Drug/Device Combinations: A Union to Deliver the Best Medical Product to Patients

FDA Small Business Regulatory Education for Industry (REdI)

Silver Spring, MD

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Who are we?

- **Kristina Lauritsen**
  - CDER Product Jurisdiction Officer
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  - (301) 796-8936

- **James Bertram**
  - CDRH Product Jurisdiction Officer
  - CDRHProductJurisdiction@fda.hhs.gov (preferred)
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What do we do?

- The Product Jurisdiction Officers in CDRH, CBER and CDER are liaisons to OCP for their Center
- Provide recommendations to OCP re: classification and assignment of combination and single-entity products
- Represent their Center on combination product and jurisdiction policies
- Work with OCP to develop guidance documents and regulations that affect their Center

What do we do?

- Participate in inter-center working groups
- Help sponsors clarify the regulatory pathway for products assigned to their Center
- Respond to internal and external inquiries

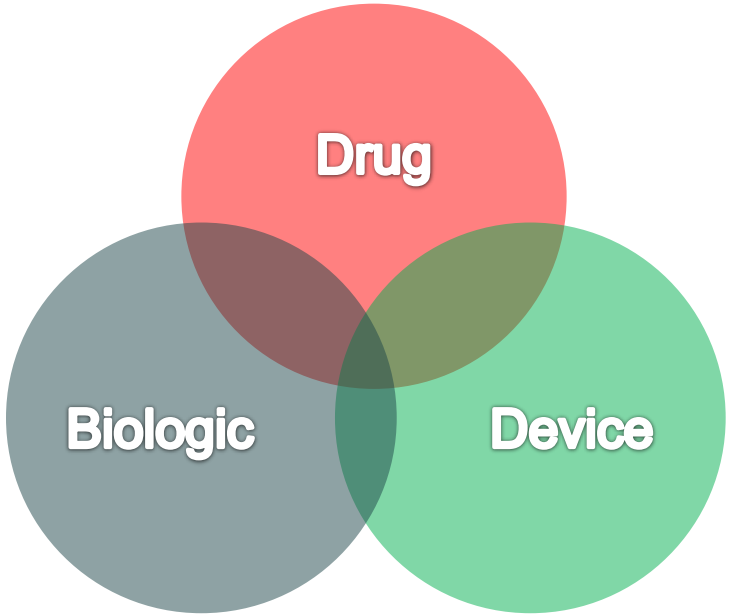
Learning Objectives

- 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

First things first... What is a Combination Product?

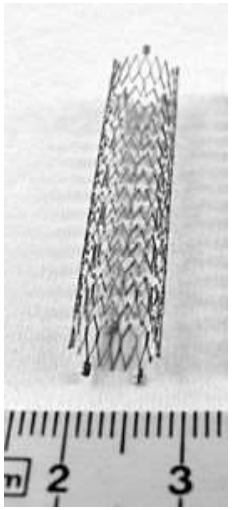
Combinations of 2 or more DIFFERENT products:

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



Combination Product... How are they combined?

- 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 & antibiotic ointment
  - Photodynamic therapy

NOT Combination Products

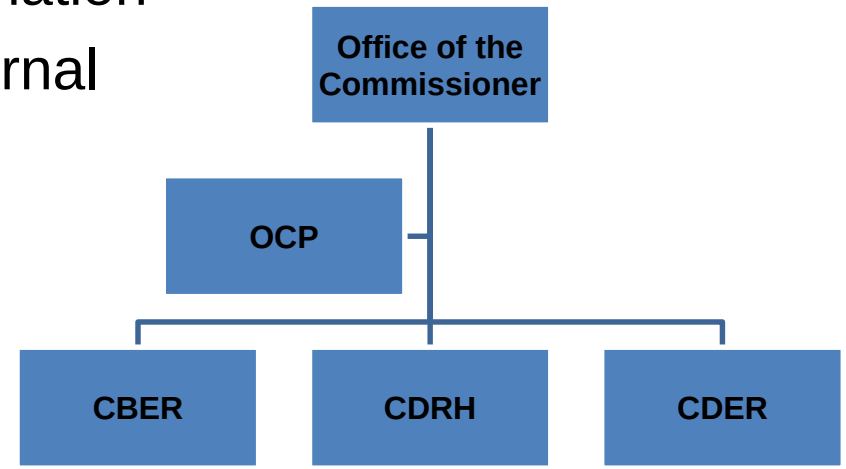
- Drug-Drug
- Device-Device
- Biologic-Biologic
- Food + Drug/Device/Biologic
- Cosmetic + Drug/Device/Biologic

I have (or think I have) a Combination Product. Now what?

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)

- Charged with assigning 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.
- Provides a focal point for combination product issues for internal / external stakeholders
- Has broad oversight responsibilities covering the regulatory life cycle of combination products



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)

Combination Product ???

