



Certificate of Compliance

(Rev C, Effective Date: 11/30/2010)

This is to certify that Bio-Tissue Inc. is a provider of human cells, tissue and cellular and tissue-based products (HCT/P) as well as a medical device manufacturer and specification developer. Bio-Tissue, Inc. meets the requirements of the United States Food & Drug Administration for the manufacture and distribution of AMNIOGRAFT® and AMNIOGUARD™ (HCT/Ps) and PROKERA® (a Class II medical device) specified in Current Good Tissue Practices (21 CFR Parts 1270, 1271), FDA & AATB Tissue Guidance Documents and Quality System Regulations for Medical Devices (21 CFR Part 820). Bio-Tissue certifies that:

- ✓ Bio-Tissue, Inc is registered and products are listed with the US FDA (*attached*)
- ✓ AMNIOGRAFT® and AMNIOGUARD™ are designated by the FDA as a Tissue Products (HCT/Ps)
- ✓ Bio-Tissue holds a Drug Master File (DMF) on file with the FDA for its HCT/P Amniotic Membrane products
- ✓ PROKERA® is classified by the FDA as a Class II medical device [510(k) clearance] (*available upon request*)
- ✓ Bio-Tissue contracts directly with only AATB accredited procurement agent(s) (*available upon request*) for the recovery of placental tissue and does not second source tissue or products
- ✓ All of Bio-Tissue's donors are live, healthy mothers and the tissue is procured after elective c-section
- ✓ Bio-Tissue's Quality Management System follows the international standards, ISO 9001:2000 and ISO 13485:2003
- ✓ Bio-Tissue's Facilities and Quality Systems are periodically inspected by the FDA and/or by qualified external auditors
- ✓ Bio-Tissue is licensed by the New York State Dept of Health (*available upon request*)
- ✓ Bio-Tissue is licensed by the California State Department of Health (*available upon request*)
- ✓ Bio-Tissue is registered with Maryland and Illinois (*available upon request*)
- ✓ Bio-Tissue is compliant with AATB and FDA guidelines for tissue processing



Product Description:

- AMNIOGRAFT[®] and AMNIOGUARD[™] are Bio-Tissue's trademark names for processed and cryopreserved human amniotic membrane tissue retrieved from donated placental tissue after elective Cesarean Section delivery. Bio-Tissue's Amniotic Membrane is designated by the FDA as a tissue product under PHS 361 HCT/P (human cells, tissues and cellular and tissue-based products). Bio-Tissue's Amniotic Membrane has therapeutic actions that promote anti-scarring, anti-inflammation and anti-angiogenesis and pain reduction. It supports epithelial healing in addition to serving as a physical barrier against the external environment on the ocular surface. The FDA has allowed these therapeutic claims for ocular surface use.
- PROKERA[®] is cleared by the US FDA (510(k) Clearance) as a class II medical device. PROKERA[®] is a corneal-epithelial device consisting of an ophthalmic conformer that incorporates amniotic membrane (AMNIOGRAFT[®]). PROKERA[®] is for physician use only and is not intended to be used by patients without a doctor's recommendation. PROKERA[®] is intended for use in eyes in which ocular surface cells have been damaged, or underlying stroma is inflamed and scarred. It can be used as a graft for ocular surface reconstruction procedures.

Tissue Place of Origin: Human amniotic membrane tissue is only retrieved from donors within the United States who have donated placental tissue after elective Cesarean Section delivery.

Donor Suitability, Selection & Testing: Placental tissues are recovered aseptically from live, healthy donor mothers after elective cesarean section under full informed consent. The donor mothers are screened at delivery for infectious, malignant, neurological and auto-immune diseases and other exposures or social habits to determine the suitability for human transplantation. The suitability of donor mothers is determined by reviewing medical records and history of possible transmissible diseases (via a standard questionnaire), performing a physical examination, and screening by serological blood tests to verify the absence of transfusion transmitted viruses. Donors are serologically tested by an independent CLIA certified lab at the time of delivery and must be found non-reactive using FDA licensed test kits for the following tests:

- HIV 1 (NAT-RNA)
- HIV 2 (antibody)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Chagas (T. Cruzi)
- Hepatitis C antibody, HCV (NAT-RNA)
- HTLV 1 & 2 antibodies
- Syphilis (RPR)
- West Nile Virus (WNV)

