SMG 4101

FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM DIRECTIVES

COMBINATION PRODUCTS

INTERCENTER CONSULTATIVE/COLLABORATIVE REVIEW PROCESS

Effective Date: June 18, 2004

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1. Purpose

The purpose of this document is to provide the procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs and biologics.

2. Definitions

Collaboration

A review activity in which reviewers in two or more Centers have primary review responsibilities, generally for a defined portion of a submission. Regulatory and scientific decisions will be made by the management of each Center for that portion of the review assigned to it, including the decision to approve or disapprove the product.

Collaborative Reviewer

The collaborative reviewer is the individual conducting the collaborative review assigned by his/her management.

Combination Product (Definition from 21 CFR Part 3, Subpart A, Section 3.2 (e)):

"Combination product includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect."

Consult

A review activity in which a reviewer in one Center requests advice from a reviewer in another Center on a specific question or issue raised in the review of a submission. The consultative review will be used to assist the requesting reviewer in making appropriate regulatory/scientific decisions.

Consulted reviewer

The consulted reviewer is the individual conducting the consultative review assigned by his/her management.

Intercenter Agreement

An agreement between two or more Centers that clarifies product jurisdictional issues by describing the allocation of responsibility for categories of products or specific products.

Letter of Designation

The written notice issued by FDA's product jurisdiction officer or the Office of Combination Product's product assignment officer in response to a formal "Request for Designation" that identifies the agency component with primary jurisdiction for a product.

Product (21 CFR Part 3, Subpart A, Section 3.2 (l))

A drug (as defined in section 201(g)(1) of the Federal Food, Drug and Cosmetic Act), device (as defined in section 201(h) of the FD & C Act); or biologic (as defined in section 351(i) of the Public Health Service Act), or combination product (as defined in 21 CFR Part 3, Subpart A, Section 3.2(e) and above).

Request Originator

The request originator is the individual originating the request for the consultative or collaborative review. This person will generally be the regulatory project manager, but may be any individual who conducts or is otherwise responsible for the review of the submission, e.g., reviewer, branch/lab chief, division director, etc.

3. Background

Each FDA Center concentrates its review activity based on its assigned product review jurisdiction. However, consultation or collaboration between Centers on certain product reviews has been traditionally performed when a unique aspect of a product's indication, formulation, design or performance raises concerns and when the expertise to review that particular aspect resides in another Center. In such instances, a consultative review of the discrete issue is requested from one Center to another. This assures a comprehensive review of the submitted application.

As medical science advances, some products submitted for FDA review utilize increasingly complex formulations, including unique and creative combinations of drugs, biologics and devices. Accordingly, combination products, by definition, may frequently require intercenter consultations or collaborations on reviews.

This SOPP has been developed to describe appropriate handling of the intercenter reviews of combination products, devices, drugs and biologics throughout the review process. The objectives are to improve intercenter communication on combination products as well as the timeliness and consistency of intercenter consultative and collaborative reviews. In addition, it is anticipated that future revisions of this SOPP will provide guidance on

suggested practices for the collaborative review process, and for improved methods for the centralized monitoring of the progress of intercenter consultations and collaborations.

This document does not establish standards for when a consultative or collaborative review is required. It should be noted that Intercenter Agreements, Letters of Designation, and standard operating procedures of the individual Centers may describe situations where consultative or collaborative review would be required. Consultative or collaborative review may be necessary in other situations.

4. Policies

- Every effort should be made to identify the need for a consultative or collaborative review as early in the review process as possible, ideally upon the first contact with a firm intending to file a submission.

- All consulted and collaborating reviewers should be held accountable and receive credit for thorough and timely expert reviews and advice. Every effort should be made to meet the due date identified by the request originator.

- The need for extensive consultation is often better handled by assigning a reviewer to the application review team.

- Reviewer communication should be frequent. Informal communication should ideally occur on a one-to-one basis without the need for prior supervisory approval. Formal communication (e.g., written review memoranda) should go through appropriate signoff procedures.

- Consultative or collaborative reviews should be tracked by each Center's tracking system, as well as the centralized method established for monitoring the progress of intercenter consultative and collaborative reviews of combination products.

