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Preconference Primer: Combination Products

FDLI Introduction to Medical Device Law and Regulation

James Boiani & Megan Robertson

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Presented by

James Boiani

Member of the Firm

jboiani@ebglaw.com

Megan Robertson

Associate

mrobertson@ebglaw.com

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What are Combination Products?

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Combination Products

Defined in 21 CFR 3.2(e) 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;
- 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**.

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Common Categories of Combination Products

- Convenience kits
- Pre-filled drug or biologic delivery systems
- Device coated with a drug
- Drug embedded with a device
- Cross-labeled products

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Regulatory Pathway

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Office of Combination Products ("OCP")

The OCP was established in 2002 by the Medical Device User Fee and Modernization Act.

OCP's role is to:

- Classify the product as a drug, device, biological product, or combination product and assign the product to one of FDA's Centers (e.g., CDER or CDRH) for premarket review.
- Help coordinate the review of such products by the Center with jurisdiction (the "Lead Center").
- Oversee the post-market activities for combination products.

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Challenges Posed by Combination Products

Combination products involve multiple components, each of which would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers (such as CDRH, CDER, CBER). Therefore, they raise challenging regulatory, policy, and review management challenges, both from an industry perspective and for FDA.

Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including:

- preclinical testing,
- clinical investigation,
- marketing applications,
- manufacturing and quality control,
- adverse event reporting,
- promotion and advertising, and
- post-approval modifications.

So, it is important to receive clarity in the beginning on which regulatory pathway will be applicable to your combination product.

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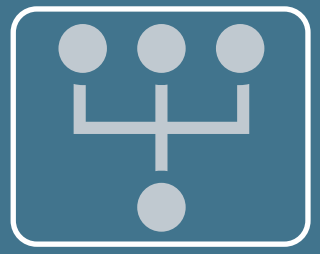
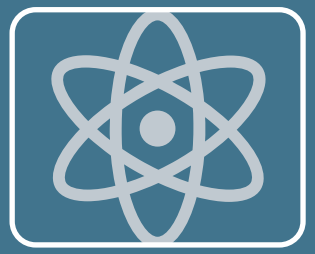
Determining Center Jurisdiction



Center jurisdiction is determined by a combination product's "primary mode of action" (or PMOA)

- Drug Primary Mode = CDER as the lead center (e.g., INDs and NDAs)
- Device Primary Mode = CDRH as the lead center (e.g., IDEs and PMAs)



PMOA is the single mode of action of a combination product **that provides the most important** therapeutic action of the combination product. 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. (21 CFR 3.2(m))

- "Mode of action" is the means by which a product achieves **an intended therapeutic effect or action**. (21 CFR 3.2(k))
- In 2016, Congress, as part of the 21st Century Cures Act, emphasized that presence of a drug effect in a combination product is not enough to require drug regulation, in response to FDA "drug" bias.

Intended therapeutic effect is primarily determined by the product sponsor and its claims

- FDA has acknowledged that two identical products with different intended uses could be regulated under two different regimes (e.g., intended use 1 = drug regulation, intended use 2 = device regulation).

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21st Century Cures Updates to Combination Product Review Process

PMOA Determination

- 21st Century Cures Act (enacted at the end of 2016 – the "2016 Cures Act") included provisions to rein in FDA bias for designating combination products for drug regulation.
- The Act provides that FDA may not determine that a combination product has a drug PMOA "solely because [it] has **any** chemical action within or on the human body"
  - To make a determination that a combination product is drug-led, FDA would appear to need evidence that the combination product's **chemical action** makes the **greatest** contribution to the overall therapeutic effects of the product
    - Without such evidence, FDA is required to look at the Center that has regulated similar combination products (i.e., those that present similar questions of safety and effectiveness)
    - If no such products exist, the product will be assigned to the Center with the most expertise to handle the review

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2016 Cures Act Updates to FDA Combination Product Review Process

Appeal of a PMOA Determination

- If a sponsor disagrees with OCP's PMOA determination, it may:
  - Request, and OCP must supply, its substantive rationale for its decision (and all scientific evidence OCP relied upon in making the determination)
  - Propose one or more studies to establish the relevance (if any) of the chemical action in achieving the product's PMOA
    - FDA and the sponsor must collaborate and reach agreement on the design of such studies (no later than 90 calendar days following the proposal)
    - If agreement is reached and the sponsor conducts the studies, OCP will consider the resulting data when re-evaluating the PMOA determination
    - While these additional studies would delay product development and entail additional costs, the potential to change the Lead Center may be worth it

