FDA Regulation of Combination Products

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Food and Drug Administration
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Four Questions

- What am I?
- Where do I go?
- What do I do when I get there?
- How do I find out?

What Is A Drug?

- Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or
- Intended to affect the structure or any function of the body.
  - 21 U.S.C. § 201(g)

What Is A Device?

Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent

which is.....

What Is A Device? (continued)

- Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or
- Intended to affect the structure or any function of the body. . .

What Is A Device? (continued)

. . .and which does not achieve its intended purposes through chemical action on man and which is not dependent on being metabolized to achieve its primary purposes.

21 U.S.C. § 201(h)

What Is A Biologic?

- Virus
- Therapeutic Serum
- Toxin or Antitoxin
- Vaccine
- Blood, Blood Component or Derivative
- Allergenic Product or
- Analogous Product
  - 42 U.S.C. § 351(i)

What Am I?

Products classified as:

- Drug
- Device
- Biologic
- Combination Product (the fourth category)

A Combination Product Is. . .

- A product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity;
- Two or more separate products packaged together;

A Combination Product Is. . .

- A product packaged separately but intended for use only with an approved, individually specified product, where both are required to achieve the intended use, indication, or effect
  - 21 CFR § 3.2(e)

Examples of Combination Products

- drug-eluting cardiovascular stent
- orthopedic implant with growth factors
- pre-filled syringe
- metered dose inhaler
- transdermal patch
- convenience kit
- ribavirin – interferon
- photodynamic therapy with laser light source

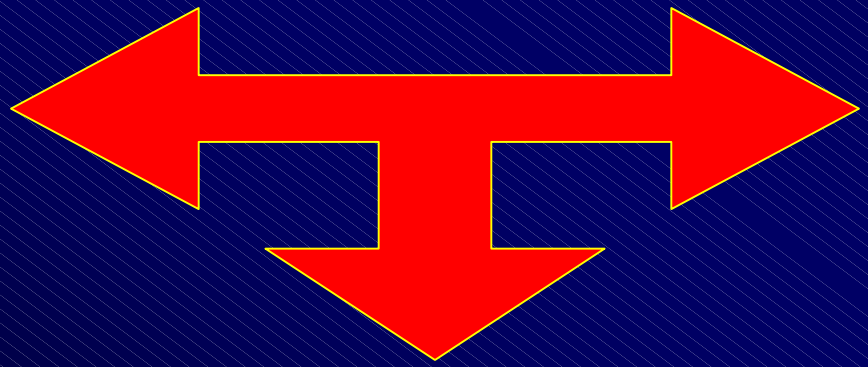
These Are Not Combination Products

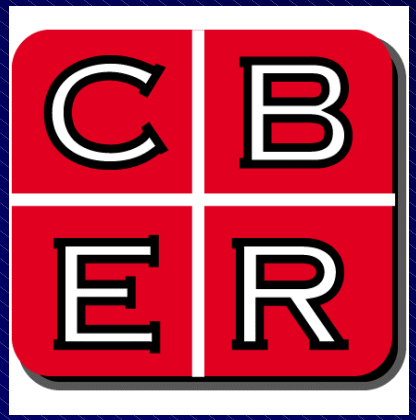
- Fixed combination drug products
- Products comprised of two biologics, two devices, or two drugs
- General drug or biologic delivery devices

I am a combination product.

Where do I go?

Drugs





Biologics

Devices

Primary Mode of Action

Primary mode of action is the statutory criterion FDA must use to determine the agency component with primary jurisdiction for the review and regulation of a combination product.

21 U.S.C. § 503(g)

PMOA continued

- PMOA not currently defined in the Act or regulations
- Proposed rule issued May 7, 2004
  69 FR 25527
  www.fda.gov/OHRMS/DOCKETS/98fr/04-10447.pdf
- Goals:
  - Simplify designation process
  - Enhance consistency, predictability and transparency

PMOA continued

- "Mode of Action" would be defined as the means by which a product achieves a therapeutic effect
- Three types of modes of action: biological product, device, drug
- Combination products typically have more than one identifiable mode of action

