Combination Products Overview: Primary Mode of Action and RFD Content

Regulatory Affairs Professionals Society
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Overview

- Role of Office of Combination Products
- Primary Mode of Action and Assignment Process
- RFD Content
- Other Considerations

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; or
  - 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)

Office of Combination Products (Established December 24, 2002)

- Resource for industry and agency reviewers
- 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

Assignment of Combination Products

- Primary mode of action (PMOA) is the statutory criterion FDA must use in assigning 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.
- Goals:
  - Simplify the designation process for sponsors
  - Enhance the consistency, predictability, and transparency of the assignment process
  - Further MDUFMA's requirement for prompt assignment of combination products, and to review/revise agreements, guidance and practices specific to the assignment of combination products

PMOA Proposed Rule: May 7, 2004 Federal Register

- "Mode of Action" would be defined as the means by which a product achieves a therapeutic effect
  - "Therapeutic" includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body
- Three types of modes of action: biological product, device, drug
- Combination products are comprised of more than one type of regulated article [or constituent part] and will typically have more than one identifiable mode of action (e.g., drug and device, device and biological product, etc.)

PMOA Proposed Rule: May 7, 2004 Federal Register -- continued

- A constituent part of a combination product has a:
  - Biological product MOA if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings…
  - Device MOA if it meets the definition of device…, it does does not have a biological product MOA, and it does not achieve its primary intended purposes through chemical action within or on the body….and is not dependent on being metabolized for the achievement of its primary intended purposes
  - Drug MOA if it meets the definition of drug…and it does not have a biological product or device MOA.

PMOA Proposed Rule: May 7, 2004 Federal Register -- 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 Proposed Rule: May 7, 2004 Federal Register -- continued

- If unable to determine the most important therapeutic action with reasonable certainty:
  - Examples: early in development (just don't know) -- or two important, independent modes of action, neither of which is subordinate to the other
  - Follow Assignment Algorithm:
    - 1st: CONSISTENCY: Assign to agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole.
    - That is, assign to the Center with *direct experience* in that type of combination product

PMOA Proposed Rule: May 7, 2004 Federal Register -- continued

- If there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as whole:
  - Examples: it is the first such combination product, or when differences in its intended use, design, formulation, etc. present different safety and effectiveness questions

- Continue with assignment algorithm:

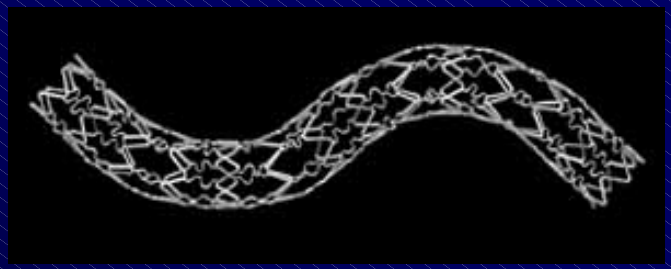
  - 2nd: SAFETY AND EFFECTIVENESS: Assign to agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product
    - That is, assign to Center with *most related experience* for that type of product

PMOA Proposed Rule: May 7, 2004 Federal Register -- continued

- Codifies criteria the agency has generally used since 1991
- Furthers MDUFMA requirements
- Framework based on an assessment of the combination product as a whole, its intended use and its effect, consistency with the assignment of similarly situated products, and safety and effectiveness issues – all of which stakeholders have been recommended as key factors to be considered
- Rule would affect RFD's submitted after effective date of any final rule based on this proposed rule
- Comment period through August 20, 2004

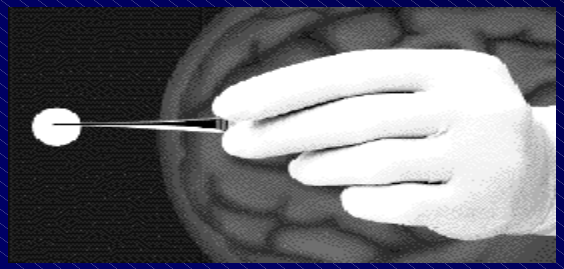
Primary Mode of Action – An Illustration

- 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
- Secondary Action
  - Local drug delivery by device
- Regulated as a Drug (NDA)

PMOA: Three Hypothetical Examples

- Vision-correcting contact lens with drug to make lens more “comfortable”
- Contact lens as drug delivery system
- Vision-correcting contact lens with concurrent delivery of glaucoma drug

PMOA Proposed Rule: Selected Stakeholder Comments

- Clarify roles of intended use, precedents, and intercenter agreements
- Clarify effect on existing products
- Provide more examples
- Post precedents on web
- Clarify some terms; issue companion guidance
- Clarify how PMOA affects regulatory authorities and need for 1 vs. 2 marketing applications

Request for Designation (RFD) - General Information

- Voluntary
- 21 CFR 3.7 has requirements -- ≤ 15 pages
- For both combination and non-combination products
  - Classification and Assignment
  - Primary Mode of Action (for combination products)
  - Clarification of Regulatory Pathway
- 60 day clock
- Email: combination@fda.gov

Who Should File an RFD?