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2016 Cures Act Updates to FDA Combination Product Review Process

FDA/Sponsor Meetings

- Once the PMOA determination is made, the sponsor may request a meeting with OCP to address the standards for approval/clearance of the combination product, postmarket modification requirements, and/or applicable good manufacturing practice requirements
- The meeting is required to occur no later than 75 days after OCP's receipt of sponsor's request

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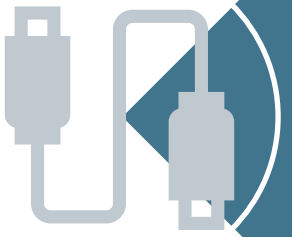
Regulatory Distinctions for Consideration: Device versus Drug



Under Section 201(h) of the Food, Drug, and Cosmetic Act, a device (or device constituent of a combination product) is one that –

(i) does not achieve their primary intended purposes through **chemical action** within the body, **and**

(ii) does not depend upon being **metabolized** for the achievement of their primary intended purposes

Products exhibit "chemical action" if they "interact at the molecular level" with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) to alter that entity's interaction with the body.

"Interaction at the molecular level" occurs through either chemical reaction (i.e., formation or breaking of covalent bonds), intermolecular forces (e.g., electrostatic interactions), or both.

The mere exchange of non-chemical energy (e.g., electromagnetic or thermal energy) between a product and the body would not constitute "chemical action".

FDA has said that the issue of whether a product "depends upon being metabolized" has not been at issue frequently in classification determinations and thus FDA has not offered specific guidance on how this requirement is interpreted (see FDA Guidance: *Classification of Products as Drugs and Devices and Additional Product Classification Issues* (2017)).

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Request for Designation Process and Considerations

- Requests for Designation are available for combination products and non-combination products
  - The product, the claims, and data about how it works matters
  - Safety data does not matter (because that is not relevant to the mode of action)
- OCP has formal and informal determination processes available
  - Request for Designation (RFD)
  - Pre-RFD
- The processes will tell you if you would be regulated as a drug, device, biological product, HCT/P, or combination product, but do not provide a determination as to the regulatory pathway
  - For example, an RFD might say a product is a device or device-led combination product, but will not address the appropriate pathway (PMA, 510(k), de novo, 510(k)-exempt)
- Other advisory processes that can be useful
  - 513(g) Process for Device Classifications
  - Tissue Reference Group for determining HCT/P vs BLA dividing line
  - Talking to a lawyer focused in FDA regulation

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Form of Submission: Pre-RFD v. RFD Process

Pre-RFD Process

- What You Get: Informal, non-binding FDA feedback regarding the classification of your product, and information about Lead Center assignment
- Timing: FDA aims to review within 60 days of receipt
- Format: No length limitation on submission; enables provision of more thorough analysis to FDA
- If You Disagree with FDA's Assessment: Can contact FDA to discuss its findings

RFD Process

- What You Get: Formal, binding FDA determination of product classification and lead Center assignment
- Timing: FDA must provide designation within 60 days of the RFD filing; if FDA misses this deadline, sponsor's recommendation for classification/assignment of the product becomes the designated classification/assignment
- Format: 15-page limit (including attachments)
- If You Disagree with FDA's Assessment: Can request reconsideration within 15 days of receipt of the designation letter; FDA will review and respond within 15 days of receipt (no new information can be considered); can also make a supervisory appeal directly to the Office of Special Medical Programs

(*In the 2018 Product Jurisdiction proposed rule, FDA proposed getting rid of the RFD reconsideration process, noting the OCP re-review is often futile)

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Key Considerations for Assessing Regulatory Strategies Involving Combination Products

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Combination Product Postmarket Obligations

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Postmarket Obligations

- Combination Products contain multiple constituent parts, each of which must comply with separate regulations, even if approved under a single classification
  - Historically, this created a lot of confusion… and still creates some, but OCP has made significant strides to clarifying the Agency's approach to these regulations
- Two examples of clarifications
  - Combination Product cGMPs under 21 CFR Part 4, Subpart A
  - Combination Product Postmarket Safety Reporting under 21 CFR Part 4, Subpart B

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Combination Product cGMPs

- cGMPs follow the constituent part that is being handled as part of the combination product process
- cGMPs can be tailored to specific operations related to manufacturing operation
- If drug and device constituents are being handled at a single facility, FDA recognized that a 'hybrid' drug-device cGMP system can address requirements for both constituents:

Additions to a 21 CFR Part 210/211 compliant system	Additions to a 21 CFR Part 820 compliant system
(i) 21 CFR 820.20 - Management responsibility. (ii) 21 CFR 820.30 - Design controls. (iii) 21 CFR 820.50 - Purchasing controls. (iv) 21 CFR 820.100 - Corrective and preventive action (v) 21 CFR 820.170 - Installation. (vi) 21 CFR 820.200 - Servicing.	(i) 21 CFR 211.84 - Testing and approval or rejection of components, drug product containers and closures. (ii) 21 CFR 211.103 - Calculation of yield. (iii) 21 CFR 211.132 - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. (iv) 21 CFR - 211.137 - Expiration dating. (v) 21 CFR 211.165 - Testing and release for distribution. (vi) 21 CFR 211.166 - Stability testing. (vii) 21 CFR 211.167 - Special testing requirements. (viii)21 CFR 211.170 - Reserve samples.

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Postmarket Safety Reporting

- For combination product applicants, postmarket safety reporting can follow constituents, so multiple reports may be required for a single combination product (e.g., an MDR report and field alert report, to satisfy device and drug reporting requirements)
  - Constituent product applicants are only required to report on their constituent
  - Combination product applications may be required to submit multiple reports
- Where there are multiple constituent part applicants, if one manufacturer receives information regarding a death or serious injury, or adverse drug experience, it must be shared with other constituent applicants within 5 days
- Associated recordkeeping requirements also apply

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Recent Developments and Looking Ahead

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2022 FDA Guidance and Notices

- Continued agency response to the 21st Century Cures Act
  - January 2022 Final Guidance: Principles of Premarket Pathways for Combination Products

- Prescription Drug User Fee Act VII (September 30, 2022)
  - FDA's commitment letter under PDUFA VII makes specific reference to advancing the development of combination products
  - October 2022: Docket No. FDA-2022-N-2335: Independent Assessment of Communication Through Product Quality Information Requests During Application Review; Statement of Work; Request for Comments

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Hot Topics Looking Ahead

- The integration of digital health and artificial intelligence with combination products
  - In the FDA PDUFA VII commitment letter, FDA commits to publish guidance on regulatory considerations for software that is distributed with a drug or integrated as part of a drug- or biologic-led combination product
- *Genus Medical Technologies v. FDA* (D.C. Cir. 2021)
  - FDA has long argued that devices are a subset of drugs, and therefore anything that was a device could be regulated as a drug as a matter of FDA discretion (this appears in 2017 draft guidance from OCP, for example)
  - The *Genus* court said that if a product meets the definition of a device, then it must be regulated as a device, i.e., FDA does not have discretion to regulated a device as a drug, as they have long held
  - FDA issued a notice in August 2021 asking for comments on potential reclassification of products as the result of the *Genus* decision

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What are the elements of a device definition?

- Key parts of the device definition 21 U.S.C. § 321(h).
  - Must be an article must be “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory….” (the “instrument clause of the device definition).
  - Intended for medical purposes, i.e.,
    - Recognized by USP/NF,
    - 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
    - Intended to affect the structure or any function of the body of man or other animals
  - Must not achieve its primary intended purposes through **chemical action** in or on the body, and
  - Must not depend upon being **metabolized** for the achievement of its primary intended purposes
- Key parts of the drug definition 21 U.S.C. § 321(g)(1)
  - Must be an article intended for medical purposes
  - *And must not meet the definition of a device, per Genus*

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Genus Raises Specter of Reclassification

- Reclassification has happened in the past, occasionally:
  - 1997 – FDA reclassified Albunex (previously classified as a device) as a drug, and transferred review of the sponsor's premarket approval application (PMA) from CDRH to CDER
  - 2005 – FDA various HCT/Ps (which were variously regulated as drugs, devices, or biologics) into a new HCT/P regulatory classification it created
  - 2006 – FDA reclassified heparin lock flush solutions a device-led combination products (previously regulated as a drug or drug-led combination product)
  - 2018 – FDA issued a notice of its intent to reclassify hyaluronic acid (HA) intra-articular products intended for treating knee osteoarthritis as drugs rather than medical devices
    - FDA noted that currently published scientific literature supports that HA achieves its primary intended purpose of treatment through chemical action within the body
  - 2022 – FDA indicated reclassification of certain ophthalmic products traditionally regulated as drug components as devices post-*Genus*

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Thank You!

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