PMOA continued

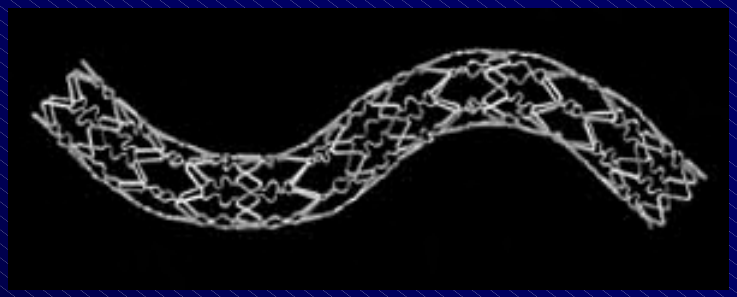
- Primary Mode of Action:
  - The single mode of action of a combination product that provides the most important therapeutic action of the combination product

PMOA continued

- If unable to determine most important therapeutic action with reasonable certainty, consider:
  - Consistency
  - Safety and effectiveness

PMOA continued
CDRH or CDER?

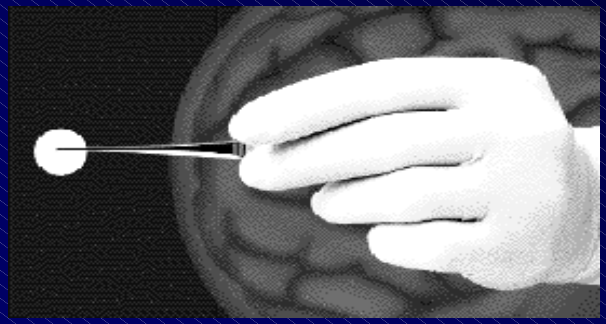
Drug Eluting Stent



- Primary Mode of Action:
  - Stent opens artery
- Secondary Action:
  - Drug prevents inflammation and restenosis of artery

- Regulated by CDRH under device provisions

Drug Eluting Disk



- Primary Mode of Action:
  - Cancer chemotherapy for brain tumor
- Secondary Actions
  - Local drug delivery of drug by device

- Regulated by CDER under drug provision

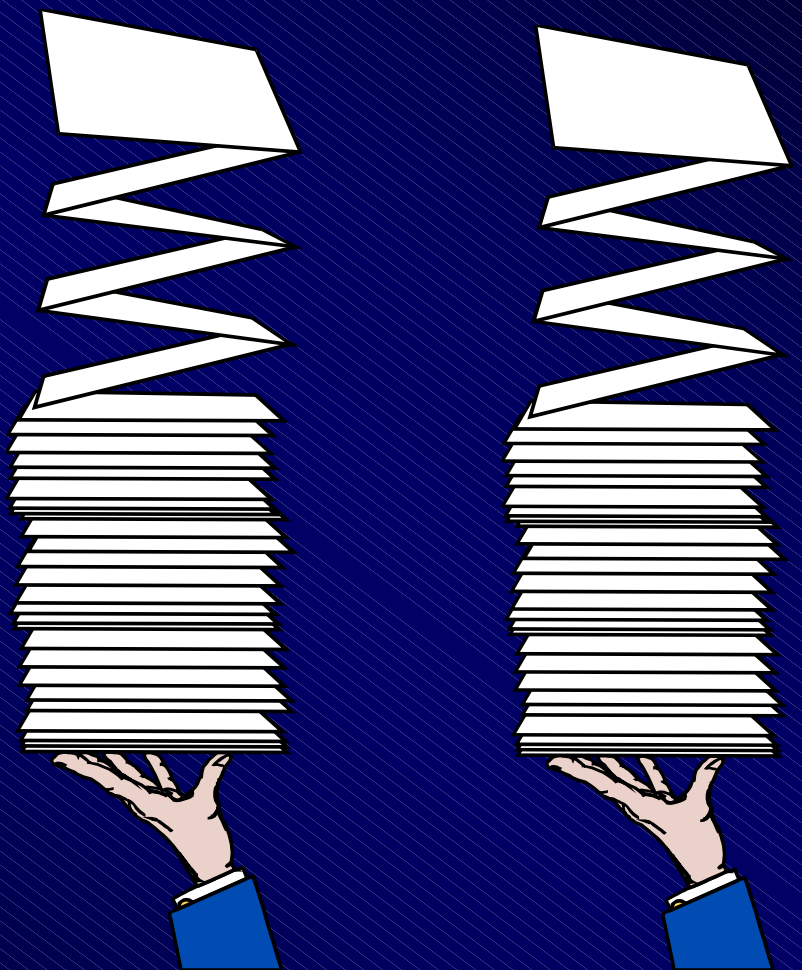
What Do I Do When I Get There?

