Background on Regulation of Combination Products

Workshop on Innovative Administration Systems for Vaccines

December 18-19, 2003

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Overview

- What is/is not a Combination Product?
- Regulation of Combination Products
- Role of Office of Combination Products
- Assignment of Combination Products/PMOA
- Premarket Review of Combination Products
- Postmarket Regulation of Combination Products
- The Future

Combination Product

- Combination Product (21 CFR 3.2(e)):
  - 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 (e.g., drug and device products); or
  - 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 and where upon approval of the proposed product, the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.
  - (Similar to 3rd bullet but both products investigational)

Examples of Combination Products

- Device coated, impregnated or otherwise physically/chemically combined with a drug or biologic
  - Drug-eluting cardiovascular stent, antimicrobial or heparin-coated catheter, condom with spermicidal coating, pacing lead with steroid-coated tip
  - Skin substitutes with cellular components, orthopedic implant with growth factors, biologically based sealants, glues and hemostatic agents
- Prefilled drug or biologic delivery device
  - Syringes, insulin/epinephrine/interferon injector pens, metered dose inhalers, transdermal patches

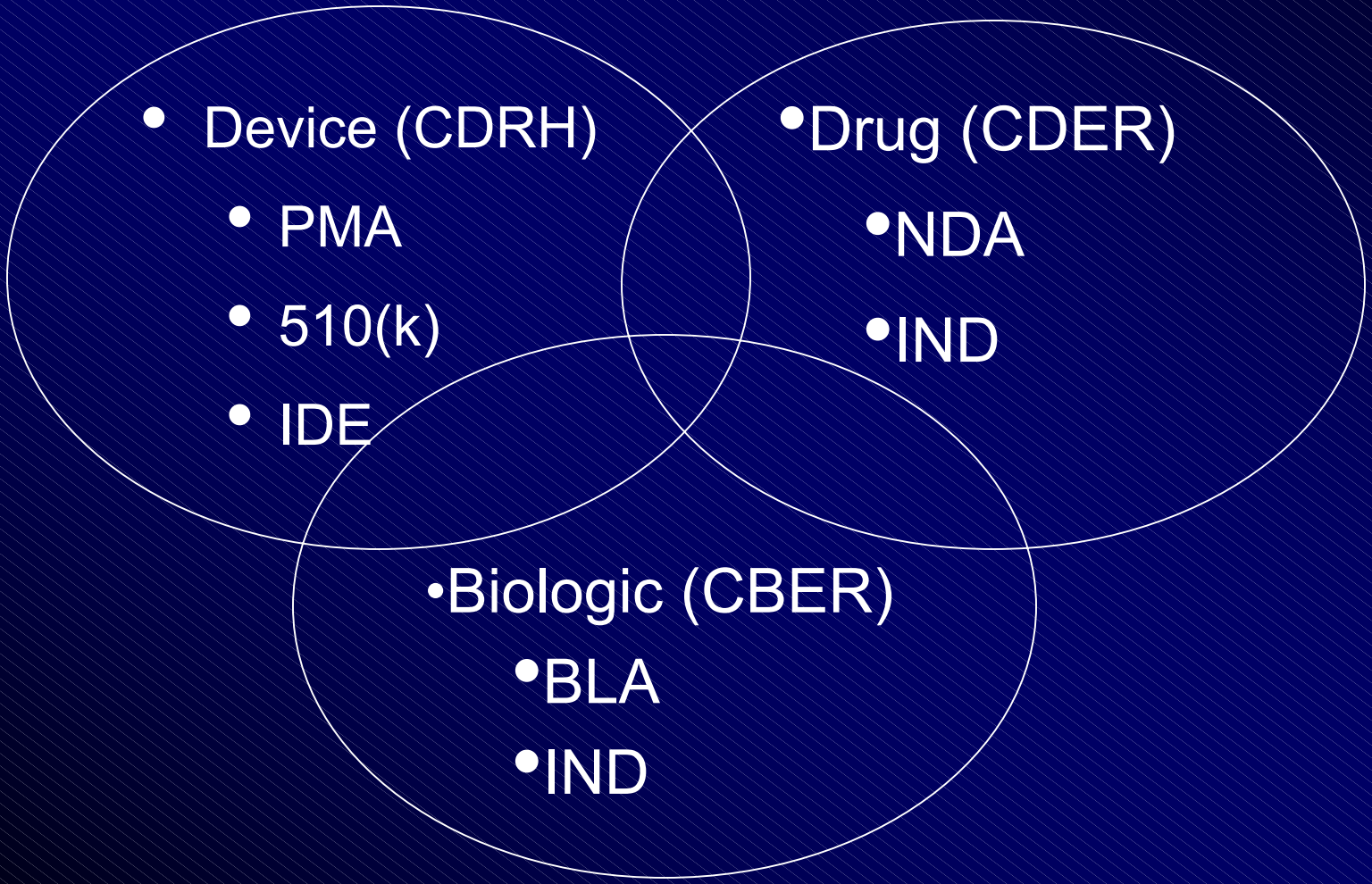
Examples of Combination Products

- Drug or biologic with applicator/delivery device
- Drug-biologic combinations
  - Radiopharmaceutical combined with biologic, monoclonal antibody combined with a chemotherapeutic drug, interferon/ribavirin
- Separate products that may constitute combination:
  - Hyperthermia device and chemotherapeutic drug, photodynamic therapy drug and laser/light source, diagnostic device requiring administration of a particular drug or biologic, drug requiring specific diagnostic device

