

● CASE STUDY

HCTP Case Presentations: Adverse Reactions and Product Deviations

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The following 12 case studies are based on actual donor situations and actions taken. They are presented for review and discussion as to potential appropriate disposition of tissue, physician and/ or patient follow up, and regulatory or medical standards compliance.

**HCTP Case Presentations:
Adverse Reactions and
Product Deviations**

UT SOUTHWESTERN
Transplant Services Center

COMPLETING
THE CIRCLE OF CARE

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● CASE STUDY/PROCEEDINGS

Slide 2:

Case 1 (1 of 2)

Corneas were transplanted from a donor who was determined to be eligible based on available information (afebrile, without leukocytosis, no signs/symptoms of sepsis).

At the time of Donor Eligibility determination, blood cultures performed by the hospital prior to death were 'No Growth' at 48 hours.

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Slide 5:

Case 1a (Discussion)

- What if one cornea recipient has developed endophthalmitis that may be attributable to the positive blood culture?
- HCT/P Deviation Report not required because there's no indication of sepsis.
- Report Adverse Reaction.

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Slide 3:

Case 1 (2 of 2)

Several days after transplant the eye bank received final blood culture results from the organ procurement organization – positive for Fusobacterium.

What do you do?

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Slide 6:

Case 2 (1 of 2)

Donor: 19 y/o female with hanging as a cause of death. Pronounced in ER after resuscitation efforts were unsuccessful.

Corneas, musculoskeletal, and cardiovascular tissue were recovered.

Based on available information, donor was determined to be eligible and both corneas were released for transplant.

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Slide 4:

Case 1 (Discussion)

- Cornea surgeons notified - Cornea recipients are without related complications.
- HCT/P Deviation Report not required because although blood cultures were positive, there's no indication of sepsis.
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 7:

Case 2 (2 of 2)

Several days later the cardiac pathology report from the heart valve processor was received - indicating the donor may have had lymphocytic myocarditis at the time of death (identified on microscopic exam).

What do you do?

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● CASE STUDY/PROCEEDINGS

Slide 8:

Case 2 (Discussion)

- Cornea surgeons notified - Cornea recipients are without related complications.
- What about skin and musculoskeletal tissue (not yet released post-preservation)?
- HCT/P Deviation report is not required because lymphocytic myocarditis is not a relevant communicable disease.
- No Adverse Reaction – no Adverse Reaction Report required.

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Notification of cornea surgeons is an organizational decision in this case. Notification decision should be based on Medical Director opinion and other organizational considerations such as relative risk to recipients, perceived risk to organizational reputation and public trust, etc.

Slide 9:

Case 3 (1 of 2)

Donor: 74 y/o male with a history of atherosclerotic cardiovascular disease (ASCVD) which was also the cause of death. Pronounced in the emergency room after resuscitative efforts were unsuccessful. Donor Risk Assessment Interview with next of kin was unremarkable beyond ASCVD.

Corneas were recovered by the eye bank. Skin and musculoskeletal tissue were recovered by the tissue bank.

Based on available information, the donor was determined to be eligible and fresh skin was released for transplant.

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Slide10:

Case 3 (2 of 2)

Approximately 1 month later the Tissue Bank reported to the Eye Bank that they had received information from the donor's primary care physician that he was treating the donor for Alzheimer's.

What do you do?

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Slide 11:

Case 3 (Discussion)

- Tissue Bank shares information with eye bank.
- Cornea surgeons notified - Cornea recipients are without related complications.
- The remaining donor tissue discarded.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

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Donor eligibility determination failed to identify the history of Alzheimer's. The donor was not free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases.

● CASE STUDY/PROCEEDINGS

Slide 12:

Case 4 (1 of 2)

Donor: 46 y/o female with Pulmonary Embolism as the cause of death.

Corneas, skin, musculoskeletal, and cardiovascular tissue were recovered.

Based on available information corneas and fresh skin were released for transplant.

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Slide 14:

Case 4 (Discussion)

- Consignees not notified of the deviation since the correct answer did not change the donor eligibility determination.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 13:

Case 4 (2 of 2)

An audit of the Donor Risk Assessment Interview revealed that one question was not asked but had been marked as “No”. The question was regarding whether the donor ‘...had or had been treated for any sexually transmitted diseases in the past twelve months...’.

