SMG 4104

FDA STAFF MANUAL GUIDES, VOLUME IV – AGENCY PROGRAM DIRECTIVES

COMBINATION PRODUCTS

INTER-CENTER CONSULTS FOR REVIEW OF HUMAN FACTORS INFORMATION

Effective Date: February 12, 2019
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1. PURPOSE

This staff manual guide (SMG) provides a framework for collaboration among the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER) for intercenter consults concerning human factors (HF) information for medical products, including combination products[1], that are subject to FDA review.

This SMG has been developed to help ensure the efficient, effective, and consistent premarket regulation of medical products, including consistent scientific and regulatory approaches to HF across applications and review teams.

2. BACKGROUND

SMG 4101: *Intercenter Consult Request Process* provides the overarching framework for this SMG. FDA staff should refer to SMG 4101 for more information regarding the process for issuing intercenter consults in general. This SMG is limited to describing the process used by the lead center to request intercenter consults from other FDA centers on HF information (i.e., protocol or study reports) for medical products, including combination products.[2]

[1] Combination products are defined in 21 CFR 3.2(e) as products comprised of any combination of a drug, a device, and/or a biological product.
[2] The specific products identified in the procedures below for CDER and CDRH represent a small proportion of total products evaluated by the respective centers. Not all products submitted to CDER or CDRH require an intercenter consult for HF because HF expertise resides in both centers.

During the product development process, Sponsors will often contact the lead center[3] (CBER, CDER, or CDRH) at multiple points to obtain advice regarding product design and HF studies. Sponsor contact can begin early in development (e.g., the pre-investigational new drug process) and can carry through to post-approval modifications to products. When intercenter consults are necessary for HF information, center representatives are expected to work collaboratively and in a timely fashion to provide a single set of recommendations issued from FDA to Sponsors.

3. POLICY

A. CBER, CDER, and CDRH will abide by the established procedures for the ICCR process.[4] The lead center is responsible for identifying when FDA receives a submission for a medical product that calls for an intercenter consult, and for initiating the intercenter consult request (ICCR) process.

B. CBER, CDER, and CDRH defined the types of medical products that may benefit from a comprehensive HF review from CDER and/or CDRH staff in sections 5.A.2, 5.B.1, and 5.C.1 of this SMG.[5] Medical products not identified in this SMG do not, as a routine matter, need intercenter consults on HF information.

C. CBER, CDER, and CDRH will periodically conduct joint meetings with representatives from each center and the Office of Combination Products (OCP) to discuss HF issues. The joint meetings will provide a regularly scheduled forum for the exchange of scientific and administrative information pertaining to the consult and review of submissions for medical products with HF information, for communication about HF-related scientific or policy matters relevant to products addressed in this SMG, and for the ongoing evaluation of the consult review process outlined in this SMG. The joint meetings will be held at minimum on a quarterly basis.

D. CBER, CDER, and CDRH will abide by requested due dates and comply with timeframes necessary to meet program goal dates for the lead center.

4. RESPONSIBILITIES

A. The Division of Medication Error Prevention and Analysis (DMEPA) is responsible for the review of HF information within CDER.

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[3] The lead center is 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.

[4] See SMG 4101: *Intercenter Consult Request Process*, available at http://inside.fda.gov:9003/downloads/aboutfda/reportsmanualsforms/staffmanualguides/ucm283569.pdf

[5] This SMG does not apply to applications for biosimilar, interchangeable, or generic products, which are governed under the agency ICCR process.

B. The Human Factors Team (HFT) is responsible for the review of HF information within CDRH.

C. CBER, CDER, and CDRH will:

1. Follow this SMG.

2. If the lead center, issue the ICCR and maintain the administrative record.

3. When consulted, abide by requested due dates necessary to meet program goal dates.[6]

4. When consulted,determine the need (if any) for additional data to further evaluate the submission of HF information as early as possible during the review cycle; if additional information is needed, notify the lead center.

5. Attend meetings as requested by the lead center or OCP, actively and constructively contributing to the discussions. The lead center and OCP will make all reasonable efforts to invite the consulted center as soon as possible to allow for the maximum amount of lead time to prepare for the meeting.

