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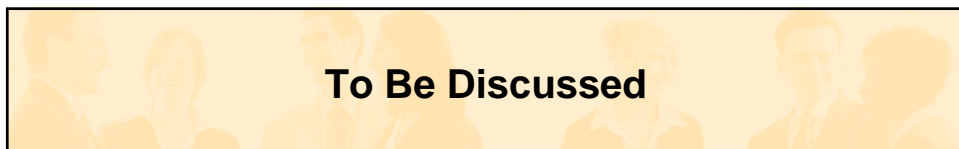
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A Little Bit Of This, A Little Bit Of That: FDA Regulation Of Combination Products

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To Be Discussed

- Definition
- Office of Combination Products (OCP)
- Primary Mode of Action
- Some FDA guidances to consider
- Suggestions on interacting with FDA's OCP

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Combination Products

Definition

- A combination product is defined to include:
 - 1) 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
 - 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

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Combination Products

Definition

(cont'd)

- 3) 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

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Combination Products

Definition
(cont'd)

- 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

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In Other Words

- Combinations of different types of products:
 - drug-device
 - device-biologic
 - drug-biologic
 - drug-device-biologic
 - not drug-drug, device-device or biologic-biologic combinations

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In Other Words

(cont'd)

- They can be:
 - physically or chemically combined
 - co-packaged in a kit
 - separate, cross-labeled products

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Some Examples Of Combination Products

- Examples of combination products where the components are physically, chemically or otherwise combined:
 - monoclonal antibody combined with a therapeutic drug

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Some Examples Of Combination Products

(cont'd)

- device coated or impregnated with a drug or biologic
 - drug-eluting coronary stent
 - pacing lead with steroid-coated tip
 - catheter with antimicrobial coating
 - condom with spermicide
 - skin substitutes with cellular components
 - orthopedic implant with growth factors

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Some Examples Of Combination Products

(cont'd)

- prefilled syringes
- insulin injector pens
- metered dose inhalers
- transdermal patches
- scaffold seeded with autologous cells

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Some Examples Of Combination Products

(cont'd)

- Examples of combination products where the components are packaged together:
 - drug or biological product packaged with a delivery device
 - surgical tray with surgical instruments, drapes and lidocaine or alcohol swabs

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Some Examples Of Combination Products

(cont'd)

- Example of combination products where the components are separately provided but labeled for use together:
 - photosensitizing drug and activating laser/light source

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Office Of Combination Products

- In 2002, the Medical Device User Fee and Modernization Act (MDUFMA) revised section 503(g) of the Federal Food, Drug, and Cosmetic Act (21 USC 353(g)) to create an office within the FDA Commissioner's Office to handle such assignment issues
 - MDUFMA also required FDA to review its combination product policies and guidance

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Office Of Combination Products

(cont'd)

- The roles of the OCP are:
 - 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 single entity (*i.e.*, non-combination) products where the jurisdiction is unclear or in dispute
 - but not to directly regulate products

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Office Of Combination Products

(cont'd)

- 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 post-market regulation of combination products
- to resolve disputes regarding the timeliness of premarket review of combination products

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Office Of Combination Products

(cont'd)

- to update agreements, guidance documents, or practices specific to the assignment of combination products
- to submit annual reports to Congress on the OCP's activities and impacts

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The Assignment Of Combination Products For Review

- A combination product is assigned to an FDA center that will have primary jurisdiction for its premarket review and regulation
- Assignment to a center with primary jurisdiction, or a *lead center*, is based on a determination of the “primary mode of action” (PMOA) of the combination product

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The Assignment Of Combination Products For Review

(cont'd)

- For example, if the PMOA of a device-biological combination product is attributable to the biological product, the FDA division responsible for premarket review of that biological product would have primary jurisdiction for the combination product
 - although it may enlist the assistance of other applicable centers

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The Assignment Of Combination Products For Review

(cont'd)

- Can submit a Request For Designation (RFD)
 - in FY 2007, OCP received 77 original RFD submissions and issued 52 decisions
 - up from 63 RFD submissions and 43 decisions in FY 2006

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FDA's Review Process For RFDs

- What is the product?
- Why would the product be used?
- How does the product work? Does it involve chemical action? Is it a combination product at all?
 - FDA plans to provide a clearer definition of “chemical action” in the future
- What data are available in the RFD?
- What does the literature say?
- What is the PMOA?
- What are the precedents?
- What safety and effectiveness issues are raised?

