



Regulation of Combination Products

NE-PDA Workshop on Development and
Commercialization of Combination Products

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Overview

- Role of Office of Combination Products
- Primary Mode of Action and Assignment Process
- Premarket Review of Combination Products
- Postmarket Regulation of Combination Products
- The Future

Combination Products Are Diverse

- Combinations of different types of regulated products (21 CFR 3.2(e))
 - Drug-device
 - Device-biologic
 - Drug-biologic
 - Drug-device-biologic
- Physically/chemically combined
- Co-package or kit
- Separate cross labeled products

Regulatory Approaches

Biologics

- BLA/IND
- GMP+
- AERS+

Primary Mode of Action
Consultation
Regulations

Drugs

- NDA/IND
- cGMP
- AERS

Devices

- PMA/510(k)/IDE
- QSR
- MDR

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
- Report to Congress

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 consistency, predictability, and transparency
 - 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

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

Resources

- Intercenter Agreements
 - CDER-CDRH; CBER-CDER; CBER-CDRH
 - <http://www.fda.gov/oc/combination/intercenter.html>

- Jurisdictional Updates
 - Recently expanded with ~70 jurisdictional determinations
 - <http://www.fda.gov/oc/combination/updates.html>

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 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

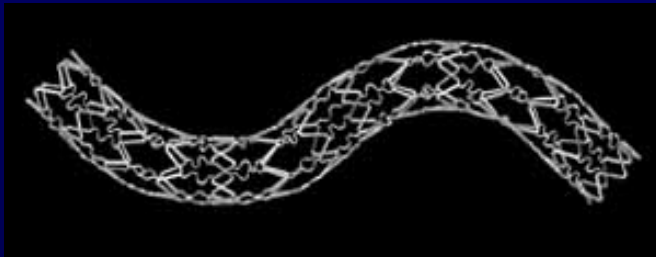
PMOA Proposed Rule:

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

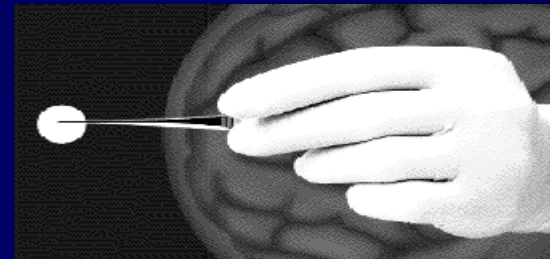
Primary Mode of Action – An Illustration

○ 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 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

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
<p>Mean Total Review Time = 38.3 days Median Total Review Time = 35 days Range of Total Review Time = 18-59 days</p>			
<p>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)</p>			
<p>* does not include requests for reconsideration nor RFDs not filed or withdrawn</p>			

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
<p>Mean Total Review Time = 46.2 days Median Total Review Time = 48.0 days Range of Total Review Time = 31-59 days</p>			
<p>Assigned to CBER: 2 (1 device, 1 biologic) Assigned to CDER: 2 (2 drug) Assigned to CDRH: 9 (9 device)</p>			
<p>* does not include requests for reconsideration nor RFDs not filed or withdrawn</p>			

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

- Developed SOP for intercenter consultation process
- Establish regulatory pathways for difficult products
- Establish and facilitate intercenter working groups
- Monitor the consultation process for combination products
- Monitor combination product review timeliness
- Advise sponsors and review staff
- Provide training and reviewer tools
- Published dispute resolution guidance
- Implemented categorization of all premarket submissions

Intercenter Consultation Requests 10/01/03 through 8/31/04

		Consulting Center		
		CBER	CDER	CDRH
Primary Assigned Center	CBER	---	3	13
	CDER	2	---	55
	CDRH	7	106	---

Dispute Resolution Guidance

- Resolution of Disputes Regarding Timeliness of Premarket Review of Combination Products <http://www.fda.gov/oc/combination/dispute.pdf>
- “Any dispute regarding the timeliness of the premarket review of a combination product may be presented to OCP for resolution, unless the timeliness of the dispute is clearly premature”
- OCP’s goal is to develop and implement policies and processes to streamline the regulation of combination products, and to ensure timely and effective premarket review
- The guidance provides procedural/process information affecting a narrow range of inquiries presented to OCP, i.e., “missed due dates” where sponsor wishes to submit formal request for timeliness dispute resolution
- OCP remains available, formally or informally, to sponsors regarding combination product issues throughout product development

Application User Fees for Combination Products – Open for Comment

- Single marketing application: fee associated with that type of application
- Sponsor chooses to submit two marketing applications when one would suffice: fee for each application (waivers/reductions possible)
- FDA requires two marketing applications: fees for each application (waivers/reductions possible)
- For innovative combination products where two applications are required: use of PDUFA barrier to innovation waiver to reduce additional fee burden associated with FDA's requirement for two marketing applications. Guidance provides factors FDA would consider.
 - MDUFMA and PDUFA applications: reduce PDUFA fee by amount of MDUFMA fee
 - Two PDUFA applications: reduce each PDUFA fee by half
- <http://www.fda.gov/oc/combination/default.htm>

Postmarket Regulation

- Statute:
 - Ensure consistency and appropriateness
- Examples:
 - Identify appropriate regulatory mechanisms
 - Coordinate Centers and field
 - Establish and facilitate intercenter working groups
 - Draft guidance (GMP's, adverse event reporting)

Current Good Manufacturing Practices for Combination Products -- Open for Comment

- CGMP and QS regulations are similar but each is tailored to the types of products for which they were designed. Manufacturers: parallel GMP operating systems are unnecessary.
- Prior to combination, each constituent part of a combination product is subject only to its governing GMP regulations. During and after combination (21 CFR 3.2(e)(1) or (e)(2)), both regulations apply.
- Compliance with both regulations can generally be achieved by using either regulation (e.g., by using the system in place at a facility)
- Guidance includes key provisions to consider in ensuring compliance with both regulations; others should be considered depending on product
 - If under CGMP: design controls, purchasing controls, CAPA
 - If under QSR: calculation of yield; expiration dating; stability testing; testing and approval/rejection of components, drug product containers and closures; testing and release for distribution; special testing requirements; reserve samples
- <http://www.fda.gov/oc/combination/default.htm>

General Considerations

- One size doesn't fit all
- Regulatory pathway and questions that need to be addressed for that pathway
- “Additive” effect of the “new” component
- Don't forget about GMP's
- Review guidance documents and approval documentation for other combination products
- Consult with FDA; get both Centers at table


What's Still Left to be Done: A Lot

- Publish and finalize remaining guidance/regulations
- Continued outreach and training
- Address “2nd tier” issues, such as
 - Post-approval changes
 - Labeling format
 - Registration & Listing
 - Promotion & Advertising
 - ...and more
- Evaluate impact of new policies and need for revisions
- Continued stakeholder input
- ...and more

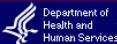
How Does the Future Look?

- 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 at meetings like this

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



U.S. Food and Drug Administration



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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 Resin/Resin Restorations 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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