Day 2 Agenda

- 9:00 – 9:50  Expedited Review & Alternate Approval Strategies
- 10:00 – 10:50  Combination Products
- 11:00 – 11:50  Current Device & Biopharma Trends
- 12:00 – 1:00  Lunch
- 1:00 – 1:50  Product Manufacturing
- 2:00 – 2:50  Product Advertising & Promotion
- 3:00 – 4:00  FDA Compliance & Enforcement
- 4:00 – 4:30  Q&A
- 4:30  Adjourn
Review

- **DRUGS**
  - OTC Monograph (over-the-counter drugs)
  - 505(b)(1) NDA (full-scale product application)
  - 505(b)(j) ANDA (generic drugs)
  - 505(b)(2) NDA (reliance on studies without a right of reference)
  - Supplemental NDA (sNDA) (for changes to approved NDA)

- **BIOLOGICS**
  - 351(a) PHSA Biologics License Application
  - 351(k)(1) Biosimilar
  - 351(k)(2) Interchangeable
  - Supplemental BLA (sBLA) (changes to approved BLA)

- **DEVICES**
  - Exempt
  - 510(k)
  - PMA
  - Determine if Class I II or III

- **Applicable to All**
  - IND or IDE
  - Registration and Listing
  - Good Manufacturing Practices/Quality System Regulation
  - Compliance
Historical Background

- Prior to 1990, FDA’s review of combination products was ad hoc and consistency in its approach across such products was elusive.

- §503(g) of the FD&C Act, created by Safe Medical Devices Act of 1990 (SMDA), allows for regulation of combination products in a rational fashion.
  - Amendments were managerial, requiring FDA to designate which center would have “primary jurisdiction” based on the product’s “primary mode of action” (21 USC 353(g)(2))
  - Does not preclude Center from requiring separate applications (e.g., NDA, PMA)
Historical Background

“Exceptional cases” can emerge that may still require separate applications filed with separate Centers.

FDA created three Inter-center Agreements (ICAs) between CDRH-CBER, CDER-CDRH, CDER-CBER.

15 years after SMDA and ICA, FDA review continued to be inconsistent, unpredictable, and lack transparency.


• Court found FDA arbitrary and capricious in assigning some contrast agents used in diagnostic equipment for cardiac dysfunction to CDER and some to CDRH.
Historical Background

- The Medical Device User Fee and Modernization Act of 2002 mandated that FDA establish the Office of Combination Products (OCP).
  - Sits within the Office of the Commissioner
  - Reporting obligations designed to ensure efficient reviews and transparent standards for all combination products
  - OCP has authority to determine which FDA Center has jurisdiction over a combination product
  - OCP also has authority to determine whether single-entity products should be regulated as drugs, biologics, or devices based on product’s primary intended effect.
Combination Product Defined

- A combination product is a one that combined a device, drug or biologic
  - No statutory definition, but statutory **distinction** in 21 USC §360bbb-2(a): “a product may be classified as a drug, device, biological product or combination product”

- 21 CFR §3.2(e)(1)-(4) articulated 4 distinct types of combination products:
  - “a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.”
Combination Product Defined

- 21 CFR §3.2(e)(1)-(4) (cont.)
  - “two or more separate products packaged together in a single package or as a unit ad comprised of drug and device products, device and biological products, or biological or 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…”
Combination Product Defined

● 21 CFR §3.2(e)(1)-(4) (cont.)
  ● “[a]ny investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect”
The Lead Center

- 21 USC §353(g)(1) requires that FDA refer a product application to a single center.
- FDA must determine the primary mode of action (PMOA) and, on that basis, choose a lead center with primary jurisdiction.
  - Example: drug PMOA will be given to CDER, but §353(g)(2) allows the agency to bring to bear any necessary resources and, accordingly, CDRH will be “consulted” on device-related aspects of the product.
  - Centers can “collaborate” or “consult”
Primary Mode of Action

“Mode of Action” (21 CFR §3.2(k))
- “the means by which a product achieves an intended therapeutic effect or action”
- Combination products have some combination of drug, biological, or device modes of action

Which is Primary? (21 CFR §3.2(m))
- “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.”
Primary Mode of Action

- What if PMOA is unclear? (21 CFR §3.4(b))
- “[i]n some situations, it is not possible to determine, with reasonable certainty, which one mode of action will provide greater contribution… to the overall therapeutic effects of the combination product.”
- FDA 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”
- If no similar combination product, then to “agency component with most expertise related to the most significant…questions posed….”
Primary Mode of Action

- PMOA Contact Lens Example:
  - contact lens combined with a drug product to treat glaucoma
  - Has both a device mode of action (to correct vision) and a drug mode of action (to treat glaucoma)
  - Both MOAs are independent; neither appears to be subordinate.
  - Application of the PMOA Algorithm as follows:
    - CDRH regulates devices to correct vision; CDER regulates drugs for glaucoma
    - No such product has been submitted for review before
    - Neither center regulates product with similar safety and effectiveness questions as a whole
    - Most important safety and effectiveness questions pertain to the drug, whereas the contact lens is routine.
    - CDER gets the assignment because CDER has most expertise.
Primary Mode of Action

