SOPP 8004: Tissue Reference Group

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for policies and procedures of the Tissue Reference Group (TRG), a working group within the Food and Drug Administration that provides recommendations to stakeholders concerning: the application of the criteria in 21 CFR 1271.10(a) to human cells, tissues and cellular and tissue-based products (HCT/Ps); whether exceptions from the requirements in part 1271 apply (see 21 CFR 1271.15); and, which regulations apply when the HCT/P does not meet the criteria in 21 CFR 1271.10(a), and when an exception in 21 CFR 1271.15 is not applicable (see 21 CFR 1271.20).

II. Scope

This SOPP outlines how the TRG (a) receives inquiries about products consisting of, derived from or containing HCT/Ps; (b) schedules and executes its meetings; and (c) prepares TRG recommendations for

signature by designated officials within CBER and the Center for Devices and Radiological Health (CDRH).

III. Background

A. As stated in the preamble to the final rule, Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, the TRG provides a single reference point and makes recommendations to the Centers regarding regulation of specific HCT/Ps (66 FR 5447).

B. The TRG is composed of three members from CBER and three members from CDRH, including the respective product jurisdiction officers. Liaisons from CBER's Office of Compliance and Biologics Quality (OCBQ), CDRH's Office of Product Evaluation and Quality (OPEQ), and Office of the Chief Counsel (OCC) assist with evaluation of the inquiries and drafting responses as needed. A liaison from the Office of Combination Products (OCP) may participate to provide information about previous Requests for Designation (RFDs) when pertinent. An Executive Secretary provides administrative support. Additional FDA staff provide consultative reviews and attend meetings on an as-needed basis.

IV. Definitions

N/A

V. Policy

A. The TRG meets on the first and third Monday of the month for approximately one hour. Additional meetings are scheduled as needed to address inquiries in a timely manner.

B. The TRG accepts inquiries from manufacturers and sponsors or their designated representatives (provided the representative identifies the represented party), regarding their existing, investigational, or proposed products containing or consisting of HCT/Ps. The TRG provides recommendations to stakeholders concerning: the application of the criteria in 21 CFR 1271.10(a) to human cells, tissues and cellular and tissue-based products (HCT/Ps); whether exceptions from the requirements in part 1271 apply (see 21 CFR 1271.15); and, which regulations apply when the HCT/P does not meet the criteria in 21 CFR 1271.10(a), and when an exception in 21 CFR 1271.15 is not applicable (see 21 CFR 1271.20).

C. Inquiries to the TRG must be submitted to the TRG in writing, either by postal mail, electronic mail, or fax.

D. Inquiries to the TRG are generally considered in the order that they are received by the Executive Secretary.

E. The TRG generally responds in writing to the inquirer within 60 days of receipt by the Executive Secretary of an inquiry that contains sufficient detail for evaluation (see IV.F., below, for the list of items considered useful for the review of TRG inquiries). The TRG may request additional information from an inquirer if the initial submission is lacking sufficient detail. The TRG is unable to provide a recommendation concerning jurisdiction and applicable regulations when a submission lacks sufficient product information.

F. The TRG addresses inquiries based on evaluation of the following information, where provided:

1. The name and contact information of the inquirer, and if applicable, the name and contact information of the party represented by the inquirer;

2. The manufacturer of the product;

3. Any proprietary names and common names associated with the product;

4. The source of the product including how the HCT/P is recovered;

5. A clear, step-by-step description of how the product is processed, packaged (including the range of product sizes, when applicable), and stored;

6. The way(s) the product is to be used and product labeling, including package inserts and any Instructions for Use documents; and

7. How the product meets all the criteria in 21 CFR 1271.10(a).

G. Inquirers who do not agree with a recommendation provided by the TRG may submit a Request for Designation (RFD) or a pre-RFD to OCP, as described in 21 CFR part 3.

VI. Responsibilities

A. TRG Members

1. Three TRG members are from CBER and three are from CDRH, including the respective product jurisdiction officers.

2. TRG members are expected to attend every scheduled TRG meeting, unless arrangements for a substitute have been made or unusual circumstances preclude attendance.

3. TRG members are responsible for reviewing submissions, response letters and meeting minutes, for participating in discussions and providing recommendations, and where applicable, for providing background information and consultations about products that are the subject of TRG inquiries.

