drugs and investigational biologics
- 21 CFR 312 - Procedures for conducting IND
- Commercial / Research
  - Phase I – first in human, dose-ranging, early effectiveness
  - Phase II – well-controlled, probable effectiveness, side-effects
  - Phase III – expanded well-controlled study for effectiveness and safety
  - Phase IV – post-approval studies

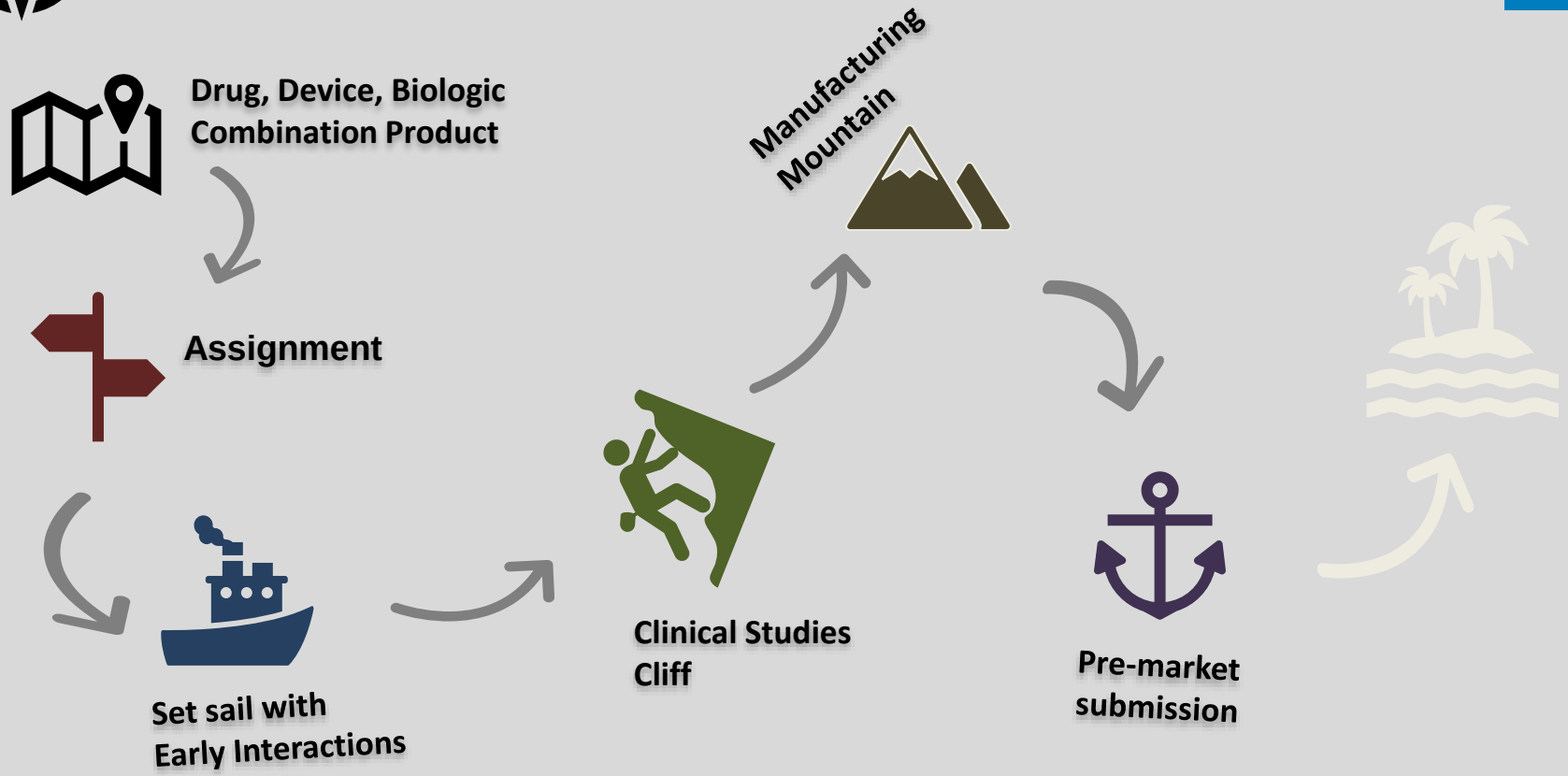
Manufacturing



CDRH / CDER - Manufacturing

- CDRH
  - Quality System Regulation (QSR)
  - 21 CFR 820
- CDER
  - Current Good Manufacturing Practices (cGMP)
  - 21 CFR 210, 211
- Combination Product
  - Streamlines requirements that would apply to each constituent part of combination product
  - Final Rule (1/22/2013) (codified in 21 CFR 4)
  - Current Good Manufacturing Practice Requirements for Combination Products (Final Guidance - 1/2015)
  - Variations to GMP requirements (draft list published in FR 6/13/2018)

Premarket Submission



CDRH - Device Classification

- Devices are classified into Class I, II, or III
- Device classification is based on controls necessary to provide a reasonable assurance of safety and effectiveness:
  - Class I – General Controls are sufficient
    - Most Class I Devices are also exempt from premarket notification (510(k)) requirements, and many are exempt from GMPs
  - Class II – General Controls and Special Controls are required (Typically require 510(k))
  - Class III – General controls and Premarket Approval are required (Typically require PMA)

CDRH - Premarket Submissions

- Premarket Notification (510(k)) [FDCA 510(k), 21 CFR 807]
  - "Clearance," vast majority of device submissions
  - "Substantially equivalent" (at least as safe and effective)
- De Novo Request [513(f)(2)]
  - "Grant"
  - No valid predicate
- Premarket Approval (PMA) application, [FDCA 515, 21 CFR 814]
  - "Approval"
- Humanitarian Device Exemption (HDE) [FDCA 510(m)(2), 21 CFR 814, Subpart H]
  - < 8,000 individuals in US/year
  - Demonstration of probable benefit