- Sponsors should be kept informed about the progress of the review of their application in accordance with existing Center/Office/Division policies. In most cases, it will also be appropriate for review staff to inform sponsors if their submission will undergo consultative or collaborative review by another Center as soon as the decision for consultation/collaboration is made.

5. Responsibilities and Procedures

This section outlines the responsibilities of each staff member involved in the intercenter consultative or collaborative review process. Appendix 2 provides

an optional checklist that can be used to assist originating and consulted reviewers in performing these steps.

Request Originator

The request originator, with input and concurrence of her/his supervisor and (if applicable) regulatory project manager/consumer safety officer (RPM/CSO) (and any Center/Office/ Division-specific procedures), should:

- Determine and specify whether they are requesting a consultative or collaborative review.

- Determine the issues of concern and the specific questions to be answered to enable the consulted reviewer to conduct an effective review within the timeframe specified. In some cases, it will be helpful for the request originator and consulting reviewer to jointly develop the issues and concerns to be addressed in the consulting review.

- Identify, via e-mail or telephone, the appropriate division director (or delegate) to whom the consultative or collaborative review request should be directed. If the division cannot be identified, contact the following for assistance:

  CBER: Associate Director for Review Management (301-827-0373)
  http://www.fda.gov/cber/inside/orgchart.pdf

  CDER: Office of New Drugs (301-594-5400)
  http://www.fda.gov/cder/cderorg.htm

  CDRH: Program Operations Staff (301-594-1190)
  http://www.fda.gov/cdrh/organiz.html

- Confirm via e-mail or telephone that the requested review can be completed in a timely manner consistent with the originating Center's review deadlines.

- Obtain via e-mail or telephone the names of the reviewer(s) who will perform the consult or collaboration.

- Identify a reasonable deadline for completion of the review, which should take into account the timeframe for Agency response to the regulatory application.

- Complete the Intercenter Request for Consultative or Collaborative Review (IRCR) Form (Appendix 1) to accompany the consult or

collaboration request. The description of the request should include relevant history and issues, including the specific questions to be answered and the specific sections of the application to be reviewed by the consulting reviewer(s).

- Forward the completed IRCR form to the consulted reviewer/consult contact (by email with a cc to the request originator who tracks review progress). Send a copy of the pertinent portion or all of the submission (if needed) to the consulted or collaborating reviewer using the courier service established for CBER-CDER-CDRH regulatory mail delivery whenever possible.

- Forward a copy of the completed IRCR form to the Office of Combination Products by email to combination@fda.gov or by fax to (301) 427-1935.

- Confirm that the consultative or collaborative review has been received by the appropriate division.

- Track the progress of the review and identify potential delays as soon as possible.

- Be available for discussion to ensure adequate communication of the product-specific issues/concerns to the consulted or collaborating reviewer, as necessary.

Consulting or Collaborating Unit

The consulting or collaborating unit should:

- Contact the request originator by telephone or e-mail immediately if a consult or collaborative review request or any aspect of the request (e.g., due date) is believed to be inappropriate or in error.

- Log review requests into the unit's document control system.

- Notify the request originator promptly if the review will be delayed, and either negotiate a new due date through the supervisory chains of both Centers, or reassign the request so that the previously established due date can be met.

- Perform a complete review of those areas specified by the request originator. If the consulted or collaborating reviewer does not have the expertise to address the identified issues, make arrangements for the review to be completed by someone with the expertise. "No comment" is not an acceptable review response.

- Assure that all consultative or collaborative reviews are in electronic review memorandum format and include a brief summary of the portion of the submission which was reviewed, recommendations for action (as necessary) and letter-ready comments and/or any requests for information to be conveyed to the firm.

- Obtain the appropriate clearances/sign-off and forward the consultative or collaborative review (email is acceptable with a notation indicating that the consulted or collaborative reviewer's supervisor concurs with the review recommendations) along with the completed IRCR form (Consulting Center use box) and the reviewed submission documentation to the request originator.

- Forward a copy of the completed IRCR form to the Office of Combination Products by email to combination@fda.gov or by fax to (301) 427-1935.

- Log the review out of the consulted/collaborating Center's document control tracking system (unless previously agreed that the consulted or collaborating reviewer's Center assumes custody of the document). Transmit the documents electronically or use the courier service established for CBER-CDER-CDRH regulatory mail delivery whenever possible.

