

DATE: October 14, 2015

TO: Associate Commissioner for Planning

FROM: Deputy Commissioner for Medical Products and Tobacco

SUBJECT: Combination Product Review, Intercenter Consult Process Study

Thank you for conducting an independent assessment of the combination product intercenter consult process and sharing with me your Combination Product Review, Intercenter Consult Process Study Report. Combination products, which combine drugs, devices, and/or biological products with one another, are a growing and important category of therapeutic and diagnostic products. Enabling and enhancing their effective, efficient, transparent, and consistent regulation is a priority for my office and the Agency.

I particularly appreciate the efforts you made to ensure substantial engagement both from regulated industry and from staff across all three medical product centers and the Office of Combination Products in developing your report. It is encouraging to see that issues identified in the report are also issues on which the medical product Centers, the Office of Special Medical Programs, and OCP have already been working together to resolve, with some improvements in place and others in process. In these respects, the report is not only instructive but reinforcing of initiatives already underway.

In particular, I note the efforts of the medical product Centers, OSMP, and OCP, consistent with report recommendations, to: issue further guidance to inform premarket reviews, including draft guidance on human factors scheduled to issue this year (see recommendation 1); simplify and rationalize access to information technology systems for staff across all three medical product Centers to enable efficient review of combination product submissions (see recommendation 2); enhance current standard operating procedures to ensure consults are issued and addressed in a timely manner (see recommendation 3); and maintain current contact information and organizational charts to ensure immediate access to the right expertise across all three medical product Centers and OC to address regulatory questions for combination products (see recommendation 4).

I endorse the report and these recommendations, direct the medical product Centers, OSMP, and OCP to continue to work on their implementation, and encourage them to look to my office as a resource to support these endeavors.

A handwritten signature in black ink, appearing to read "R. Califf", written in a cursive style.

Robert M. Califf, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. Food and Drug Administration

Combination Product Review
Intercenter Consult Process Study
October 14, 2015

Office of Planning
Office of Policy, Planning, and Legislation
Office of the Commissioner

Table of Contents

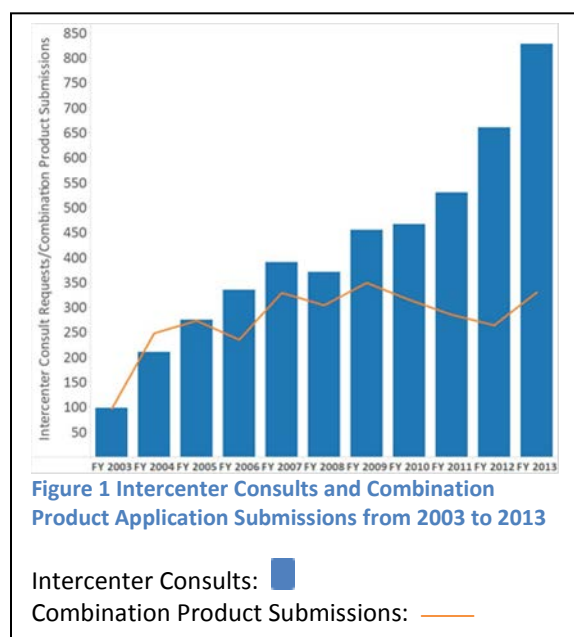
I.	Background	3
II.	Methodology	4
III.	Findings	4
A.	Different Policies, Practices, and Application Types	4
B.	Separate Review and Tracking Systems Between Centers	5
C.	Unclear Communication Channels Between Centers	5
D.	Lack of Resources to Review Consults	5
IV.	Conclusions/Recommendations	5
V.	Appendix A: Questions Asked of Interview Participants	7

I. Background

As defined in 21 CFR 3.2(e), a combination product is any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Interest in combination products is high due to opportunities they offer to enhance product safety and efficacy, market drivers, and technological advances that continue to merge product types.

Because combination products are products composed of two or more separate products and regulated under different types of regulatory authorities, and by different FDA Centers, intercenter consulting raises challenging regulatory, policy, and review management issues. These challenges have been exacerbated as the number of intercenter consults has increased. Figure 1 below shows that although the number of original application submissions for combination products has remained fairly steady since 2007, the number of intercenter consults has increased dramatically since the Office of Combination Products (OCP) started tracking them in 2003.