CDER - Premarket Submissions

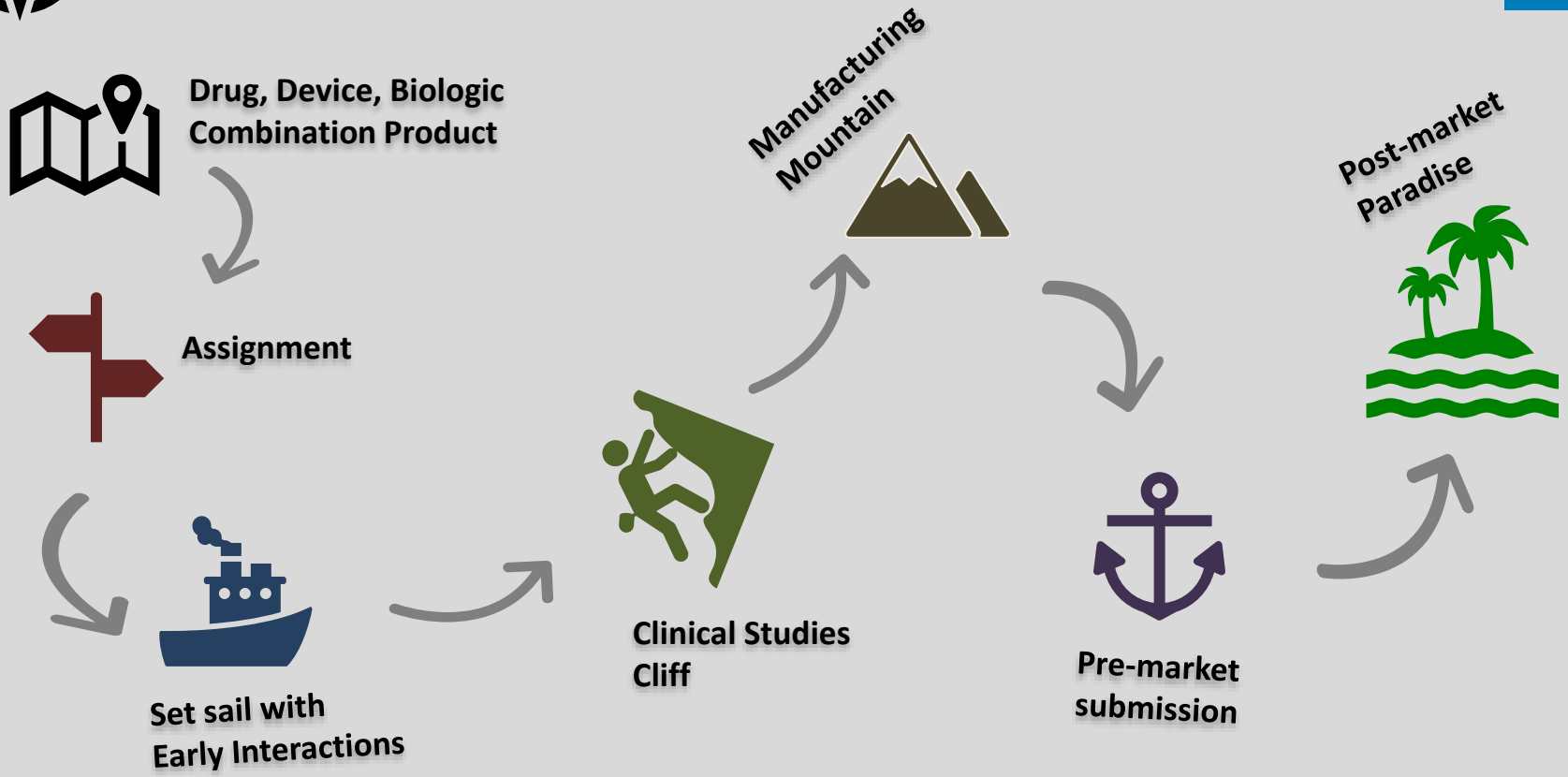
- NDA - section 505 of the FDCA describes three types of new drug applications
  - 505(b)(1) – full report of safety and effectiveness
  - 505(b)(2) – full report of safety and effectiveness, *but* some data comes from studies not conducted by the applicant (e.g., published literature)
  - 505(j) - identical in active ingredient, dosage form, use, route of administration, etc., to a previously approved product (*abbreviated* NDA or ANDA) – generic drug
- BLA (original) – section 351(a) of the PHS Act
- BLA (Biosimilar) – section 351(k)

User Fees

- No separate user fee paradigm for combination products

- Fees depend on type of application submitted (e.g., PMA vs NDA)

Post-market


Drug, Device, Biologic Combination Product
Assignment
Set sail with Early Interactions
Clinical Studies Cliff
Manufacturing Mountain
Pre-market submission
Post-market Paradise

CDRH - Post-market

- Changes to your legally marketed device
  - PMA
    - Panel Track Supplement- Typically a change in IFU or design requiring new clinical data
    - 180 day Supplement – various modifications (design change to trade name change)
    - Real-Time Supplement (90 days) – minor design change
    - 30 day notice/135 Day Supplement - manufacturing changes
    - Annual Reports
  - 510(k)
    - Traditional - Affects indication for use or could affect S&E
    - Special – Summary level data. Does not affect the intended use of the device and does not alter the fundamental scientific technology of the device
    - Abbreviated - Relies on the use of guidance documents, special controls, and recognized standards

CDER - Post-Market

- Changes to your NDA or ANDA
  - Manufacturing sites/process, specifications, container closure, labeling, etc.
    - major changes - Prior Approval Supplement
    - moderate changes -Changes Being Effected (CBE) supplement
      - » CBE
      - » CBE-30
    - minor changes - Annual reports
- Annual reports

Post-Market Safety Reporting (PMSR)

- While PMSR regulations share many similarities, each has distinct requirements
  - Meant to ensure consistency and completeness, but avoid duplication.

