PDA / FDA Joint
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Combination Products: A Multi-Center Challenge for FDA and Industry

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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
  - Resource to sponsors and review staff

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

Combination Product Regulatory challenges

- What is it?
- Where does it go?
- How is it regulated?
- How is it developed / reviewed?
- How is consistency, appropriateness, timeliness ensured?
- What if I don’t know or disagree?

Background

- What is and is not a Combination Product?

Background: Things that are not Combination Products

- Most concomitant use of drugs, devices and biologics
- Drug-drug, device-device, or biologic-biologic combinations; e.g.,
  - Products with two biologics, even if shared CDER and CBER role
- General devices intended for use with a class or otherwise unspecified drug /biologic products
  - Unfilled syringe or diagnostic test without specifying a particular drug

Background: Combination Products

- 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
  - provided separately but intended for use together where both are required to achieve the intended use, indication, or effect and where mutually conforming labeling is needed.

Examples of Combination Products

- Physically, chemically / otherwise single entity
  - Biologic monoclonal antibody with a therapeutic drug;
  - Device coated, impregnated with a drug or biologic
    - Drug-eluting stent, pacing lead steroid-coated tip
    - Skin substitutes w. cellular components, orthopedic implant w. growth factors
  - Prefilled drug or biologic product delivery device
    - Syringes, insulin injector pens, metered dose inhalers, transdermal patches

Examples of Combination Products, cont'd

- Co-packaged
  - Drug / biologic product packaged with a delivery device, or packaged with a diagnostic test

- Separately marketed, both are required and when mutually conforming labeling is needed
  - Photodynamic therapy drug and laser/light source,
  - Drug requiring specific device for administration
  - Diagnostic device required for use of a specific drug or biological product

Challenges

- Where does it go?
  - What center / organizational unit has the lead for premarket review and regulation?

Assignment of Combination Products

- Office of Combination Products:
  - Determines the product classification
  - Determines the primary mode of action
  - Identifies lead center
  - Identifies premarket regulatory pathway
  - Provides preliminary information on postmarket authorities

Assignment of Combination Products, cont'd

- Formal process for RFD submissions to OCP
  - Time frame (60 days)
  - Appeal process (15 days)
  - Decisions are binding

Assignment of Combination Products, cont'd

- PMOA: statutory criterion FDA must use to assign an agency component with primary jurisdiction for premarket review and regulation of a combination product.
  - PMOA is not currently defined in the Act or regulations.

Assignment of Combination Products, cont'd

- Intercenter agreements (1991) provide some information on primary mode of action (PMOA)

- **PMOA proposed rule, May 7, 2004**
  - www. fda.gov/OHRMS/DOCKETS/98fr/04-01447.pdf
  - Comment period closes August 20, 2004

PMOA Proposed Rule

- PMOA:

The single mode of action of a combination product that provides the most important therapeutic action of the combination product.

PMOA Proposed Rule, cont'd

- Mode of Action: the means by which a product achieves a therapeutic effect
  - Therapeutic: any effect / action intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body
- Three modes of action: biological product, device, drug
- Combination products: More than one constituent part → usually more than one mode of action

PMOA Assignment Algorithm: For the lead agency component

- PMOA = determinable → assign there; stop
- PMOA = uncertain →
  - Is there an agency component with CPs that raise similar S&E questions for CP as a whole?