B. TRG Chairperson

1. One of the CBER members is the Director of the Division of Human Tissues (DHT) in the Office of Cellular Therapy and Human Tissues-CMC (OCTHT-CMC), Office of Therapeutic Products (OTP). S/he also serves as the TRG Chairperson.

2. The TRG Chairperson is responsible for calling TRG meetings to order, for facilitating the discussion of matters before the TRG, and for working with the Executive Secretary to draft the TRG meeting agenda, in addition to performing the other duties of a TRG member.

C. CBER and CDRH Product Jurisdiction Officers

Two members are the CBER and CDRH product jurisdiction officers, who provide information about how products that are similar to those under review by the TRG have been regulated by their respective offices, in addition to performing the other duties of a TRG member.

D. Executive Secretary

1. The Executive Secretary serves as the primary administrator for the TRG.

2. Included among his/her responsibilities are managing incoming submissions, tracking incoming and outgoing correspondence, scheduling meetings, drafting meeting agendas, distributing and collecting consult requests, preparing background summaries,

preparing meeting minutes, drafting, finalizing and mailing response letters, and archiving documents.

E. Liaisons

1. Liaisons from CBER's OCBQ and CDRH's Office of Compliance provide relevant information pertaining to any current or previous compliance and/or enforcement issues relating to the product and/or the establishment under discussion by the TRG.

2. A liaison from OCC provides input to the TRG on legal matters pertaining to TRG inquiries and recommendations.

3. As needed, a liaison from OCP answers questions from the TRG about the RFD process or decisions that have been issued.

F. CBER and CDRH Policy Staff

Staff from OCTHT/OPT in CBER and OPEQ policy staff in CDRH, as designated by the respective office designated officials, review and clear the final response letters.

G. Designated Officials, OCTHT CBER and OPEQ CDRH

The designated officials review the inquiry and upon approval, sign the TRG's response letter and return it to the Executive Secretary for finalization and mailing.

VII. Procedures

A. Receiving Inquiries

1. All inquiries addressed to the TRG are forwarded to the Executive Secretary.

2. Upon receipt, an inquiry is assessed for sufficient detail for TRG evaluation by the Executive Secretary who acknowledges receipt of the inquiry and, if the email address used by the requestor is not secure, requests that the inquirer establish secure email with the FDA. The Executive Secretary enters the inquiry into the TRG log with the following information:

   a. Date that the inquiry was received by the Executive Secretary

b. Inquirer's contact information, and if inquiring on behalf of another party, the manufacturer or sponsor they are representing

c. Basic information about the product that is the subject of inquiry

3. If the inquiry lacks sufficient detail for evaluation, the Executive Secretary contacts the sender to request that the missing information be provided in written form to the TRG.

4. After the inquiry is logged, DHT staff prepares a backgrounder summarizing the product that is the subject of the inquiry, the questions posed to the TRG, and relevant precedents from TRG files.

5. Inquiries are placed on the agenda for the next scheduled meeting, generally no later than two weeks after receipt by the Executive Secretary. Each inquiry is listed on the agenda as one of the following:

a. New Request for Recommendation

b. Pending Request for Recommendation

6. After the TRG Chairperson and Executive Secretary finalize the agenda, the Executive Secretary distributes the agenda and any associated documents to the TRG members and other participants no later than two working days before the meeting, to allow for sufficient time for evaluation and preparation of TRG members' recommendations and consultations.

B. Meetings

1. The Executive Secretary takes attendance and the TRG Chairperson calls the meeting to order. Note: TRG members that cannot attend a meeting because they are on leave, or for other reasons, are expected to designate a substitute who can present their comments and recommendations for each item on the agenda.

2. The TRG Chairperson facilitates discussion of each agenda item, assuring that the TRG members have adequate information to evaluate the inquiry, including description of the product, questions posed by the inquirer, and relevant precedents. Each TRG member then presents their comments

and recommendations for the response, including the rationale for their recommendations.

3. Sometimes, after the initial discussion, the TRG may determine there is insufficient information to respond to the inquiry. The Executive Secretary communicates this to the sponsor or manufacturer and the TRG discusses any additional information provided to FDA at the next available meeting, generally within two weeks of submission of the additional information.