Recall the Statute (FDCA 503(g))…

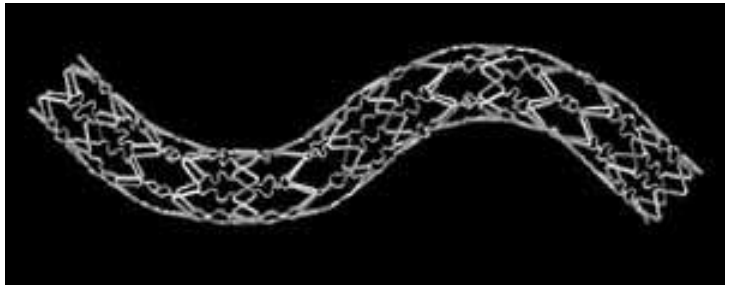
Combination products are assigned based on the primary mode of action (PMOA). If the Secretary determines that the primary mode of action is that of ---

(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***

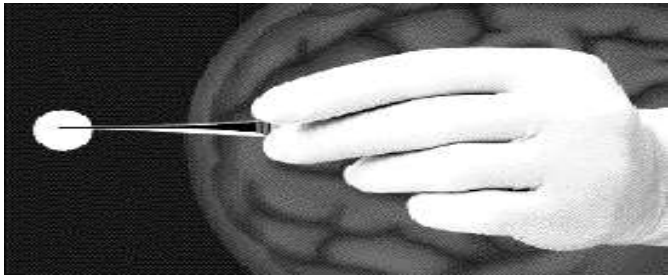
(C) a biological product, the agency center charged with premarket review of biological products shall have primary jurisdiction. --- ***CBER or CDER***

PMOA Examples



Drug Eluting Stent

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



Drug Eluting Disk

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

But…PMOA may be difficult 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 the PMOA with reasonable certainty, OCP will then consider…

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

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

(21 CFR 3.4)

Algorithm Assignment example

Contact lens coated with glaucoma drug

- MOA: Lens corrects vision
- 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 guidance:
  - Email: combination@fda.gov
  - Simple issues, uncertainty, process concerns
  - Determine whether an RFD is needed
  - Non-binding; can submit RFD if disagree with informal guidance
- Formal process:
  - Submit a Request for Designation (RFD)
  - Formal, binding determination – **60** days
  - Complex issues or dispute / uncertainty
  - Requirements in 21 CFR 3.7

RFD process

- 15 page limit, including attachments
- Complete product description
- Amount and purpose of ingredients/components
- Indications for use
- Developmental work
- MOA and PMOA
  - How it works (mechanism), not just what it does
  - Rationale – supported by data, reference to literature
- Sponsor's recommendation for classification / assignment

When to submit an RFD or informal inquiry?

Submit an RFD or informal inquiry **BEFORE** any submission (i.e., presubmission / pre-IND, marketing submission)