- One application or two?
- Intercenter consultation/collaboration
- Postmarket regulatory authorities
- Timeliness dispute resolution

One Application or Two?

In appropriate cases, FDA may require two applications.

21 CFR § 3.4(b)



Intercenter Consultation/Collaboration

SOP Review Process

Provides the policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs and biologics.

www.fda.gov/oc/ombudsman/intercentersop.pdf

Postmarket Regulatory Authorities

- cGMP
- QSR
- Adverse Events

Timeliness Dispute Resolution

- Premarket review
- PDUFA and MDUFMA time frames
- Purpose is to obtain review as quickly as possible
- Guidance document
  www.fda.gov/oc/combination/dispute.html

How Do I Find Out?

- Office of Combination Products
- Center Jurisdictional Liaisons
- Intercenter Agreements/ Jurisdictional Updates
- Request for Designation

Office of Combination Products

- Classifies products as drugs, devices, biologics, or combination products
- Assigns combination products to an FDA center
- Ensures timely premarket review
- Reviews/updates guidance, agreements, practices

OCP continued

- Reports to Congress annually
  www.fda.gov/oc/combination/Congressreport.pdf
- Assures consistent and appropriate postmarket regulation of combination products
- Serves as a resource to sponsors of combination products throughout development and review of product
- OCP website: www.fda.gov/oc/combination

Office of Combination Products

Overview of the Office of Combination Products

Quarterly Progress Reports to Stakeholders

- First Quarterly Progress Report to Stakeholders: January - March 2003

Review of Combination Products

Intercenter Consultative/Collaborative Review Process PDF [82KB] HTML

Assignment of Combination Products/Product Jurisdiction Program - Revised 6/13/2003

June 23, 2003 Final Rule NEW!

Intercenter Agreements

Jurisdictional Updates

- Drug-Eluting Cardiovascular Stents
- Dental Prophylaxis Pastes with Drug Components

General Information

Definition of a Combination Product

November 25, 2002 Public Hearing on Regulation of Combination Products

- Federal Register Notice
- Agenda and Presentations
- Transcript of Nov. 25, 2002 Public Hearing - PDF [213KB] HTML

Regulation of Combination Products: FDA Employee Perspectives

PDF [74KB] [HTML]

Selected Guidance Documents Applicable to Combination Products.

Recent Examples of Combination Product Approvals

Press Release

FDA Establishes Office of Combination Products, Dec. 31, 2002

Contact Us

We are interested in your comments and suggestions about combination products issues. Please contact:

New address 6/19/2003
Mark D. Kramer, Director
Office of Combination Products
Food and Drug Administration
15800 Crabbs Branch Way (HFG-3)
Suite 200
Rockville, MD 20855
(301) 827-9229
(301) 827-9230 fax
email: combination@fda.gov

Center Jurisdictional Liaisons

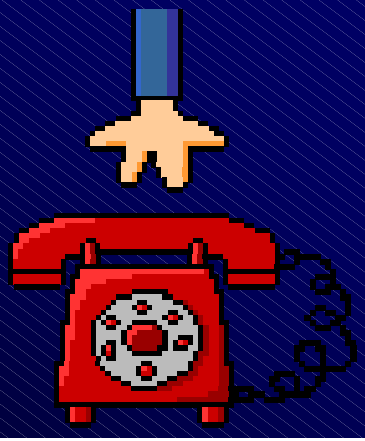
- Informal approach
- Not necessarily binding on agency
- Contact Jurisdictional Liaisons

Center Jurisdictional Liaisons

CBER: Sherry Lard 301-827-0379

CDER: Warren Rumble 301-594-5480

CDRH: Gene Berk 301-594-1190



InterCenter Agreements

- Three agreements:
  - CDER – CBER
  - CBER – CDRH
  - CDER – CDRH
- Written in 1991
- www.fda.gov/oc/combination/intercenter.html

