

FDA STAFF MANUAL GUIDES, VOLUME IV – AGENCY PROGRAM DIRECTIVES

COMBINATION PRODUCTS

INTER-CENTER CONSULT REQUEST PROCESS

Effective Date: June 11, 2018

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**1. PURPOSE**

The purpose of this document is to describe the procedures for when and how to request, receive, process, and track the progress of Inter-Center Consult Requests (ICCRs) between the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH). Henceforth, this will be referred to as the ICCR process. This SMG outlines the standardized ICCR process across the medical product Centers to enable efficient and effective collaboration.<sup>1</sup>

**2. SCOPE**

The ICCR process covers inter-center consults that occur between CBER, CDER, and CDRH for combination products and non-combination products.<sup>2</sup> If staff have

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<sup>1</sup> CBER, CDER, CDRH, and OCP also coordinate on regulations and guidance that pertain to combination products. See [SMG 4103 Expectations and Procedures for Engagement among Medical Product Centers and Office of Combination Products on Regulations and Guidance Pertaining to Combination Products](#).

<sup>2</sup> Combination products are defined in 21 CFR 3.2(e). The term Part 3 combination product (hereafter “combination product”) includes:

- (1) 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;
- (2) 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;

questions about this document, they should contact their Center Product Jurisdiction Officers (PJOs) or the Office of Combination Products (OCP).

In addition to describing the ICCR process, this document describes:

- Roles and responsibilities for the Lead Center, the Consulted Center(s), and OCP;
- The process for determining if an inter-center consult is needed;
- Critical steps in the ICCR process; and
- Standard critical elements to be included in a consult request.

### 3. BACKGROUND

Consultation with another Center may be needed for the review of a product. Such consultation between Centers, for example for premarket applications<sup>3</sup> or in postmarket, may occur when a unique aspect of a product's indication, formulation, design, or performance raises concerns that require review by another Center, or when the expertise to review a particular aspect of the product resides in another Center. In such instances, a consult is requested by one Center to another. This ensures a comprehensive review of the product.

In 2015, an [external study](#) identified the need for a comprehensive strategy for managing combination product review and underscored the importance of cross-center collaboration. This study highlighted issues that had the potential to delay approval. The findings of the external study were confirmed by an [internal study](#). A comprehensive assessment revealed several opportunities for improvement related to combination product review processes.

To address the issues identified in the studies and facilitate inter-center interactions, FDA developed and piloted a new ICCR process for premarket combination product

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(3) 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

(4) 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.

<sup>3</sup> For purposes of this SMG, unless otherwise stated, the term premarket application includes investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), investigational device exemption (IDE), premarket approval application (PMA), premarket notification (510(k)), humanitarian device exemption (HDE), biologics license application (BLA), request for classification submitted under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (De Novo request), presubmissions (e.g., pre-NDA, Q-submission) or supplements/amendments to any of these applications (as applicable).

review beginning in [August 2016](#). The objectives of the pilot were to improve inter-center coordination for combination products and enhance the timeliness and consistency of inter-center reviews. Based on outcomes of the pilot and internal stakeholder feedback, the new process was implemented throughout CBER, CDER, CDRH, and relevant groups in FDA's Office of the Commissioner (OC), and the process was expanded to all inter-center consults. The process outlined in this SMG is based upon the results of the pilot and addresses the mandate in Section 3038 of the [21st Century Cures Act](#) to ensure timely and effective review that involves more than one Agency Center.

#### 4. ROLES AND RESPONSIBILITIES

- A. **Lead Center**: The Center that has primary review responsibility for the product. This Center is responsible for identifying early in the review process whether the application or product issue necessitates an inter-center consult.<sup>4</sup>
- B. **Lead Center Consult Requester**: The person in the Lead Center who fills out and submits an ICCR. The consult requester serves as the administrative point of contact for the consult request (e.g., location of review materials) and when additional information is needed from the external stakeholder (sponsor/applicant/manufacturer).
- C. **Lead Center Submission Contact**: The person(s) in the Lead Center who serves as the point of contact for technical questions regarding the application or issue. The Lead Center Submission Contact and the Lead Center Consult Requester may or may not be the same.
- D. **Consulted Center**: The Center that will provide the necessary expertise to the Lead Center. After the consult is completed, the Consulted Center is responsible for closing out the ICCR.
- E. **Consulted Center Receiver**: The person(s) in the Consulted Center who is assigned to receive ICCRs (e.g., by monitoring a specific email inbox) and assist with triage and reviewer assignment within the Consulted Center.
- F. **Assigned Consulted Center Reviewer**: The person in the Consulted Center who is assigned to conduct the review and provide a review memo or other deliverable in response to the consult request.