6. Work closely with other centers to ensure a collaborative, well-managed, and timely review process.

7. Follow good review management principles and practices as specified for each center.[7] [8]Strive to reach alignment on key decisions and recommendations during review of the HF information; identify areas of disagreement and engage the relevant parties in other centers in constructive dialogue to resolve them as quickly as possible.[9]

5. PROCEDURES

A. When CDER is the lead center:

a. CDER receives HF information, and the Office of Surveillance and Epidemiology Safety Regulatory Project Manager (OSE SRPM) managing the

[6] Program goals include performance goals agreed to by the HHS Secretary in FDA's various user fee programs.
[7] See MAPP 6030.9: Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review, available at https://www.fda.gov/media/85790/download
[8] See guidance for review staff and industry: Good Review Management Principles and Practices for PDUFA Products, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf.
[9] See SMG 9010.2: Cross-Center Dispute Resolution at the FDA, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM380522.pdf.

submission consults appropriate member(s) of DMEPA per internal OSE procedures.

b. CDER evaluates the incoming HF information and determines whether it is for a combination product that contains one of the following device constituent parts:

   (1) Gas delivery device

   (2) Hyperbaric chamber

   (3) Nebulizer

   (4) Implantable infusion device

   (5) Body-worn infusion device

   (6) External infusion device (such as infusion pumps and elastomeric pumps)

   (7) Software-driven medication dispenser

   (8) Reusable auto-injector intended for multiple patient use, auto-injector with external electronic components (e.g., LCD display screen) or mobile technology applications that meet the device definition that do not fall under enforcement discretion as outlined in existing policies, guidance and/or regulations[10]

   (9) Inhaler (pressurized metered dose and dry powder) with external electronic components (e.g., LCD display screen) or mobile technology applications that meet the device definition that do not fall under enforcement discretion as outlined in existing policies, guidance and/or regulations

c. If the combination product contains one of the device constituent parts listed in Section 5.A.2, an ICCR for HF is issued from CDER to CDRH.[11]

d. CDRH abides by the requested due date specified in the consult request and performs a HF review accordingly.

e. CDRH sends the completed consult review to CDER.

[10] See the CDRH digital health page at https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm for more information.

[11] There may be combination products not specifically identified in this section where input from CDRH may be needed. In such circumstances, the appropriate subject matter experts in CDER will determine whether an ICCR should be issued to CDRH.

(1) CDER will review the completed consult and determine if there are any questions that need to be forwarded to CDRH.

(a) Within 2 business days of receipt of request for clarification or questions, CDRH staff provide a substantive response to any questions, discussion requests, etc., from CDER related to CDRH's review.

(2) If any differences of opinion between centers are noted, every attempt is made to resolve differences at the lowest organizational level possible. CDER and CDRH staff discuss and seek to reach agreement in a timely and mutually agreed upon manner. As a best practice, all affected parties agree to discuss the comments at the reviewer level first and make reasonable attempts to reach an agreement. The outcome of this negotiation is documented in the administrative record maintained by CDER.

(a) If resolution cannot be achieved at the lowest organizational level, the matter is brought to the attention of the next level of management in the affected centers. As discussed in SMG 9010.2, *Cross-Center Dispute Resolution at the FDA,* dispute resolution may continue as an informal process or convert to a formal dispute resolution, if needed, at any point in the process.

f. The OSE SRPM archives the completed HF consult review from CDRH in the administrative record.

g. CDER references the archived CDRH review in the final CDER HF review.

h. CDER incorporates the CDRH recommendations into the CDER HF review or meeting responses, as appropriate.

(1) For a HF review, CDER references the CDRH review.

(2) For preliminary meeting comments, CDER incorporates the CDRH HF recommendations into DMEPA's meeting preliminary question responses as appropriate.

i. CDER finalizes its HF review or meeting responses in the appropriate electronic archive and notifies CDRH.

B. When CDRH is the lead center:

1. CDRH receives a submission containing HF information and evaluates it to determine whether it is for a combination product with a device constituent part or a standalone device that meets any of the following criteria:

a. A device that is intended for a specific use with a drug or biological product[12] (e.g., an insulin syringe indicated for delivery of a novel concentration of insulin or a device intended to instruct a patient on dosing for a specific insulin product);

b. The proposed device indication for use, as described in the labeling, appears to be or is inconsistent with the drug/biologic labeling or monograph that the device is intended to be used with (e.g., device that administers a drug by a new route of administration not already described in the drug/biologic labeling);

a. A device that is intended to minimize the risk for abuse or misuse of drug products (e.g., opioids); or

d. A device that is intended to treat or assist in the treatment of substance use disorder of drug products.