- The sponsor of:
- (1) Any combination product the sponsor believes is not covered by an intercenter agreement; or
- (2) Any product where the agency component with primary jurisdiction is unclear or in dispute.

When Should an RFD be submitted?

- Before filing an application for premarket review (investigational or marketing application)
- As soon as there is sufficient information for the agency to make a determination

RFD Content

- Less than 15 pages, including attachments
- Sponsor information
- Product description, including:
  - Regulatory status of components and discussions between sponsors
  - Chemical, physical, or biological indications
  - Proposed Use and indications
  - Schedule and duration of use, dose and route of administration of drug or biologic

RFD Content-- continued

- Status and reports of the results of developmental work
- Description of the manufacturing process
- Description of all known modes of action, the sponsor's identification of the primary mode of action, and the basis for that determination
- Sponsor's recommendation as to which agency component should have primary jurisdiction, with accompanying

RFD Processing

- Email: combination@fda.gov
- 60-day Clock
- Request for Reconsideration
  - Submit within 15 days
  - Less than 5 page submission
  - FDA response within 15 days

OCP Assignments of Combination Products (10/1/03 through 8/31/04)

Requests for Assignment Submitted	Assignments Issued	% Issued within 60 days	Pending (not overdue)
27*	26*	100%	1

Mean Total Review Time = 38.3 days
Median Total Review Time = 35 days
Range of Total Review Time = 18-59 days

Assigned to CBER: 3 (2 dev/biol, 1 drug/dev/biol)
Assigned to CDER: 6 (5 drug-device, 1 dev/biol)
Assigned to CDRH: 17 (15 drug-device, 2 dev/biol)

*does not include requests for reconsideration nor RFDs not filed or withdrawn

OCP Classification Decisions (Non-Combination Products (10/1/03 -- 8/31/04)

Requests for Classification Submitted	Classifications Issued	% Issued within 60 days	Pending (not overdue)
19*	13*	100%	6
Mean Total Review Time = 46.2 days Median Total Review Time = 48.0 days Range of Total Review Time = 31-59 days			
Assigned to CBER: 2 (1 device, 1 biologic) Assigned to CDER: 2 (2 drug) Assigned to CDRH: 9 (9 device) *does not include requests for reconsideration nor RFDs not filed or withdrawn			

Resources

- Intercenter Agreements
  - CDER—CDRH
  - CDER—CBER
  - CBER—CDRH
  - Jurisdictional Updates

Review of Combination Products

- Resource to sponsors and review staff
- SOP on Intercenter Consultation Process
  - **www.fda.gov/oc/ombudsman/intercentersop.pdf**
- Monitoring Intercenter Consultations
- Tracking and Reporting of Other Combinations
  - Categorization of premarket submissions
- Reviewer tools and training
- Submission Format and Content
- Resolution of Disputes Regarding Timeliness of Review
  - **http://www.fda.gov/oc/combination/dispute.pdf**

Postmarket Regulation

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

General Considerations

- Combination products regulated as devices are not devices; those regulated as drugs are not drugs
- One size doesn't fit all
- Regulatory pathway and questions that need to be addressed for that pathway
- "Additive" effect of the "new" component
- Review guidance documents and approval documentation for other combination products
- Consult with FDA; get both Centers at the table

In Progress

- Primary Mode of Action
- Transparency of Jurisdictional Process
- GMP/QSR
- Adverse Event Reporting
- 1 vs. 2 Applications
- Submission Format & Content
- Cross Labeling
- …and more

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
- Continued opportunities for stakeholder input

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

Office of Combination Products: Annual Report to Congress
PDF (251KB)
HTML

Quarterly Progress Reports to Stakeholders

NEW! FY04 OCP Review Performance: Formal Requests for Designation Submitted by Industry

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

Instructions for Submitting a Request for Designation (RFD)

June 23, 2003 Final Rule

Intercenter Agreements

NEW! Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research

Jurisdictional Updates

- **NEW!** Jurisdictional Update: Drug-Biologic Combination Products
- Human Demineralized Bone Matrix
- Drug-Eluting Cardiovascular Stents
- Dental Prophylaxis Pastes with Drug

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

NEW! Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges: Summary of July 8, 2003 FDA Workshop

Regulation of Combination Products: FDA Employee Perspectives
PDF [74KB] [HTML]

Selected Guidance Documents Applicable to Combination Products.

Review of Combination Products

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

NEW! Draft Guidance for Industry: Combination Products, Timeliness of Premarket Reviews: Dispute Resolution Guidance [PDF]

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:

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Contact Us:
Agency Jurisdictional Experts

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301-427-1934

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CDER:	Warren Rumble	301-594-5480
CDRH:	Gene Berk	301-594-1190

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