Jurisdictional Updates

- Statement of past classification and/or assignment decisions
- Not policy statements
- Four issued to date
- www.fda.gov/oc/combination/updates.html

Request for Designation

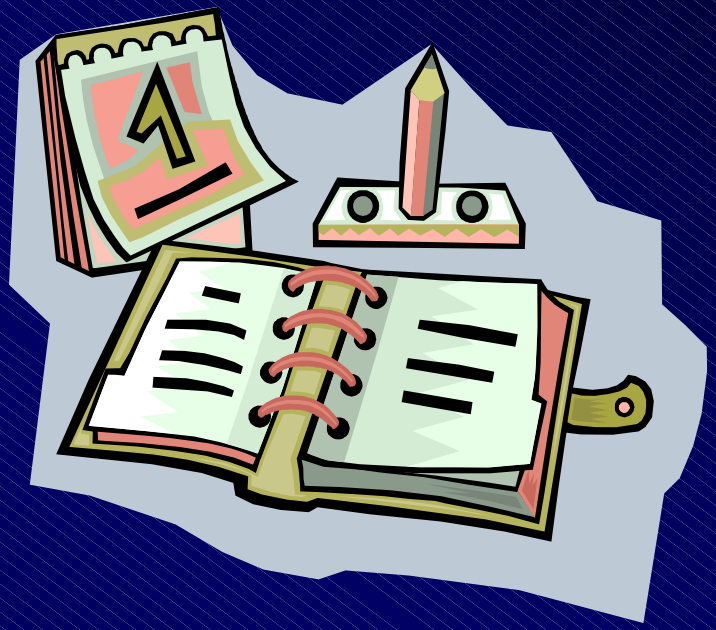
- Voluntary
- 21 CFR Part 3
- Classification and Assignment
- Clarification of Regulatory Process

Who Should File an RFD?

- The sponsor of any product when the identity of the product as a drug, device, biologic, or combination product is unclear or in dispute
- The sponsor of any combination product where the Center with primary jurisdiction is unclear or in dispute.
- FDA may stay the review clock while a determination is being made.

When Should I Submit an RFD?

- Before filing any application for premarket review
- *As soon as* there is sufficient information for FDA to make a determination



RFD Content

- ✓ Sponsor information
- ✓ Product description
- ✓ Proposed use and indications
- ✓ Description of primary mode of action
- ✓ Recommendation on product classification and Center with primary jurisdiction

21 CFR § 3.7 (c)

RFD Processing

- OCP consults with Centers and Office of Chief Counsel
- Written response
- FDA 60-day clock
- Or sponsor's recommendation takes effect

RFD Processing continued

- Designation in RFD letter may be changed without the consent of sponsor only to protect the public health or for another compelling reason.

- 21 CFR § 3.9(b)

RFD Processing continued

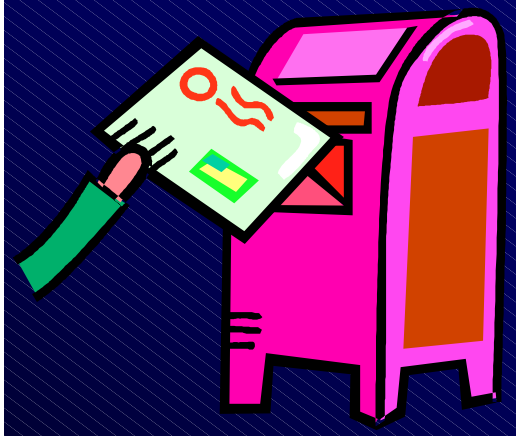
Request for Reconsideration

- Submit within 15 days
- Less than 5-page submission
- FDA response within 15 days

FDA does change decisions upon reconsideration

21 CFR § 3.8(c)

Contact Us



Office of Combination Products
15800 Crabbs Branch Way
(HFG-3)
Rockville, MD 20855

Director: Mark Kramer
Product Assignment Officer: Leigh Hayes
Product Classification Officer: Suzanne O'Shea

Contact Us

(301) 827-9229

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