
  
THE FUSION OF EXPERTISE

## Combination Products: Managing Regulatory and Business Risks

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### Rewards Associated with Combination Products

- Breakthrough technologies
- Substantial improvements in health
- Improvements in safety due to local administration of the drug product
- Addition of new indications for use of existing drug products

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### Risks Associated with Combination Products

- Science – multiple technologies, multiple components
- Manufacturing – multiple technologies, multiple components
- Regulatory – multiple regulatory frameworks, fewer precedents, less clarity

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**A Drug is defined as:**

- (A) articles recognized in the official USP...
- (B) articles intended for used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than Food) intended to affect the structure or any function of the body of man or other animals; and
- (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts or accessories

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**A Biologic is defined as:**

- ...a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, 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" [42 U.S.C. 262(i)].

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**A Medical Device is defined as:**

- "an 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 USP, 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 any of its principal intended purposes.**"

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**A Combination Product is defined as:**

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

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**A Combination Product is defined as:**

- 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

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**A Combination Product is defined as:**

- 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

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### Examples of Combination Products

- Drug coated stents
- Growth factor associated with a spinal fixation device
- Wound care products with antibacterial agents
- Extracorporeal processing systems

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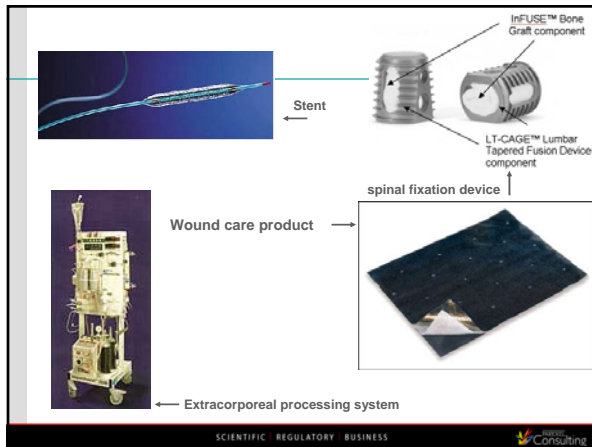
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### Other Examples of Combination Products

- Metered dose inhalers
- Pen injectors with customized cartridges
- Cultured skin wound care products
- Pharmacogenetic assays
- Delivery devices for gene and stem cell therapies

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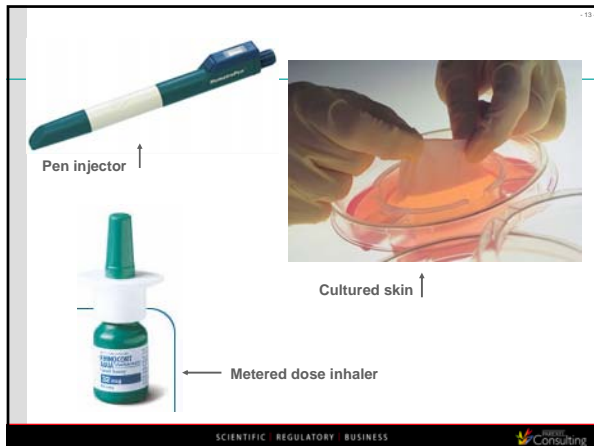
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### The Current Situation

- The 3 1991 Intercenter Agreements provide the foundation
- 21CFR 3, Product Jurisdiction describes the regulatory process
- The process is administered by the Office of Combination Products and Product Jurisdiction Officers in each of the 3 centers

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### Is It Always Necessary to Use the RFD Process?

- How certain do you need to be?
- Consider regulatory and business risks
- How many precedents have been established?
- Are there other downstream issues regarding product testing and manufacturing issues?

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Primary Mode of Action

- What does the product do? How does it do it?
- Is the most important action mechanical? Electromagnetic?
- Or is it chemical?
- Or, is the Primary Mode of Action unclear?