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<sup>4</sup> To aid in determining whether an Inter-Center consult is needed for certain combination products, agreements between the Centers exist that outline circumstances when a consult is or is not needed. When the Lead Center is unsure whether a combination product is covered by such an agreement, the Lead Center should contact its PJOs for a determination. In addition, when a combination product is not covered by any agreement and the Lead Center is considering not issuing a consult, the Lead Center should consult its PJOs, who should work with the relevant Center(s) to determine whether a consult is necessary.

- G. **Center Product Jurisdiction Officers (PJOs)**: The contact(s) within each Center for product classification, Center jurisdiction, and combination product information. The PJOs also serve as administrative support for Center stakeholders using the ICCR process.
- H. **Office of Combination Products (OCP)**: The Agency office that administers the overall ICCR process and assists the Centers, when needed. For combination products, OCP oversees the statutory requirements for coordinating inter-center reviews by overseeing the timeliness of premarket reviews and the alignment of Centers' feedback to industry. OCP may serve in the same capacity for non-combination products, typically at the request of Centers.

## 5. PROCEDURES

The figure in Attachment A illustrates the general flow of the ICCR process, including the specific roles and responsibilities of the Lead Center, Consulted Center, and OCP. OCP and each Center's PJOs are resources for Center staff regarding the ICCR process. The Center PJOs should typically be contacted first for questions related to whether a product is a combination product, for assistance in identifying the appropriate Consulted Center Receiver, or for questions related to a Center's internal process for managing ICCRs. Center PJOs will engage OCP when needed in these discussions.

The ICCR process in brief is as follows:

a. **Identify the product as a combination product or a non-combination product (Lead Center)**

This should be done within the first few days of the receipt of the application or issue and, when applicable, documented within the Lead Center's records system.

b. **Identify need for expertise and initiate consult (Lead Center)**

The specific expertise needed for the consult, where that expertise resides, and the complexity of the request dictate the process for the request (see section d. below). Every effort should be made to identify the need for a consult as early in the review process as possible.<sup>5</sup> The Lead Center should provide the Consulted Center adequate time to complete the review while still ensuring that necessary due dates are met (e.g., any user-fee goal dates associated with the submission). OCP participation in discussions may be requested directly by the external stakeholder or by either the Lead or the Consulted Center(s).

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<sup>5</sup> Staff should refer to internal process documents for specific timelines.

c. **Draft/prepare consult request (Lead Center)**

At a minimum, the Lead Center Consult Requestor should include the following information in an ICCR to enable the Consulted Center to efficiently assess the scope of the request and identify appropriate reviewer(s):

- i. Application and product information (application number and type (if applicable); product name(s); indications for use; and description of the product(s));
- ii. Specific questions for which expertise is being requested and what is needed (i.e., deliverables being requested) from the Consulted Center;
- iii. Location of review materials (e.g., links to electronic documents) and specific details on where the question/relevant product information can be found (sections, page numbers, etc.);<sup>6</sup>
- iv. Requested due date for the Consulted Center's review or other deliverable, established to allow Lead Center to meet applicable user-fee commitments or other Center or Agency policies or requirements;
- v. Any known interim milestones before consult completion (e.g., internal meetings, external stakeholder meetings, interactive review due dates, filing decision dates, draft memos, slides, minutes) for which feedback or participation from the Consulted Center may be needed; and
- vi. Contacts (e.g., Lead Center Submission Contact) for the Consulted Center to follow up with if additional information is needed.

d. **Submit consult (Lead Center)**

- i. For routine consults,<sup>7</sup> the consult request is sent to the relevant Consulted Center Receiver. OCP maintains a list of Consulted Center Receivers accessible to all staff. If the Lead Center Requester has questions about the Consulted Center Receiver, he/she can contact the Lead Center PJOs for assistance.

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<sup>6</sup> When access to electronic systems and databases is needed to complete a consult review, the process to gain access to the Lead Center's electronic systems and databases should be expedited. Staff with questions about such access may contact their PJOs or OCP.

