FlexHD Acellular Dermal Matrix

TISSUE SAFETY ANALYSIS

FlexHD is a ready-hydrated biologic dermal allograft that provides the advantages of a biologic prosthetic with demonstrable safety properties for clinical applications.

FlexHD Acellular Dermal Matrix (ADM) is derived from allograft human skin that is minimally processed using proprietary procedures developed by MTF[†]. Allograft skin is decellularized, removing the epidermal layer and cells, leaving an acellular dermis that is disinfected and packaged.

FlexHD ADM is packaged hydrated in 70% ethanol solution. It does not require rehydration or rinsing prior to use. Testing has shown that acellular dermis in this packaging configuration is stable up to 18 months at ambient conditions and does not require refrigerated storage.

The FlexHD allograft is used to cover and reinforce damaged or inadequate integumental, connective, and soft tissues. It serves as a framework to support cellular repopulation, and vascularization at the surgical site. FlexHD's acellular properties were designed to minimize risk of specific and nonspecific inflammatory responses. Acellular dermal matrix has passed vigorous safety testing and demonstrates desired biomaterial properties for its intended use.

WHY MTF?

Since our inception in 1987, **MTF has distributed over 2.5 million grafts without incident,** and we maintain an unrivaled safety record. Because of all of the safety steps instituted by our Board of Directors and Medical Board of Trustees, **MTF has become the number one tissue bank in the nation.** MTF takes every precaution to insure safety and we are not bound by anyone other than our surgeons who demand the highest safeguards.

- MTF's donor safety criteria is among the most stringent of any tissue bank. MTF meets and exceeds the standards and regulations of the American Association of Tissue Banks (AATB) and the FDA.
- MTF employs the latest technologies (such as Nucleic Acid Testing) to conduct serological tests on all donors.
- MTF rejects more donors every year than any other tissue bank as the tissues of these donors fail to meet our strict acceptance criteria.

DONOR SCREENING

Every potential donor must pass a thorough Quality Assurance process. First, standardized age criteria must be met (female age 12–70; male age 12–70), helping to ensure the selection of tissues with dense, strong cancellous constructs more commonly found in that range. Soft-tissue age criteria was determined based on the clinical research of the mechanical integrity of tissue through a range of ages.

Prior to donation, the donor's medical/social history is screened for medical conditions or disease processes that would contraindicate the donation of tissues in accordance with current policies and procedures approved by the MTF Medical Advisory Board.

MTF is the only tissue bank that employs Registered Nurses to screen potential donors as standard practice. The Vice President of Technical Operations then reviews medical charts along with the Medical Director who determines donor suitability.

[†] U.S. and international patents pending

All donor information is maintained at MTF and is sufficient to indicate that the donor eligibility criteria current at the time of recovery has been met and is also in compliance with current FDA regulations.

Donor blood samples taken at the time of recovery are tested by a CLIA licensed facility for:

- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C antibody
- HIV-1/2 antibody
- HTLV-I/II antibody
- Syphilis

In addition to the testing listed above, HIV and HCV Nucleic Acid Amplification Testing (NAT) are performed. The results of all serological testing must be negative to enable the release of the dermal allograft tissue for transplantation.

Prior to the release of tissue for processing, all donor records are reviewed and approved in writing by the MTF Medical Director and Technical Director. The donor record includes:

- Legal next-of-kin consent
- Medical history and Behavioral Risk Assessment documentation
- Autopsy report (if an autopsy was performed)
- Tissue recovery information
- Blood and tissue culture results
- Serologic testing results
- Donor Quality Assurance Documentation
- Description of the preservation methods indicating the duration between death and tissue recovery.
- Physical assessment
- Plasma dilution documentation

TISSUE RECOVERY AND PROCESSING

MTF's manufacturing processes are designed and validated to prevent the contamination or cross-contamination of tissues in accordance with FDA current Good Tissue Practices (cGTP).[1] MTF maintains a documented quality management system designed and implemented to fulfill requirements of the FDA regulations and AATB standards. MTF is an accredited member of AATB.

