Combination Products

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Office of Combination Products (OCP)
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Overview

- Background
- Classification / Assignment of Products
- Development considerations for combination products
- Update on current efforts
Background

- Mandated by the Medical Device User Fee and Modernization of 2002 (MDUFMA)
- Office established December 24, 2002

- Office of the Commissioner, Office of Special Medical Programs (OSMP)
Currently, we are a staff of 8:

- Thinh X. Nguyen - Director
- Patricia Y. Love, MD., MBA. - Deputy Director
- John (Barr) Weiner, J.D. - Associate Director for Policy
- Leigh Hayes, J.D. – Senior Counsel, Product Jurisdiction Program
- Kristina J. Lauritsen, Ph.D. - Scientific Reviewer
- Joseph Milone, Ph.D. - Scientific Reviewer
- Michael Berman, Ph.D. - Scientific Reviewer
- Bibi K. Jakrali - Management Analyst
OCP’s Role

• What is it?

• Where does it go?

• What do you do when it gets there?
What is it?
What is it?

Classification

• Drug
• Device
• Biological Product
• Combination Product
Classification – Drug and Biologic

- **Drug**: articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles intended to affect the structure or any function of the body of man or other animals (FDCA, 201(g))

- **Biological product**: a 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. (PHSA, 351(a))
Classification - Device

- **Device**: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is 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 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 (FDCA, 201(h))
Classification – Combination Product

• Combinations of 2 or more DIFFERENT products:
  – Drug + Device
  – Device + Biologic
  – Drug + Biologic
  – Drug + Device + Biologic

• How are they combined? (21 CFR 3.2(e))
  – Physically or chemically into a single entity
  – Co-packaged / Kit
  – Sold separately and labeled for use together
Combination Product Examples

- Bandage with antimicrobial coating
- Bandage packaged with tube of antibiotic ointment
- Pre-filled delivery device, e.g., syringe or inhaler that contains drug or biologic (EpiPen, Advair)
- Antimicrobial coated catheter
- Drug-eluting stent (Taxus, Xience)
- Antibody-drug conjugates (Mylotarg)
- Light source and photo-activated drug (Photofrin)
NOT combination products:

- Drug-Drug
- Device-Device
- Biologic-Biologic
- Food + Drug/Device/Biologic
- Cosmetic + Drug/Device/Biologic
Where does it go?
Where does it go?

Assignment / Jurisdiction

• Drug - CDER
• Device - CDRH
• Biological Product – CBER or CDER
• Combination Product - ???
Assignment / Jurisdiction

• Non-combinations are assigned based on classification
  – Exceptions:
    • Devices that create a biologic at the point of care (devices regulated by CBER)
    • Therapeutic proteins, antibodies (biological products regulated by CDER)

• Combination products are assigned based on the primary mode of action (PMOA)

(FDCA, Section 503(g))
Assignment / Jurisdiction

• Mode of Action (MOA) – “the means by which a product achieves its intended therapeutic effect or action” – drug, device, biologic definitions (21 CFR 3.2(k))

• PMOA – “the single mode of action of a combination product that provides the most important therapeutic action … The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…” (21 CFR 3.2(m))
Assignment / Jurisdiction

- PMOA = device = CDRH
- PMOA = drug = CDER
- PMOA = biologic = CBER (or CDER)
Assignment / Jurisdiction

• PMOA may be difficult to identify
  – Early development (just don’t know)
  – Two (or more) completely different modes of action, and neither is subordinate to the other
Assignment Algorithm

• If unable to determine the PMOA with reasonable certainty, then consider...

• FIRST: Consistency (Tier 1)
  – Assign the product to the Center that regulates other combination products that present similar questions of safety and effectiveness

• SECOND: Safety and Effectiveness (Tier 2)
  – When FIRST does not apply, assign the product to the Center with the most expertise related to the most significant safety and effectiveness questions

(21 CFR 3.4)
PMOA Examples

Drug Eluting Stent
- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Assigned to CDRH

Drug Eluting Disk
- PMOA – chemotherapy for brain tumor (drug)
- Secondary MOA – local delivery of drug by the device
- Assigned to CDER
Algorithm Assignment example

• Contact lens coated with glaucoma drug – CDER
  – MOA: Lens corrects vision
  – MOA: Drug treats glaucoma
  – Device and drug have independent modes of action – Algorithm:
    • First of its kind product: Tier 2 = CDER
      – In this hypothetical example, the most significant safety and effectiveness questions are related to the characterization, manufacturing, and clinical performance of the drug component, while the safety and effectiveness questions raised by the vision-correcting contact lens are considered more routine.
    • Other products like this: Tier 1 = CDER
How do you know?

Classification or Assignment / Jurisdiction

• Submit a Request for Designation (RFD)
  – Formal, binding determination
  – Complex issues or dispute / uncertainty
  – Requirements in 21 CFR 3.7

• Email: combination@fda.gov
  – Informal, non-binding
  – Simple issues, uncertainty, process concerns
  – Determine whether an RFD is needed
RFD process

- 15 page limit
- Complete product description
- Amount and purpose of ingredients/components
- All MOAs and which is the PMOA
  - How it works (mechanism), not just what it does
  - Rationale – supported by data, reference to literature
- Recommendation
  - Classification - what it is (drug, device, biologic, combination product)
  - Assignment - where it goes (CDER, CBER, CDRH)
- 60 days

21 CFR 3.7
When to submit an RFD or informal inquiry?

Submit an RFD or informal inquiry BEFORE any submission (preIDE/IND, marketing submission)

Why?
FDA may stay the review clock while a determination is being made (21 CFR 3.10)
Classification = Combination Product

What do you do when it gets there?
What do you do when you get there?

