

SOPP 8508: Procedures for Handling Adverse Reaction Reports Related to "361" Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Version #2

Effective Date: March 26, 2008

1. Purpose

This SOPP describes the procedures that the Center for Biologics Evaluation and Research (CBER) should routinely follow when receiving reports of adverse reactions associated with HCT/Ps. This SOPP also will address the necessary framework for efficient communication between points of contact in the Office of Biostatistics and Epidemiology (OBE), Office of Cellular, Tissue, and Gene Therapies (OCTGT), Office of Compliance and Biologics Quality (OCBQ), Office of the Director (OD) and the Office of Communication, Training and Manufacturers Assistance (OCTMA), and between other appropriate Food and Drug Administration (FDA) staff, and non-FDA participants.

2. Definitions

HCT/P

An HCT/P is an article containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient [21 CFR 1271.3(d)]. An HCT/P is regulated solely under section 361 of the Public Health Service (PHS) Act and applicable regulations in 21 CFR Part 1271 if it meets all of the criteria described in 21 CFR 1271.10(a). An HCT/P that falls into this category is sometimes referred to as a "361" HCT/P.

If the HCT/P does not meet the criteria in 1271.10(a), then the HCT/P is regulated as a drug, medical device, or biological product under the Federal Food Drug and Cosmetic Act and/or section 351 of the PHS Act and other applicable regulations in Title 21 CFR in addition to applicable regulations in 21 CFR Part 1271.

MedWatch

MedWatch is the FDA safety program for reporting adverse reactions/events and problems associated with medical products, including HCT/Ps (<http://www.fda.gov/medwatch>). Manufacturers use form FDA 3500A for mandatory reports. Consumers, health professionals, and other respondents use Form FDA 3500 for voluntary reports.

Adverse Reactions for "361" HCT/Ps per 21 CFR 1271.350(a)

An adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response [21 CFR 1271.3(y)].

Any adverse reaction involving a communicable disease related to an HCT/P made available for distribution must be investigated [21 CFR 1271.350(a)(1)] by the manufacturer that made the HCT/P available for distribution.

An adverse reaction involving a communicable disease related to an HCT/P made available for distribution must be reported to FDA if the adverse reaction:

1. Is fatal;
2. Is life-threatening;
3. Results in permanent impairment of a body function or permanent damage to body structure; or
4. Necessitates medical or surgical intervention, including hospitalization.

HCT/Ps regulated as drugs, medical devices, or biological products

The TST only reviews adverse reaction reports for “361” HCT/Ps. The websites below are being provided for your information only. The appropriate regulations for reporting pre- and post- marketing medical device reports and adverse experience reports for HCT/Ps that are regulated as drugs, medical devices, or biological products are:

Medical devices:

IDE

21 CFR 812

http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr812_07.html

Approved/cleared device

21 CFR 803

http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr803_07.html

<http://www.fda.gov/cdrh/mdr/mdr-general.html>

Biological products and drugs:

IND

21 CFR 312.32 and 21 CFR 312.64

http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr312_07.html

BLA

21 CFR 600.80

http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr600_07.html

Recall

21 CFR 7.3(g) defines a recall as a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers and against which FDA would initiate legal action. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority.

Market Withdrawal

21 CFR 7.3(j) defines a market withdrawal as a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA or which involves no violation.

Tissue Safety Team

The Tissue Safety Team (TST) consists of CBER representatives from OBE, OCTGT, OCTMA, OCBQ and OD. The primary purpose of the TST is to provide a coordinated process for the review, investigation, and communication of reports of HCT/P adverse reactions. The TST develops procedures and policies to facilitate rapid and comprehensive responses by FDA and other agencies, as appropriate, to reported adverse reactions. Other activities include outreach and education, and development of recommendations regarding tissue safety.

3. Background

CBER has received reports of a number of adverse reactions associated with the use of "361" HCT/Ps. CBER asserts that it is important to investigate, track, and monitor these events to minimize public health risks. The Current Good Tissue Practice regulations [21 CFR 1271.350(a)] require manufacturers of HCT/Ps to report certain adverse reactions involving communicable disease to FDA.

To ensure that the responsibilities for addressing reported adverse reactions associated with HCT/Ps are clearly established, CBER formed a Tissue Safety Team (TST) in 2004 to monitor these adverse reaction reports and to coordinate any related activities. This SOPP delineates responsibilities and identifies points of contact within CBER as well as other FDA components and HHS agencies.

