Combination Products Coalition

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VIA FEDEX & ELECTRONIC SUBMISSION

September 28, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2020–N–1550 New Drugs Regulatory Program Modernization: Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's *New Drugs Regulatory Program Modernization: Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation* and appreciates FDA's objective to more effectively communicate the basis for its decision on applications.

The comments provided herein and further detailed in Appendix A provide responses to several questions posed by FDA for the October 30 virtual workshop and are in addition to CPC's initial comments submitted on August 26, 2019 on this topic (Docket No. FDA-2019-N-2012: *New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication*).

Furthermore, prior to submitting these comments, CPC provided feedback to ONDPublicMTGSupport@fda.hhs.gov requesting an additional Integrated Review example that includes reviews on a combination product as without such an example (and knowing the level of detail that would be included in an integrated review memo for combination product-related topics such as clinical data, including PK comparability studies and real-life patient handling studies, human factors studies, design verification and validation activities, bridging-related information, etc.), it was difficult for CPC to respond to several of FDA's proposed questions.

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

While the CPC supports the integrated review template and acknowledges the value of implementing a system that effectively communicates the basis for new drug approvals, CPC is concerned that the proposed integrated review template will lack the level of detail currently provided in the discipline-specific review memos. CPC members regularly reference these publicly available discipline-specific review memos for combination products to better understand the Agency's current thinking on a variety of combination product submission requirements. For example, DMEPA and CDRH review memos are referenced for human factors testing, risk documentation, and labeling requirements; CDRH review memos are referenced for device constituent and combination product performance and testing requirements; CDER clinical/cross discipline team review memos are referenced for clinical data and real-life patient handling study requirements; Clinical Pharmacology review memos are referenced for bioequivalence/bioavailability study requirements; and DMPP review memos are referenced for labeling and Instructions for Use requirements, including formatting and usability-related topics.

Additionally, these review memos may include justification for why a specific request has been made and would typically provide insights regarding the types of responses that FDA finds acceptable for a given request. Also, knowing the source of the request can help industry understand the context and scope of the request. As such, CPC strongly requests that, as FDA implements the integrated review document, the discipline-specific review memos remain publicly available to ensure full transparency and understanding of the Agency's current thinking with respect to combination product requirements. The availability of these FDA review memos has been extremely valuable to industry, FDA, and ultimately combination product users as the review memos facilitate more complete filings, which leads to fewer FDA concerns and shorter FDA review and approval timelines, thus reducing time-to-market for combination products designed to positively impact patient experiences and outcomes. This information is particularly important as policies and regulatory requirements for combination products continue to evolve.

Furthermore, although CPC members are most concerned with the combination product-related information listed above, our member companies are also interested in continued access to all information currently made publicly available following a drug/biologic approval. This information includes, but is not limited to, pre-submission correspondence, inquiries and responses, review memos, and inspection report summaries or decisions to defer inspections.

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We appreciate the opportunity to provide input on the questions posed by FDA and look forward to participating in the October 30 virtual workshop.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

CC: ONDPublicMTGSupport@fda.hhs.gov

Appendix A: Responses to FDA Questions Regarding Integrated Review Documentation

FDA Question	CPC Recommendation and Rationale
1. We are interested in preserving for stakeholders what they find most useful in FDA reviews.	
a. Comparing the Integrated Review to previous reviews, is there any information you are having difficulty locating?	As noted above, since the two example reviews provided minimal combination product-related content, CPC has no comment at this time.
b. Are you able to use the Integrated Review for the same purpose that you used previous reviews? If not, please provide specific examples.	As noted above, since the two example reviews provided minimal combination product-related content, CPC has no comment at this time.
2. We are interested in specific recommendations about any areas of the Integrated Review documentation of the Integrated Assessment that can be improved to meet the needs of stakeholders.	a. For combination products approved by CDER as supplements to NDAs/BLAs, Integrated Reviews should be provided if a new device constituent part was approved. Supplement review memos of these new product presentations have only been rarely provided in the past. b. To facilitate location of combination product and device-related content in the integrated review, o provide a specific section for reviews of information related to combination products including device constituent parts; and o add a specific section for FDA information requests (and include in the table of contents) c. FDA information requests should include: o reason for the request;