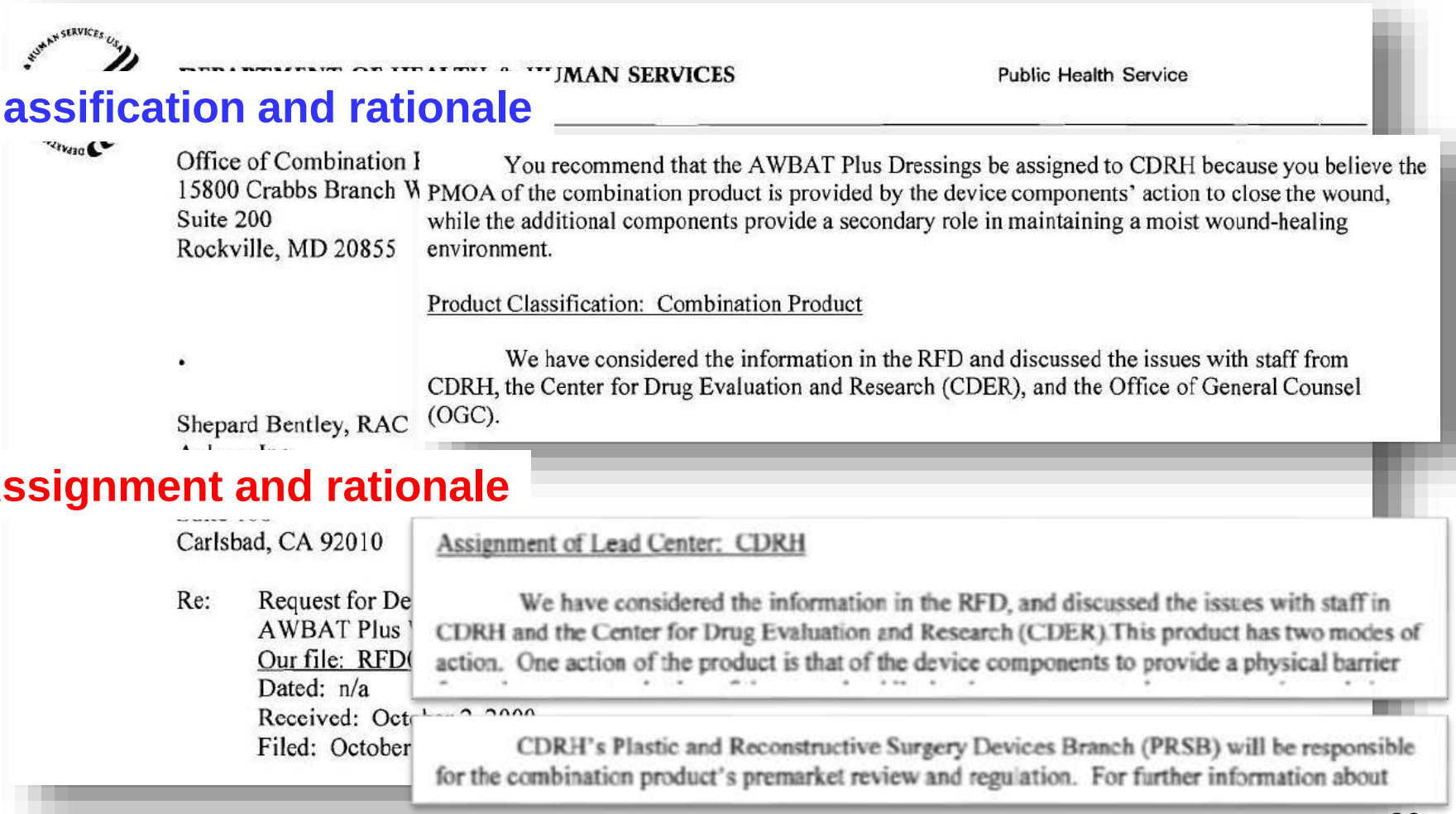
<u>Why?</u>

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

RFD Decision Letter

Classification and rationale

Assignment and rationale



...JMAN SERVICES Public Health Service

Office of Combination I
15800 Crabbs Branch W
Suite 200
Rockville, MD 20855

Shepard Bentley, RAC

Carlsbad, CA 92010

Re: Request for De
AWBAT Plus
Our file: RFD(
Dated: n/a
Received: Oct
Filed: October

You recommend that the AWBAT Plus Dressings be assigned to CDRH because you believe the PMOA of the combination product is provided by the device components' action to close the wound, while the additional components provide a secondary role in maintaining a moist wound-healing environment.

Product Classification: Combination Product

We have considered the information in the RFD and discussed the issues with staff from CDRH, the Center for Drug Evaluation and Research (CDER), and the Office of General Counsel (OGC).

Assignment of Lead Center: CDRH

We have considered the information in the RFD, and discussed the issues with staff in CDRH and the Center for Drug Evaluation and Research (CDER). This product has two modes of action. One action of the product is that of the device components to provide a physical barrier

CDRH's Plastic and Reconstructive Surgery Devices Branch (PRSB) will be responsible for the combination product's premarket review and regulation. For further information about

What's next?

Classification

Assignment

What do I do when I get there?

- Early Interactions and Feedback
- Clinical Trials
- Manufacturing
- Premarket Submissions
- Post-market Requirements
- Other Considerations

Product Development

Product Development

Early Interactions & Feedback

CDRH- Early Interaction / Feedback

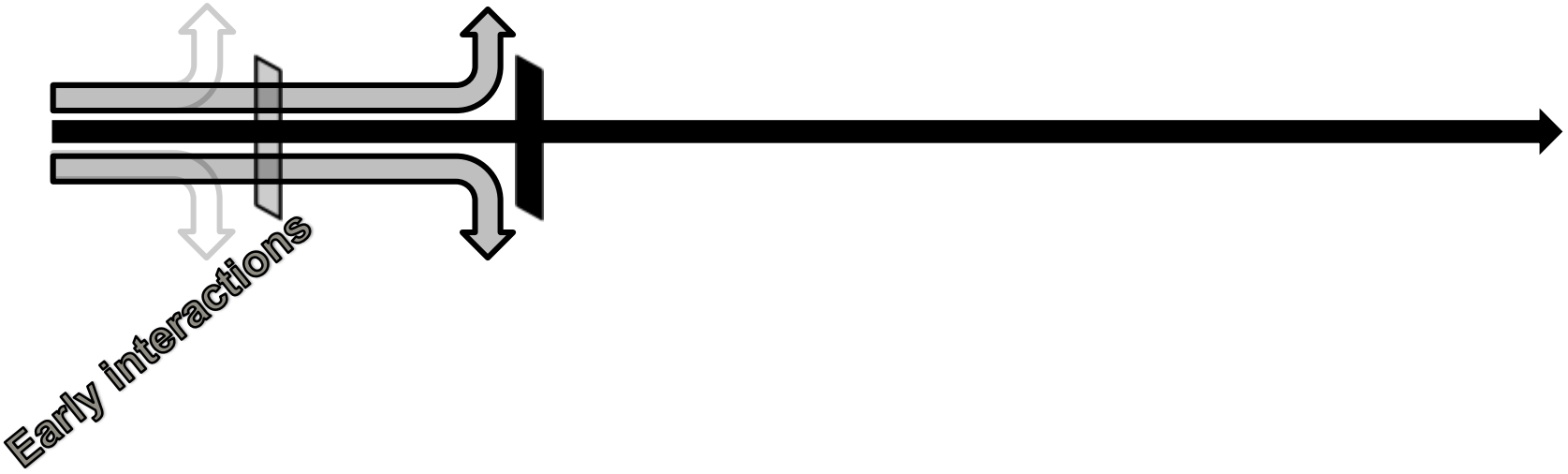
Q-Submission Type	Meeting	Timeframe for Meeting/Teleconference/Feedback (from receipt of submission)
Pre-Submission	Upon request	75-90 days
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Scheduled within 30 days of request
Submission Issue Meeting	Yes	21 days
Day 100 Meeting	Yes	100 days (from filing of PMA)

