Combination Products Determination and Review Processes: Impact of 21st Century Cures Act and Recent FDA Initiatives

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Agenda

- 21st Century Cures
  - Definitions
  - Procedural mechanisms
  - 1 v. 2 applications
  - Additional provisions
- FDA initiatives
  - Combination Products Policy Council
  - Pre-RFD submission
- PDUFA commitments
  - Including, inter-center communications

21st century cures and regulatory definitions

1. What Am I?

- Drug
- Device
- Biological Product

- Combination Product

A device cannot achieve its *primary intended purposes* through chemical action. Section 201(h) of the Act.

What does achieve mean?

2. Where Do I Go?

If the *primary mode of action* (PMOA) of a combination product is attributable to the:

- Drug constituent part, then CDER has primary jurisdiction
- Device constituent part, then CDRH has primary jurisdiction
- Biological product constituent part, then CBER or CDER has primary jurisdiction.

Section 503(g)(1)(D) of the Act.

PMOA

Mode of action expected to make greatest contribution to overall therapeutic effect of product.

Section 503(g)(1)(C)

In determining PMOA, FDA cannot choose drug "solely because the combination product has any chemical action."

Section 503(g)(1)(E)

21st Century Cures: §3038 Combination Product Innovation

New Procedural Mechanisms

- In determining the primary Agency center for review of a combination product, FDA may not determine that the product's primary mode of action (PMOA) is that of a drug or biological product solely because it has any chemical action within or on the human body.
- If a combination product sponsor disagrees with FDA's PMOA determination, the sponsor may request, and FDA must provide, a substantive rationale for the determination that references the scientific evidence relied upon by FDA. The sponsor then may propose 1 or more studies (which may be clinical, nonclinical, or both) to establish the relevance, if any, of chemical action in achieving the PMOA of the combination product. If the sponsor and FDA agree on the study design and the sponsor conducts such studies, then FDA must consider the data in reevaluating the PMOA.

21st Century Cures: New Procedural Mechanisms cont.

- If a combination product sponsor submits a written meeting request, FDA generally must meet with the sponsor within 75 calendar days. This meeting may address the standards and requirements for market approval or clearance, post-market modifications, and applicable good manufacturing practices for the combination product.
  - FDA may, however, defer addressing issues if scientific or other information is not available or agreement is not feasible when the meeting is requested.
  - Any agreement reached in the meeting must remain in effect except upon: (1) the written agreement of FDA and the sponsor; or (2) a decision by the director of the review division of the primary agency center (or someone more senior) that an "issue essential to determining whether the standard for market clearance" or another applicable statutory standard is met was identified after the agreement or that deviating from the agreement is "otherwise justifiable based on scientific evidence, for public health reasons."

21st Century Cures: Additional Provisions

Approved Constituent Part

- FDA may require that the sponsor of a combination product containing an "approved constituent part" submit only those data and information that FDA deems necessary to meet the statutory standard for marketing authorization.
- FDA must consider any incremental risks and benefits posed by the product, "using a risk-based approach and taking into account" prior findings of safety and effectiveness or substantial equivalence for the relied-upon "approved constituent part."

21st Century Cures

Approved Constituent Part

- Device submissions that rely on an "approved drug" constituent part must include patent certifications or statements as are required for section 505(b)(2) applications and comply with the notice provisions regarding paragraph IV certifications.
- The timeline for approval of these applications will depend on the type of patent certification made by the applicant.
- Approval of the combination product also must await expiry of any blocking new chemical entity exclusivity, three-year Hatch-Waxman exclusivity, pediatric exclusivity, qualified infectious disease product ("QIDP") exclusivity, and orphan drug exclusivity applicable to the "approved drug."

21st Century Cures

Approved Constituent Part

- Section 520(h)(4) of the FDCA previously authorized FDA to rely on data in a PMA six years after its approval in approving a subsequent device or reclassifying a device.
- This section was amended to provide that no information in a PMA may be used to approve or clear another device submission for a combination product containing an approved drug constituent part unless the submitter complies with the patent certification and notice requirements that would apply to a section 505(b)(2) applicant, and that the subsequent device submission is subject to the exclusivity rights applicable to the approved drug.

21st Century Cures

Office of Combination Products

- OCP must:
  - oversee the alignment of feedback regarding reviews involving multiple agency centers
  - ensure that there is a designated primary point of contact in the lead center for a combination product sponsor
  - ensure that meetings between FDA and a combination product sponsor are attended by each agency center involved in the review "as appropriate," and that each consulting center follows applicable guidance
  - ensure that each consulting center completes its premarket review and provides the results to the lead center "in a timely manner"
- Communications from the primary agency center shall be considered communications from the FDA on behalf of all agency centers involved in the review "to the extent consistent with other provisions of law and the requirements of all affected agency centers"

21st Century Cures

Required Guidance and GMP

- Within 4 years of enactment and after public comment, FDA must issue final guidance addressing:
  - (1) the structured process for managing pre-submission interactions with sponsors developing combination products;
  - (2) best practices for ensuring that agency feedback in such interactions represents FDA's best advice based on the information provided; and
  - (3) procedural matters for the meetings described above and agreements reached therein.
- Within 18 months of enactment, FDA must publish a proposed list of combination products and manufacturing processes for which GMP requirements may vary from 21 C.F.R. section 4.4 or for which the requirements of section 4.4 can be satisfied through alternative or streamlined mechanisms. After a public comment period, FDA must publish a final list in the Federal Register and then periodically review it.