<sup>7</sup> A routine consult is one in which Lead Center staff knows which group(s) in the Consulted Center has/have the desired expertise. One application or issue may require multiple routine consults within the same Consulted Center (e.g., separate consult requests issued for facility inspection, clinical, and/or product design considerations).

- ii. For non-routine consults,<sup>8</sup> ICCRs are initially sent to OCP. Prior to sending such a consult request to OCP, the Lead Center Requester should contact their Center PJOs for assistance. OCP schedules and coordinates a consult orientation meeting with the Lead Center and potential Consulted Center(s). During the consult orientation meeting, the Centers and OCP will discuss what expertise from the potential Consulted Center(s) is necessary for review of the product and/or issue.

After the consult orientation meeting, the Lead Center will submit any necessary consult requests to the identified Consulted Center(s) as discussed during the orientation meeting. Once all necessary ICCRs are submitted, the process and engagement between Centers follow that of a routine consult, outlined below.

e. **Assign reviewer (Consulted Center)**

Upon receipt of an ICCR, the Consulted Center Receiver assigns a reviewer in the ICCR electronic tracking system, which will automatically notify the Lead Center of the reviewer assignment. If an assigned reviewer cannot address all the questions in the consult request or if an ICCR has been sent to the wrong Consulted Center Receiver, the Consulted Center should expeditiously communicate the issue to the Lead Center so that the ICCR can be reassigned or redirected.<sup>9</sup>

Assigned reviewers from the Consulted Center are considered members of the Lead Center review team. The Lead Center will inform assigned reviewers from the Consulted Center of the other review team members. The Lead Center will invite assigned reviewers from the Consulted Center to internal and stakeholder meetings. Their supervisors may also be invited to these meetings.

f. **Consult review (Consulted Center)**

The scope of the Consulted Center's review should include the specific requests from the Lead Center and be limited to these requests. If a Consulted Center believes there are additional review considerations for which the Lead Center did not request a consult and for which the Consulted Center has expertise, the scope of the consult should be discussed with the Lead Center. If the Lead Center determines that additional expertise is

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<sup>8</sup> A non-routine consult is any consult where another Center's input is needed, but the interaction is not straightforward. Non-routine consults typically occur when the scope of the consult is large/complex (e.g., multiple groups may need to interact), or when novel products or issues that present challenging questions regarding the scope or content of the consult or groups that may need to provide input are involved.

<sup>9</sup> Staff should refer to internal process documents for specific details and timelines.

necessary to inform the regulatory decision-making process, then additional consult requests may be issued.

The Lead Center is responsible for communication with the external stakeholder in accordance with the Lead Center's processes. This includes sending requests on behalf of the Consulted Center for additional information or clarification to the external stakeholder. The Lead Center should expeditiously notify the Consulted Center when the response is received. The Consulted Center's review of the information obtained does not require a new ICCR and should be incorporated into the final deliverable provided by the Consulted Center. New ICCRs are required for review of responses in a resubmission after an action has been taken (e.g., Complete Response, major deficiency).

User-fee and other goals are commitments that apply to the entire Agency. Therefore, the Consulted Center and its Assigned Reviewer(s) should make every effort to meet the consult due date identified by the Lead Center to ensure that goal dates are met. If the Consulted Center anticipates that a due date will be missed, the Consulted Center must notify the Lead Center to discuss alternatives as soon as possible and, as necessary, update the ICCR with a new due date.

g. **Complete consult (Consulted Center)**

Centers may choose to interact with each other on draft or informal work products prior to finalizing the consult, and this can be done on an as-needed basis. Final deliverables (e.g., final written review, response to meeting questions) should go through appropriate signoff procedures within the Consulted Center before being provided to the Lead Center. Assigned Consulted Center Reviewers are responsible for ensuring their management has appropriate documentation to ensure timely signoff (e.g., application, previous consulting reviews) by the requested consult due date. Once the consult is complete, the Consulted Center sends the final deliverable to the Lead Center and closes out the ICCR in the ICCR electronic tracking system.

h. **Incorporate consult (Lead Center)**

If the Lead Center accepts the Consulted Center's consult recommendation, the Lead Center incorporates the recommendation in developing communications with the external stakeholder, determining application approvability, or taking other FDA action. If the Lead Center disagrees with the recommendations, it should reach out to the Consulted Center to discuss the disagreement prior to taking a regulatory action. If disagreements cannot be resolved, see i. below.