MTF employs an Audit Team whose sole purpose is to audit our recovery partners on a regular basis and ensure compliance.

RECOVERY

Allograft tissue used by MTF to manufacture FlexHD acellular dermis is recovered in an aseptic environment using aseptic surgical techniques as outlined in the *MTF Technical Manual* and the Association of Operating Room Nurses (AORN) standards. All tissue recovery procedures comply with the current AATB standards. Blood samples for serological and microbiological testing are obtained prior to tissue recovery.

Every tissue is computer-tracked with the Tissue Trace® system—from recovery through testing, processing, packaging, and distribution—from the donor to each medical facility. Upon completion of the tissue-recovery procedures, individual tissues are aseptically packaged and labeled with a unique 8-digit donor-identification number and tissue description. The donor number and MTF tissue ID number are applied to the outer transport container. Labeling includes the lot number, expiration date, product code, quantity (volume), and other pertinent information.

[1] 21 CFR 1271 Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement — effective May 25, 2005

All labeled and packaged recovered tissues, blood specimens, culture tubes and documentation are transported to the MTF facility via overnight courier. All tissues are transported in insulated coolers on wet ice. A sample of the solution used to transport the recovered graft (transport sample) is obtained upon arrival of the tissues at MTF. This transport sample is representative of the unprocessed skin prior to preparation and is cultured in accordance with current USP Sterility Test method <71>.

The tissue is then placed in a -40^{o}C or below freezer or storage container for storage until the tissue is released for processing.

MTF donors are released to processing after all charts and records are carefully reviewed by one of our Medical Directors who are all physicians with infectious disease or pathology backgrounds.

PROCESSING

Processing and packaging of tissue is performed aseptically in sterile ISO Class 4 [Class 10 (Certified)] Clean Rooms — eliminating the need for terminal sterilization, which has been shown to compromise the biological and biochemical integrity of allograft tissue. Antibiotic soaks, surfactant treatments, and ethanol soaks are also utilized in processing.

Aseptic processing at MTF is performed in accordance with the current AATB standards as published by the AATB.[2] MTF's environmental monitoring program includes:

- Critical areas — Daily air sampling for non-viable particles and viable microorganism in the air and on work surfaces.
- Non-critical areas — Weekly air sampling for non-viable particles and viable microorganism in the air and work surface.
- Personnel — Monitoring of personnel is done on a quarterly basis using agar touch plates of gowned personnel.
- Water — Purified water sampling for Trace Organic Content (TOC), conductivity and microorganisms are conducted on a daily basis in accordance with current USP Purified Water requirements.

Clean Room and laminar flow hoods certification is conducted on a semi-annual basis and monitored in accordance with current ISO Standards.[3]

MTF maintains a documented quality management system designed and implemented to fulfill requirements of 21CFR Parts 1270 & 1271 and the Validation Guidance of the FDA, as well as the current AATB standards.

TISSUE DISINFECTION

MTF has successfully achieved a millionfold (6-log) reduction in microbial levels with a validated disinfection process to consistently reduce bacterial levels in our acellular dermis. The microbial inactivation included the evaluation of a panel of the most common microorganisms found in the body or on the skin, which includes both aerobic and anaerobic species of bacteria, mold, yeast, and fungi: *Escherichia coli, Candida albicans, Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa, Bacillus subtillis, Clostridium sporogenes,* and *Streptococcus pyogenes.*

The disinfection of the dermal matrix is accomplished through an extended disinfection solution soak-agitation validated process, followed by a thorough, controlled purified water rinse.[4]

Using aseptic techniques, acellular dermis was processed up to the disinfection step. Sections of MTF's acellular dermis were forwarded to a contract test laboratory for the study. Samples of acellular dermis

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2 AATB Standards for Tissue Banking, 11th edition, 2002.

3 ISO 14644-1:1999 — Clean Rooms and Associated Controlled Environments — Part 1: Classification of Air Cleanliness. PART 2: Specifications for Testing and Monitoring to prove continued compliance with ISO 14644-1, and ISO 14644-4:2001 — Cleanrooms and Associated Controlled Environments.