- Final rule issued on 12/20/16 (81 FR 92603)
  - codified in 21 CFR Part 4

- Draft Guidance (Mar 2018)

- FDA intends to delay enforcement of these provisions
  - 07/31/2020 – FAERS/eMDR (drugs/devices/biologics)
  - 01/31/2021 – VAERS (vaccines)

Is there anything else out there?

- Digital Health, Devices and Drugs
- Combo Product Submission Identification
- Intercenter Consultation
- General Considerations
- Regulatory Challenges

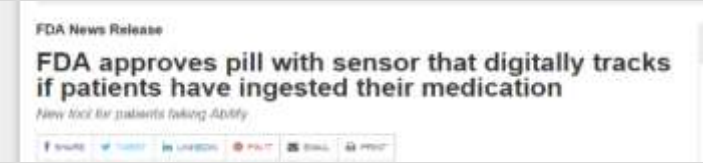
Not All Software is a Device

The law amended the definition of “device” in the Food, Drug and Cosmetic Act to exclude certain software functions intended...

- *(A) for administrative support;*
- *(B) for maintaining or encouraging a healthy lifestyle;*
- *(C) to serve as a electronic patient records;*
- *(D) for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results and certain other related information; and*
- *(E) to provide recommendations to health care professionals for clinical decisions, where the user can independently review the basis of the recommendation.*

Drugs and Digital Health

- Growing experience with drugs and software


FDA News Release

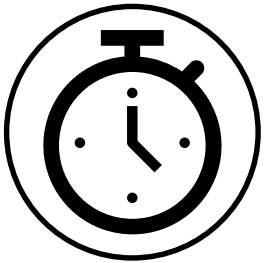
FDA approves pill with sensor that digitally tracks if patients have ingested their medication

New tool for patients taking Abilify

- CDER established an internal digital health working group
  - Representation from across CDER and including CDRH
  - Addressing policy issues for software used with drugs
  - Resource for review teams with application-specific questions
  - Goal is risk-based approach that also considers existing CDRH policies on software as a medical device

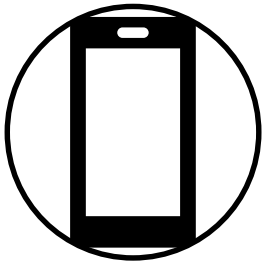
Possible Drug and Software Continuum

Ingestion of Drug with Device Enables Tracking and Results in Clinically Meaningful Benefit



Ingestion of Drug with Device Enables Tracking

Use of Device Enables Tracking but Drug Product Unchanged



Patient-input Required Tracking (via mobile app)

Required Drug Labeling ← → **Promotional Drug Labeling**

PDURS

What: Proposed framework for Prescription Drug Use Related Software (PDURS) disseminated by or on behalf of drug sponsors for use with one or more of their prescription drug products.

Why: Provide prescription drug sponsors the flexibility to develop and disseminate innovative software, while maintaining appropriate Agency oversight over the sponsors' communications about their products.

Goal: Development of guidance based on feedback

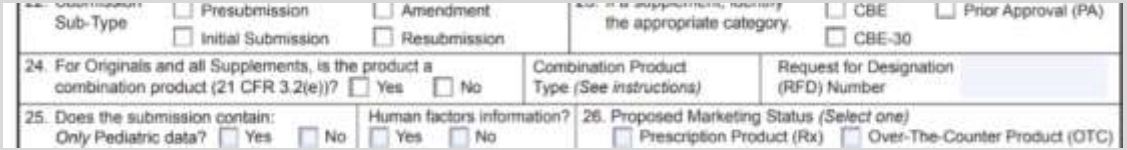
When: Closed April 29 (Docket No. FDA-2018-N-3017)

Identify Combo Product Applications

21st Century Cures Act of 2016 requirement:

- all applicants identify combination product submission

- CDER and CBER - 356h & 1571 forms



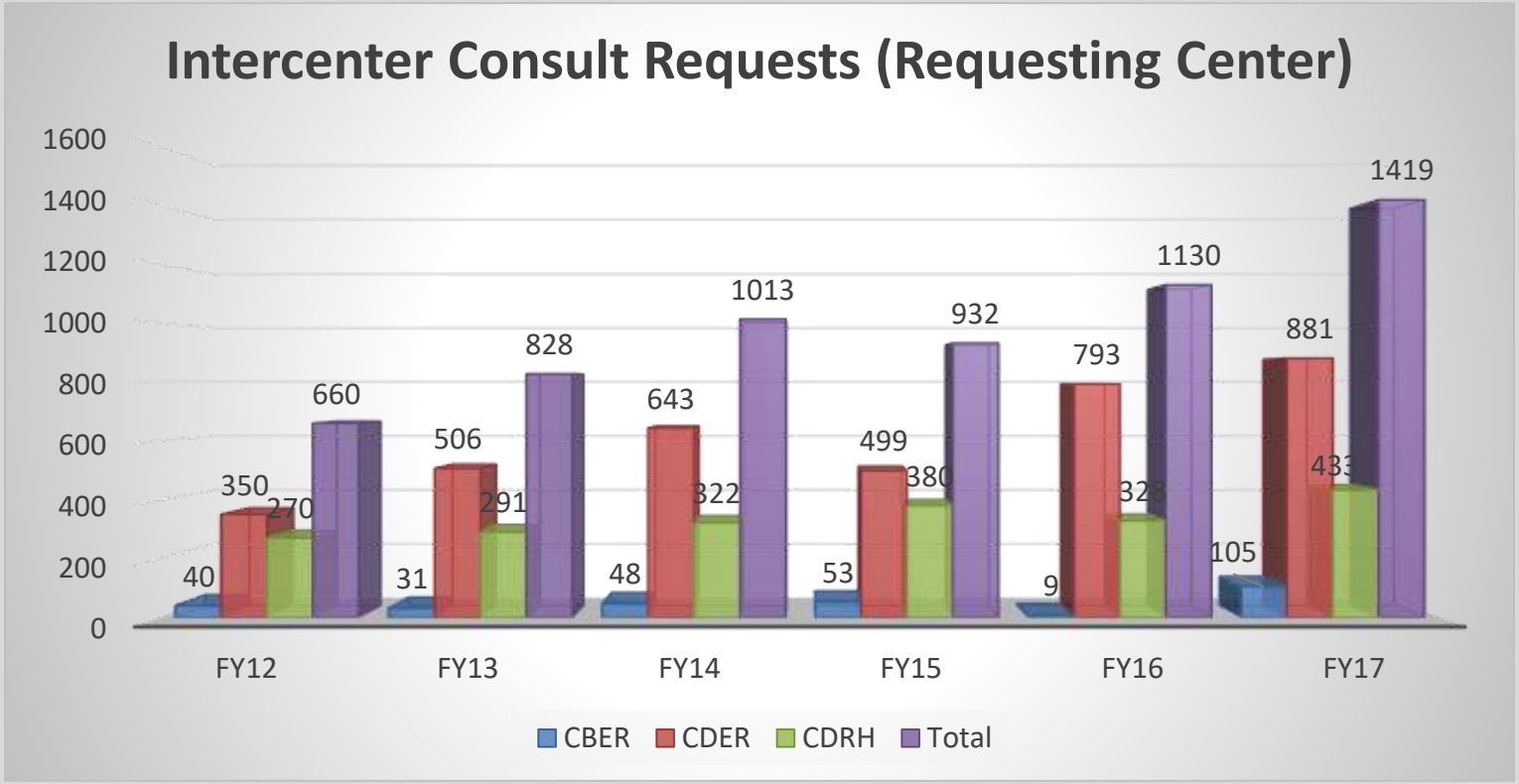
- CDRH – Refuse to Accept Guidances

10.	Submission identifies the product as a combination product.	☐	☐	

Intercenter Consultation

- Enhanced internal process – includes IT updates and resources for staff
- Staff Manual Guide for Intercenter Consults (SMG 4101)
- FDA reviewers more aware of combination product review issues than ever before
- Request specific input and expertise
- Center consultation and collaboration ongoing throughout product life-cycle
- Lead center facilitates interactions with sponsor and consulting center

