

FDA & the Changing Paradigm for HCT/P Regulation

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ABSTRACT

The Pharmaconference, Inc. hosts annual cellular and tissue conferences. The 11th Annual FDA and Changing Paradigm for HCT/P Regulations, held March 23-25, 2015, included presentations from FDA and industry on labeling and accompanying record requirements for cells, and musculoskeletal and ocular tissues. The FDA gave a general session presentation detailing requirements according to 21 CFR 1271. During breakout sessions, industry speakers from cells and musculoskeletal and

ocular tissues gave presentations describing their industry specific requirements, i.e., according to their respective accreditation bodies. The content here is the presentation given for requirements of eye banks accredited by the Eye Bank Association of America (ocular tissue).

Keywords: EBAA, Medical Standards, labeling, tissue report form, package insert form, preservation type, processing type, predistribution shipment

LABELING & ACCOMPANYING RECORDS FOR HCT/Ps (Ocular)

FDA & the Changing Paradigm for HCT/P Regulation

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Figure 1

Slide 2:

Objectives

- Labels
 - All Tissues
 - Short- and Intermediate Term Preserved Tissue
- Documentation to Accompany Donor Tissue
 - Tissue Report Form
 - Package Insert Form
 - Pre-distribution
- Case Study – LVG’s halo Label

Figure 2

This presentation will focus on the Eye Bank Association of America’s (EBAA) labeling and accompanying documentation requirements, which are in addition to FDA requirements. We will review what information has to be included in the label that’s applied to the tissue container and the content required to be included in the paperwork that is sent with the tissue to the consignee. There is a difference in what has to be on the label and in the paperwork depending on 1) how the tissue is preserved, and 2) how the tissue was processed. Lastly, we’ll review an example of how, even with the most thoughtful approach, mistakes can be made when navigating through all the many requirements.

Slide 3:

Preservation Differences

- Short Term Preservation
 - Eye tissue preservation techniques that maintain viability and/or ultrastructure for less than 5 days. Refrigeration requirement of 2°-8°C.
 - Example: Whole eyes preserved for surgeon manual dissection in OR

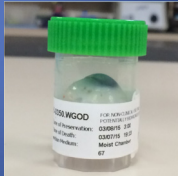


Figure 3

First let’s talk about the different types of preservation detailed by the EBAA Medical Standards. There are three types: short term, intermediate term, and long term. The difference between the three are related to the tissue expiration date, which is determined either by the storage media or the length of time the tissue may be in storage before its viability is compromised. Short-term preservation applies to eye tissue that will be transplanted within 5 days of recovery of the tissue. This is typically a whole eye that the surgeon will manu-

ally dissect in the OR. To give you an example, in the picture here you see the cornea at the top of the globe. The surgeon will excise a portion of the cornea from the globe in the OR. Lions VisionGift does not provide short-term preserved tissue, which is why you see ‘for non-clinical use’ on the label.

Slide 4:

Preservation Differences

- Intermediate Term Preservation
 - Cornea or corneal section preserved in solution that maintains cellular and/or ultrastructure viability for 14 days. Refrigeration requirement of 2°-8°C.
 - Example: Corneal-scleral rim preserved tissue that may or may not have undergone processing.




Figure 4

The second and most common type of ocular tissue preservation is intermediate term. For this type of preservation, corneas are excised from the globe by eye bank technicians and stored in a solution that contains antibiotics and nutrients necessary to maintain the tissue’s viability. The expiration countdown of 14 days starts once the cornea is placed in the media.

Slide 5:

Preservation Differences

- Long Term Preservation:
 - Cornea or corneal section stored in a solution that is designed to maintain tissue ultrastructure for greater than 5 days and up to 5 years depending on the technique. Viability is not maintained.
 - Example: Tissue preserved in glycerin or that has undergone terminal sterilization.

Figure 5

Long term preservation refers to tissue where endothelial cell viability is either not maintained or not relevant. The Medical Standards call out corneal tissue, but it applies to any tissue the eye bank manufactures. It most often applies to scleral tissue preserved in alcohol or corneas preserved in glycerin, but also applies to tissue that has been irradiated.