4. Alternatively, after initial discussion the TRG may sometimes determine that consultation of other FDA staff may be needed to develop a recommendation. The Executive Secretary prepares the consultation request and the consultant provides their comments and recommendation, including the rationale for their recommendation at the next available meeting, generally within two weeks of the initial discussion.

5. If additional time is required to obtain information or for consultation (see above), the item is placed on the agenda for the next meeting.

6. The Chairperson summarizes the proposed recommendation or recommendations and asks all TRG members to comment, to determine whether there is agreement. If there is a consensus recommendation, the draft response is outlined and the agenda item is concluded. If there is not a consensus, the Executive Secretary may schedule a briefing for designated officials of affected Offices to generally occur within the following two weeks. After the briefing, the designated officials advise on the preparation of the response letter for their signatures, or other steps for addressing the inquiry.

7. Updates on HCT/P inquiries, jurisdictional issues, and compliance activities that have been addressed or engaged in by the participating offices are presented at the beginning of each meeting. The purpose of the updates is to share jurisdiction decisions, compliance activities, and other matters that may inform TRG evaluations.

C. Responding to Inquiries

1. The Executive Secretary drafts the response letter and submits it for review by the TRG.

2. TRG may inform the inquirer that should s/he disagree with the TRG's recommendation, an RFD or a pre-RFD may be submitted to OCP, as provided under 21 CFR part 3, when such information is relevant to the inquiry.

3. If the TRG concludes that a given product does not meet the criteria for regulation solely under section 361, the TRG may direct the inquirer to the Center at the Agency that is responsible for review of that HCT/P, where sufficient information is provided to support that referral and the TRG members, including both jurisdiction officers, are in agreement about the referral.

4. When the draft response is cleared by the TRG, the Executive Secretary presents the letter to the designated officials of OCTHT and OPEQ for their respective signatures.

5. The Executive Secretary sends the signed letter to the inquirer by secure e-mail or, if secure email has not been established, by US Mail.

6. Some inquiries of a limited nature, such as information requests, may be addressed directly by e-mail or telephone call between the Executive Secretary and the inquirer.

7. The Executive Secretary logs the date that the TRG recommendation or other response was mailed or otherwise conveyed to the inquirer.

VIII. Appendix

N/A

IX. References

A. References below can be found on the Internet:

1. Proposed Approach to the Regulation of Cellular and Tissue-based Products

2. Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement: Proposed Rule (FR Vol. 66, No.5, 1508, January 8, 2001)

3. Human Cells, Tissues, and Cellular Tissue-Based Products; Establishment Registration and Listing, Final Rule (FR Vol 66, No. 13, 5447, January 19, 2001)

4. Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

5. Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

6. 21 CFR 1271

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Bruce Crise Scott Brubaker	Katie Rivers, Acting Chief RABOB/DROP/ORO	February 23, 2023	6	Revised to incorporate an updated list of information used to evaluate a submission, and for changes due to the 2023 CBER reorganization.
Denise Zavagno Andrew Yeatts Scott McNamee Jean Makie Sherry Lard Katherine Kavlock Deborah Hursh Bruce Crise Scott Brubaker	Darlene Martin, MS, PMP	January 16, 2020	5	Revised to incorporate new formatting, addition of acknowledgement of receipt and request to establish secure email, and edits to RFD, pre-RFD, website links, office name change (ODE to OPEQ), and use of term ‘designated officials.’

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Denise Zavagno Scott McNamee Jean Makie Sandra Magera Sherry Lard Katherine Kavlock Deborah Hursh Yong Fan Bruce Crise Scott Brubaker James Bertram	Christopher Joneckis	September 5, 2018	4	Revised to update existing procedures (see 82 FR 54290) and references, and to address Office name change (OCTGT to OTAT)
Charlene Cho Angela Krueger Sherry Lard Ellen Lazarus Scott McNamee TRG SOPP Working Group	Christopher Joneckis	April 25, 2013	3	Revised to clarify existing procedures and to add new procedures in response to comments.
Marty Wells Sharon Risso Diane Maloney Jill Warner Areta Kupchyk Ruth Solomon Marybeth Jacobs	Robert Yetter	June 7, 2002	2	This change incorporates language of the final rule (21CFR1271.10) published in January 2001, clarification of timeframes, staff responsibilities and formatting.
	Rebecca Devine	July 28, 1998	1	Original