Intercenter Consultation Requests



↑55%*

***FY17 Compared to previous 5-year average (913)**

General Considerations

- No single developmental paradigm – NOT a one size fits all approach
- Existing guidance for constituent parts are a starting point only
- Need to address issues for product as a whole
- Very few combination product guidance documents:
  - Drug-eluting stents (*draft*)
  - Pen injectors

General Considerations

- Authorization to reference drug (DMF) or device (MAF) master files
  - Permit submission of proprietary information so that parties, other than owners of that information, may rely on it

- Outstanding drug/device issues

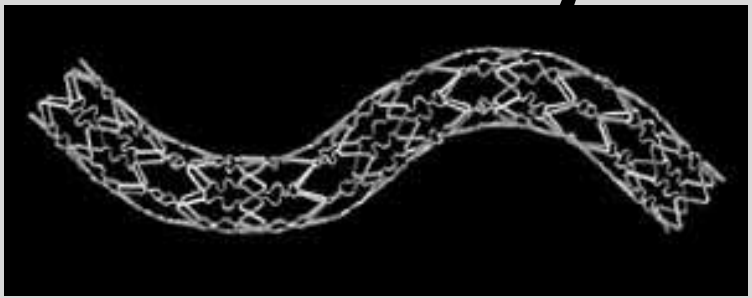
- Only one investigational application for a combination product

Regulatory Challenges Today

- Diverse regulatory considerations among device, drugs, and biologics
- Premarket expectations for combination products – draft guidance
- Regulatory and scientific approach for single-entity product
- Learning curves – FDA and industry
- Appropriate leveraging of available information
- Appropriate pre-clinical testing and clinical trial design
- Jurisdiction

Seasoned traveler…

Case Study



Drug Eluting Stent (DES)

- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Device/Drug constituent parts
- Assigned to **CDRH**

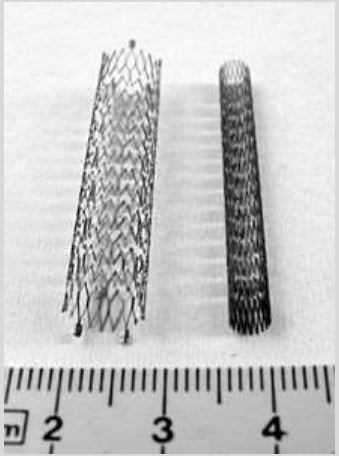
Device Classification

Device	Stent, Superficial Femoral Artery, Drug-Eluting
Definition	Stent, superficial femoral artery, drug-eluting – a metal scaffold with a drug coating placed via a delivery catheter into the superficial femoral artery artery to maintain the lumen. The drug coating is intended to inhibit restenosis.
Review Panel	Cardiovascular
Product Code	NIU
Premarket Review	Office of Device Evaluation (ODE) Division of Cardiovascular Devices (DCD) Vascular Surgery Devices Branch (VSDB)
Submission Type	PMA
Device Class	3

Device	Coronary Drug-Eluting Stent
Definition	Stent, coronary, drug-eluting – a metal scaffold with a drug coating placed via a delivery catheter into the coronary artery or saphenous vein graft to maintain the lumen. The drug coating is intended to inhibit restenosis.
Review Panel	Cardiovascular
Product Code	NIQ
Premarket Review	Office of Device Evaluation (ODE) Division of Cardiovascular Devices (DCD) Interventional Cardiology Devices Branch (ICDB)
Submission Type	PMA
Device Class	3

Components of DES

- **Device**
  - Stent platform
  - Delivery device
- **Drug**
  - Active ingredient
- **Polymer/carrier**