In addition to reports from manufacturers, CBER may receive voluntary reports of adverse reactions from other sources including other FDA Centers or HHS agencies, health care professionals, hospital personnel, and consumers. Some reports may not have a MedWatch form associated with them (for example, a consumer injury complaint reported to a district office or to OCTMA). CBER will track and monitor adverse reaction reports received (regardless of the format or reporting mechanism used) and initiate and coordinate investigations as appropriate. When HCT/P adverse reactions are reported to FDA in a format other than MedWatch, reporters will be contacted and encouraged to submit a MedWatch report.

Examples of “361” HCT/Ps that meet the criteria in 21 CFR 1271.10(a), and for which reporting is required, are:

- Amniotic membrane when used alone or without added cells
- Bone
- Cartilage
- Cornea
- Fascia
- Ligament
- Pericardium
- Peripheral or umbilical cord blood stem cells (for autologous use or use in a first or second degree blood relative)
- Sclera
- Skin
- Tendon
- Vascular graft, except when used in association with organ transplantation and labeled as such
- Heart valves
- Dura mater

The following HCT/Ps meet the criteria in 21 CFR 1271.10, but adverse reaction reporting currently is not required. Voluntary reports may be submitted using Form 3500:

- Semen
- Oocytes
- Embryos

Adverse reaction reporting also is not required for “361” HCT/Ps procured before 21 CFR 1271.350 became effective (i.e., before May 25, 2005). Voluntary reports may be submitted using Form 3500.

4. Policy

It is CBER’s policy that all HCT/P adverse reaction reports will be investigated, tracked, and monitored by the TST Working Group (WG), which is composed of a subset of representatives of the full TST. On a monthly basis and when deemed necessary on a case-by-case basis, the TST WG will brief the TST regarding ongoing investigations. On a quarterly basis and when deemed necessary on a case-by-case basis, the TST will brief the OD/CBER regarding ongoing investigations. The TST will develop any internal and external communications necessary regarding adverse reactions.

5. Responsibilities and Procedures

A. MedWatch Reports

OBE Responsibilities

OBE is the official contact for MedWatch reports involving HCT/Ps. OBE is responsible for processing and epidemiologic review of the reports, as well as for making reports available to the appropriate contacts within CBER for review and follow-up.

Upon receipt of a report of an adverse reaction associated with an HCT/P, the OBE staff person receiving the report will forward it to the OBE point of contact for the TST WG (see Appendix 1). OBE will open a record in the Adverse Event and Product Problem (AEPP) database and enter pertinent details for review by other TST WG members. However, reports of adverse events for CDRH-regulated devices, reports submitted as part of an Investigational New Drug (IND) protocol, and biological product deviation reports are not entered into AEPP, and are forwarded as appropriate. All MedWatch reports for HCT/Ps and other CBER-regulated products are stored in the Adverse Events Reporting System (AERS) database; OBE maintains a list of HCT/P active ingredients for designation of products within AERS.

OBE will notify the OCBQ POCs of reports that may need manufacturer follow-up. OBE will immediately notify the TST WG on any urgent matters (such as infections in multiple recipients of tissue from the same donor, infections involving virulent pathogens, recipient fatalities, product contamination). OBE will forward adverse reaction reports involving cell and cellular-based products to the OCTGT POC for cell reports for clinical follow-up.

OBE will assess the adverse reaction report to determine the need to conduct a clinical follow-up investigation (e.g., if details are needed about the time to onset of symptoms or the recipient outcome). If additional information is needed, OBE will contact the reporter and ask appropriate clinical questions. OBE will summarize the information received from the reporter and enter the summary into AEPP. OBE will immediately notify the TST WG on any urgent matters that arise from follow-up investigation.

OBE's POC will set up bi-weekly meetings of the TST WG (Appendix 1) as needed to discuss open reports and other issues related to the operation of the TST. For TST Quarterly meetings, OBE will present a descriptive summary of the number and types of reports received in the previous quarter, and will present selected cases.

OCBQ Responsibilities

OCBQ will contact the HCT/P manufacturer, when necessary. The decision to contact the manufacturer will be based on historic precedent or, when faced with a new scenario, will be consultative among members of the TST WG. OCBQ will request additional relevant information regarding the tissue involved (e.g. information regarding donor eligibility or tissue processing). Information received from the manufacturer will be reviewed and summarized by OCBQ and entered into AEPP. OCBQ will notify the OCTGT and OBE POCs if OCBQ determines that the

information obtained from the manufacturer needs their review prior to the next TST WG meeting (for example, to review and interpret donor clinical information). OCBQ will immediately notify the TST WG on any urgent matters that arise from follow-up investigation.

If it is determined that a directed inspection assignment is warranted, OCBQ will write the assignment and shepherd it through the approval process.

OCTGT Responsibilities

OCTGT is responsible for the medical/scientific assessment of each case. The OCTGT POC will obtain scientific information about the microorganism involved, in order to determine its significance. OCTGT will share this information with other TST WG POCs. OCTGT will review donor information received from the tissue manufacturer, such as donor eligibility records and autopsy reports, if necessary or upon request by OCBQ.