- Multiple Marketing Applications for Combination Product (21 CFR §3.4(c))
  - “designation of one agency component as having primary jurisdiction for the premarket review and regulation of a product does not preclude...in appropriate cases, the requirement by the FDA of separate applications.”
- FDA has stated that this would be the “exception rather than the rule” and those reviews would be “coordinated to the greatest extend possible” (56 Fed. Reg. at 58,755)
Choice of Legal Authorities

- FDA is silent regarding whether the choice of Center requires application of that Center’s legal authorities.
- “discretion to decide which statutory authorities it [will] use in regulating a particular combination product”
- Many questions re: application of post-marketing regulations for combination products
  - 2013: OCP issued Final Rule on Application of GMPs to Combination Products (codified at 21 CFR pt. 4, Subpart A)
  - 2009: OCP issued proposed rule on adverse event reporting framework for combination products (not final)
    - Follows the premarket application type? If two, which one?
Request for Designation (RFD)

- Submitted where center jurisdiction for combo product or single entity product is in question for purposes of determining jurisdiction.
- Should be submitted prior to submission of a pre-approval application.
- 21 CFR §3.7(b) elements must be included:
  - Product description, intended use, sponsor’s recommendation
- OCP Guidance for Industry, How to Write a Request for Designation (RFD) (April 2011)
Request for Designation (RFD)

- **RFD Process**
  - 15 page limit
  - Submit to OCP
  - OCP will review for administrative completeness and determine if sufficient to determine jurisdiction
  - OCP will issue letter to Sponsor acknowledging filing or the information needed to complete the RFD.
  - If FDA does not respond to the RFD within 60 days, the Sponsor’s recommendation becomes the center with jurisdiction.
  - 15 days to ask FDA to reconsider its designation
Definitions Revisited

- OCP tasked with making jurisdictional decisions about single entity drugs or devices
- FD&C Act statutory definitions play key role
  - Drug = “article intended to prevent, treat, or diagnose disease”
  - Device = “does not achieve its primary intended purposes through chemical action within or on the body of man...and which is not dependent on being metabolized for the achievement of its primary intended purposes”
- What is “chemical action”?

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Definitions Revisited

- Draft Guidance, Interpretation of the Term “Chemical Action” in the Definition of Device under Section 201(h) of the FD&C Act (June 2011)
- Draft Guidance, Classification of Products as Drugs and Devices & Additional Product Classification Issues (June 2011)
  - If chemical action is unrelated to primary purpose, it can still be a device.
  - If chemical action is primary purpose, but occurs outside the body, it may be a device
  - If chemical action relates to any primary purpose, it must be a drug
Definitions Revisited

- PREVOR Litigation
  - PREVOR makes Diphoterine Skin Wash, a liquid substance intended to help prevent chemical burn injuries that occur due to accidental exposure to chemical agents. “First response” method to spray DSW onto skin to physically and mechanically remove or wash away offensive chemical.
  - Secondary purpose is to neutralize acids and bases washed off the skin.
  - OCP ruled it’s a drug-device combination product with a drug PMOA.
Definitions Revisited

- PREVOR Litigation (cont.)
  - Prevor I
    - Court held that FDA’s guidance mentioning “any purpose” for drug designation impermissible altered statutory device definition, which centers on “primary”
    - “even in part” was also erroneous because that is not equivalent to “primary intended purpose.”
    - Case remanded to FDA for scientific justification
  - Prevor II
    - FDA responded with “meaningfully contributes” threshold.
    - Court held that this was lower that “achieves” standard in statute and, again, remanded.
Cross-Labeling Challenges

- FDA regulation of product labeling is a central tenet of the regulatory paradigm
- “Type 3” Combination Products (where the approval of one modality requires a corresponding labeling change to a previously approved product) present labeling challenges
  - Conforming changes require the cooperation of the manufacturer of the previous product (e.g., contrast agent used in imaging device)
  - Right of reference often required
  - Often little or no incentive for cooperation
Cross-Labeling Challenges

- Potential Work-arounds Introduce Problems
  - Broad indications on device w/o naming specific drugs (thereby not being true combo, but yet advertising/promotion issues are vexing)
  - Device company can include substantial information about the drug product administration on its label w/o mentioning specific drug (but still may need right of reference so FDA can review the drug data; end user confusion is labels are different)
  - “Umbrella Labeling” allows new indication for imaging drug to be added to device labeling even if the indication is not in the drug labeling
Cross-Labeling Challenges

- Potential Work-arounds Introduce Problems (cont.)
  - Device company could submit an NDA under 505(b)(2) of the FD&C Act (where no right of reference is required) but that company would need to be prepared to manufacture the drug component.

- Congressional Action likely required to remedy the cross-labeling issue; reform urgently needed as status quo hinders innovation.