Need a comprehensive evaluation of components AND finished combination product

Preclinical Considerations – Bench Testing

Device

- Polymer coating integrity
- Particulate matter
- Simulated use
- Stent integrity
- Corrosion resistance
- Delivery system functionality
- Leachables / extractables
- Polymer & stent material chemistry
- Shelf life
- MR compatibility

Drug

- Chemistry (purity / impurities)
- Loading
- Elution profile (polymer/carrier)
- Toxicology (cell culture)
- Structure
- CMC
- Stability

Preclinical Considerations - *in vivo* / animal studies

Device

- Biocompatibility
- Stent integrity and performance in clinically relevant model
- Handling characteristics (delivery / deployment)
- Compare / contrast bare metal to polymer coated to drug+polymer coated

Drug

- Local / regional / systemic toxicities (e.g., NOAEL)
- Dose ranging / finding studies
- Pharmacokinetics (PK) studies
- Acute / chronic exposure

Clinical Considerations

- Primary and secondary endpoints to support safety and effectiveness of DES
- Additional Drug studies / parameters
  - Depends on previous experiences (NME, previously approved or studied under IND)
  - Depends on results from preclinical studies (e.g., IV administration of drug alone needed?)
  - IV dose escalation studies
  - Metabolic studies
  - Drug interaction studies
  - Release kinetics

Manufacturing Considerations

Device

- Specifications for device component(s)
- QSR (21 CFR 820)

Drug

- Specifications established to control quality of drug
- GMP (21 CFR 210/211)

Summary

- No single developmental paradigm – NOT a one size fits all approach
- Need to consider product as a whole
- Identify what is and isn't a combination product
- Understand best practices for combination products and navigating the FDA

Questions?

Final Thoughts

- No single developmental paradigm – NOT a one size fits all approach
- Work with FDA early in your development process to establish jurisdiction / classification
- 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)
- Recommend early interactions with FDA when developing your combination product

Industry Education Resources

Acts, Rules and Regulations
www.fda.gov/combination-products/guidance-regulatory-information/acts-rules-and-regulations

Combination Product Guidance documents (final and draft)
www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents

Office of Combination Products
www.fda.gov/combination-products

References

- **Meetings/Presubmissions**
  - CDER/CBER: Formal Meetings Between the FDA and Sponsors or Applicants
    www.fda.gov/media/72253/download
  - CDRH: 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
- **Changes to an Approved NDA or ANDA**
  www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda
- **Current Good Manufacturing Practice Requirements for Combination Products**
  www.fda.gov/media/90425/download
- **Principles for Premarket Pathways for Combination Products (Draft Guidance)**
  www.fda.gov/media/119958/download
- **Compliance Policy for Combination Product Postmarketing Safety Reporting (Draft Guidance)**
  www.fda.gov/media/111788/download

Abbreviations

- AE – adverse event
- ANDA – abbreviated new drug application
- BLA – biologic license application
- CBE – changes being effected
- CBER – Center for Biologics Evaluation and Research
- CDER – Center for Drug Evaluation and Research
- CDRH – Center for Devices and Radiological Health
- CFR – Code of Federal Regulations
- cGMP – current Good Manufacturing Practices
- DES – drug eluting stent
- FDA – Food and Drug Administration
- FDCA – Food, Drug, and Cosmetic Act
- HDE – Humanitarian Device Exemption
- IDE – Investigational Device Exemption
- IND – Investigational New Drug
- IV - intravenous
- MOA – mode of action
- NME – new molecular entity
- NDA – New Drug Application
- NOAEL – no observed adverse effect level
- OCP – Office of Combination Products
- OSMP – Office of Special Medical Programs
- PHSA – Public Health Services Act
- PK - pharmacokinetics
- PMA – premarket approval
- PMOA – primary mode of action
- QSR – quality systems regulations
- RFD – request for designation


FDA
U.S. FOOD & DRUG
ADMINISTRATION