Slide 6:

J1.000 Labeling

- All tissues
 - Name of source eye bank
 - Type of tissue (e.g., cornea, whole eye, sclera)
 - Type of storage solution
 - Processing info, if applicable
 - Single patient use only
 - Sterility claims
 - ISBT 128 info (by Jan 1, 2016)

Figure 6

As noted earlier, the labeling and documentation requirements are different depending on the type of preservation. The Medical Standards call out what has to be on the label accompanying paperwork for all tissues, and then for short and intermediate term tissues. The additional labeling requirements for short and intermediate term preserved tissue is detailed in Figure 8.

The labeling requirements for all tissue need to have what's listed here (Figure 6). Eye banks sometimes import corneas from other eye banks. If the imported tissue will undergo processing, the importing eye bank will likely have to generate and apply new labels to the container. The name of the source eye bank (typically the eye bank that performed eligibility determination) has to be included on the label, so the importing eye bank needs to have the ability to include this information on labels they generate and apply to imported tissue. The label needs to list the type of storage media the tissue is in and indicate the tissue is for single patient use only.

The labeling and documentation requirements are also different depending on the type of processing that was performed on the tissue, if any. I'll get into more detail about this in next slide (Figure 7). The label also needs to indicate if the tissue is considered sterile or not. For any tissue that hasn't been sterilized by a validated irradiation process, the label needs to indicate the tissue "should not be considered sterile". Eye banks are required to adopt ISBT coding by the end of the year, which has very specific labeling requirements.

Slide 7:

J1.000 Labeling

- All tissues, continued.



Figure 7

As I said before, the label also needs to indicate if the tissue underwent processing. Corneas can be processed for different surgical uses depending on the physical qualities of the tissue. If the tissue underwent processing by the eye bank, the container needs to indicate what type. The examples here (Figure 7) show that this tissue was processed for Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty.

Slide 8:

J1.000 Labeling

- Short and intermediate term preserved tissues
 - Date and time of donor's death
 - Date and time of initial corneal/scleral preservation

Cornea OD 2015-0397.CNOD	Date Time of Preservation: 03/18/15 0:16 Date Time of Death: 03/17/15 12:08 Age: 63 Source Eye Bank: Lions VisionGift 2201 SE 110th Ave Portland, OR 97214 503.808.7070	Medium: Optisol GS Exp. Date: 04/01/15 STORAGE: 4-8° CELSIUS - DO NOT FREEZE SINGLE PATIENT APPLICATION ONLY - NOT STERILE	Patient's Chart Copy Cornea OD 2015-0397.CNOD Single Patient Use Only - Not Sterile Lions VisionGift 503.808.7070
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Figure 8

In addition to the requirements for all tissue, labels for short and intermediate term preserved tissue also need to have the date and time of donor's death and date and time of initial cornea or sclera preservation. The Lions VisionGift label you see here (Figure 8) is an example of a label for intermediate term preserved tissue that includes all the required information. (Note: The section you see at the right of the label is a tear-off portion that the consignee may use to place in the recipient's chart. This is a customer service Lions VisionGift provides to surgeons and is not required by EBAA.)

Slide 9:

LI.100 Tissue Report Form

- All Tissues
 - Source eye bank contact info
 - Tissue ID (also ISBT Jan 1, 2016)
 - Type of storage solution
 - Name and EBAA Accreditation status of any org performing a step
 - Processing info, if applicable, to include specific tissue qualities

Figure 9

On to the requirements for accompanying documentation. Again, remember that just as the requirements are different based on preservation type, the requirements are also different if processing occurred. Remember that this presentation only details the requirements that are in addition to FDA requirements; the FDA requirements are not listed here.

EBAA requires a tissue report form be sent with all tissue. Much of the content required to be included in the tissue report form is the same as the labeling requirements and is consistent based on preservation type and processing. For all tissue, EBAA requires eye banks to include the source eye bank's contact information and the indicate the storage media the tissue is in. Additionally, the EBAA also requires eye banks report the name and EBAA accreditation status of any establishment that performs a manufacturing step for that tissue, including recovery, processing, storage, evaluation, donor eligibility determination and distribution. For example, not all eye banks process tissue. If they send their tissue to be processed by another entity, the tissue report form needs to include the name of that entity and whether or not the entity is accredited by the EBAA.

