Multimodal Therapies for Brain Disorders: Session II Regulatory and Reimbursement Considerations

Combination Products at US FDA

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June 14, 2016

Discussion Topics

Within the spectrum of multimodal therapies for brain disorders…

- When are multimodal products combination products?
- What are combination product implications for the FDA regulatory review process?

What is the basis of Product Classification?

- Biological product; PHS Act 351(a)*
- Device; FD&C Act, 201(h)*
- Drug; FD&C Act, 201(g)*
- Combination Product; FD&C Act 503(g)

*See reference slides

What is a combination product?

- A combination product is:
  - A product comprised of two or more different types of medical products (e.g., drug and device, drug and biological product, device and biological product, or all three together).
  - Constituent part: A drug, device, or biological product that is part of a combination product. (*See* 21 CFR 3.2(k) and 21 CFR 4.1.)
- A combination product is not:
  - A product comprised of only two or more of the same type of human medical product (e.g., drug - drug, device - device, or biologic - biologic).
  - A human medical product combined only with a non-medical product (e.g., drug with a food or cosmetic).

Combination Product: Definition

- 21 CFR Part 3
  - Physically or chemically into a single entity; §3.2(e)(1)
  - Co-packaged (Kit); §3.2(e)(2)
  - Sold separately and labeled for use together; §3.2(e)(3) or (e)(4)

21 CFR Part 3.2(e) - Details

- (e)(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological 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; or

- (e)(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect

Separately Provided Products: Labeling Jargon

- General labeling: Broad use - does not restrict to a particular drug or device
- One-way labeling:
  - Brand Drug A for use with Brand Device A
  - Brand Device A for use with drugs with certain characteristics, or labeled for use with Device A
- Two-way labeling (cross-labeling; combination Product)
  - Brand Drug A for use with Brand Device A
  - Brand Device A for use with Brand Drug A

Combination Product Examples

- (e)(1) Chemically / physically combined single entity CP
  - Drug-eluting stent
  - Antibody-drug conjugates
  - Pre-filled disposable drug / biological delivery device
- (e)(2) Co-package
  - Drug with empty syringe, diluent, and transfer pack
  - Drug-device implant with implantation tools
- (e)(3) or (e)(4) Separately provided and cross-labeled
  - Dedicated light source and dedicated photo-activated drug
  - Dedicated drug and dedicated infusion pump

For a Combination Product …

Assignment / Jurisdiction of CP

- Combination Product (CP)
  - CDER, CBER, or CDRH
  - Assigned based on the primary mode of action (PMOA)* or algorithm**

*FD&C Act, Section 503(g);
**21 CFR 3.2(m)

Assignment / Jurisdiction of CP, Cont'd

- Mode of Action (MOA) – "the means by which a product achieves its intended therapeutic effect or action, …" § 3.2(k)
  - Action is based on the drug, device, biologic definitions
- PMOA – "the single mode of action of a combination product that provides the most important therapeutic action …
  - Most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…;" § 3.2(m)

Assignment / Jurisdiction Cont'd

- When the PMOA is uncertain, use the assignment algorithm:*
  - Assign to center with combination products raising similar S/E questions for CP as a whole (Tier-1)
  - If there aren't similar combination products, then Assign to center with most expertise in the most significant safety and effectiveness questions for the CP (Tier-2)

*21 CFR 3.4

What Happens After Assigned?

- Product is still a combination product; it does not change classification to that of the type of products customarily in that center.
  - The constituent parts retain their identity and their applicable requirements apply to the combination
- Lead center is the point of contact
  - Use the communication procedures and timelines of the lead center submission type
  - Selection of submission type considers what is needed for the entire combination product; e.g., comply with applicable regulations / requirements of both constituent parts without being contrary or confounding.
- Data: use cross-center due diligence to address the scientific questions to ensure safety and effectiveness for the combination product as a whole and its constituent parts

Combination Product: General Regulatory Approach

- Premarket
  - Apply consistent standards to assess safety and effectiveness regardless of Center assignment
  - Use consistent and appropriate regulatory pathways
  - One investigational application (i.e., the one used by the lead center)
  - One marketing application for most combination products but might vary based on the marketing configuration

Combination Product: Consistency Considerations for Safety & Effectiveness - Examples

- Indication for Use: same or different from approved / cleared labeling(s)
- Drug changes; e.g., dose, rate, route or method of administration; dosing regimen or frequency
- Device changes; e.g., modality or exposure differences;
- Drug-Device interactions; preclinical, non-clinical, biocompatibility
- Human factors
- Safety or other labeling revisions for new use

Premarket Review Observations

- What is the appropriate regulatory pathway to market; e.g.,
  - Type of marketing application(s)
  - Does the label of a marketed product need to change?
  - Resolving potential differences in data requirements

Premarket Review Observations, Cont'd

- Managing changes to the product configuration during the premarket review (e.g., how to leverage existing data)
- Managing different review processes, different application types, and different review times
- Assessing combination product CGMPs* and scheduling of inspections

*21 CFR Part 4

What Else Happens After Assigned?

- OCP provides assistance in:
  - Responding to questions from industry or FDA staff
  - Attending internal meetings and meetings with sponsors when requested
  - Hosting OCP-cross center meetings at industry requests
  - Identifying and resolving CP regulatory/policy review issues (small or large).
  - Facilitate resolution of scientific / process issues

Postmarket Regulation / Review

- Postmarket Combination Product Changes
  - Compliance with regulatory requirements for each constituent part while avoiding redundancy
  - Ensure consistent compliance and inspectional standards
  - Ensure consistent standards and regulatory review pathways for postmarket changes

What is similar regardless of combination product or non-combination status?

- Centers and OCP continue to work together to
  - Determine if the product is appropriately classified and in the appropriate center
  - Identify and assess the scientific and technical data
  - Consider the labeling that is appropriate to ensure safe and effective use of the product(s) for the proposed indication
  - Achieve consistency and transparency
  - Speak with one agency voice

Contact Us –
We're Here to Help!

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Reference slides

Classification Definitions: Drug or Device

- 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. (FD&C Act, 201(g))
- Device: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man…, or intended to affect the structure or any function of the body of man …, and does not achieve its primary intended purposes through chemical action within or on the body of man … and is not dependent upon being metabolized for the achievement of its primary intended purposes. (FD&C Act, 201(h))

Classification Definition: Biological Product

- 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.

*PHS Act, 351(a)

Useful Assignment Information

- Guidance documents and regulation*
  - PMOA Rule, 21 CFR Part 3 revision – 2005
  - Chemical Action (draft) – 2011
  - Classification (draft) – 2011
  - How to Write an RFD - update 2011

* http://www.fda.gov/CombinationProducts/default.htm