Combination Products: A Regulatory Challenge

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Combination Products

- One item composed of two or more differently regulated products
- Two or more differently regulated items that MUST be used together to achieve the expected outcome:
  - Often packaged together – but not always
  - Being labeled for required use together
- Often offer unique therapeutic advantages

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Examples of Combinations

- Drug-eluting cardiovascular stent
- Spinal fusion cage coated with therapeutic protein for disc disease
- Scaffold seeded with cells for organ replacement
- Interferon and ribavirin combination for Hepatitis C

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Why Regulation is a Challenge

- Differences between drugs, devices and biologics:
  - Design and development
  - Testing
  - Manufacturing
  - Post-market monitoring
- Regulatory processes also differ

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Characteristics of Drugs

- Discovered
- Stable formulation developed
- Highly mechanized manufacture
- Consumed by use
- Systemic toxicity
- Large populations of exposure
- Patient can choose to stop use

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Characteristics of Devices

- Designed
- Constant improvements/changes
- Often manufactured by hand operations
- Available for study after use
- Adverse events most often local in nature
- Relatively limited populations of exposure
- Most are for professional use

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Regulatory Differences Based on Types of Data Needing Evaluation

- Drugs:
  - Chemical assessment: purity, consistency
  - Animal testing for toxicity; early controlled human exposure for efficacy
  - Large clinical trials for statistical evaluation of safety and efficacy – no direct measures
- Devices:
  - Material selection and testing; device design and experience
  - Bench testing for performance; animal testing for procedural assessment
  - Small to medium human trials to confirm expectations, often with direct means of observation or measurement

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Issues for Regulations

- One size does not fit all products
- How products will be used and by which health care professionals is important
- The product's most important therapeutic benefit is useful for deciding how to regulate combinations
- The additive effect of the other component(s) is important
- The entire lifecycle of the product needs to be considered

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Goals of Combination Product Regulations

- Effective regulation of the combination – each contributing characteristic
- Scientifically appropriate assessments
- Not duplicate or unnecessary extra oversight
- Reasonable timeframes for bringing these important products to market

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How the Combination is Reviewed Is Important

- Major issue for how the materials are developed, submitted, and reviewed
- Rules for assignment needed

  US - Primary mode of action for assignment
- How well the second/third component is understood for market approval is planned as well

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Regulating a Device as a Drug and a Drug as a Device

- Blending of requirements
- Selection of key areas of focus for testing
- Determination of clinical data needed and size of clinical trial
- Manufacturing oversight for each component
- Labeling designed for best use; education
- Post-market assessments as appropriate – focus on expected, low rates of risk or failure

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US Review of Combination Products

- FDA Statute (law):
  - Ensure timely and effective premarket review by overseeing timeliness of and coordinating reviews involving more than one agency Center
- FDA Regulation
  - Provides a clear mechanism for deciding how the combination will be reviewed

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Primary Mode of Action: Key Element of FDA Assignment Decision

- "Primary Mode of Action":
  - *The single mode of action of a combination product that provides the most important therapeutic action of the combination product*

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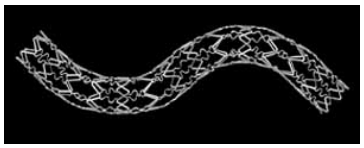
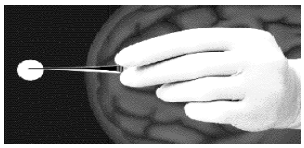
Primary Mode of Action

Drug Eluting Stent



Is it regulated as a drug, or a device?

Drug Eluting Disk



Is it regulated as a drug, or a device?

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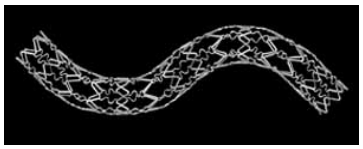
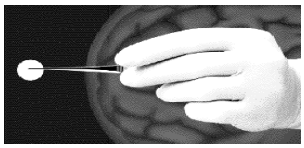
Primary Mode of Action

- 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 for brain tumor
- Secondary Actions
  - Local drug delivery of drug by device
- Regulated as a drug (NDA)

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More Examples

- Contraceptive sponge – drug activity is the primary mode of action
- Drug pumps – general use - not labeled for a specific drug or pre-filled with a drug
- Most therapies even if used together are not regulated as combinations

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Summary

- Combination products pose challenges
- Regulatory differences are based in underlying product differences
- Choosing the path for regulatory review needs to be consistent and predictable
- Processes should address actual risks and benefits of the combination
- Actual review work needs to have oversight for timeliness and consistency
- Combination products offer therapeutic benefits

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