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Primary Mode Of Action

- August 2005 Final Rule
- The rule codifies a definition for PMOA as the principal consideration for assigning jurisdiction for a combination product to a particular FDA review center
- PMOA is defined as “the single mode of action that provides the most important therapeutic action of the combination product”
- FDA considers the sponsor’s intended use – not other potential uses – in making PMOA determinations

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Primary Mode Of Action

(cont'd)

- The Final Rule stated that, “The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product”
- FDA explained that the rule focuses only on providing a mechanism for making a primary review center assignment – not for making other regulatory decisions, such as what type of application will be required or whether a sponsor will need to follow drug, device or biologic adverse event reporting requirements

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Examples

- The Final Rule provided examples, including:
 - a spinal fusion device coated with a therapeutic protein for treating degenerative disc disease
 - assigned to the device center
 - a scaffold seeded with human cells for organ replacement
 - assigned to the biologics center
 - a vertoplasty implant with an extended-release analgesic
 - assigned to the device center

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The Hmmm Factors

- One of the most significant components of the rule was that it put on paper the algorithm that the agency has been using in cases where PMOA is unclear or cannot be determined
- The algorithm directs that, in the event PMOA cannot be determined with “reasonable certainty,” the product will be assigned to the center that regulates other combination products with similar safety and efficacy questions

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The Hmmm Factors

(cont'd)

- What is “reasonable certainty”?
 - when the PMOA is not in doubt among knowledgeable experts, and can be resolved to an acceptable level in the minds of those experts based on the data and information available to FDA at the time an assignment is made

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The Hmmm Factors

(cont'd)

- If no similar product exists, FDA will assign the product to the center with the best expertise to evaluate the most significant safety and effectiveness issues
 - if the combination product is the first of its kind
 - when differences in its intended use, design, formulation or other characteristic present unique safety and effectiveness questions
 - if the combination product's actions are independent of each other

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Example

- Contact lens combined with a drug to treat glaucoma
- The contact lens' function is vision correction and the drug's function is the treatment of glaucoma
 - they are independent actions
- No one has submitted an application for this type of combination product, so FDA has no precedent to follow in the assignment of the center's review

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Example

(cont'd)

- FDA would refer the application to the Center for Drug Evaluation and Research, because the drug's safety and effectiveness issues are more significant than those of the contact lens, which the agency considers "routine"
- In contrast, FDA's Center for Devices and Radiological Health regulates drug-eluting stents
 - here, the function of the drug is secondary and supports the artery-opening function of the stent

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Example

(cont'd)

- FDA, with the sponsor's input, can change the review assignment during product development if data show that a product is incorrectly assigned, thereby creating a public health concern
- FDA's current regulations allow a change in review assignment

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Questions To Ask

- The Final Rule sought to give stakeholders more insight into how the agency identifies a product's most significant safety and effectiveness issues when making the primary review center assignment

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Questions To Ask

(cont'd)

- Questions routinely asked by FDA include:
 - what is the therapeutic effect of the product as a whole?
 - does the device component incorporate a novel or complex design or have the potential for clinically significant failure modes?
 - has either of the components been previously approved or cleared?

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Types Of Marketing Applications Required For A Combination Product

- Depending upon the type of combination product, its approval, clearance or licensure may be obtained
 - through submissions of a single marketing application, or
 - through separate marketing applications for the individual constituent parts of the combination product

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Types Of Marketing Applications Required For A Combination Product

(cont'd)

- For most combination products, a single marketing application is sufficient for the product's approval, clearance or licensure
- In some cases, however, a sponsor may choose to submit two marketing applications for a combination product when one application would suffice

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Types Of Marketing Applications Required For A Combination Product

(cont'd)

- For example, a sponsor may choose to submit two applications in order to receive some benefit that accrues only from approval under a particular type of application, e.g.,
 - new drug product exclusivity
 - orphan status
 - proprietary data protection when two firms are involved