CDER- Early Interaction / Feedback

Meeting Request	Meeting Topic	Timing of Meeting
Type A	Stalled development, Dispute resolution, Clinical holds, Special Protocol Assessment (SPA)	Meet within 30 days of request (briefing package submitted 2 weeks ahead)
Type B	preIND, end of Phase (1)/2/3, preNDA/BLA	Meet within 60 days of request (briefing package submitted 4 weeks ahead)
Type C	Any other meeting	Meet within 75 days of request (briefing package submitted 4 weeks in advance)

Product Development

Clinical Trials



CDRH- Clinical Trials

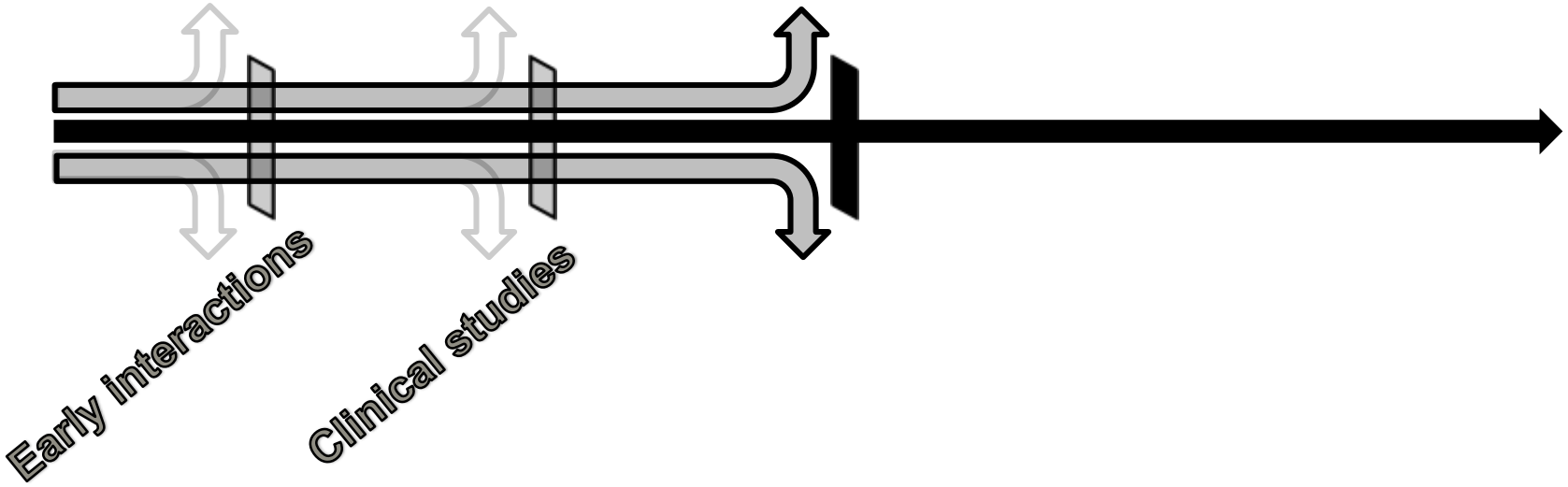
- Investigational Device Exemption (IDE)
  - 21 CFR 812 - Procedures for conducting IDE
  - Often conducted in support of a PMA application and small percentage of 510(k)s
  - Feasibility Study
    - Early & Traditional feasibility studies
    - Capture preliminary safety and effectiveness (S&E) / Not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