Again, if the tissue is processed, the tissue report form must include the type of processing or the indicated use, along with the post-processing tissue qualities (see Figure 11).

Slide 10:

LI.100 Tissue Report Form

- Short and Intermediate Term Preservation
 - Donor age, COD, Death date and time
 - Initial preservation date and time
 - Ocular cooling information
 - Recovery, processing and evaluating technician name(s)
 - Processing info, if applicable, to include specific tissue qualities

Figure 10

The tissue report form for short and intermediate term preserved tissue needs to include information about the donor and tissue recovery. It needs to include the donor's age, cause of death, and date and time of death. It needs to include the date and time of initial preservation and the time ocular cooling or refrigeration time began after death.

The tissue report form must also include the names of the eye bank technicians that recovered, processed (if applicable), and evaluated the tissue. Figure 11 lists the EBAA requirements for what information needs to be included in the tissue report form based on type of processing (if applicable), which is summarized here. If a cornea was processed, the tissue report form must also include the type of processing or indicated use and a description of the cornea's physical qualities after it underwent processing (e.g., post-processing endothelial cell count).

Slide 11:

LI.100 Tissue Report Form

Matrix II: Post-Processing Reporting Requirements

Processing Type	Morphology and Dimensions of Cut	Diameter of Cut	Pachymetry	Pre/Post-Processing Slit Lamp Exam	Pre/Post-Processing Endothelial Cell Density Reports
LAK	Yes	No	No	Yes	Yes
DSEK	No	Yes	Yes	Yes	Yes
DMAEK	No	Yes	Yes	Yes	Yes
DMEK	No	No	No	Yes	Yes
ALK	No	Yes	Yes	Yes	No
Short Term Preservation	As above	As above	As above	Yes*	Yes**
Intermediate Term Preservation	As above	As above	As above	Yes*	Yes**
Long Term Preservation	As above	As above	As above	Yes*	Yes**

*only for tissue intended for optical, as opposed to tectonic surgeries
 **only for tissue deemed suitable for procedures in which the transplant outcome is dependent upon viable endothelium

EBAA Medical Standards June 2015

Figure 11

Slide 12:

LI.200 Package Insert Form

- Storage recommendations
- Consignee receiving inspection instructions
- Statement about warranty as to the tissue's merchantability or fitness for use – there is none
- Notification if eye bank performs pre-surgical microbiological cultures and request for results if performed by transplanting surgeon
- Recipient tracking requirements
- Infectious disease tests performed, at a CLIA and FDA registered laboratory, and statement about test kits used.

Figure 12

The Tissue Report Form, as the name of the document suggests, is a report detailing information specific to a tissue and, if applicable, the donor it was recovered from. In addition to a Tissue Report Form, the eye bank must also send a Package Insert Form with every tissue. The Package Insert Form includes more general information that typically doesn't change from one donor or tissue to the next. Because the requirements differ based on tissue type (e.g., sclera vs cornea), many eye banks have a different Package Insert Form for each type of tissue they offer.

Regardless of tissue type, the Package Insert Form needs to include storage recommendations and instructions to consignee on what to expect when they receive the tissue. For instance, the consignee should evaluate the color of the storage solution (for intermediate term tissue), confirm the tamper evident seal is intact, the conditions of the shipping container, etc. It needs to include a statement that there is no warranty as to the tissue's merchantability or fitness for use, i.e., the final suitability determination rests with the surgeon.

Eye banks need to inform the surgeon whether or not they perform pre-surgical microbiological cultures – most do not. However, many ophthalmologists do and the eye banks want to know those results and request the results be forwarded to them. The Package Insert Form must advise the consignee that are responsible for tracking specific recipient information, including name, a unique ID number, age or date of birth, date, location, and type of surgery, and the name of the transplanting surgeon.