    Yes, then → assign there; stop

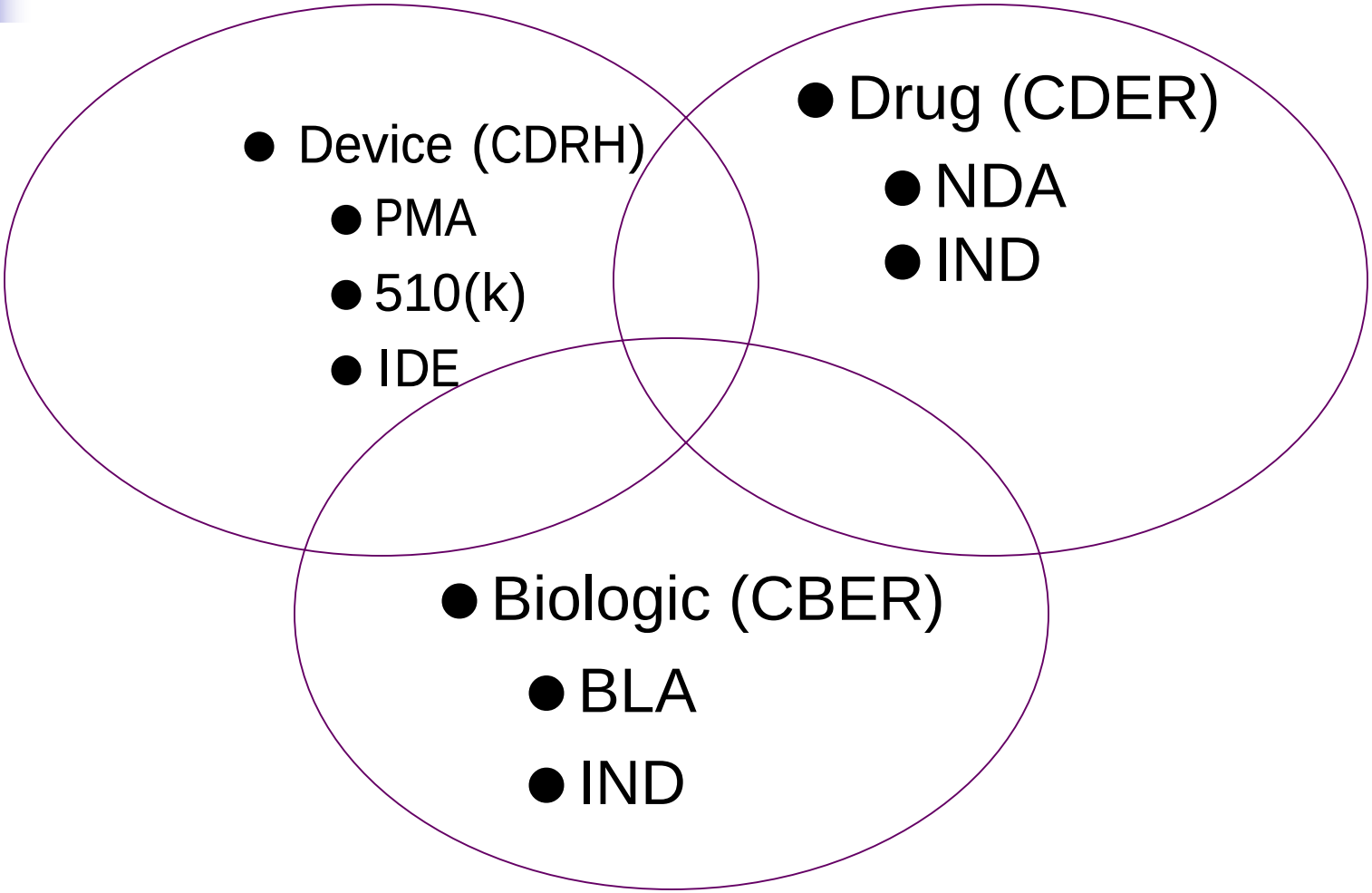
    No, then ...
  - Which agency component has the most expertise related to the most significant S&E questions for the CP?

    → Assign there

Challenge

- How is it regulated?

Regulatory Approaches



Challenge: How is it regulated?

- Number of marketing applications

Number of Marketing Applications

- Drafting guidance anticipates the following
  - One application will be sufficient for most combination products
    - Chemically, physically, or otherwise combined into a single entity; and most co-packages
  - Two applications may be
    - Required by FDA in some circumstances
    - Requested by industry and possibly accepted by FDA in some circumstances

Challenge: How is it regulated?