CDER- Clinical Trials

- Investigational New Drug (IND) application
  - 21 CFR 312 - Procedures for conducting IND
  - Commercial / Research
  - Phase I – first in human, dose-ranging, early effectiveness (20-80 patients)
  - Phase II – well-controlled to establish probable effectiveness, side-effects (100-300 patients)
  - Phase III – expanded well-controlled study for effectiveness and safety (1000-2000 patients)
  - Phase IV – post-approval studies

Product Development

Manufacturing

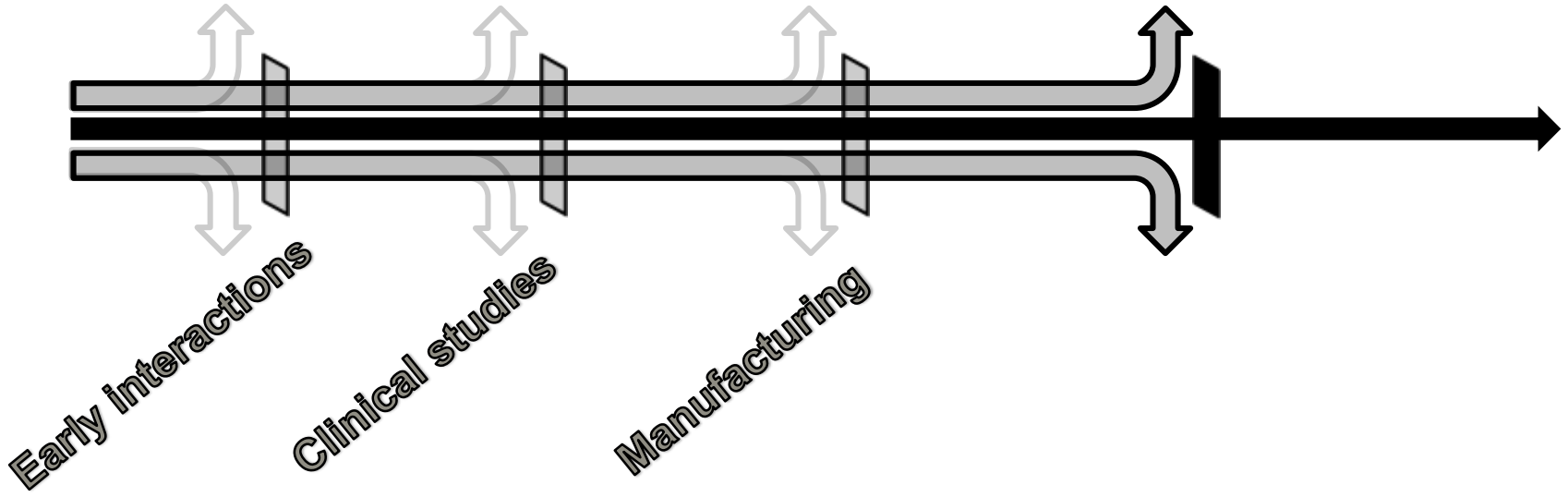


CDRH/CDER- Manufacturing

- 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)
  - Draft Guidance (1/2015)- *Current Good Manufacturing Practice Requirements for Combination Products*

Product Development

Premarket Submissions



CDRH- Device Classification

- Devices are classified into Class I, II, or III
- Device classification is based on the 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, ~4,000/year
  - "Substantially equivalent" (at least as safe and effective)
- De Novo [513(f)(2)]
  - "Grant," ~30/year
  - No valid predicate
- Premarket Approval (PMA), [FDCA 515, 21 CFR 814]
  - "Approval,"
  - Reasonable assurance of safety and effectiveness
  - Original PMAs ~40/year
- Humanitarian Device Exemption (HDE) [FDCA 510(m)(2), 21 CFR 814, Subpart H]
  - < 4,000 individuals in US/year
  - Exempt from effectiveness requirements of PMA