FDA Question	CPC Recommendation and Rationale
	○ identification of who (which Division or Center) originated the request; and ○ sponsor response, consulting reviewer feedback and resolution. d. Include enhanced summaries of pre-submission correspondence to highlight the FDA issues that were discussed prior to the submission and therefore, would not be otherwise apparent to industry. e. Include summary of bridging/leveraging (per FDA guidance *Bridging for Drug-Device and Biologic-Device Combination Products*) (e.g., human factors data, clinical data, design verification data, etc.) along with a summary of FDA's determination of acceptability or non-acceptability. f. Include consistent summaries of clinical requirements and submitted clinical data with the combination product or why clinical data was not necessary. g. Include consistent summaries of human factors requirements and submitted human factors data for the combination product or why human factors data was not necessary. h. To facilitate understanding of all issues pertinent to the combination product and/or device approval, include a full review of the associated issues (e.g., clinical requirements (including real-life patient handling and pharmacokinetic (PK) comparability studies), device delivery requirements, human factors, essential performance requirements (EPRs), summary of design verification and validation activities (including test result tables where relevant, CDRH and DMEPA review checklists, summary of release testing, quality systems, manufacturing, etc.)). i. Further details on specific topics pertinent to combination products that would aid sponsors in proactively addressing future FDA concerns during combination product development are listed below. ○ Combination product PK comparability study(ies) ▪ study subjects (healthy subjects vs. patients; male vs. female)

FDA Question	CPC Recommendation and Rationale
	▪ study designs (crossover vs. parallel) ▪ injection sites (single injection site vs. multiple injection sites) ▪ sample size (including whether statistically powered vs. empirically determined) ▪ primary and secondary endpoints ▪ statistical analysis methods (e.g., ANOVA, ANCOVA) ▪ summary of whether bioequivalence (i.e., 0.80-1.25) was demonstrated • summary for why a non-bioequivalent PK comparability study for a combination product study is acceptable or summary of subsequent data required for approval ▪ PK-related information requests, including the reason for the request and associated sponsor response o Real-life patient handling study ▪ summary of data submitted and why it was considered acceptable for approval ▪ relevant study design details including: • number of participants • length of study • primary and secondary endpoints • number of injections per participant / total number of injections • questionnaires administered or interviews conducted (at what visit were they administered, what type of information was requested) • overview of training received o Human factors validation ▪ study objective(s) ▪ test environment and conditions of use ▪ whether training was provided

FDA Question	CPC Recommendation and Rationale
	▪ user group details (number and type of test participants), including justification for selection of user groups ▪ user tasks description and categorization (including tasks identified as critical tasks) ▪ summary of findings and conclusions, including issues observed and risk mitigation measures employed ▪ FDA's analysis and opinions about the sponsor's data/analysis for each task ▪ human factors-related information requests, including the reason for request and associated sponsor response (including human-factors-related labeling requests, rationale for requiring a drug-only/non-combination product) usability study, etc.) o Labeling ▪ patient labeling (DMPP) reviews (applicable for all products including combination products with device constituent parts) ▪ FDA's methods and criteria for assessment of the format, layout, and wording of patient Instructions for Use and Quick Start/Reminder Guides ▪ requested changes to the Instructions for Use and how they were resolved ▪ requested changes to the product and carton labeling j. If the integrated review approach is applied to generic products, clarification regarding FDA's determination for the regulatory pathway and 'sameness' criteria for complex generic products that are combination products. k. Discuss use of any digital recording methods used during clinical studies.
3. We are interested in stakeholders' views regarding the advantages and disadvantages of an interdisciplinary assessment presentation of key review	<u>Advantages</u> CPC identified several advantages with the new integrated review approach. Specifically, the integrated review memo eliminates duplication of content and makes location of information easier as all information regarding a submission

FDA Question	CPC Recommendation and Rationale
issues and the resultant integration of the assessments of multiple disciplines into a single Integrated Review document.	is in one document and more easily searched (if included in the integrated review), whereas currently, content may be located in multiple review memos. CPC found it easier to locate the following information: o Submission regulatory history o Benefit-risk assessment o FDA review team o Key review issues o Consult review requests <u>Disadvantages</u> As noted above, since the two example reviews provided included minimal combination product-related content, it was difficult to know what level of detail would be included for combination product-related topics. As such, there is the potential that integrated reviews lack the level of detail currently provided in the discipline-specific review memos. For example, information regarding why a specific request has been made and why FDA found the response acceptable may be missing. As such, CPC requests that individual review memos be maintained in case useful information is missing from the integrated review memo.
4. We would like to know whether the new format of the Integrated Review documentation for the Integrated Assessment provides clarity of benefit-risk assessments and informs your knowledge of FDA's basis for making decisions.	If the information that we have requested is provided, CPC confirms that the Integrated Assessment has the potential to provide clarity of benefit-risk assessments and inform sponsor knowledge of FDA's basis for making decisions.