Overview of FDA Regulation of Combination Products

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Definition of Combination Products

Combination products are defined in 21 CFR 3.2(e). The term combination product includes:

• 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;

• 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

• 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.
Examples of Types of Combination Products

Examples of combination products where the components are physically, chemically or otherwise combined (21 CFR 3.2(e)(1)):

- Monoclonal antibody combined with a therapeutic drug
- Device coated or impregnated with a drug or biologic
  - Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide
  - Skin substitutes with cellular components; orthopedic implant with growth factors
- Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches

Examples of combination products where the components are packaged together (21 CFR 3.2(e)(2)):

- Drug or biological product packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs

Examples of combination products where the components are separately provided but labeled for use together (21 CFR 3.2(e)(3) or (e)(4)):

- Photosensitizing drug and activating laser/light source
- Iontophoretic drug delivery patch and controller
Office of Combination Products (OCP)

OCP created in 2002 under Medical Device User Fee and Modernization Act.

- To serve as a focal point for combination product issues for agency reviewers and industry.
- To develop guidance and regulations to clarify the regulation of combination products.
- To assign an FDA center to have primary jurisdiction for review of both combination and non-combination products where the jurisdiction is unclear or in dispute.
- To ensure timely and effective premarket review of combination products by overseeing the timeliness of and coordinating reviews involving more than one agency center.
- To ensure consistency and appropriateness of postmarket regulation of combination products.
- To resolve disputes regarding the timeliness of premarket review of combination products.
- To update agreements, guidance documents, or practices specific to the assignment of combination products.
- To submit annual reports to Congress on the Office’s activities and impacts.
- To provide training to FDA staff and regulated industry on combination product regulation.
Intercenter Consult Process Study
October 2015

Findings
• Different policies, practices and application types
• Separate review and tracking systems between centers
• Unclear communication channels between centers
• Lack of resources to review consults

Recommendations
• Establish clear guidance for the review of common combination product types
• Provide reviewers with access to other Centers' systems or create a unified data system
• Update SOPP (standard operating procedures and policies) manual
• Create and maintain a current org chart and contact directory
• Create a mechanism for better tracking time spent on intercenter consults
Recent Developments and New Guidance

Post Market Safety Reporting (Final rule) (12/2016)
• Describes the postmarketing safety reporting requirements that apply to combination product applicants and constituent part applicants when the combination product or its constituent parts have received FDA marketing authorization.
• Minimizes duplicative reporting.

Current Good Manufacturing Practice Requirements for Combination Products (1/2017)
• The cGMP requirements that apply to each of the constituent parts apply to the combination product they constitute.
• Applies to all combination products.

How to Prepare a Pre-Request for Designation (Pre-RFD) (1/2017)
• Enables a sponsor to obtain a preliminary nonbinding assessment of the (1) regulatory identity or classification of a product as a drug, device, biologic or combination product and (2) determination of which center will regulate product if it's a non-combination product or which will have primary jurisdiction for the premarket review and regulation if it is a combination product.