2. If the medical product meets one of the criteria listed in section 5.B.1, then an ICCR for HF is issued from CDRH to CDER.[13]

3. CDER abides by the requested due date specified in the consult request and performs a HF review accordingly.

4. CDER sends the completed consult review to CDRH.

   a. CDRH will review the completed consult and determine if there are any questions that need to be forwarded to CDER.

      (1) Within 2 business days of receipt of request for clarification or questions, CDER staff provide a substantive response to any questions, discussion requests, etc. from CDRH related to CDER's review.

   b. If any differences of opinion between centers are noted, every attempt is made to resolve differences at the lowest organizational level possible. CDER and CDRH staff discuss and seek to reach agreement in a timely and mutually agreed upon manner. As a best practice, all affected parties agree to discuss the comments at the reviewer level first and make reasonable attempts to reach an agreement. The outcome of this

[12] See guidance for industry: General/Specific Intended Use, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf.

[13] There may be medical products, including combination products, not specifically identified in this section where input from CDER may be needed. In such circumstances, the appropriate subject matter experts in CDRH will determine whether an ICCR should be issued to CDER.

negotiation is documented in the administrative record maintained by CDRH.

(1) If resolution cannot be achieved at the lowest organizational level, the matter is brought to the attention of the next level of management in the affected centers. As discussed in SMG 9010.2, *Cross-Center Dispute Resolution at the FDA*, dispute resolution may continue as an informal process or convert to a formal dispute resolution, if needed, at any point in the process.

5. The final HF consult review from CDER is archived in the administrative record by CDRH.

6. The archived CDER review is referenced in the final CDRH review.

7. CDRH incorporates the CDER recommendations into the CDRH review or meeting responses as appropriate.[14] [15]

   a. For a HF review, CDRH references the CDER review.

   b. For preliminary meeting comments, CDRH incorporates the CDER HF recommendations into CDRH's preliminary question responses as appropriate.

8. CDRH finalizes the HF review or meeting responses in the appropriate electronic archive and notifies CDER.

C. When CBER is the lead center:

1. CBER receives a submission containing HF information and evaluates it to determine whether it is for a combination product with a device constituent part that meets any of the following criteria, then an ICCR will be issued from CBER to CDER or CDRH for the following:[16]

[14] See guidance for industry and FDA staff: *Types of Communication During the Review of Medical Device Submissions*, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm341948.pdf.

[15] See guidance for industry and FDA staff: *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.

[16] There may be medical products, including combination products and standalone biologics or devices, not specifically identified in this section where input from either CDER/DMEPA or CDRH or both may be needed. In such circumstances, the appropriate subject matter experts in CBER will discuss the product with the consulting center(s), as appropriate, and determine whether an ICCR should be issued only to CDER or CDRH, or to both centers.

a. If the combination product contains one of the following device constituent parts, then an ICCR will be issued from CBER to CDER:

(1) Prefilled syringe

(2) Auto-injector

(3) Nasal or oral delivery device

(4) Inhaler

(5) Transdermal patches/micro-needles for drug/biologic delivery

(6) Software where output is appropriate for review as part of product labeling

b. If the combination product contains one of the following device constituent parts, an ICCR will be issued from CBER to CDRH:

(1) Gas delivery device

(2) Hyperbaric chamber

(3) Nebulizer

(4) Implantable infusion device

(5) Body-worn infusion device

(6) External infusion devices (such as infusion pumps and elastomeric pumps)

(7) Software-driven medication dispenser

(8) Reusable auto-injectors intended for multiple patient use, auto-injector with external electronic components (e.g., LCD display screen) or mobile technology applications that meet the device definition that do not fall under enforcement discretion as outlined in existing policies, guidance and/or regulations[17]

(9) Inhalers (pressurized metered dose and dry powder) with external electronic components (e.g., LCD display screen) or mobile technology applications that meet the device definition that do not fall under

[17] For example, see guidance for industry and FDA staff: Mobile Medical Applications, available at https://www.fda.gov/media/80958/download.

enforcement discretion as outlined in existing policies, guidance and/or regulations

2. CDER and CDRH abide by the requested due date specified in the consult request and perform a HF review accordingly.

3. When the consult review is completed, CDER and/or CDRH sends the completed consult review to CBER.

    a. CBER will review the completed consult and determine if there are any questions that need to be forwarded to CDER or CDRH.