Figure 1



Individual companies as well as industry groups have expressed concerns regarding the consistency and clarity of FDA's communications related to combination product review. In August 2014, the Combination Products Coalition¹ shared with FDA the results of their 2014 Industry Survey, highlighting several sponsor² reported experiences of FDA Centers not coordinating or communicating well internally, which they say led to confusion and delays in the review process.

Because of such concerns and internal awareness of the unique challenges combination products pose for FDA's premarket review processes, a study team from FDA's Office of Planning (OPL) examined procedures and processes associated with intercenter consult requests for premarket submissions for combination products.

¹ [For more information regarding CPC's 2014 Industry Survey, please visit <http://combinationproducts.com/wp-content/uploads/2014/07/May-23-2014-CPC-Paper-Improving-Patient-Care.pdf>]

² "Sponsor" refers to the entity seeking premarket authorization from FDA to market a new medical product.

Study Objectives

- 1) To examine intercenter consult coordination within FDA, including management, timing, timeliness, and workload challenges.
- 2) To investigate interactions between applicants and FDA around combination product applications; specifically, to look at the standard operating procedures, intercenter connections and contacts for combination product applications and the timeframes for these interactions.

II. Methodology

The study was conducted from September 2014 to January 2015 at FDA's White Oak, MD campus. The study team first received input from industry representatives affected by combination product review; specifically, FDA reached out to the Combination Products Coalition (CPC) and to the Advanced Medical Technology Association (AdvaMed). The study team used internal and external source documents to develop the questions that were posed to internal focus group and interview participants. The key topics were pertinent to reviewing policies, responsibilities, key barriers, strengths, examples, and review structures.

Four focus group discussions were held; two each with staff from the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER) respectively. Groups were comprised of individuals that were regularly involved in the review of premarket submissions for combination products.

Eighteen semi-structured interviews were conducted with additional FDA stakeholders in leadership positions for overseeing and troubleshooting the review process, as well as FDA staff in key roles related to combination product review, such as product jurisdiction officers, compliance officers, OCP staff, and Office of Chief Counsel (OCC) attorneys who work on combination product issues.

An interview guide (see Appendix A) was designed to cover all topics while providing flexibility for interviewees to raise additional topics, and for interviewers to ask supplementary questions, especially when identifying additional unanticipated relevant information. Following data analysis, the study team evaluated the findings and developed recommendations for inclusion in this report.

III. Findings

The issues most frequently identified by study participants were:

A. Different Policies, Practices, and Application Types

Differing review timelines, and differing approaches to managing the review process (e.g., using project managers or not) between Centers make it difficult for reviewers to develop a shared understanding of priorities and timelines during a review and thus inhibit effective coordination between Centers.

Differences in application review standards – particularly between 510(k) submissions and approval applications – and in data requirements and expectations among Centers create complexities that make

it difficult to achieve consistency in the outcome of a combination product review and present challenges to timely response.

B. Separate Review and Tracking Systems Between Centers

Being unable to access other Centers' data systems in a timely manner and lack of a shared technical platform were seen as a significant source of delays and inefficiencies in the consult process. The lack of rapid access to review information and application tracking systems present challenges to effective project management and results in communication gaps and reduced traceability of combination product submissions.

C. Unclear Communication Channels Between Centers

There is a lack of clarity regarding cross-center communication channels, resulting in problems where staff are not sure where to direct consult requests or how to appropriately follow-up on prior requests. In addition, consult requests are often incomplete and have insufficient specificity, requiring additional follow-up and resulting in response delays.

D. Lack of Resources to Review Consults

Lead Centers do not reimburse time spent by staff of other Centers on intercenter consult requests, presenting workload challenges for the consulting Center. The increasing demand for intercenter consults without any additional funds has stretched already limited resources.

IV. Conclusions/Recommendations

The following are recommendations addressing some of the issues identified in the study, to improve the overall efficiency, consistency, and predictability of the intercenter review of combination products.

Recommendation 1: Establish clear guidance for the review of common combination product types.