21st Century cures -- separate marketing applications

FDA shall conduct the premarket review of any combination product under a single application, whenever appropriate.

Section 503(g)(1)(B) of the Act.

Nothing in this subsection shall be construed as prohibiting a sponsor from submitting separate applications for the constituent parts of a combination product, unless FDA determines that a single application is necessary.

Section 503(g)(6) of the Act.

The designation of one agency component as having primary jurisdiction … does not preclude … in appropriate cases, the requirement by FDA of separate applications.

21 CFR 3.4(c)

Number of Marketing Applications for a Combination Product

… for most combination products, a single marketing application is sufficient for the combination 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.

In certain circumstances … a single marketing application is the only feasible option, such as: … combination products that are chemically, physically, or otherwise combined ….
Drugs and devices are generally approved or cleared only as finished products, not as components for further manufacture.

Number of Marketing Applications Concept Paper

FDA Initiatives

Combination Products Policy Council—established April 2016

- The Combination Products Policy Council provides a senior-level forum to establish combination product policy across the FDA and ensures that policy is implemented in a consistent manner throughout the Agency.
- The Council is chaired by the Deputy Commissioner for Medical Products and Tobacco (OMPT) or his/her designee, comprised of the following members:
  - the Center Directors or their designee and one representative from CDER, CDRH, and CBER
  - the Office Directors or their designee from the Office of Combination Products and the Office of Special Medical Programs.

FDA Initiatives

Combination Products Policy Council cont.

- The Council's charter states that:
  - the Council will prospectively identify regulatory and scientific policy issues to address and function as a forum for developing guiding principles related to combination products, cross-labeled products, and medical product classification
  - the Council will resolve disagreements among Centers, the Office of Combination Products (OCP), and/or sponsors on activities and policies related to medical product classification and the clearance/approval of combination products and cross-labeled products
  - the Council does not meet directly with sponsors

FDA Initiatives

Combination Products Policy Council Docket

- Docket established in January 2017 to receive suggestions, recommendations, and comments for topics from interested parties, including academic institutions, regulated industry, patient representatives, and other interested organizations, on policy issues that may be considered by the Council.
- These comments are to help the Agency identify and address combination product policy issues that need clarification through guidance, notice and comment procedures, or other means.
- Comment period closed in April 2017.

FDA Initiatives

Combination Products Policy Council FR Notice-Establishment of Docket

- FDA envisions a variety of combination product policy topics that may be appropriate for consideration by the Council, which typically would meet one or more of the following criteria:
  - A novel combination product policy issue requiring senior management input;
  - An identical issue on which FDA seems to have taken inconsistent combination product policy positions;
  - An existing combination product policy position that should be reconsidered in light of scientific or regulatory advances; or
  - A combination product policy that may be triggered by a specific combination product, but that will be applicable to other combination products.

FDA Initiatives

Pre-RFD Submission—Draft Guidance for Industry, January 2017

- A Pre-RFD is a clear and concise written submission that a sponsor may submit to OCP to request FDA's preliminary, nonbinding assessment of:
  - (1) the regulatory identity or classification of a product as a drug, device, biological product, or combination product, and/or
  - (2) whether CBER, CDER, or CDRH will regulate the product if it is a non-combination product, or which of those Agency Centers will have primary jurisdiction for the premarket review and regulation, if it is a combination product.
- OCP will determine if the submission contains information to make an assessment within business 5 days and will provide a written preliminary classification and/or jurisdictional assessment of the product within 60 calendar days of receipt, or will advise that additional review time is needed.

FDA Initiatives

Pre-RFD Submission—no page limit

- The Pre-RFD should include:
  - a description of a product,
  - proposed use or indications,
  - and a description of how a product achieves its intended therapeutic/diagnostic effects.
- The Pre-RFD may also include:
  - relevant data/studies,
  - a description of related products,
  - and/or a sponsor recommendation as to a product's jurisdiction or PMOA if it's a combination product.

PDUFA Commitments

More efficiently, effectively and consistently review CP submission

- Expand staff capacity and capability in Centers and OCP: cGMP, engineering, HF, bridging studies and labeling
- Streamline consult processes, develop MAPPs
- Identify Points of Contact in OCP, Centers
- Review HF protocols within 60 days
- Train staff in CP development
- Engage 3rd party to assess review practices
- Publish draft guidance or updates: bridging studies and IFU