Golf vs. Basketball
Sept 14, 2016 MDG Forum

READING YOUR MIND
Understanding Your Brain Through Physical Responses

You Are Invited!

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Drug Meets Device: The Power of Combination Products

Speakers:

• **Richard Anders, JD**, Founder, Executive Director, Mass Medical Angels

• **Andrew Bellinger, MD, PhD**, Chief Scientific Officer, Lyndra Co.

• **Jonathan C. Bretz, OT/L, MBA**, RAC President & Founder, RSQM Associates, LLC

• **John Keating, DVM, DACVP**, Director of Pathology, CBSET Inc

Moderator:

• **Ibraheem (Ib) T. Badejo, PhD**, Senior Director, New Ventures (Medical Devices), Johnson & Johnson Innovation Center
Combination Products

Jonathan C. Bretz – President
RSQM Associates, LLC
May 19, 2016
FDA defines Combination products as...

1. A product comprised of two or more regulated components:
   - drug/device
   - biologic/device
   - drug/biologic
   - drug/device/biologic
   that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together:
   - in a single package or as a unit
   - and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that...
   - 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;

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.
What is or isn’t a combination product?

- Drug-Eluting Stent
- Drug packaged with a syringe or injector pen
- Controlled-release drug delivery device
- Metered dose inhalers
- Orthopedic implant coated/packaged with biologic growth factor
- Chemotherapy drug and monoclonal antibody (biologic) conjugate
- Intraoperative drug plus detecting device
- In-vitro diagnostic test to select patients for a specific biological product therapy
- Photosensitizing drug and activating light source
- Bandage with antimicrobial coating

- Device - device
- Drug - drug
- Biologic - biologic
- Food + Drug/Device/Biologic
- Cosmetic + Drug/Device/Biologic
Where does your product belong?

• Type?
  – Device
  – Drug
  – Biologic
  – Or Combination?

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

• Primary Mode of Action (PMOA)
  – Single mode of action, which contributes “the most important therapeutic action of the combination product”
  – Makes “greatest contribution to the overall intended therapeutic effects of the combination product” (21 CFR 3.2(m))

• Jurisdiction
  – PMOA = device = CDRH
  – PMOA = drug = CDER
  – PMOA = biologic = CBER (or CDER)
What if PMOA is difficult to determine?

• This is true if product is...
  – In early development and you just don’t know
  – Made with two (or more) completely contrasting modes of action, and neither is secondary to the other

• Submit an email to: combination@fda.gov
  – Informal, non-binding
  – Determine if RFD is needed

• Submit Request for Determination (RFD)
  – Formal, binding determination
  – Requirements in CFR 21 3.7
Possible changes on the horizon...

• Combination Product Regulatory Fairness Act of 2015-2016
  – Require FDA to provide sponsor scientific rationale for determining product is not medical device
  – Prohibits FDA from determining product is drug solely because has chemical reaction

• 21st Century Cures Act
  – Enhancing Combination Products Review
    • Describe responsibilities of agency center
Addendum
Where in FDA is OCP?

Food and Drug Administration

- Office of the Commissioner
  - Office of Medical Products and Tobacco
    - Office of Special Medical Programs
      - Office of Combination Products
        - Center for Devices and Radiological Health (CDRH)
        - Center for Biologics Evaluation and Research (CBER)
        - Center for Drug Evaluation and Research (CDER)
FDA & Combination Products

- Safe Medical Devices Act of 1990 (SMDA)
- Device to be assigned to lead agency center based on its ‘primary mode of action’ (PMOA)
- 1991 - SMDA Implemented
- 2003 – Office of Combination Products (OCP)
  - Prompt assignment to ‘lead center’
  - Premarket review
  - Postmarket regulation
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

*“Combination Products,” Kristina J. Lauritsen, Ph.D., Office of Combination Products
PMOA/Assignment Algorithm*

Identify the combination product modes of action
- Drug and Device
- Drug and Biologic Product
- Device and Biologic Product
- Drug, Device and Biologic Product

Which mode of action is the primary mode of action of the combination product?

DEVICE
STOP
Device Primary Mode of Action. Assigned to agency component with responsibility for that type of device.

DRUG
STOP
Drug Primary Mode of Action. Assigned to agency component with responsibility for that type of drug.

BIOLOGICAL PRODUCT
STOP
Biological Primary Mode of Action. Assigned to agency component with responsibility for that type of biological.

UNABLE TO DETERMINE WITH REASONABLE CERTAINTY

Is there an agency component that regulates either combination products that present similar questions of safety and effectiveness with regards to the combination products as a whole?

YES
STOP
Assign to the agency component with responsibility for regulating other combination products that present similar questions of safety and effectiveness with regards to the combination product as a whole.

NO

Which agency component has the most expertise related to the most significant safety and effectiveness questions presented by the combination product?

STOP
Assign to the agency component that has the most expertise related to the most significant safety and effectiveness questions presented by the combination product.

*Mark Kramer – Master Control
Resources

- FDA Office of Combination Products
- Draft Guidance: Human Factors Studies and Related Clinical Study Considerations in Combination Product: Design and Development
- Current Good Manufacturing Practice Requirements for Combination Products
- Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products
- Combination Products Guidance Documents
- Application User Fees for Combination Products
Drug-Device Product Development

*integrated target product profiles*

**MARKET ATTRACTIVENESS**
- Clinical Benefit
- Price Support
- Reimbursability
- Competitive Landscape
- Follow-on Products

**OPERATIONAL FEASABILITY**
- Technical
- Manufacturing Scalability and COG
- Regulatory Pathway
- Freedom to Operate (IP)
- Speed to Market
Improving biocompatibility in DES

- Alteration of polymer coatings - both durable and biodegradable
- Minimizing polymer-tissue contact
- Biodegradable scaffolds
- Polymer free stents

Sustained Crystalline Drug Retention Despite Fast Coating Degradation
RENAL DEVERVATION
Tzafriri et al, Innervation patterns may limit response to endovascular renal denervation. JACC, 2014.
LESSONS
Upcoming MassBio Forums

June 1: Cannabinoids: Curse or Cure?  FDD
June 2: The Biosimilars Race: Are You Still at the Starting Line?  L&R
June 29: Case Studies in Clinical Trial Outsourcing: Do’s, Don’ts & Lessons Learned;  CRO/CMO

Digital Healthcare Forum Series

June 21: The Digital Healthcare Landscape

July TBD: “Mobilizing” Clinical Trials: New Technologies for Accuracy, Efficiency & Real Time Data Capture

August 4: The Promise of Digital Healthcare: Commercialization & Beyond