Product Classification, Jurisdiction, Combination Products, and In Vitro Diagnostics Issues

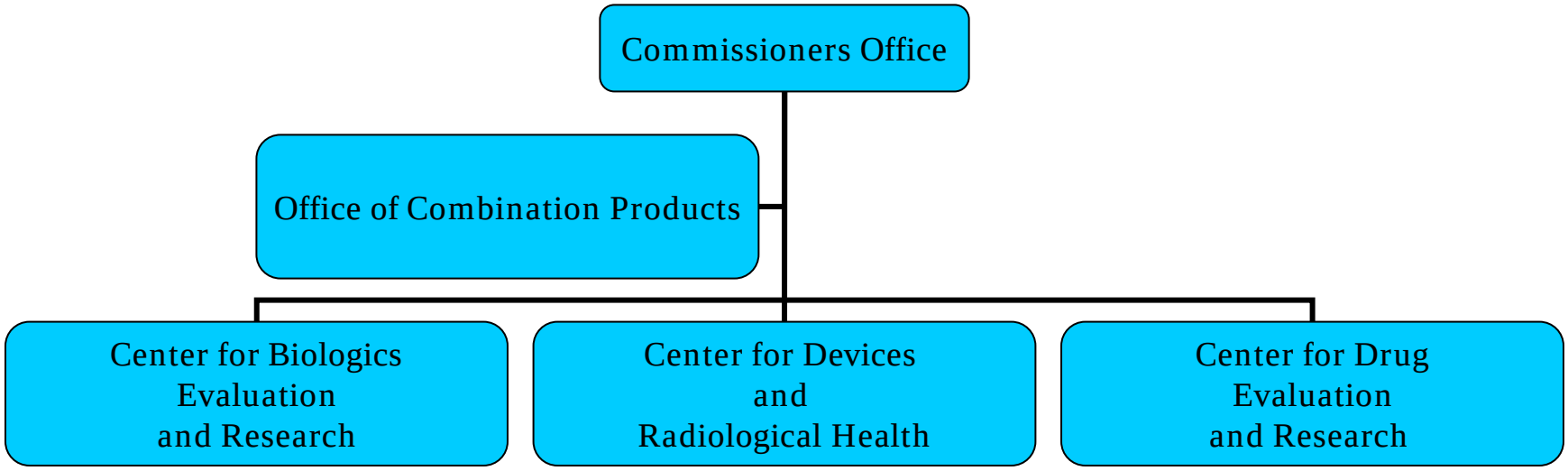
Joseph Milone, Ph.D.
Biologist
Office of Combination Products (OCP)

Medical Device Manufacturers Association
510(k)/OIVD Workshop
April 25, 2011

Presentation outline

- About OCP
- Product Classification and Jurisdiction
- Assignment Process
- Intercenter Combination product review
- In vitro diagnostics (IVD) combination products
- Contact information

Where is OCP?


Commissioners Office
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Center for Drug Evaluation and Research

Who's in OCP?

Currently, we are a staff of 9:

1 Engineer/Director: Thinh Nguyen

2 Physicians: Patricia Love and Lana Shiu

3 Scientists: Kristi Lauritsen, Michael Berman, and Joe Milone

2 Attorneys: Barr Weiner and Leigh Hayes

1 Administrative Assistant: Bibi Jakrali

OCP's Roles:

- Make product classification and jurisdictional determinations
- Oversee / help coordinate premarket review
- Ensure consistent / appropriate postmarket regulation
- Develop policy, guidance, and regulations
- Serve as a resource for industry and review staff
- Resolve timeliness disputes
- Report to Congress annually

Product Classification and Jurisdiction

What Type of Product Do I Have?

OCP will classify a product based on the definitions of drug, device, and combination product as stated in the Food and Drug Cosmetic Act and the definition of a biological product as stated in the Public Health Service Act

Definition of a Drug

- The term "drug" means:

  (A) articles recognized in the US Pharmacopoeia, Homeopathic Pharmacopoeia, or National Formulary;

  (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;

  (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals.

Definition of a Device

Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -

(1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, **and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.**

Definition of a Biological Product

- Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings

PHS Act § 351(i); 42 U.S.C. § 262(i)

To Summarize:

- The drug definition is the broadest
- The drug and device definitions address:
  - What a product is intended to do
  - How a product works (device cannot achieve its primary intended purposes through chemical action or by being metabolized)
- The biological product definition is based on what a product is
- Based on such considerations we determine the classification of a product

Where Does My Product Get Reviewed?