Lastly, the Package Insert Form must include a statement that infectious disease testing was performed by a FDA and CLIA registered laboratory using test kits that were approved for cadaveric blood when available.

Slide 13:

Pre-distribution Shipment

- Shipment of tissue in quarantine within an establishment or between establishments (recovering eye bank to processing eye bank) of tissue that has not been released for distribution. Tissue must be shipped in quarantine.

Figure 13

The Medical Standards define a pre-distribution shipment according to Figure 13. This typically applies to tissue being transported from recovery site to eye bank, but also applies to tissue sent from one eye bank to another for processing before eligibility determination is performed. In both cases, the tissue needs to have 'in quarantine' on the container to clearly show the tissue is not released for transplant.

Slide 14:

Case Study – LVG's halo label



Figure 14

In April 2014 Lions VisionGift started offering sterilized cornea, sclera, and pericardium for transplant (figure 14). We primarily use our own ocular tissue, but we also work with three other eye banks who provide corneas for us to process. We import pericardium from an AATB accredited tissue bank who performs the tissue recovery and donor eligibility determination, and we process, store, and distribute it. We dissect the cornea into up to four pieces and punch square pieces from sclera and pericardium. A sclera can be dissected into about 10 different pieces and pericardium can render close to 100. These have been used by surgeons in glaucoma surgeries to cover up 'blebs'.

Our challenge was to figure out how to get all the information that FDA and EBAA required to send with tissue to the consignee who

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receives the tissue. We had to decide what information would be on the label, what would be on the package insert. At the time, the requirements for label and accompanying documentation content was the same for all preservation types. EBAA Medical Standards did not differentiate between long term preserved and intermediate term preserved tissue. Even though a lot of the information didn't apply or wasn't relevant, all requirements for intermediate term and short term preserved tissue, including cause of death, names of recovery and processing technicians, processing information and tissue characteristics post-processing – all of it had to either be on the label or accompany the tissue. We were the second eye bank to offer a sterilized tissue. Ever. So the EBAA didn't really have a reason to address it. In June 2014, the EBAA Medical Standards were revised to differentiate the requirements for short and intermediate term tissue from long term preserved tissue. These are the requirements you learned about today.

Slide 15:

Case Study – LVG's halo label

Language	Container	Accompany Tissue**	Put it here*
Name of source eye bank	ebaa J1.000	ebaa L1.100	L2
Location of eye bank		ebaa L1.100	PI
Telephone # for eye bank		ebaa L1.100	PI
Tissue ID #	both	ebaa L1.100	L1
Type of tissue/description	both		L1
If tissue		both (L1.200) (ebaa requires we include FDA registered along with CLIA)	
Date at	SOR: statement "communicable disease testing performed by CLIA certified laboratory" (no need to include the name of lab who did testing)		PI
Expirat	SOR: list and interpretation of results of all communicable diseases performed	both (L1.200)	PI
Single	Age of donor	ebaa L1.100	L2
Type of	Cause of Death	ebaa L1.100	L2
Establish	Time of ocular cooling/body refrig	ebaa L1.100	L2
storage	Name of technicians who recovered, processed and evald tissues	ebaa L1.100	L2
statement	slit lamp report with date of eval	ebaa L1.100	L2
testing	spec report with date of eval	ebaa L1.100	L2
summary	Name and accredited status of each establishment that performs any of the following steps ...	ebaa L1.100	L2
determin			

Figure 15

We decided we didn't want to wait for the Medical Standards to be revised before we started distributing this tissue. So down we sat to figure out where to put what information. We outlined all the EBAA and FDA requirements in a matrix (figure 15). Logistically, it would have been very difficult – if not impossible – to print out a tissue report form for each graft. So we decided to put all the information required to be on the tissue report form on the label, including some FDA requirements that aren't required to be on the label but must in the paperwork that accompanies the tissue.