CDER- Premarket Submissions

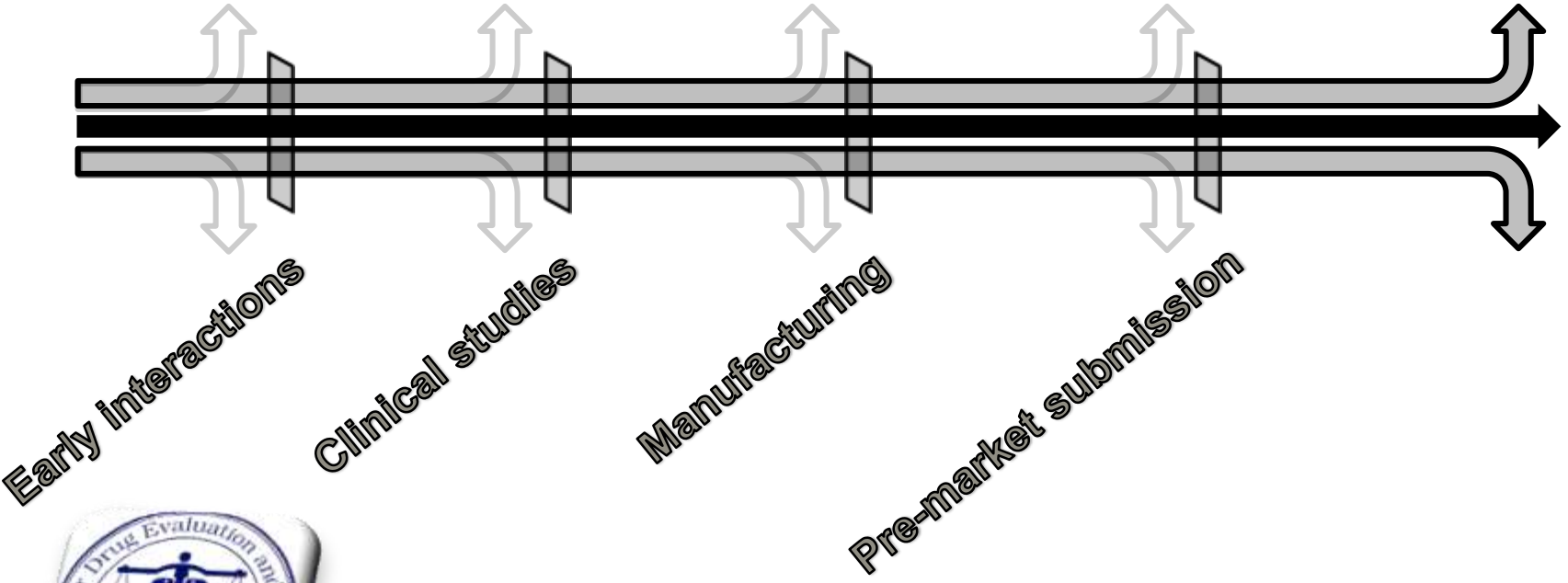
- NDA - section 505 of the FDCA describes three types of new drug applications
  1. 505(b)(1) – full report of safety and effectiveness
  2. 505(b)(2) – full report of safety and effectives, *but* some data comes from studies not conducted by the applicant (e.g., published literature)
  3. 505(j) - identical in active ingredient, dosage form, use, route of administration, etc., to a previously approved product (abbreviated NDA or ANDA)
- BLA – section 351 of the PHS Act describes biologic license applications

User Fees

- No separate user fee paradigm for combination products
- Fees depend on type of application submitted (e.g., PMA vs NDA)

Product Development

Post-market Requirements



CDRH- Post-market

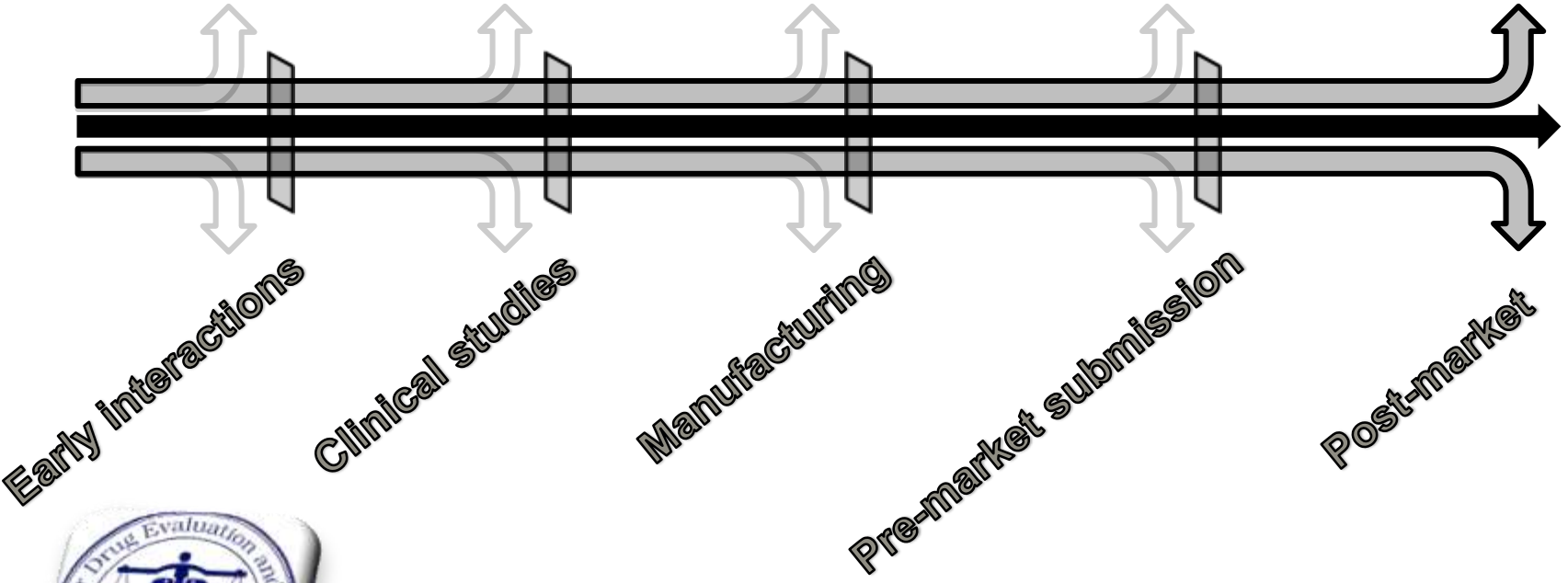
- Changes to your legally marketed device
  - PMA supplements
    - Panel Track- Typically a change in IFU or design requiring new clinical data
    - 180 day Supplement – various modifications (design change to trade name change)
    - Real-Time Supplement (90 days) – minor design change
    - 30 day notice/135 Day Supplement - manufacturing changes
  - 510(k)
    - Traditional - Affects indication for use or could affect S&E
    - Special - Does not affect the intended use of the device and does not alter the fundamental scientific technology of the device
- Adverse Event (AE) reporting (21 CFR 803) (both PMA & 510(k))
- PMA annual reports

