

U.S. Food and Drug Administration

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Regulatory perspectives on Combination Therapy for Cancer

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Premises

- The term “combination” can have multiple perceptions.
 - A regulatory definition is based on product type according to legal definitions
- The FDA has established mechanisms for working with combination products
- Education is required to minimize misperceptions and utilize existing regulatory mechanisms

Common Questions

- What is meant by the term “combination product”?
 - Regulatory definition: Two or more articles of different product types combined in particular ways outlined in the Code of Federal Regulations (21CFR3)

It all depends on the definition

- Product- an article that is a drug, device or biologic
- Biological Product- any product from a source list that is applicable to the prevention, treatment, or cure of a disease or condition of human beings
- Drug- articles that meet one of three conditions intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals or intended to affect the structure or any function of the body of man or other animals
- Device –same as drug but 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

Variations in the system

- Some centers regulate multiple product types; for example, CBER regulates some device such as cell sorters and CDER regulates some biologics such as monoclonal antibodies

Regulatory Definition of Combination Product

Combination products are defined if they meet any of four conditions

- Single entity
- Single package
- Intended for use with an approved product
- Intended for use with an investigational product

Regulatory Expectations

- Combination products will be assigned a primary review center at FDA
- Mechanisms for determining the primary review center are based on:
 - Primary mode of action, if known
 - *or*
 - Regulatory precedent with reference to similar products
 - *or*
 - Center with the most expertise in the safety and effectiveness questions related to the combination

Mode of Action for Combination Products

- Formal definition of mode of action is the means by which a product achieves an intended therapeutic effect or action
- If multiple modes of action are supported, one will take precedence as the primary mode of action based on criteria in the applicable regulations

Designation based on primary mode of action

21 CFR Food and Drugs CHAPTER I SUBCHAPTER A GENERAL
PART 3 -PRODUCT JURISDICTION Subpart A
3.4 Designated agency component.

- (a) To designate the agency component with primary jurisdiction for the premarket review and regulation of a combination product, the agency shall determine the primary mode of action of the product. Where the primary mode of action is that of:
- (1) A drug (other than a biological product), the agency component charged with premarket review of drugs shall have primary jurisdiction;
 - (2) A device, the agency component charged with premarket review of devices shall have primary jurisdiction;
 - (3) A biological product, the agency component charged with premarket review of biological products shall have primary jurisdiction.

Designation when primary mode of action cannot be determined

- (b) In some situations, it is not possible to determine, with reasonable certainty, which one mode of action will provide a greater contribution than any other mode of action to the overall therapeutic effects of the combination product.

In such a case, the agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole.

When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the agency will assign the combination product to the agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product.

Interactions between FDA components

The designation of one agency component as having primary jurisdiction for the premarket review and regulation of a combination product does not preclude consultations with other agency components or, in appropriate cases, the requirement by FDA of separate applications.

Office of Combination Products

- Established in 2002 as part of Medical Devices User Fee and Modernization Act.
- Official duties include:
 - assigning an FDA Center to have primary jurisdiction for review of a combination product
 - ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one agency center
 - ensuring consistency and appropriateness of postmarket regulation of combination products
 - resolving disputes regarding the timeliness of premarket review of combination products
 - updating agreements, guidance documents or practices specific to the assignment of combination products

Guidance Document on Request for Designation (RFD)

- Published August 2005
- Available at:
 - <http://www.fda.gov/oc/combinacion/howtowrite.html>
- Contents include:
 - What information must I include in my RFD?
 - What format should I follow for my RFD?
 - What information does FDA recommend that sponsors provide in RFD submissions?
 - How can I limit my submission to 15 pages including attachments as required by the regulation, and still provide all the information FDA needs to make its decision?

Common Questions

- How do FDA Centers coordinate review practice?
 - Designation of one Center as primary
 - Other Centers may perform a collaborative or consultative role. Precedent and mechanisms exist for each.
 - Sponsor submission of documents is only to the primary Center and Division. Internal sharing of documents is expected.

Common Questions

- How is an FDA Center chosen for a combination product?
 - If possible on the basis of primary mode of action, which is defined in the Code of Federal Regulations
 - If primary mode of action cannot be used, then the selection is based on precedents and experience with similar products
 - If no precedents exist, then the selection is based on expertise in the therapeutic questions

Common Questions

- What is expected to initiate a Phase I study with a combination product?
 - Following designation of a primary center, submission of an IND application
 - Pre-IND meetings are an option once the primary center has been designated
 - The FDA will internally arrange any collaborations or consultations

Common Questions

- What is expected to initiate a Phase I study with a **multi-component** product?
 - Submission of an IND to the FDA Center that regulates the type of product
 - Pre-IND meetings are an option once the primary center has been designated

Common Questions

- How are protocols submitted?
 - To the primary IND
- How are adverse events reported?
 - To the IND under which the protocol is filed

Common Questions

- Is there a need for single dose initial clinical studies for each component of a multi-component product or each product in a combination product?
 - Not necessarily. Factors include novelty of products, existence of prior clinical data from similar products, results of pre-clinical studies

Common Questions

- Does modification of one component of a multi-component product require filing a new IND?
 - Possibly. Determinations are made on a case by case basis.

Common Questions

- Can multi-component products and combination products qualify for incentives?
 - The usual programs of Fast Track, Orphan Status (with possibility of qualifying for development grants), Pediatric Exclusivity, Priority Review and Accelerated Approval can all apply using the relevant criteria

Summary

- Primary regulatory challenge may be a need for education of research community about definitions and programs