The next of kin was immediately re-contacted and asked the question – the answer was ‘No’.

What do you do?

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Slide 15:

Case 4a (Discussion)

Suppose the answer had been ‘Yes’ the donor had been treated for a sexually transmitted disease in the past twelve months?

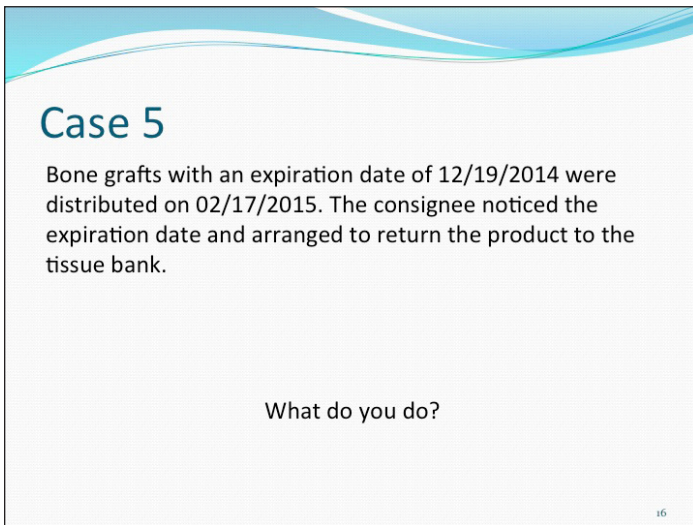
- Notify consignees.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

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Consignee notification is required because there were risk factors for relevant communicable disease agents.

● CASE STUDY/PROCEEDINGS

Slide 16:



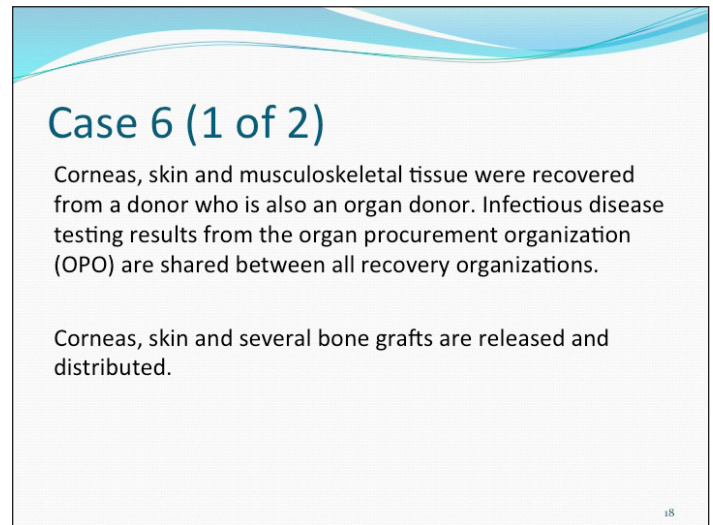
Case 5

Bone grafts with an expiration date of 12/19/2014 were distributed on 02/17/2015. The consignee noticed the expiration date and arranged to return the product to the tissue bank.

What do you do?

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Slide 18:



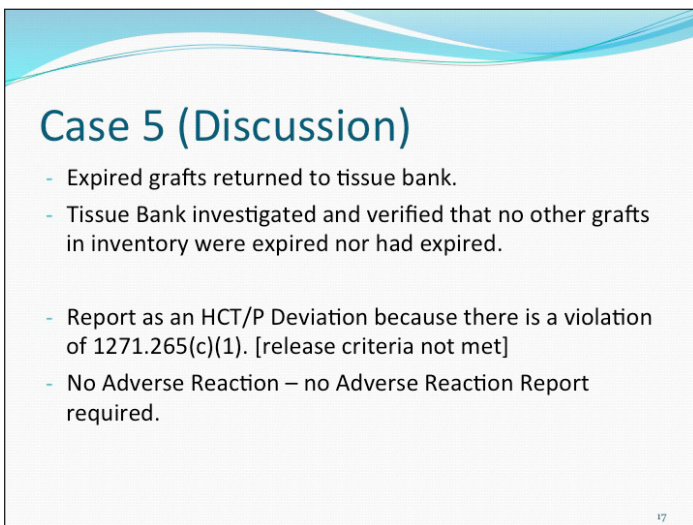
Case 6 (1 of 2)

Corneas, skin and musculoskeletal tissue were recovered from a donor who is also an organ donor. Infectious disease testing results from the organ procurement organization (OPO) are shared between all recovery organizations.