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
- AE reporting (21 CFR 314)

Product Development

Other considerations



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 guidances:
  - Drug-eluting stents (*draft*)
  - Pen injectors

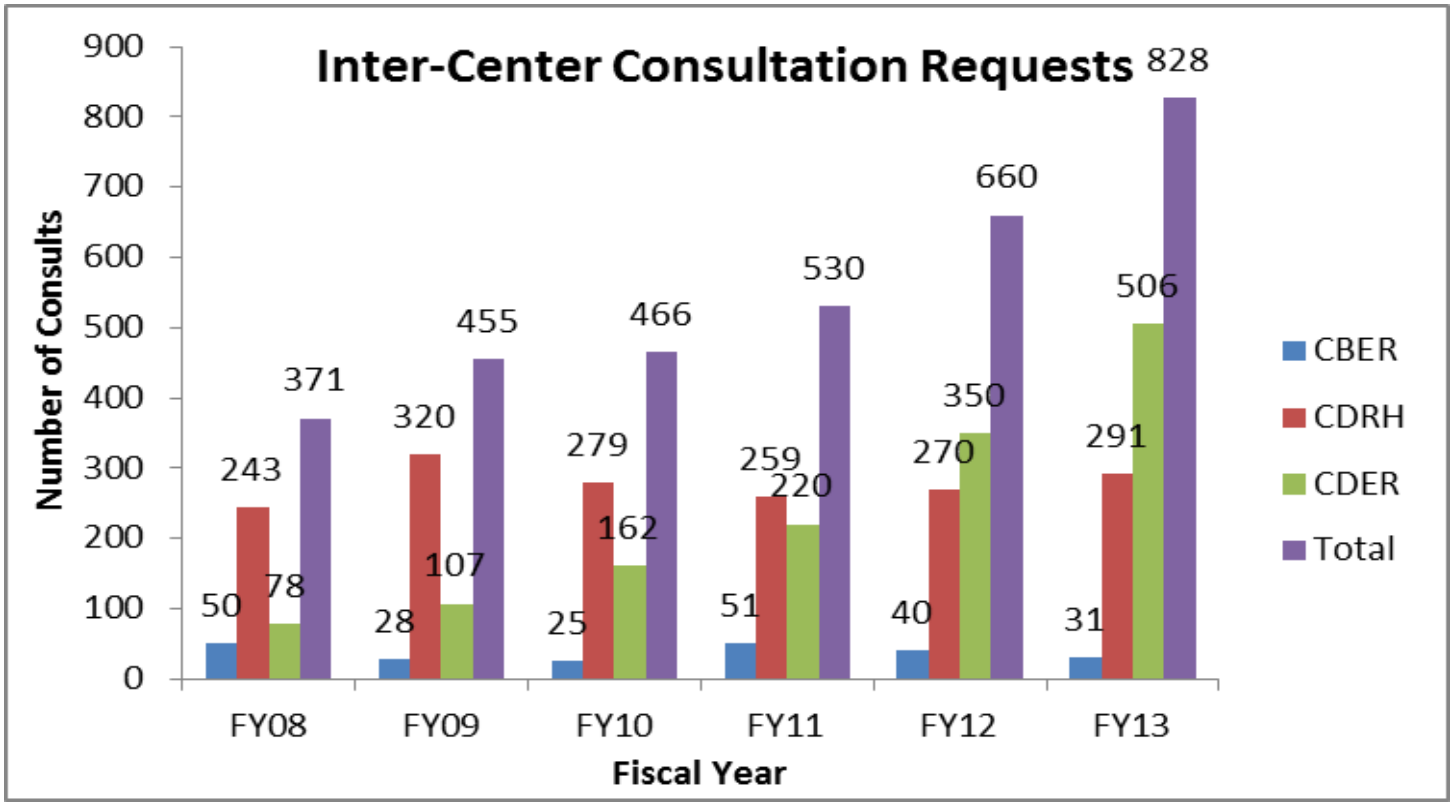
General Considerations

- Authorization to reference drug (DMF) or device (MAF) masterfiles
  - Permit the submission of proprietary information so that parties other than the owners of that information may rely on it
- Outstanding drug/device issues
- Only one investigational application for a combination product