4 MTF Validation -290 Disinfection of Acellular Dermis, Validation Protocol and Report

were inoculated with an individual microorganism and a mixture of organisms. Tissue sections were inoculated with at least 10^6 CFU of the challenge organism or mixture of them for the disinfection process and < 100 CFU for the neutralization validation. The panel of organisms used was representative of different groups of organisms commonly found in the environment.

The inoculated tissue sections were exposed to a prepared disinfection solution. The disinfection process was executed following the nominal process.[5] Following completion of the preset exposure time and rinse steps, one tissue section was assessed for viability of the selected organism(s).

Two tissue sections were tested for each organism or mixture. One (1) sample for Pre-Disinfection process count and one (1) sample for Post-Disinfection process count. The obtained results are summarized in the following table:

Inoculated Organism	**Log Reduction**
Staphylococcus aureus	>6.1
Staphylococcus epidermidis	>5.7
Streptococcus pyogenes	>6.7
Escherichia coli	>5.6
Bacillus subtilis	>5.7
Candida albicans	>7.7
Pseudomonas aeruginosa	>6.7
Clostridium sporogenes (spore)	>6.0
Mixture of above organisms-1	>6.5
Mixture of above organisms-2	>6.5

STERILITY TESTING

The FlexHD allograft is tested for sterility in accordance with procedures in the current United States Pharmacopeia (USP) <71>,[6] which utilizes a 14-day, 2-media, 2-temperature protocol or equivalent method. All microbiologic cultures used for culturing transport sample must allow for growth of anaerobic and aerobic organisms. All positive cultures are subcultured, and any organisms are identified to the genus level. MTF has performed a validation study of the sterility sampling procedure for MTF's acellular dermis and the test method used for sterility testing.[7]

The sterility test method used for acellular dermis was qualified by a Bacteriostasis and Fungistasis (B&F) test. The B&F test demonstrates that the test article itself is not inhibitory to the growth of microbial contaminants that can be present in the test sample. The Direct Transfer method was employed for the test. The assay reflected the actual sterility test methodology that was used on the sample.

MTF has validated its processing procedure to prevent contamination and cross-contamination of human tissues distributed by MTF. **Final sterility cultures must be negative before the tissue is released.**

BIOCOMPATIBILITY TESTING

In addition to meeting USP sterility requirements and demonstrating effective inactivation of bacterial load, biocompatibility testing has been conducted in accordance with ISO 10993, further establishing safety of tissue, which is above and beyond the minimum requirements for AATB compliance. FlexHD Acellular Dermal Matrix has been subjected to a panel of eight tests for biocompatibility and has been

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5 MTF Validation — 403 Process Validation Report Sterilization of Acellular Dermis

6 Current United States Pharmacopeia (USP) <71> Sterility Test Method

7 MTF Validation Study: Sterilization of Acellular Dermis, Final Report, July 19, 2005

demonstrated to be non-cytotoxic, non-hemolytic, and non-mutagenic, confirming that there are no adverse immunologic responses at the acute, sub-chronic, and chronic levels.

North American Science Associates, Inc. (NAmSA) designed the biocompatibility testing of MTF's acellular dermis in accordance with the International Organization for Standardization (ISO 10993) guidelines for medical implants designed for long-term use. A brief description of the testing and results are summarized the table that follows:

Test Description	**Results**	**Criteria**
Cytotoxicity via ISO MEM Elution	Grade 0	Must be less than Grade 2, or less than 50% lysis
ISO Maximization Sensitization	No evidence of sensitization observed	Sensitization evaluated on a scale of 0 (no edema/erythema) to 4 (severe edema/erythema)
ISO Intracutaneous	Sesame oil extract: 0.0 Saline extract: 0.0 No significant irritation observed	Irritation evaluated on a scale of 0 (negligible) to 8.0 (severe)
ISO Systemic Toxicity	No mortality or evidence of systemic toxicity from extracts	Systemic toxicity demonstrated by animal death, abnormal behavior, such as convulsions or prostration, or weight loss > 2 grams
Genotoxicity — In Vitro Chromosomal Aberration	Non-genotoxic to Chinese hamster ovary cells	$p \leq 0.01$ demonstrates significant chromosomal aberration
Genotoxicity — Bacterial Reverse Mutation	Saline extract: nonmutagenic to *S. typimurium* and *E. coli* Sesame oil extract: nonmutagenic to *S. typimurium* and *E. coli*	Evidence of mutagenic response with 2-fold increase in number of revertants
In Vitro Hemolysis — Direct Contact	0% hemolysis	Hemolysis evaluated based on index of 0% (non-hemolytic) to above 40% (severely hemolytic)