Process Controls: Final product is processed in Bio-Tissue's GMP Clean Room Facility using aseptic methods under Class 100 biological safety cabinets. Final product is released after microbiological testing for aerobic, anaerobic and fungal organisms by an independent CLIA certified lab shows no growth. Additionally, technical review and Quality Assurance approval is performed before product release. Process validations of aseptic processing, container and closure integrity testing of the final packaging system and antimicrobial effectiveness of the



final packaging system have been performed and found to be acceptable. With the exception of the human tissue, all starting materials and reagents used to manufacture the tissue products are sterile however, due to the nature of human tissue with biologic activity, terminal sterilization is not feasible.

Stability/Solutions: Bio-Tissue's Amniotic Membrane products (AMNIOGRAFT[®], PROKERA[®] & AMNIOGUARD[™]) are preserved in a validated and patented storage medium made of Dulbecco's Modified Eagle Medium and Glycerol (1:1) containing Ciprofloxacin and Amphotericin B. The tissue has been stored between -85°C and -50°C prior to distribution. Cryopreservation is vital for maintaining the integrity and biologic activity of amniotic membrane. The biological functions of Bio-Tissue's Amniotic Membrane products are retained with Bio-Tissue's cryopreservation methods. Validation studies have been conducted to establish the expiration date of Bio-Tissue's Amniotic Membrane products at 4°C, -20°C and -80°C and the results are reflected in the storage requirements established for this product. Validation studies included analysis of frozen sections followed by morphological staining of test and control tissue samples as well as package and container closure integrity validation of final packaging systems.

Labeling & Tracking: Each finished product (HCT/P or medical device) is assigned and labeled with a unique identification code that relates the final product to the donor. There is a system established and maintained to track the final product from the consignee to the donor and from the donor to the consignee or final disposition.

Packaging/Shipping: See individual Product Inserts for packaging information. The shipping containers (NanoCool systems) have been validated via simulated and actual shipping condition testing. The validation studies concluded that the shipping containers currently in use by Bio-Tissue for final product distribution and shipment effectively maintain temperatures below 21°C for up to 72 hours when tested against the ISTA-7D seventy-two hour summer profile. These studies also provide objective evidence that the package integrity is maintained throughout transit therefore providing sufficient protection to the product during the transportation process.

Voluntary Recall Procedures: Bio-Tissue has detailed procedures in place to respond appropriately to product concerns that may affect health and safety of the end-user. Our current tracking system facilitates any recall event that may occur. All affected customers will be immediately notified by verbal or electronic communication. Formal written notification will also be issued.

Storage: Bio-Tissue's Amniotic Membrane products (AMNIOGRAFT[®], PROKERA[®] & AMNIOGUARD[™]) are stored at -80°C (-112°F) before shipping to retain its natural function and integrity. Bio-Tissue's Amniotic Membrane products are shipped in validated NanoCool shipping systems. If it is not used immediately, the following guidelines should be followed for the storage of Bio-Tissue's Amniotic Membrane products:



Usage after receipt of Tissue/Device:	Storage Temperature:	Acceptable Storage Location:	Storage Time:
Few hours after package arrival	Below 21°C (69.8°F)	NanoCool Shipping Container	Within the expiration date printed on the outer shipping box.
Within 3 months of receipt (no freezer available)	1 to 10 °C (33.8 to 50°F)	Standard Home Refrigerator	Within 3 months of placing in the refrigerator or until expiration date printed on outer packaging, whichever comes first.
Within 1 year of receipt	-49 to 0°C (-56.2 to 32°F)	Standard Freezer (Home or general use)	Within 1 year of placing in the freezer or until expiration date printed on the outer packaging, whichever comes first.
Long term storage	-85 to -50°C (-121 to -58°F)	-80°C Freezer	Until expiration date printed on the outer product packaging (shelf-life is 2 years from date of manufacture).

Refer to Bio-Tissue's Amniotic Membrane individual Product Inserts for more details.

Dr. Topaz Kirlew
Executive Vice President Technical & Regulatory Affairs
(Quality Management Representative)

11/30/10

Date