Regulatory Process and Development Considerations
  – General
  – Constituent parts
  – Clinical Investigations
  – Manufacturing
General Considerations: Application Type

- **CDRH**
  - preIDE
  - IDE
  - 510(k)
  - PMA
  - HDE

- **CDER**
  - preIND
  - IND
  - NDA
  - (BLA)

- **CBER**
  - preIND
  - IND
  - BLA
  - (PMA)
  - (510(k))
General Considerations: Marketing Applications

• Typically require only one
• Two applications (generally not required)
  – Platform technology
• Confidentiality
  – Existing application
  – Master files
  – Authorization to cross-reference
General Considerations: User Fees

• One application: subject to the fee associated with the type of application required
  – Eligible for same fee-waivers as non-combination products (e.g., small business)

• Two applications: fee assessed for each
  – Innovative combination product waiver could reduce the fee burden associated with the requirement for two marketing applications
    • Essentially pay the equivalent of one fee – for example, if both a PMA and NDA are required, the NDA fee would be reduced by the amount of the PMA fee

• Guidance document: Application User Fees for Combination Products
General Considerations: Review Process

- Review process very much like non-combination products except that more than one Center is involved in the review
  - Submit application (preIND/IDE, IND/IDE, 510(k)/PMA/NDA/BLA)
  - Review team assigned (intercenter consult process)
  - Meeting held or letter issued
General Considerations: New Products

• No single developmental paradigm – NOT a one size fits all approach
• Existing guidance for constituent parts are a starting point only
• Need to address issues for product as a whole
• Very few combination product guidances:
  – Coronary Drug-Eluting Stents - Nonclinical and Clinical Studies (Draft)
  – Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (Draft)
Constituent Parts

• Consider broad range of interactions of constituent parts

• Consider what is currently available or known for a constituent part
  – Prior approval or clearance
  – Same or new intended use, population
  – Formulation, dose, route of administration
  – Location of use
  – Consider in the context of the NEW indications for use
  – Existing guidance for constituent parts
Constituent Parts

• Device
  – Leachables/extractables into drug/biologic
  – Change in stability
  – Adhesion/absorption
  – Manufacturing residues

• Drug / Biologic
  – Changes in formulation, strength, route of administration, delivery method
  – Local / regional toxicity
  – Pharmacokinetic studies
  – Dose ranging and dose finding studies
Clinical Investigations

• Only 1 investigational application should be submitted
  – IND or IDE – depends on lead Center
  – Consider safety concerns for EACH constituent part, regardless of lead Center

• Largely similar considerations to non-combination products
  – Trial design, sample size, statistical methods, endpoints
  – Evaluate drug/device interactions
  – Human factors – evaluation/testing of device use (user/environment/interface)
Manufacturing

• Consider both constituent parts and combination
  – Stability of constituent parts may change when combined
  – Drug / biologic altered by terminal sterilization

• Consider changes in manufacturing
  – Concentration, inactive ingredients
  – Cellular incubation time and methods may affect performance characteristics
  – Important to establish arrangement for interaction between manufacturers of constituent parts in Post-approval change protocol
Proposed cGMP Rule

• Current Good Manufacturing Practices
  – Federal Register, September 23, 2009
  – Final rule anticipated in 2012
• Streamlined approach – avoid duplicative or parallel manufacturing process
• Adopt a baseline system and tack on certain additional procedures
• Guidance will follow final rule
Proposed AE Rule

• Postmarket Safety Reporting (adverse events)
  – Federal Register, October 1, 2009
  – Follow reporting rules associated with the application type
  – Other requirements as specified in proposed rule:
    • 5-day device reports
    • 30-day device malfunction reports
    • 15-day alerts for drugs and biologics
    • 3-day field alert reports for drugs
    • Expedited blood fatality reports for blood/biologics
  – Guidance will follow
OCP’s role pre/postmarket

- Facilitate
- Intercenter consults
- Timeliness
- # of marketing applications
- Regulation and guidance development

Center responsibility:
- Application type
- Test methods, pre-clinical/clinical requirements
Current Efforts

• Finalize proposed cGMP and AE rule
• Guidance development
  – Imaging devices for use with contrast agents (draft)
  – Autoinjectors – technical/scientific considerations (draft)
  – Chemical action (draft)
  – Classification of drugs and devices (draft)
  – Autoinjectors – regulatory pathway (in development)
  – cGMP – revision of 2004 draft (in development)
  – Post-approval supplements (in development)
  – Cross-labeling (in development)
Contact Us
We’re Here to Help!

combination@fda.gov

Please provide brief product description and intended use or summary of the issue.

Website:

www.fda.gov/CombinationProducts/default.htm

Address: Office of Combination Products
White Oak
Bldg 32, Rm 5129
References

- Acts, Rules and Regulations
  [http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109108.htm](http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109108.htm)

- Guidance documents (final and draft)

- Proposed rules:

- Office of Combination Products
  [http://www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm)
Abbreviations

- AE – adverse event
- CBER – Center for Biologics Evaluation and Research
- CDER – Center for Drug Evaluation and Research
- CDRH – Center for Devices and Radiological Health
- CFR – Code of Federal Regulations
- cGMP – current Good Manufacturing Practices
- FDCA – Food, Drug, and Cosmetic Act
- MOA – mode of action
- OCP – Office of Combination Products
- OSMP – Office of Special Medical Programs
- PHSA – Public Health Services Act
- PMOA – primary mode of action
- QSR – Quality Systems Regulations
- RFD – request for designation
Application/Submission types

- 510(k) – premarket notification
- PMA – premarket approval
- IDE – investigational device exemption
- HDE – humanitarian use device exemption
- NDA – new drug application
- ANDA – abbreviated new drug application
- IND – investigational new drug application (also used for investigational biological products)
- BLA – biologic licensing application