Copies of any communications with the external stakeholder (e.g., minutes, action letters) that are related to or result from the consult should be sent electronically to the Consulted Center in a timely manner.

i. **Informal and Formal Dispute Resolution (Lead and Consulted Centers)**

If the Consulted Center feels that rejection of information provided in a consult will affect the assessment of safety, efficacy, and/or quality of the product under review, it is encouraged to try to resolve these disagreements informally at the inter-center review team level and continue through the next level signatory if agreement cannot be reached. The outcome of any such discussions should be documented in the administrative record of the application. If the Lead Center and Consulted Center(s) cannot resolve the difference of opinion informally, the cross-center scientific or regulatory dispute resolution process may be initiated (see SMG 9010.2 Cross-Center Dispute Resolution at the FDA).

j. **Archive consult (Lead Center)**

The Lead Center is responsible for archiving the final deliverable from the Consulted Center (e.g., written consult memorandum) in the appropriate Lead Center administrative file. The Lead Center is also responsible for confirming that the combination product code in the Lead Center systems and databases appropriately reflects the type of combination product (see 5.a. above).

Communication between staff in the Lead and Consulted Centers should be frequent. Informal communication should ideally occur on a one-to-one basis between review staff, without the need for prior supervisory approval. For complex products and development programs, the Lead Center should schedule additional planning meetings as necessary to ensure an efficient review process. Such communications may involve discussion of updates to the product application, information requests to and from external stakeholders, attendance and discussions at milestone/review meetings, and interim review findings, among others.

## **6. PROCESS MONITORING AND IMPROVEMENT**

OCP will maintain centralized resources on the Agency intranet for staff, including training materials on the ICCR process. OCP and the Centers will periodically review and update these resources as needed. The Centers will ensure that established timelines for ICCR activities are clear and predictable and will communicate target timelines for identifying the need for an inter-center consult, submitting a consult request, and assigning a reviewer for the consult.

Quantitative and qualitative data will be collected by OCP and the Centers to evaluate the need for process improvements. Data collected may include:



- Number of inter-center consults requested;
- Circumstances under which consults are needed for combination products;
- Timeliness of consult interactions, as compared to any established benchmarks (e.g., time from application receipt to consult request submission, time from consult request submission to reviewer assignment);
- Input on ICCR format and usability (e.g., through staff feedback, audits, monitoring users request for assistance with ICCR tasks); and
- Quality of the consult requests or reviews (e.g., through staff feedback, audits, collection of user complaints).

OCP will periodically review ICCR data and conduct additional assessments (audits, etc.) as needed to ensure the ICCR process supports timely, consistent, and effective review of combination products.

## 7. REFERENCES

U.S. Food and Drug Administration. Combination Product Review Inter-Center Consult Process Study. April 17, 2015. Available at: <http://www.fda.gov/downloads/CombinationProducts/GuidanceRegulatoryInformation/UCM467128.pdf>. Accessed October 31, 2016.

## 8. EFFECTIVE DATE

The effective date of this guide is June 11, 2018.

## 9. Document History – SMG 4101, “Inter-Center Consult Request Process”

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIALS
Initial	7/31/02	N/A	N/A	Steering Committee: J. Morrison, K. Cook, S. Lard, H. Rosecrans S. Unger Center Directors: K. Zoon J. Woodcock D. Feigal
Revision	2/14/03	Added interim procedures for	M. Kramer	D. Feigal J. Goodman

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIALS
		combination products tracking; Modified IRCR Form to denote type of product		J. Woodcock M. Kramer
Correction	7/1/03	Updated fax number of Office of Combination Products	M. Kramer	New approval not required; technical correction to OCP fax number only
Correction	6/18/04	Updated fax number of Office of Combination Products	M. Kramer	New approval not required; technical correction to OCP fax number only
Revision	6/11/18	Substantive revision of entire document to reflect revised inter-center consult process.	Office of Combination Products (OCP) <a href="mailto:combination@fda.gov">combination@fda.gov</a>	Jonette Foy, Associate Director for Policy, CDRH Diane Maloney, Associate Director for Policy, CBER Thinh Nguyen, Office Director, Office of Combination Products Douglas Throckmorton, Deputy Center Director for Regulatory Programs, CDER Rachel Sherman, Principal Deputy Commissioner

# SMG 4101, Attachment A - Inter-Center Consult Request Process Map