TESTING

As an accredited member of the AATB, all of our testing and processing of donated tissue meet or exceed all AATB standards and FDA regulations, and we maintain an unequalled safety record. All test results are evaluated by a team of specialists and physicians — all of whom are from the infectious disease, pathology and tissue banking fields. Since 1991, we have approved and processed more than 50,000 donors and distributed more than 2.5 million allografts.

All tissue and blood samples are tested for infectious diseases, including testing for AIDS with Nucleic Acid Testing (NAT by TMA) — the newest and most reliable test to confirm the presence or absence of HIV and HCV early following exposure.

MTF set the precedent for tissue banks to utilize HIV DNA by Polymerase Chain Reaction (PCR) testing on every donor. PCR is the most reliable test to confirm the presence or absence of HIV. MTF also requires a comprehensive battery of testing that includes, but is not limited to, the following:

HIV-1, HIV-2 and HIV-1 NAT are tests designed to detect for the virus responsible for AIDS infection.

HTLV I & II are tests designed to detect for the human T-cell lymphotrophic virus.

HB core and HBsAg are tests designed to detect for hepatitis B virus infection. This identifies exposure to the virus and also past immunity to it conferred from the vaccine for the virus.

RPR is the test used for detecting for syphilis; HCV-Ab and HCV-NAT for detecting the hepatitis C virus.

BIOMECHANICAL PROPERTIES

In comparison with the leading competitor's dermal matrix material, FlexHD Acellular Dermal Matrix demonstrated superior biomechanical properties, including: average tensile strength, maximum load, and tensile modulus (ability to resist deformation). Suture retention testing showed that our acellular dermal matrix was equivalent to the competitor material in testing.

Its biomechanical advantages are significant when considering applications such as abdominal wall repair, where material strength is required to promote healing and prevent additional failures at the wound repair site. Please refer to the FlexHD *Biomechanical Properties* white paper for further information.

HISTOLOGY

Immunochemical evaluation of FlexHD Acellular Dermal Matrix confirms that the major components of our extracellular matrix, including collagen, elastin, and major components responsible for promoting cell attachment and growth are preserved such that the allograft's histomorphological integrity is maintained after processing. Cells are effectively removed, leaving the original dermal matrix architecture intact.

Its acellular biologic properties provide a matrix with proven, desirable qualities for revascularization and overall tissue integration. Please refer to the separate white paper on *Histology: In Vivo and In Vitro Studies* for further information.

CONCLUSION

FlexHD Acellular Dermal Matrix is made available through the Musculoskeletal Transplant Foundation, a not-for-profit organization that is a national consortium of medical schools, academic institutions and recovery organizations involved in the recovery, processing and distribution of bone and related soft tissue for use in transplant surgery. Our quality and safety standards have been developed by leading physicians, transplant surgeons, and specialists in the fields of science and medicine.

MTF's quality and safety standards consistently meet or exceed the requirements of the American Association of Tissue Banks and the current regulations published by the federal Food and Drug Administration. MTF is also in compliance with established Good Tissue Practices and the International Standards Organization. MTF uses the most complete and technically advanced testing available, including Nucleic Acid Testing (NAT), for detection of transmittable diseases such as HIV and hepatitis, to assure the safety of every allograft we supply.

FlexHD provides an allograft with proven safety qualities that couples the histological advantages of an acellular biological matrix with the expediency of not requiring rehydration.

Save time. Work more efficiently. Use FlexHD Acellular Dermal Matrix.

Please visit our website at mtf.org, or **contact MTF at 1-800-433-6576** for further information.