6. Appendices

Appendix 1

Intercenter Request for Consultative or Collaborative Review Form

Appendix 2

Process Checklist

7. Effective Date

Revision 4 of this SOPP is effective on June 18, 2004.

Approved by:

Jesse L. Goodman, M.D., M.P.H.
Director
Center for Biologics Evaluation and Research

_____ Date: _____

David Feigal, Jr., M.D., M.P.H.
Director
Center for Devices and Radiological Health

_____ Date: _____

Janet Woodcock, M.D.
Director
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Director
Office of Combination Products

_____ Date: _____

8. Document History -- SMG 4101, Intercenter Consultative/Collaborative Review Process

Drafted/ Revision	Approved By	Effective Date	Version Number	Comment
L. Wilson, H. Rosecrans, M. Dillon Parker, T. Forfa, M.Kramer, R. Lawlor, M. Hare, J. Morrison	**Steering Committee:** J. Morrison, K.Cook, S.Lard, H. Rosecrans S. Unger **Center Directors:** K. Zoon J. Woodcock D. Feigal	7/31/02	1	Original
K. Colangelo M. Kramer H. Rosecrans L. Wilson	D. Feigal J. Goodman J. Woodcock M. Kramer	2/14/03	2	Added interim procedures for combination products tracking; Modified IRCR Form to denote type of product
M. Kramer	New approval not required; technical correction to OCP fax number only	7/1/03	3	Updated fax number of Office of Combination Products
M. Kramer	New approval not required; technical correction to OCP fax number only	6/18/04	4	Updated fax number of Office of Combination Products

Appendix 1

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center:
Division:
Mail Code: HF___-
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center:
Division:
Mail Code: HF___-
Requesting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request:_____

Requested Completion Date:_____

Submission/Application Number:_____
(Not Barcode Number)

Submission Type_____
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:
___Drug device combination
___Drug-biologic combination
___Device-biologic combination
___Drug-device-biologic combination
___Not a combination product

Submission Receipt Date:_____

Official Submission Due Date:_____

Name of Product:_____

Name of Firm:_____

Intended Use:_____
_____

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

_____
_____
_____

Documents to be returned to Requesting Reviewer? ____Yes____No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear.

Attach extra sheet(s) if necessary:

Type of Request: __Consultative Review__Collaborative Review

Appendix 2

(Optional) Process Checklist
Intercenter Consultative/Collaborative Review Process for Combination Products, Devices, Drugs and Biologics

Request Originator

— Confirm the need for the request for consulting or collaborative review with a supervisor/team leader

— Provide specific instructions to the consulting reviewer

— Sections of the submission to be reviewed by the consulting reviewer

— Issues of concern and specific questions to be addressed by the consulting reviewer

— Confirm receipt by the appropriate Division and consulted reviewer

— Confirm that the consulting reviewer can complete the review within the timeframe requested

— Provide submission sections, instructions, and Intercenter Request for Consultative or Collaborative Review (IRCR) form. Use the courier service established for CBER-CDER-CDRH regulatory mail delivery whenever possible

— Forward a copy of the completed IRCR form to the Office of Combination Products by email to combination@fda.gov or by fax to (301) 427-1935

— Stay in contact with consulted or collaborating reviewer to ensure adequate communication and early resolution of questions or issues that may arise

Consulting Reviewer/RPM/CSO

—Confirm that the review can be completed within the time frame requested

— Conduct complete review as requested by the request originator

— Sections of submission identified by request originator

— Issues of concern and specific questions identified by request originator

— Immediately advise request originator of any areas where consulting reviewer does not have expertise to address the issues identified (if applicable)

— Prepare typewritten review memorandum to the file that addresses:

- Brief summary of portion(s) of submission reviewed
- Recommendations for action (as necessary)

- Letter-ready questions to be conveyed to firm

— Obtain supervisory clearance/sign-off in accordance with Center/Office/Division procedures

— Complete the “For Consulted Center’s Use only” box on the IRCR Form

— Forward completed review to request originator using the courier service established for CBER-CDER-CDRH regulatory mail delivery whenever possible. If forwarding review by email, provide supervisory concurrence with review recommendations

— Forward a copy of the completed IRCR form to the Office of Combination Products by email to combination@fda.gov or by fax to (301) 427-1935