Corneas, skin and several bone grafts are released and distributed.

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Slide 17:

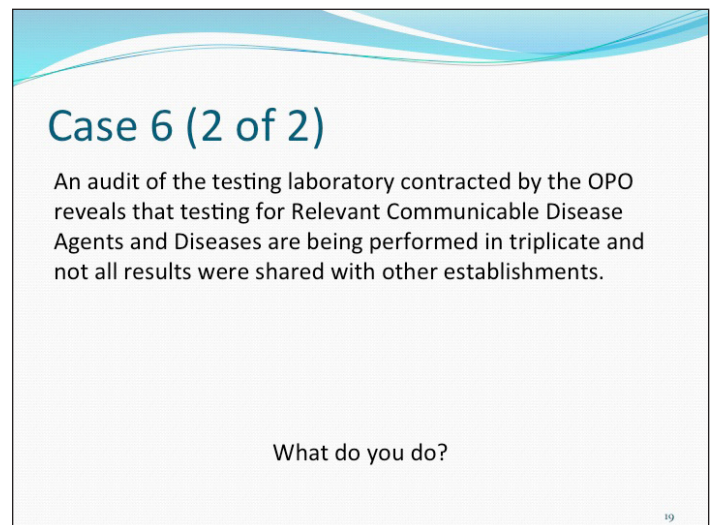


Case 5 (Discussion)

- Expired grafts returned to tissue bank.
- Tissue Bank investigated and verified that no other grafts in inventory were expired nor had expired.
- Report as an HCT/P Deviation because there is a violation of 1271.265(c)(1). [release criteria not met]
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 19:



Case 6 (2 of 2)

An audit of the testing laboratory contracted by the OPO reveals that testing for Relevant Communicable Disease Agents and Diseases are being performed in triplicate and not all results were shared with other establishments.

What do you do?

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The tissue bank failed to identify that all release criteria had been met prior to distribution (e.g. tissue had passed its established expiration date). Before making an HCT/P available for distribution, you must review manufacturing and tracking records pertaining to the HCT/P, and, on the basis of that record review, you must verify and document that the release criteria have been met. A responsible person must document and date the determination that an HCT/P is available for distribution.

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Case 6 (Discussion)

- Obtain and review triplicate test results (they're all found to be non-reactive).
- Notify consignees.
- HCT/P Deviation report is not required for OPO not sharing results that were negative.
- If results were positive, an HCT/P Deviation report would be required - violation of 21 CFR 1271.80(c) [testing]
 - Notify Consignees.
- No Adverse Reaction – no Adverse Reaction Report required.

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This scenario is more complex than it may initially appear as the slightest variation(s) in the facts of similar scenarios could render completely different reporting requirements. Work closely with FDA staff in determining appropriate reporting. However, be aware that decisions are ultimately the responsibility of the HCT/P establishment.

Slide 21:

Case 7

Several lots of cancellous bone chips are labeled with a 3 year expiration date. The tissue bank's SOP specifies a 2 year expiration date. Grafts from involved lots have been released to inventory but have not been distributed.

What do you do?

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Slide 22:

Case 7 (Discussion)

- Investigate and document deviation.
- HCT/P Deviation report is not required because the products were not distributed.
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 23:

Case 8

Several lots of cancellous bone chips are labeled with a 3 year expiration date. The tissue bank's SOP specifies a 2 year expiration date. Grafts from involved lots have been released to inventory and several **have been distributed**.

What do you do?

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Slide 24:

Case 8 (Discussion)

- Investigate and document deviation.
- Notify consignees.
- No adverse outcomes reported.
- Report as an HCT/P Deviation because there is a violation of 1271.260(c). [expiration dating]
- No Adverse Reaction – no Adverse Reaction Report required.