Intercenter Consultation

- FDA reviewers are more aware of combination product review issues than ever before
- Formal intercenter consultation process: http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm119234.htm
- Request specific input and expertise
- Center consultation and collaboration is ongoing throughout product life-cycle
- Lead center facilitates interactions with sponsor and consulting center

Inter-center Consultation Requests



↑ 67%*

*FY 13 Compared to 5-year average

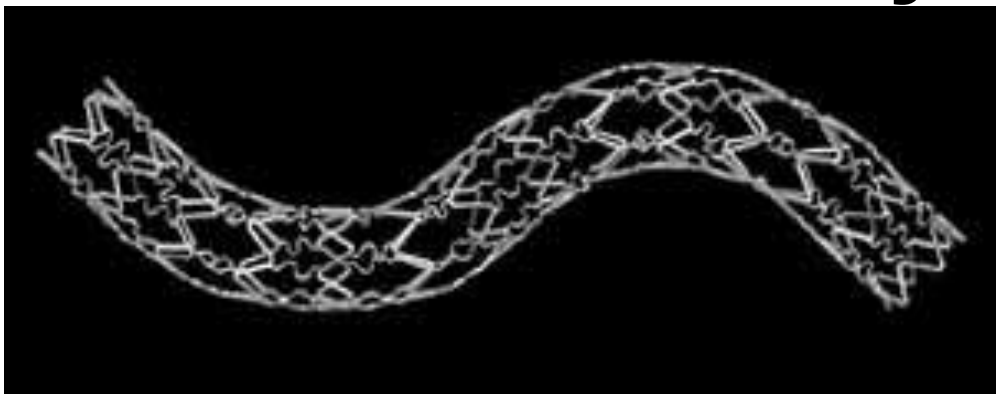
Regulatory Challenges

- Jurisdiction
- Disparity in statutory and regulatory requirements between CDRH & CDER/CBER
- Learning curves – FDA and industry
- Appropriate leveraging of available information
- Appropriate pre-clinical testing and clinical trial design
- Regulatory and scientific approach for single-entity product ≠ device+drug/biologic

OCP can help!

- Manage the intercenter consult process to ensure timeliness of submission review
- Tracks and monitors all intercenter consult requests
- Facilitates any disputes between the centers regarding combination products
- Develops policies and processes for improving intercenter consultation

DES Case Study



Drug Eluting Stent

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

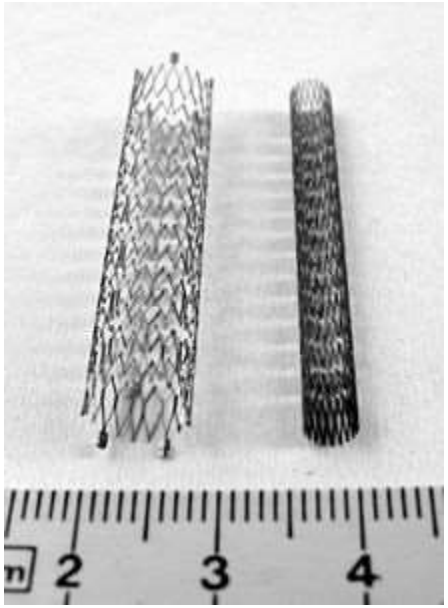
Device Classification

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 [6](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 [6](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

Considerations from a preclinical perspective (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

Considerations from a preclinical perspective (*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

Considerations from a clinical perspective

- Primary and secondary endpoints to support safety and effectiveness of the 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

Considerations from a manufacturing perspective

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
- 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 the Agency when developing your combination product

Industry Education Resources

- **Acts, Rules and Regulations**

http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109108.htm

- **Combination Product Guidance documents (final and draft)**

http://www.fda.gov/RegulatoryInformation/Guidances/ucm122047.htm

- **Office of Combination Products**

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

References

- **Meetings/Presubmissions**
  - CDER/CBER: Formal Meetings Between the FDA and Sponsors or Applicants http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf
  - CDRH: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- **Changes to an Approved NDA or ANDA** http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf
- **Current Good Manufacturing Practice Requirements for Combination Products (DRAFT)** http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf
- **Drug-Eluting Stents (DRAFT)** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072193.pdf

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

Questions?

Please complete the session survey:

surveymonkey.com/r/2015-Plenary