FDA's Office of Combination Products: A Progress Report

Society for Biomaterials: Biomaterials in Regenerative Medicine: The Advent of Combination Products

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Overview

- Combination Products are Diverse
- Role of Office of Combination Products
- What We've Done
- What We're Doing
- What's Left to Do
- Additional Slides for Reference

Combination Products Are Diverse

- 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

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

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

What We've Done

- Surveyed agency reviewers and industry to identify key combination product issues to be addressed
- Worked within existing statutory provisions
- Improved Assignment Process:
  - Published proposed rule on primary mode of action
  - Issued 100% of our formal assignment decisions on time
  - Provided more guidance in assignment letters
  - Provided informal jurisdictional guidance on wide variety of products
  - Improved internal assignment process and documentation
  - Published ~70 jurisdictional determinations to make jurisdictional process more transparent

Assignment of Combination Products

- Based on a determination of the primary mode of action (PMOA) of the combination product
- PMOA is not currently defined in the Act or regulations.
- Proposed Rule published May 7, 2004. Goals:
  - Simplify the designation process for sponsors
  - Enhance the consistency, predictability, and transparency of the assignment process

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

What We've Done -- continued

- Facilitated the premarket review process
  - Developed SOP for intercenter consultation process
  - Established regulatory pathways for difficult products
  - Established and facilitated intercenter working groups
  - Monitored the consultation process for combination products
  - Monitored combination product review timeliness
  - Advised sponsors and review staff

What We've Done -- continued

- Facilitated the premarket review process (continued)
  - Published dispute resolution guidance (regarding review timeliness)
  - Published user fee guidance (mechanism to reduce fees for innovative combination products for which two marketing applications are required)
  - Provided training and reviewer tools
  - 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	---

What We've Done -- continued

- Ensured "consistent and appropriate" postmarket review
  - Identified appropriate regulatory mechanisms
  - Coordinated Centers and Field Offices
  - Established and facilitated intercenter working groups
  - Drafted guidance
- Outreach
  - Internally
  - Industry

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

What We're Doing

- All of the preceding
- Developing additional guidance:
  - Adverse Event Reporting
  - 1 vs. 2 Applications
  - Cross labeling
  - Submission format/content
- Developing additional training
- Implementing automated consultation tracking system
- …and more

What's Still Left to be Done: A Lot

- Publish and finalize preceding 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 or legislative fixes
- Continued stakeholder input
- …and more

General Considerations

- Combinations regulated as devices are not devices
- One size doesn't fit all
- "Additive" effect of the "new" component
- Review guidance documents and approval documentation for other combination products
- Discuss GMP issues with FDA early on
- Consult with FDA; get both Centers at the table

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

Additional Reference Slides

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)

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, antibiotic bone cement, 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, nasal flu vaccine

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

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

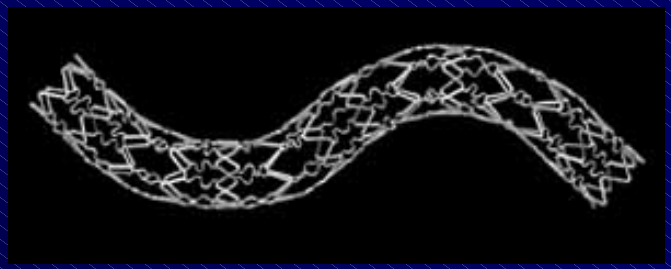
- A constituent part of a combination product has a:
  - Biological product MOA if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings…
  - Device MOA if it meets the definition of device…, it does 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

- Codifies criteria the agency has generally used since 1991
- 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 recommended as key factors to be considered
- Comment period closed August 20, 2004

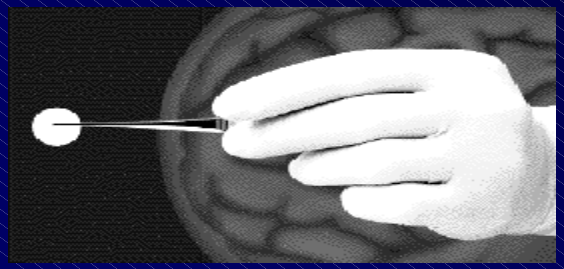
Primary Mode of Action – An Illustration

- 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 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

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

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

Prevalence of Combination Products – A Snapshot (4/1/03 – 7/31/03)

	Combination Product Category									
Application Type	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTALS**
Original NDA		2								**2**
Original BLA			2							**2**
Original PMA										**0**
510(k)				1			2		1	**4**
Original IND	2	6	5		3	4	4	4	4	**32**
Original IDE	1		1	1	3	0	2		1	**9**
Original HDE										**0**
TOTALS	**3**	**8**	**8**	**2**	**6**	**4**	**8**	**4**	**6**	**49**

KEY:
1= convenience kit or co-package
2= prefilled drug delivery device/system
3= prefilled biologic delivery device/system
4= device coated/impregnated/otherwise combined with drug
5= device coated or otherwise combined with biologic
6= drug/biologic combination
7= separate products requiring mutually conforming labeling
8= possible combination based on mutually conforming labeling of separate products
9= other type of combination product

4/1 - 7/31/03

Product Review – Preliminary Performance (4/1/03 – 7/31/03)

			COMBINATION PRODUCTS			
APPLICATION TYPE			**Applications Received (#)[1]**	**Application Reviews Completed (#)**	**Review Time (Days)**	**Reviewed On Time (%)**
Original NDAs	Priority		0	---	---	---
	Standard		2	0	---	---
Original BLAs	Priority		0	---	---	---
	Standard		2	0	---	---
Original PMAs	Regular		0	---	---	---
	Expedited		0	---	---	---
510(k)s	Traditional	90 days	3	3	34, 39, 90	100%[2]
	Special	30 days	1	1	45	100%[2]
	Abbreviated	90 days	0	0	---	---
TOTALS			**8**	**4**		**100%**

[1] The cut-off date for data collection was July 31, 2003. The number of original PMA and 510(k) applications received during this period may change due to CDRH's practice of tracking/reporting at application close-out.

[2] Considers whether FDA review time remained within 90 days (30 days for Special 510(k)s), with FDA's review clock being reset to zero whenever additional information is received in accordance with 21 CFR 807.87(l).

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

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

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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 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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