The OCTGT POC for cells will perform clinical and manufacturer follow-up on cell reports as needed and present these cases at TST WG meetings. If the POC for cells is not available to perform follow-up in a timely manner, the OCTGT POC for all other reports will perform follow-up.

The OCTGT POC will arrange monthly meetings with the entire TST (Appendix 2), as needed, to discuss selected cases and policy issues. The OCTGT POC also will arrange quarterly meetings of the TST and the Immediate Office of the Director (OD) (Appendix 4), as needed, to discuss significant cases and policy issues, and brief OD on other TST activities.

OCTMA Responsibilities

If OCTMA receives information about an adverse reaction from a consumer, healthcare professional, consignee, or manufacturer, OCTMA will forward this information to the OBE POC (Appendix 1).

TST Joint Responsibilities

The TST WG (Appendix 1) will meet bi-weekly, as needed. It will evaluate all HCT/P reports submitted to FDA and information collected during follow up investigation, if any. The TST Chair will determine when the investigation by the TST is complete and seek concurrence with others on the TST WG. The TST Chair or designee will close the case in AEPP, indicating that the TST investigation is complete and, based on the information, no further action is warranted. Cases may be re-opened if new information that warrants further action becomes available.

If the TST Chair is notified about an urgent matter (e.g. through OBE or OCBQ notification of the TST WG), the TST Chair will determine whether the TST

(Appendix 2) and the CBER OD (Appendix 4) should be notified of the event, and will carry out such notification.

If the TST WG determines that the investigation of, or response to a report requires involvement of contacts outside of CBER (Appendix 3), the TST Chair will assign to TST WG members responsibility for initiating these contacts.

OD Responsibilities

If the Emergency Operations Manager (EOM) from the CBER OD receives information about an Emergency/Serious Adverse Reaction or safety issue from the Office of Crisis Management/Office of Emergency Operations, the EOM will disseminate this information to the TST WG. The EOM will also communicate general information about the TST activities to CBER OD Senior Management as needed.

Interaction with CDC

CDC may provide infectious disease expertise and/or laboratory testing (e.g., cultures of donor and/or recipient tissues and/or materials; identifying and/or genetic typing of isolates, etc.). When necessary, CDC also may notify consignees of potential safety risks, in coordination with state and local health departments. Information exchanges between FDA and CDC will be consistent with the principles and procedures outlined in the Memorandum of Understanding between FDA and CDC (MOU Number 225-06-8401).

Communication with Foreign Government Regulatory Authorities

In the event of consignee notification involving HCT/Ps distributed to foreign countries, the OCBQ Director will notify the International Affairs Advisor in the Office of the Director (Appendix 5). The International Affairs Advisor will perform/coordinate any necessary notification of foreign regulatory authorities. If communications are needed with foreign regulatory authorities for other reasons, the International Affairs Advisor also will coordinate those on behalf of the TST.

B. Recalls and Market Withdrawal

OCBQ's Division of Case Management (DCM) is the official contact in CBER for recalls. If OCBQ/DCM is informed of a firm's decision to notify consignees of a distributed product involved in or related to a potential or actual communicable disease transmission, OCBQ/DCM will immediately inform the TST Chair. The TST Chair will determine whether the TST (Appendix 2) and the CBER OD (Appendix 4) should be notified of the event, and will carry out such notification.

C. Other Reports

The CBER Office that is contacted by an outside agency (e.g. CDC or HRSA), the public, or other FDA component about an adverse reaction involving an HCT/P should follow the procedure above. The outside reporter will be encouraged to file a MedWatch report.

D. Discussion with CBER Upper Management

The TST Chair will contact CBER OD (Appendix 4) about any important HCT/P safety concerns. At TST quarterly meetings, the OD will be briefed on all significant cases and policy issues.

6. Effective Date

March 27, 2008

7. History

Written By	Approved By	Approval Date	Version Number	Comments
Laura St. Martin	Robert Yetter	March 26, 2008	2	Administrative procedures updated
Martha Wells Anita Richardson	Robert Yetter	February 28, 2005	1	Original version

Appendices

- [Appendix 1: Tissue Safety Team Working Group & Points of Contact \(POCs\) \(PDF - 23KB\)](#)
- [Appendix 2: Tissue Safety Team \(PDF - 25KB\)](#)
- [Appendix 3: Points of contact for other agencies or personnel within FDA \(PDF - 28KB\)](#)
- [Appendix 4: CBER Office of the Director \(PDF - 19KB\)](#)
- [Appendix 5: International Affairs Advisor \(PDF - 14KB\)](#)