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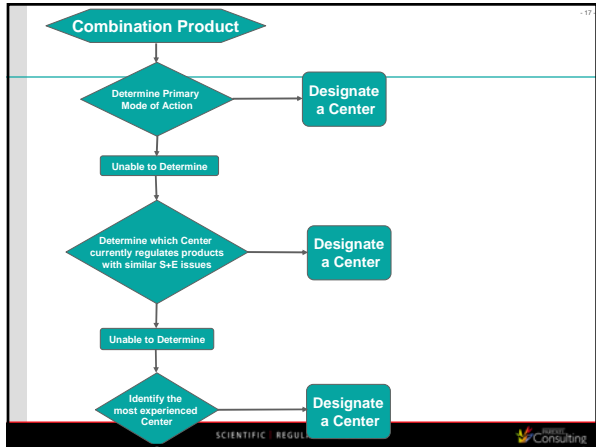
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Points to Keep in Mind

- FDA can apply *any* of their regulations to your product or process
- There is room to propose your own strategy
- FDA is bound by both scientific considerations and precedents
- Precedents may not be publicly available

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### The RFD Process

- Determine your indication for use
- Understand your technology
- Conduct informal discussions with FDA to identify key issues
- Prepare your point of view
- Know the precedents that apply to your product and indication
- Prepare the RFD

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### RFD Contents

- Identification of the sponsor, product and any related products that have received FDA review
- Description of the product
- Status of preclinical and clinical testing of the product
- Description of the manufacturing process and sources of components

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### RFD Contents

- Proposed indication for use
- Mechanism of action/Primary mode of action and rationale
- Schedule and duration of use, route of administration
- Description of related products and their regulatory status
- Sponsor recommendation for primary jurisdiction

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### RFD Process

- FDA suggests the RFD should be 15 pages or less
- FDA will issue a decision with 60 days, or, if no decision is made, then the sponsor's proposal is accepted
- FDA may request a meeting with the sponsor during the review period
- The sponsor may appeal a designation decision
- The decision in the Designation Letter is binding on FDA, unless there is a compelling public health reason to change it

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### Possible Designations

- Simple designations: Drug, Biologic or Device
- One product, linked by either labeling or packaging to another product: a drug that will only be sold with a specific device
- Most device designations lead to PMAs, although some drug/biologic delivery devices have been designated as 510(k) products
- Frequently, if a simple device is linked via labeling with a drug, the device will not be cleared or approved until the drug is approved

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### Business Issues for Combination Product Developers

- Differences between pharma and device companies
  - Cultural
  - Financial
  - Time lines/Product Life Cycle/ROI
  - Toleration of risk

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Preapproval Issues for Combination Product Developers

- Regulatory Differences between the pharma device paths
- Product development time: Years vs. months
- cGMP vs. Quality System Regulation including Design Controls
- Software development and validation
- Preclinical testing per ICH guidance or ISO 10993 plus product specific testing
- Multiple clinical trials vs. one trial
- Clinical trial design: masking, investigator training, payment for test articles

Seven horizontal lines for notes.

Post Approval Issues for Combination Product Developers

- Product modification procedures
- Adverse event reporting process
- Marketing Exclusivity
- Periodic reports

Seven horizontal lines for notes.

Risk Limitation Strategies for Biotech Product Developers

- Recognize as early as possible if your product may potentially be a combination product
- Remember regulatory definitions are not harmonized internationally; your product may be a device in the U.S. and a drug in the EU
- Keep technology limitations of the device component in mind as the pharma component is developed and dosing is determined
- Do not under estimate the complexity of device development, especially computer controlled products
- Good communication between pharma and device development teams along with fully integrated project management is essential


Seven horizontal lines for notes.

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## Useful References

- Primary Mode of Action Information:  
<http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm>
- FDA Combination Products Information:  
<http://www.fda.gov/oc/combination/>
- Getting Started with a Combination Product  
<http://www.devicelink.com/mddi/archive/03/03/018.html>  
<http://www.devicelink.com/mddi/archive/03/04/019.html>

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**Thank you!**

Any questions?

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