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● CASE STUDY/PROCEEDINGS

Slide 25:

Case 9

Several lots of cancellous bone chips are labeled with a 3 year expiration date. The tissue bank's SOP specifies a 2 year expiration date. Grafts from involved lots have been released to inventory and several have been distributed. The tissue bank has just completed a process validation that demonstrates a 3 year expiration but has not yet incorporated those results in SOPs.

What do you do?

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Slide 27:

Case 10

Cancellous bone chips are labeled with a 3 year expiration date according to the tissue bank's SOPs that have been in place for several years. Many lot numbers have been distributed and transplanted under this protocol. Re-verification of the package aging testing reveals that the appropriate expiration should be 2 years rather than 3 years.

What do you do?

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Slide 26:

Case 9 (Discussion)

- Investigate and document deviation.
- Consignee notification not required
- No adverse outcomes reported.
- HCT/P Deviation Report is required because there's a violation of 1271.265(c)(3) [departure from procedure]
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 28:

Case 10 (Discussion)

- Investigate and document deviation.
- Notify consignees.
- No adverse outcomes reported.
- HCT/P Deviation Report is required because there is a violation of 1271.260(c). [expiration dating]
- No Adverse Reaction – no Adverse Reaction Report required.

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The HCT/P establishment failed to record and approve this departure prior to making the HCT/P available for distribution. You must not make available for distribution any HCT/P manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission, unless a responsible person has determined that the departure does not increase the risk of communicable disease through the use of the HCT/P. You must record and justify any departure from a procedure at the time of its occurrence. Had the departure been approved prior to making the HCT/P available for distribution, this would not have been a reportable HCT/P deviation.

Although the HCT/P establishment established expiration dating, it failed to establish appropriate expiration dating. Where appropriate, you must assign an expiration date to each HCT/P based on the following factors:

- (1) HCT/P type;
- (2) Processing, including the method of preservation;
- (3) Storage conditions; and
- (4) Packaging.

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Slide 29:

Case 11

An eye bank receives a post-transplant report from a cornea surgeon that the recipient has developed a *Candida glabrata* infection.

In the course of investigating the complaint, the eye bank finds out that the recipient of the mate cornea also has an infection with the same infectious agent

What do you do?

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Slide 32:

Case 12 (Discussion)

- Investigate adverse reactions involving a communicable disease related to an HCT/P that they made available for distribution - 21 CFR 1271.350(a)(1)
- Notify other consignees
- Notify other organizations thought to be involved in the donation.
- Adverse Reaction Report is required - 21 CFR 1271.330 (Submit MedWatch Form 3500A to FDA within 15 days of initial receipt of information)
- HCT/P Deviation Report is required because there is a violation of 21 CFR 1271.80(c) [testing]

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Slide 30:

Case 11 (Discussion)

- Investigate adverse reactions involving a communicable disease related to an HCT/P that they made available for distribution - 21 CFR 1271.350(a)(1)
- Medical intervention was required to treat the infections.
- Adverse Reaction Report Required - 21 CFR 1271.330 (Submit MedWatch Form 3500A to FDA within 15 days of initial receipt of information) 21 CFR 1271.350(a)(2-3)
- If investigation does not reveal a deviation, HCT/P Deviation Report not required.

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Slide 33:

Case 13

A tissue manufacturer receives complaint that during surgery, the surgeon discovers the graft is mislabeled and is the wrong size. Surgeon must cut the graft and this prolongs the surgical procedure. Patient does well.

What do you do?

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Slide 31:

Case 12

A recipient of a tendon develops symptoms 3 months post-transplant and tests positive for HCV. In the course of the investigation, the tissue bank discovers that the HCV testing was not performed correctly.

What do you do?

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Slide 34:

Case 13 (Discussion)

- Investigate deviation - 21 CFR 1271.350(b)(1)
- HCT/P Deviation Report not required because it's not related to the prevention of communicable disease or HCT/P contamination.
- No Adverse Reaction – no Adverse Reaction Report required.

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