Priorities of the Combination Products Coalition

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What is the CPC?

Formed in 2003

CPC member companies represent the drug, device and biologics industries

Mission: Improve the regulatory environment for combination products

How?

- Develop and advocate policy positions related to combination product regulation
- Engage with FDA through educational programs to work through complex regulatory issues impacting combination products
CPC 2014 Combination Product Survey

Participants are all manufacturers of various types of combination products:

- 84
  - Represented 84 separate product experiences with FDA review process

- 3
  - Three participants submitted 10 or more combination products for pre-market review in the past 5 years
CPC Survey: Results

Have you encountered problems during FDA review?

100%
CPC Survey: Results

What were the origins of the problems?

- 54% CDER did not follow CDRH advice
- 15% CDRH did not follow CDER advice
- 54% Lack of adequate coordination among reviewing Centers
- 77% Requests received late in review process
CPC Survey: Results

In which areas did you receive conflicting information?

- Human factors testing: 64%
- Actual-use Testing: 31%
- Instructions for use: 54%
- Other: 31%
Which was true when you had a conflict during review?

- 84% CDER supported its position using scientific evidence
- 8% CDER offered little or no explanation for its position
- 8% Other
FDA Issues Identified

Issues distilled from survey and interviews with willing participants:

1. Lack of coordination between FDA groups, across Centers and within Centers
2. Insufficient communication with sponsors
3. Inadequate scientific and regulatory justification for decisions
CPC Key Focus Areas (FY 2017)

1. FDA Process
2. Marketing Submissions
3. Human Factors
4. Clinical Trials
5. Cross-Labeled/Co-Packaged Combination Products
6. Postmarket Safety
FDA Process

Issue:

- Policymaking in the combination product area can take too long, given the need to forge a consensus among different centers.
- Varying requirements for different application types make it challenging for FDA to coordinate consistent and efficient combination product reviews.
- Uncertainty in how the combination product provisions from the 21st Century Cures Act will be interpreted.
FDA Process

Priorities:

- Streamline policymaking
- Improve intercenter coordination and communication during combination product reviews
- Develop a strategy to engage with FDA with respect to the implementation of the combination product provisions of the Cures Act
FDA Process and 21st Century Cures

This is an important area for guidance development

- FDCA 503(g)(1)(E): “In determining the primary mode of action of a combination product, the Secretary shall not determine that the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body.”
- Establishes a new process for dispute resolution to complement 21 C.F.R. 10.75.
  - Allows for sponsors to “propose one or more studies (which may be nonclinical, clinical, or both) to establish the relevance, if any, of the chemical action in achieving the primary mode of action of such product.”
  - Directs FDA and sponsor to work toward agreement on such studies.
Marketing Submissions

**Issue:**
- Inconsistent regulatory expectations with respect to the content, structure and requirements for both marketing and post-approval submissions for combination products

**Priorities:**
- Advocate for consistent and predictable submission requirements
- Collaborate with FDA on an approach for postmarket changes for combination products
- Influence regulator positions on location of device-related content within CTD based regulatory submissions
Marketing Submissions

Sample Activities

- Met with FDA in 2016 to discuss concerns surrounding the eCTD Technical Conformance Guide
- Developed a template eCTD reviewer’s guide
  - Guide aims to assist manufacturers in developing roadmaps to allow FDA reviewers to easily navigate the device and combination product related content in NDA and BLA submissions
- Developed document outlining guiding principles and examples for handling postapproval changes
- Submitted comments on EMA’s concept paper re: developing a guideline on quality requirements for combination products
Human Factors

**Issue:**
- Inconsistent and late-stage IFU feedback creates a burden for industry

**Priorities:**
- Influence the IFU review process to enable earlier, more consistent and data driven health authority input on instructional material
- Collaborate with European health authorities to work toward global regulatory consistency in HF approach for combination products
Human Factors

Sample Activities

- Provided comments to FDA’s draft guidance documents re: (1) HF studies for a combination product submitted in an ANDA and (2) demonstrating interchangeable with a reference product

- Similar comments on both draft guidances

- Key feedback to FDA:
  - Improve alignment between the draft guidances and existing FDA human factors guidance and recognized US and international standards
  - Focus comparative analyses on risk, not use error rates
  - Describe human factors studies as qualitative research (to assess adequacy of the product user interface) rather than quantitative research (to assess the capabilities of users)
Clinical Trials

Lack of clarity with respect to:

- The clinical data requirements when bridging to a new drug or device component for the combination product; and

- Allowable leveraging of prior clinical experience based on established device platforms, similar drug component attributes and/or representative user group
Clinical Trials

Key Questions

- When is new bridging data required for a submission of a new combination product?
- If new bridging data is required for a submission, what data is required?
- If new bridging data is required, can a company obtain or create such data outside of the clinical trial setting?
Clinical Trials

Priorities

- Develop consolidated industry position on bridging requirements from comparability bench testing to clinical safety and efficacy studies
- Develop criteria for when appropriate to include leveraging of existing clinical device/drug experience in support of the introduction of a new drug or device component
- Prepare case studies that illustrate successful comparability testing scenarios in building the scientific bridge to present at CPC-RAPS educational program to be held in November 2017
Clinical Trials and 21st Century Cures

FDCA 503(g)(3): “For purposes of conducting the premarket review of a combination product that contains an approved constituent part . . . the Secretary may require that the sponsor of such combination product submit to the Secretary only data or information that the Secretary determines is necessary to meet the standard for clearance or approval, as applicable, under this Act or the Public Health Service Act, including any incremental risks and benefits posed by such combination product, using a risk-based approach and taking into account any prior finding of safety and effectiveness or substantial equivalence for the approved constituent part relied upon by the applicant . . .

This is another key area for guidance development – bridging in the context of combo products is often an areas of concern for developers due in part to differences of Center philosophies.
Cross-Labeled/Co-Packaged Combination Products

**Issue:**

- Lack of clarity and consistency in the application of FDA policies and regulations for cross-labeled combination products (e.g., Digital Health products; differences between cross-labeled vs. co-development products; one-way vs. two-way labeled products)

**Priorities:**

- Assist industry in preparing for FDA questions and provision of evidence related to cross-labeled combination product expectations/requirements

- Advocate for greater clarity, transparency and predictability in FDA cross-labeling policies and application of combination product regulation
Postmarket Safety

Issue:

- Challenges in industry implementation of the 2016 final rule on postmarket safety reporting for combination products
- Divergence in thinking and approach between FDA and the world (EU, Japan, Australia) on the topic of postmarket safety

Priorities:

- Engage with FDA to explore the challenges and preparation necessary for implementation of the 2016 final rule on postmarket safety reporting
- Advocate for alignment in global approach to postmarket safety as the industry rapidly evolves
Three case studies on software with pharmaceuticals:

- Adherence Enhancing Digital Health Products
- Disease Management Digital Health Products
- Clinical Guideline Interpretation Products

Presently no clear guidance

Presented 34 questions covering:

- Scope of FDA regulation
- Requirements if regulated
QUESTIONS