- Manufacturing controls

PMOA and Manufacturing Control Challenges

- PMOA can lead to like combination products in different lead centers (different marketing applications); e.g.,
  - Drug eluting stent
    - Device PMOA → CDRH (PMA / 510(k))
    - Drug PMOA → CDER (NDA)

Manufacturing Control Challenges

- Manufacturing control regulations are associated with the marketing application, inspection practices, premarket review requirements & practices, post approval changes, etc
  - QS regulations ... PMA, HDE, 510(k)
  - CGMP regulations ... NDA
  - Biologic product regulations ... BLA

Manufacturing Control Challenges, cont'd

- Historically, most manufacturing sites use either QS or CGMP (not both).
  - Both are appropriate to ensure the quality of the type of product for which they are customarily used, but they do so in different ways.
- Different compliance review and inspection processes / expectations may confound the inspection process.
  - CGMP / QS rarely discussed during product development;

Manufacturing Control Challenges, cont'd

- Recognize that there is some overlap in regulatory provisions (especially general vs. detailed requirements)
- Manufacturers do not want to maintain to separate systems
- But, need to ensure appropriate control of certain processes.

Draft Guidance: GMP/QS Combination Products

- Plan to identify how GMP / QS would be applied to the constituent parts & the combination product as a whole
  - Guidance will focus on information for combination products that are:
    - Chemically, physically, or otherwise combined into a single entity
    - Co-packaged

Draft Guidance: GMP/QS Combination Products, cont'd

- Communication = most important activity during combination product development
  - Manufacturers of constituent parts
  - FDA intercenter team
    - Product reviewers
    - GMP/QS experts
    - Field inspectors
    - OCP

Draft Guidance: GMP/QS Combination Products, cont'd

- Status:
  - Nearing completion

Challenge: How is it regulated?

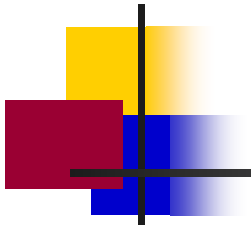
- Safety reporting requirements, postmarket

Safety Reporting: post market

- § 314.80, Adverse Drug Experience (ADE)
- § 600.80, Biological product adverse experience
- § 606.170, Blood component adverse experience
- § 600.81, Vaccine adverse events
- § 803, Medical Device Reporting (MDR)

Safety Reporting

- Centers maintain different safety reporting data bases
- Draft guidance on what and how to submit safety reports for combination products
  - Nearing completion



Challenge

- How reviewed?
- How ensure timely and effective reviews?

Intercenter Review Process

- Statute: OCP to ensure timely and effective premarket review by overseeing timeliness and by coordinating reviews involving more than one agency Center
  - Established Intercenter Consultation / Collaboration SOP (July, 2002; Revised February, 2003)
    - Consults count; same priority as assigned products
    - Team agreement on timing
    - www.fda.gov/oc/ombudsman/intercentersop.pdf

Combination Products Evolution of Processes

- Active monitoring/facilitation; web-enabled database
- Tracking and Reporting of Other Combinations
  - Categorization of premarket submissions
- Reviewer tools and training
- Resource to sponsors and review staff

Challenge

- What if I disagree or have a dispute?

Combination Product Dispute Resolution Guidance, draft

- Combination Products: Timeliness of Premarket Reviews Dispute Resolution Guidance, draft
  - (www.fda.gov/oc/combination/dispute.pdf)
  - Procedural/process for sending formal disputes to OCP
- OCP remains available to discuss (formally or informally) any combination product issues throughout development

Other OCP Initiatives

- Policy - Guidance Initiatives:
  - Definition of Primary Mode of Action, proposed rule
  - 1 vs. 2 marketing applications
  - Good manufacturing controls
  - Postmarket safety reporting
  - Dispute resolution, draft guidance
  - Format and content of marketing applications

What if I want to know more? Update of OCP Activities

- Progress Report to Stakeholders
  - http:www.fda.gov/oc/combination/default.html
- Annual Report to Congress
  - http://www.fda.gov/oc/combination/congressreport.html

What if I have a combination product?

- **Seek early collaboration / interaction**
- **Ask questions**
  - Involve all components
    - Device and drug/biologic product firms
    - Both centers and OCP
    - Meetings with FDA throughout developmental process
      - Include relevant industry firms and all FDA components

Contact Us – Office of Combination Products

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