Industry Perspectives on Combination Products - Challenges and Opportunities

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EXAMPLES

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

• Catheter with antimicrobial coating
• 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

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
Combination Products

• Can impact regulatory processes for all aspects of product development and management
  – Preclinical testing
  – Clinical investigation
  – Marketing applications
  – Manufacturing/quality control
  – Adverse event reporting
  – Promotion and advertising
  – Post-approval modifications
Device Industry Perspective

• Combination product review process can be complex and daunting
  – 510(k) products have shorter development cycles than drugs
  – Extensive quantity and depth of data (especially for CDER review)
  – May require different type of technical/scientific and regulatory expertise
  – Potentially conflicting requirements (Quality Systems-stability, process validation, etc.)
Industry Challenges

• “Culture shock” for those who may be working with CDER for the first time
  – CDRH viewed as more accessible
  – More limited access to CDER reviewers and management
  – More formal/prescriptive engagement process with CDER
  – Lack of familiarity with “Rules of Engagement” for each Center
General Regulatory Differences

• Each Center has a different set of laws and regulations acting as the basis for its authority
  • Food, Drug and Cosmetic Act
    – Drugs and Devices
  • Public Health Services Act Biologics
  • Code of Federal Regulations (21 CFR)
    – 314 Drug
    – 600 Biologics
    – 800 Device

• Each Center is organized differently

• Least Burdensome provisions of the FDA Modernization Act do not apply to the complete combination product (only apply to the device component(s))
General Regulatory Differences

• Types of meetings
• Clinical studies
  – CDER- IND (Phase 1, 2 and 3)
  – CDRH- IDE (feasibility, pilot, pivotal)
• Different application review timelines
• Different requirements and timelines for post market changes (e.g., manufacturing, new facility, sterilization)
• Different user fees
Complexities

• No consistent application format
• High degree of regulatory uncertainty
  – Regulatory path
  – Data Requirements
  – Timeframe to approval
  – Requirements established on a “case by case” basis

• Unknown or limited applicability of precedence
Goals

• Improve the consistency of combination product reviews and address delays in the review process
  – Greater clarity regarding designation of combination products (PMOA)
  – Better coordination and agreement among FDA Centers- data requirements and timeliness
  – Greater certainty and predictability of the review process
FDA Initiatives

• FDA efforts to improve the process
  – Formation of the Combination Products Policy Council
  – Lean process mapping
  – Commissioning of the Intercenter Consult Process Study for Combination Product Review, whose results were published in October, 2015

• Highlighted the lack of consistency and clarity of the review process, including:
  – Different policies, practices and review standards among Centers
  – Separate review and tracking systems between Centers
  – Unclear communication channels
  – Lack of resources for consult reviews
21\textsuperscript{st} Century Cures

• The 21\textsuperscript{st} Century Cures Act (Act) was passed by the House on November 30, 2016, and the Senate on December 7, 2016

• It was signed into law on December 13, 2016

• The Act contains three primary titles that address acceleration of medical product innovation, development, and delivery
21st Century Cures

- Will modify meeting evidentiary standards for combination products based on incremental risk
- Should complement FDA efforts to streamline and implement process improvement
  - Policy and actions of the Combination Products Policy Council are not binding
  - Statutory changes are necessary to ensure fundamental changes in approach (e.g., the determination of PMOA based on chemical action)
Combination Products § 3038

• Plan similar to Pre-sub
• PMOA not based on any degree of chemical action
  – Agreement to work with sponsor to determine
• Incremental Risk
• Data reference for approved drug
• Flexibility on cGMP
• Likely to need implementing regulation and/or guidance
“Pre-Sub” Meetings

• Everyone must be at the table and decisions are binding
  – Historically, CDER could overturn past decisions by CDRH

• Different review interaction processes
  – CDRH- No new questions permitted later in review unless triggered by new data or information
  – CDER- Does not have this same restriction
Primary Mode of Action

• Not based on *any* degree of chemical action (default to CDER)

• Requirement for FDA to provide scientific rationale for classification decisions
  – If disagreement, sponsor needs to do a study to determine PMOA (binding)

• Current FDA draft guidance will need to be withdrawn in light of 21st CC
Incremental Risk

• Focus on the relevant questions of safety and effectiveness (i.e., incremental risk)
  – New questions posed by combination product

• Incremental, risk-based approach and process
  – Increase certainty and efficiency around the regulatory review and lifecycle for combination products (including post market modifications)
Data Reference for Approved Drug

• Reliance on existing safety and effectiveness information (e.g., drug and device)
  – 505(b)(2) process allows an approved drug w/o patent protection or exclusivity to be referenced in application (e.g., lidocaine)
  – Not allowed for Biologics
  – Could reference existing publically available data
Flexibility on cGMPs for Combination Products

Provides a streamlined approach to comply with cGMP requirements

- *Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (Issued Jan 2017)*

- Single entity combo product - two ways to demonstrate compliance with cGMPs
  - Meet all QS requirements (21 CFR 820 and 21 CFR 211) or
  - Choose a streamlined approach (comply with either reg provided that additional specific aspects of other GMP framework are also incorporated)
  - FDA guidance on adverse event reporting
Dispute Resolution

• Formal dispute resolution process
  – Include timelines to provide sponsors with additional clarity and predictable timelines

• Sponsor involvement throughout regulatory review process
  – In best position to provide information and frame issues
Thank you for your attention
QUESTIONS
FDA’s Implementation of 21st Century Cures

• How does FDA plan to implement 21st CC?
• Will FDA need to change the regulation or issue new guidance?
• How can industry participate in the implementation process?
FDA Internal Process Reform

• How do FDA’s internal process reforms seek to align the review policies between the respective Centers?

• What reporting procedures and level of transparency does the CPPC intend to use when implementing these activities?

• How will the CPPC interact with the OCP?

• Can sponsors request participation of key FDA staff if they present their issues to the CPPC?

• What are the criteria for the issues to meet the threshold for consideration by the CPPC?