Guidance documents specific to commonly submitted combination products that detail data expectations and other critical review considerations are needed. OCP leadership is appreciated by the Centers, and OCP should ensure a well-coordinated, timely, cross-center process for the development of these guidances, together with relevant subject matter experts from the involved Centers. Subject matter experts from OCP and the Centers should develop a list of potential topics for these guidances.

Recommendation 2: Create new simplified processes for access to CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) and CDRH's Image 2000 for consulting reviewers; this access should be pre-approved, expedited, and long-lasting.

The study team strongly recommends that reviewers involved in intercenter review of combination products be provided access to other Centers' systems. Unless a unified data system is developed and implemented, reviewers who work with combination products should be granted an expedited pathway to system access without short-term expiration of their access.

Recommendation 3: Update the Intercenter Consultative/Collaborative Review Process Standard Operating Procedures and Policies (SOPP) Manual and Intercenter Consult Request form and make them easily accessible on the OCP website.

FDA established a Manual of SOPP for the Intercenter Consultative/Collaborative Review Process, and the latest version (v. 4) was revised June 18, 2004. The manual provides an overview of the intercenter consult and collaborative review process and is available on the external FDA website.³ Since it has been more than 10 years since this manual has been updated, the study team recommends having an intercenter working group review and update it as needed and then share the updated version broadly within Centers, as newer reviewers may not be aware that it exists. The study team encourages the working group to incorporate guidance to improve communication practices into the SOPP, promoting early communication wherever possible.

The study team also recommends a similar update to the Intercenter Consult Form, following a discussion with subject matter experts regarding the form's current utility and purpose. Study participants differed in their opinions of whether the form was still required or if computer systems might be adapted to collect the same information. If still needed, the form should be updated with input from reviewers and project managers who use the form regularly to ensure its usefulness.

Recommendation 4: Create and maintain a combination-product-specific organizational chart and contact directory, keeping personnel changes current.

FDA staff involved in the intercenter review process would benefit from a contact directory specific to combination products, with information indicating the issues and products that should be directed to each office. This directory should be regularly updated and available on OCP's website.

Recommendation 5: Establish a mechanism for estimating time spent on intercenter consults so resources can be allocated appropriately to organizational units to assure adequate review performance.

The fact that reviewers are unable to obtain additional resources to review intercenter consults means that these consults are sometimes given a lower priority than their own Center user fee work, though most groups are still able to meet the deadlines requested of them to date. The study team recommends developing a mechanism for tracking time spent on intercenter consults, built into existing workload tracking systems, which then could be used to help with resource allocation.

³ www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126016.pdf

V. Appendix A: Questions Asked of Interview Participants

1. What are your office's policies for interacting with other Centers/offices when leading the review of a combination product?
 - o 1a. What are the important roles and responsibilities in the review process? How are these assigned?
 - o 1b. Is there a set policy on when, how, and what to communicate to the sponsor?
 - o 1c. How and when in the process is OCP involved?
2. What policies do you have for interacting with other Centers/offices when you are consulting on the review of a combination product?
 - o 2a. What are the important roles and responsibilities in the consult process? How are these assigned?
3. Can you give an example of a significant issue or problem that you became involved with when your office was **leading** the review of a combination product?
 - o 3a. How was the issue resolved?
4. Can you give an example of a significant issue or problem that you became involved with when your office was **consulting** on the review of a combination product?
 - o 4a. How was the issue resolved?
5. Can you describe a time that a combination product review or consult went especially well?
 - o 5a. What specific practices were most useful or helpful?
6. What types of documents or manuals would assist you and your staff during the review process?
 - o What type of training would better equip members to manage consults/reviews?
7. Have you noticed a change in your office's workload related to combination products (either in leading application reviews or in consult requests) over the past three years? Please describe the change, if any.
 - o 6a. *(If applicable)* How has the change in workload affected your policies for handling combination product reviews and/or consults?
 - o 6b. *(If applicable)* How would you ideally address the change?
8. How do you track the time that your employees spend on consults?

Closing Questions

9. What is the single most important action you believe could be taken to improve the communication or coordination of combination product review?
10. Is there anything I should have asked that I did not, or that you would like to add?