Admittedly, we could not fit all the information the EBAA required on the tissue report form on the label, so we intentionally did not include only the items that we thought the EBAA would agree didn't meet the spirit of the requirement. For example, ocular cooling is really important to surgeons transplanting short and intermediate term preserved tissue as it has affects the level of tissue degradation prior to placement in media. Because it's been irradiated, ocular cooling is not relevant to halo tissue grafts or their potential uses. The same logic applies to specular data. Corneas intended for surgeries that require a healthy endothelium are required to have a specular microscopy, which is required info to be put on the tissue report form. The tissue we are processing doesn't have an endothelium anymore and won't have a specular count. We chose to leave that off the label because it didn't apply. We thought the EBAA would agree with us if it came down to it. The Standards

were changed a couple months after the product was released, so we weren't living in non-compliance long.

Slide 16:

The diagram shows a tissue label with several key sections and callouts:

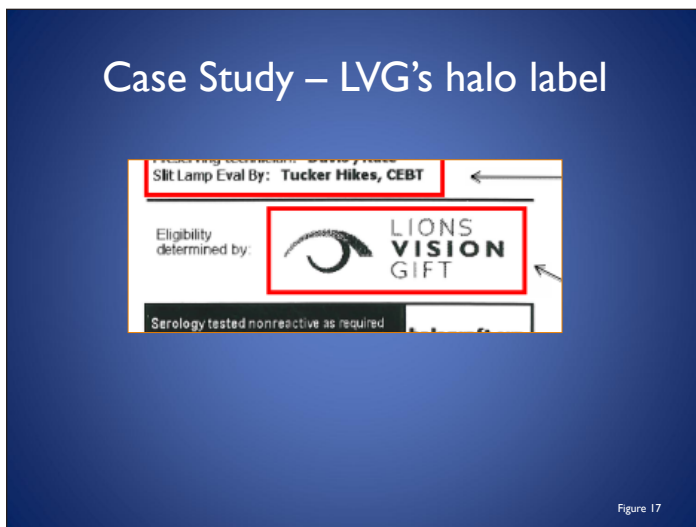
- QR code:** QR code containing all label information to facilitate packaging and tracking.
- Cornea:** Tissue type may be either cornea, sclera or pericardium.
- Half Moon Full Thickness:** Graft type and size of epithelium used to make graft. Graft type is n/a for sclera and pericardium. Expiration date based on date of irradiation.
- VG12.1243.DH.002.001:** Storage medium is 20% HSGA for cornea or 0.9%NS for sclera and pericardium.
- Donor Information:** Unique tissue QR according to SOP 20.000 Labeling.
- Donor Information (Detailed):** Donor information required by EBAA to be on Tissue Report Form that is to be used with the tissue to complete. Slit lamp is n/a for sclera and pericardium.
- Lions Vision Gift:** Logo indicating the source eye bank making final eligibility determination.
- halograftLong:** Logo indicating the source eye bank making final eligibility determination.
- Accreditation:** Accreditation status dependent on source eye bank vs eye & tissue bank (e.g. AATB).

This is what we can up with (Figure 16). All of the data in red changes based on the circumstances of the tissue. For instance, the media cornea grafts are stored in is different than the media the pericardium and sclera is stored in. The storage media that prints on the label changes based on the tissue type. The same thing happens with the donor information, as well as the information regarding the source eye bank or tissue bank providing the tissue, including accreditation status. (Note: This label is an example. The cause of death wasn't entered for this donor and, hence, isn't reported here.)

So can anyone tell me what's missing from this label that is a FDA requirement? Remember that all the tissue and donor specific information that is required to accompany the tissue will be on the label, including FDA requirements. Remember that we import tissue from other eye banks and one tissue bank, who perform the eligibility determination. So where you see Lions VisionGift in this example, you'd see the name of the entity who provided the tissue and determined eligibility, because that information would change. And remember that the package inserts are pre-printed with general information about the product.

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Slide 17:



Here’s a closer look at where the problem is (Figure 17).

During an FDA inspection, it was discovered our halo label was missing information required by the FDA. FDA requires that name of the organization that determined eligibility be included in the paperwork that accompanies the tissue, but they also require the organization’s ADDRESS also be included. We corrected the problem immediately and made it through the inspection without a 483 because of our quick corrective and preventive actions.