Not Combination Products

- Drug-drug, device-device, or biologic-biologic combinations, such as:
  - Fixed combination drug products
  - Products comprised of two biologics, even if review responsibility shared between CDER and CBER
- Most concomitant use of drugs, devices and biologics
- General drug or biologic delivery devices (e.g., unfilled syringe or infusion pump) not intended for use with specified drug or biologic product

Regulatory Approaches



Regulation of Combination Products

- Assigned to lead Center based on "primary mode of action"
- Intercenter consultation/collaboration
- Premarket regulatory authorities
- One application vs. two
- Postmarket regulatory authorities

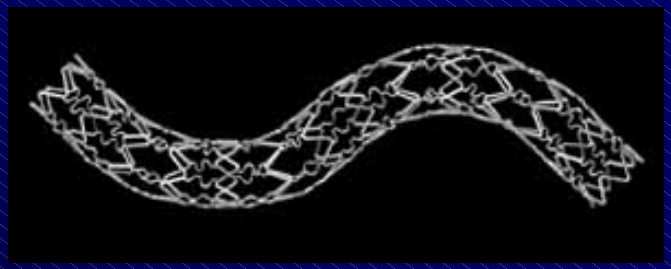
Office of Combination Products (Established December 24, 2002)

- Assignment of combination products
- Ensure timely and effective premarket review
- Consistent and appropriate postmarket regulation
- Dispute resolution (timeliness vs. substance)
- Review/update guidance, agreements, practices
- Reports to Congress

P. L. 107-250 -- enacted 10-26-02

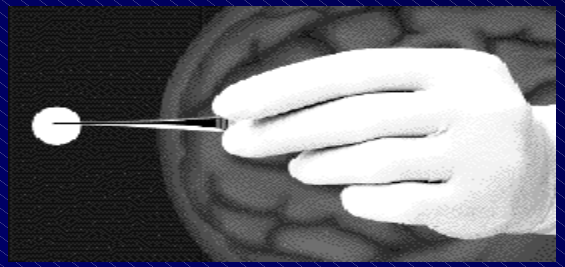
Primary Mode of Action

- Drug Eluting Stent



- Primary Mode of Action:
  - Stent opens artery
- Secondary Action:
  - Drug prevents inflammation and restenosis of artery
- Regulated as a Device (PMA)

- Drug Eluting Disk



- Primary Mode of Action:
  - Cancer chemotherapy for brain tumor
- Secondary Actions
  - Local drug delivery of drug by device
- Regulated as a Drug (NDA)

Assignment of Combination Products

- Statute:
  - Promptly assign an agency Center
- Goals:
  - Efficient Request for Designation (RFD) process
  - More consistent, predictable, and transparent process

OCP Assignments of Combination Products (12/24/02 – 9/30/03)

Requests for Assignment Submitted	Assignments Issued	% Issued within 60 days	Pending (not overdue)
15*	13	100%	1
Mean Total Review Time = 38.0 days Median Total Review Time = 40 days Range of Total Review Time = 18-47 days *Additional RFD Withdrawn = 1			
Assigned to CBER: 2 (1 drug-biologic, 1 device-biologic) Assigned to CDER: 3 (3 drug-device) Assigned to CDRH: 8 (8 drug-device)			

Assignment of Combination Products

- Initiatives:
  - Definition of Primary Mode of Action
  - Selection of premarket authorities
  - 1 application vs. 2
  - RFD Process and 21 CFR Part 3
  - RFD Documentation
  - Intercenter Agreements

Review of Combination Products

- Statute:
  - Ensure timely and effective premarket review by overseeing timeliness of and coordinating reviews involving more than one agency Center

Review of Combination Products

- SOP on Intercenter Consultation Process
  - www.fda.gov/oc/ombudsman/intercentersop.pdf
- Monitoring Intercenter Consultations
  - Active monitoring/facilitation
  - Web-enabled database
- Tracking and Reporting of Other Combinations
  - Categorization of premarket submissions
- Resource to sponsors and review staff
- Reviewer tools and training
- Submission Format and Content

Product Evaluation – General Considerations

- Elucidate primary mode of action (jurisdiction)
- Considerations:
  - Regulatory pathway and questions that need to be addressed for that pathway
  - Approaches normally taken by lead Center
  - “Additive” effect of the “new” component
- One size doesn’t fit all
- Review guidance documents
- Consult with FDA early – get both Centers at table

Postmarket Regulation

- Statute:
  - Ensure consistency and appropriateness
- Initiatives:
  - RFD Letters
  - GMP's
  - Adverse Event Reporting
  - Other Issues (e.g., registration and listing)

How Does the Future Look?

- Numbers and types of combination products will continue to grow
- Consultation process more systematized
- Clearer, more predictable process for assignment, premarket review and postmarket regulation

OCP Website: http://www.fda.gov/oc/combination/

FDA U.S. Food and Drug Administration — Department of Health and Human Services

FDA Home Page | Search FDA Site | A-Z Index | Contact FDA

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
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