        (1) Within 2 business days of receipt of request for clarification or questions, CDER or CDRH staff provide a substantive response to any questions, discussion requests, etc. from CBER related to their review.

    b. If any differences of opinion between centers are noted, every attempt is made to resolve differences at the lowest organizational level possible. CBER, CDER, and/or CDRH staff discuss and seek to reach agreement in a timely and mutually agreed upon manner. As a best practice, all affected parties agree to discuss the comments at the reviewer level first and make reasonable attempts to reach an agreement. The outcome of this negotiation is documented in the administrative record maintained by CBER.

        (1) If resolution cannot be achieved at the lowest organizational level, the matter is brought to the attention of the next level of management in the affected centers. As discussed in SMG 9010.2, *Cross-Center Dispute Resolution at the FDA*, dispute resolution may continue as an informal process or convert to a formal dispute resolution, if needed, at any point in the process.

4. The final HF consult review(s) is archived in the administrative record by CBER.

5. The archived review(s) is referenced in the final CBER review.

6. CBER incorporates the CDER/DMEPA and/or CDRH/HFT recommendations into their review or meeting responses[18] as appropriate.

    a. For HF review, CBER references the CDER and/or CDRH review.

[18] See SOPP 8101.1: *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*, available at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm.

b. For preliminary meeting comments, CBER incorporates CDER and/or CDRH recommendations into CBER's preliminary question responses as appropriate.

7. CBER finalizes the HF review or meeting responses in the appropriate electronic archive and notifies the consulted party (CDER/DMEPA and/or CDRH/HFT).

6. AMENDMENT OF THIS STAFF MANUAL GUIDE

The originating office may edit this SMG and issue the revision without full Agency clearance in limited circumstances.[19] SMG management is described in FDA SMGs 3280.1 and 3280.2.

1. The circumstances allowing originating office edits to this SMG without full Agency clearance are constrained to:

   - Making corrections or office information updates
   - Adding or updating references to section 7, References
   - Documenting, via a dated attachment, specific program governance agreements (for example, a multi-office council that will approve compliance programs)

2. In making edits, the office:

   - Documents the change in the clearance form FDA 2306 and obtains clearances from other affected centers and offices, if any
   - Adds appropriate information in SMG section 10, Document History
   - Does not change the SMG's effective date
   - Informs non-affected centers and offices of the edits

[19] The originating office is the Office of Surveillance and Epidemiology within the Center for Drug Evaluation and Research.

7. REFERENCES

A. SMG 4101: *Intercenter Consult Request Process*, available at http://inside.fda.gov:9003/downloads/aboutfda/reportsmanualsforms/staffmanualguides/ucm283569.pdf.

B. MAPP 6030.9: *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM349907.pdf

C. Guidance for review staff and industry: *Good Review Management Principles and Practices for PDUFA Products*, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf

D. SMG 9010.2: *Cross-Center Dispute Resolution at the FDA*, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM380522.pdf

E. Guidance for industry and FDA staff: *Mobile Medical Applications*, available at https://www.fda.gov/media/80958/download

F. Guidance for industry: *General/Specific Intended Use*, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf.

G. Guidance for industry and FDA staff: *Types of Communication During the Review of Medical Device Submissions*, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm341948.pdf

H. Guidance for industry and FDA staff: *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

I. SOPP 8101.1: *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*, available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM324381.pdf

J. SMG 3280.1: *Directives Management: FDA Administrative Directives*, available at

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM275301.pdf

K. SMG 3280.2: *Directives Management: FDA Program Directives System*, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM275328.pdf

8. EFFECTIVE DATE

The effective date of this guide is February 12, 2019.

9. Document History – SMG 4104, Inter-center Consults for Review of Human Factors Information

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	02/08/2019	N/a	DMEPA within CDER/OSE	Dr. Janet Woodcock, Director CDER
Change	02/08/2021	URLs in Ftnt. 7 and 17; and Sect. 7.E.	CDER/OSE/RAS	Dr. Irene Chan, Research Officer, CDER/OSE/OMEPRM/DMEPA

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