- For products that are comprised of a single type of product the answer is easy – the product is reviewed in the Center that has responsibility for the type of product
  - CDER for drugs (also some biologics)
  - CBER for biologics (also some devices and drugs)
  - CDRH for devices
- Where do products comprised of more then one type of product (combination products) go?

Definition of Combination Product

- The Secretary shall in accordance with this subsection assign an agency center to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of—
- (A) a drug (other than a biological product), the agency center charged with premarket review of drugs shall have primary jurisdiction,
- (B) a device, the agency center charged with premarket review of devices shall have primary jurisdiction, or
- (C) a biological product, the agency center charged with premarket review of biological products shall have primary jurisdiction.

21 U.S.C. 353

What is a Combination Product?

- Combinations of different types of products:
  - Drug-device
  - Device-biologic
  - Drug-biologic
  - Drug-device-biologic
  - Not drug-drug, device-device or biologic-biologic combinations
  - Not a food or cosmetic

- They can be:
  - Physically or chemically combined
  - Co-packaged in a kit
  - Separate, cross-labeled products
  - Defined in 21 CFR 3.2(e)

Examples of Combination Products

- Drug-eluting coronary stent
- Prefilled drug/biologic delivery system
- Metered dose inhalers
- Drug/biological product packaged with a delivery device
- Photosensitizing drug and activating light source

I Am a Combination Product

Primary Mode of Action

Primary mode of action is the statutory criterion FDA must use to determine the agency component with primary jurisdiction for the review and regulation of a combination product.

21 U.S.C.§ 503(g)

PMOA Continued

- PMOA not defined in statute, now defined in regulations:
  21 CFR 3.2(k) and (m).

- Final Rule issued on August 25, 2005 and can be accessed at:
  http://edocket.access.gpo.gov/2005/pdf/05-16527.pdf

Primary Mode of Action

Primary mode of action is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

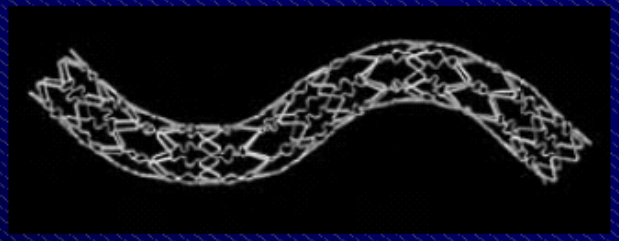
21 CFR 3.2(m)

PMOA Algorithm

- If unable to determine most important therapeutic action with reasonable certainty, consider:
- Consistency: is there an agency component that regulates other combination products presenting similar questions of safety & efficacy with regard to the combination product as a whole?
- Safety and Effectiveness: which agency component has the most expertise related to most significant safety & efficacy questions presented by the combination product?

PMOA
CDER or CDRH?

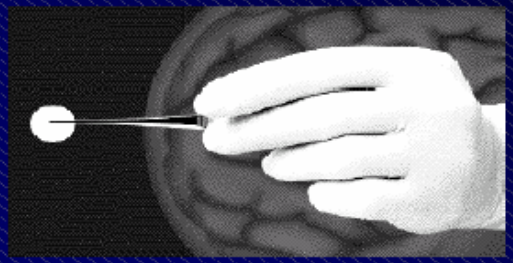
Drug Eluting Stent



- Primary Mode of Action:
  - Stent opens artery
- Secondary Action:
  - Drug prevents inflammation and restenosis of artery

- Regulated by CDRH under device provisions

Drug Eluting Disk



- Primary Mode of Action:
  - Cancer chemotherapy for brain tumor
- Secondary Actions
  - Local drug delivery of drug by device

- Regulated by CDER under drug provision

Assignment Process

How Does a Sponsor Get a Classification/Jurisdiction Assignment?

- Two main processes
  - Formal Request for Designation route
  - Informal guidance route
- Contact OCP first for advice on which route is appropriate for your product

Request for Designation (RFD)

- Voluntary formal process
- 21 CFR Part 3
- Classification (What am I?)
- Assignment (Where do I go?)
- Clarification of regulatory pathway (What do I do when I get there?)

Review Timelines and Jurisdictional Decisions

FDA may stay the review clock while a determination is being made.