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Types Of Marketing Applications Required For A Combination Product

(cont'd)

- In other cases, FDA may determine that two marketing applications are necessary
 - e.g., when one of the individual constituent parts of a combination product is already approved for another use, and where the labeling of the already approved product will need to be changed to reflect its new intended use in the combination product

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Some Combination Product Guidances

- April 2005 – “Application User Fees for Combination Products” (www.fda.gov/oc/combination/userfees.html) (among other things)
 - explains where sponsors would be eligible for conventional user fee waivers in cases where two applications are voluntarily submitted for a combination product

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Some Combination Product Guidances

(cont'd)

- also defines what might qualify for an “innovative combination product” partial fee waiver when two applications are required
- recommends that applicants explore alternative Premarket Approval Application (PMA) paths as a means to lower user fee costs

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Some Combination Product Guidances

(cont'd)

- April 2005 – “Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product” (www.fda.gov/oc/combination/dispute.html)
 - advises sponsors to seek dispute resolution only after the applicable timeframe has expired (e.g., the user fee date) or if there is specific advance warning from the FDA reviewing division that deadlines will not be met

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Some Combination Product Guidances

(cont'd)

- if there are no relevant user fee deadlines, a sponsor should contact the OCP to determine suitable timing for a complaint, according to the document

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Some Combination Product Guidances

(cont'd)

- The document also provides further clarification on user fee timeliness disputes for a single combination product reviewed under two types of applications
- Such dispute requests will be reviewed separately
- If a device user fee timeline is past due, for example, but the drug user fee date has not yet occurred, “a timeliness dispute resolution request covering the device application would not be premature”

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Some Combination Product Guidances

(cont'd)

- So, for a combination product being reviewed under two separate applications, the sponsor can file a dispute resolution request to the OCP once the first of the two action dates has passed

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Some Other Guidances To Consider

- August 2005 – “How to Write a Request for Designation”
(www.fda.gov/oc/combination/howtowrite.htm)
!)
- provides recommendations for information needed for each required section of an RFD
- key sections to focus on:
 - what is your product?
 - why would your product be used?
 - how does your product work?

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Some Other Guidances To Consider

(cont'd)

- what is your product's most important therapeutic action?
- what is the basis for your PMOA determination?
 - data are often helpful
- how do you think your product should be assigned? Why?
 - use assignment algorithm (if appropriate)

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Some Other Guidances To Consider

- September 2006 – “Early Development Considerations for Innovative Combination Products” (www.fda.gov/oc/combination/innovative.html)
- Intercenter Agreements that describe jurisdictional information (www.fda.gov/oc/combination/intercenter.html)

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Some Other Guidances To Consider

(cont'd)

- To come – guidance on contrast agents
 - premarket and postmarket review and labeling recommendations for diagnostic imaging devices that are used with imaging contrast agents or radiopharmaceuticals

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Interacting With The Office Of Combination Products

- Be prepared
 - review FDA's regulations and guidances to understand the rules and the agency's current thinking
 - have a gameplan if you have a preference for a particular course of action

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Interacting With The Office Of Combination Products

(cont'd)

- Be proactive
 - if you have a question, ask and do it sooner rather than later
 - request a meeting or a conference call to make sure FDA understands your questions and the product itself
 - you might need to educate the agency

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Some Challenges

- Little guidance in the law beyond PMOA, for example
- Proposed rules on combination product good manufacturing practices and adverse event reporting have yet to be issued
 - FDA indicating draft regulations expected to be released in May 2008
 - FDA stated in 2006 that the proposed rule on GMPs will “allow manufacturers the flexibility to select either the [drug] cGMP or [device] quality system regulation” and “avoid the necessity to fully implement both sets of cGMP regulations when manufacturing combination products”

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Some Challenges

(cont'd)

- Co-packaging, claims, cross-labeling
 - the OCP plans to release in 2008 a concept paper on cross-labeling
 - where two separately packaged products, possibly with different manufacturers, might each contain labeling explicitly indicating a combined use of the product

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Freebie

- We've written an article about combination products. If you'd like a courtesy copy, please give me your card or email me at alan.minsk@agg.com.

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