21 CFR 3.10

RFD Content

- Sponsor information
- Product description
- Proposed use and indications
- Description of PMOA
- Recommendation of product classification and the center with primary jurisdiction
- Also see guidance document on how to write a RFD (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm)

RFD Processing

- OCP reviews RFD's for completeness (within 5 business days of receipt)
- If complete, OCP sends acknowledgement letter to sponsor, and copy of RFD's to three Center Liaisons
- Center recommendations due to OCP in 21 days
- Consultation among OCP, Centers, and Office of General Counsel as appropriate
- Decision reached, response letter prepared, necessary clearances obtained, letter issued by day 60
- Decision is binding

What If I Disagree With an RFD Decision?

Request for Reconsideration:

- Submit within 15 days
- Less than 5 page submission, no new information
- FDA response within 15 days

21 CFR 3.8(c)

Intercenter Combination Product Review

Intercenter Review Process

- Standard operating procedures and policies for intercenter review
  - Provides review framework and process
  - Defines responsibilities and roles of consulting and reviewing centers
  - Available at the following link: http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm119234.htm

- Two types of intercenter consults
  - Collaborative
  - Consultative

Consultation

- A reviewer in one center requests advice from a reviewer in another center
- The review will be used to assist the lead center in making appropriate regulatory and/or scientific decisions
- Final decision rests with lead center

Collaboration

- A review activity in which reviewers in two or more centers have primary review responsibilities, generally for a defined portion of a submission
- Regulatory and scientific decisions will be made by each center for that portion of the review assigned to it, including the decision to approve or disapprove the product

IVDs as combination products

Most IVD products are not combination products

Component 1	Component 2	Intended Use	PMOA	Lead	Consult
MICROPLATE READER AND AUTOMATIC WASHER	ANTINUCLEAR ANTIGEN, ANTI-HUMAN IgG CONJUGATE, TBM ENZYME SUBSTRATE	DIAGNOSIS OF AUTOIMMUNE DISEASE	N/A	CDRH	N/A
MULTIPLEX BEAD SUSPENSION	AFFINITY PURIFIED HUMAN IgG , POLYCLONAL GOAT IgM ANTIBODY	RHEUMATOID FACTOR	N/A	CDRH	N/A

IVDs as combination products

- In vitro diagnostics by themselves are not combination products
- In vitro diagnostics can become a combination product when combined with a drug or biologic
- Most common types of IVD combination products are convenience kits, co-packaged products, and separate products requiring cross labeling.

Two specific examples of IVD combination products

- IVD requiring administration of a particular drug (device primary)
  - Breath tests requiring ingestion of a labeled drug
  - Jurisdictional update for breath test combination products
    - http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103134.htm
- Drug requiring use of a specific diagnostic device (drug primary)
  - Specific pharmacogenomic test used to identify candidates for therapy or to modify drug dosing

Issues impacting IVD combination products

What happens when a diagnostic test is used to determine treatment of a drug?

- Often involves separate manufacturers and different products
- May require co-development
- May require co-labeling

Final Guidance - New Contrast Imaging Indications for Devices and Approved Drug and Biological products

- Labeling needs to be consistent.
- New indications likely require labeling changes for both device and companion drug or biological products (and vise versa)
- Labeling likely would not need to change for uses that are covered by the existing labeling
- Guidance also discusses:
  - The number of submissions
  - Type of submissions
  - Type of data that would be needed for approval

Final Guidance - New Contrast Imaging Indications for Devices and Approved Drug and Biological products

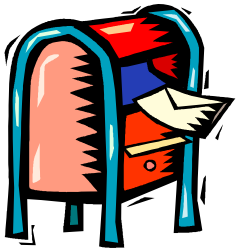
- Guidance available at the following link:
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM195951.pdf

How to find out...

- The final rule on PMOA
- Proposed rules for postmarket safety reporting and current good manufacturing requirements
- Information about RFD process, jurisdiction and classification
- Examples of recently approved combination products
- Combination product guidance documents
- See our website: http://www.fda.gov/CombinationProducts/default.htm/

Perhaps the easiest way to find out...Contact Us!

New



- Office of Combination Products
  WO32, Hub/Mail Room #5129
  10903 New Hampshire Avenue
  Silver Spring, MD 20993

New

- 301-796-8930

- combination@fda.gov