

## Patient Safety Through Redundant Safeguards

The safety of tissue is contingent on three stages - donor history screening, laboratory testing and tissue preparation processes validated to eliminate potential disease transmission. In the event that any one of these stages is challenged, RTI's tissue processing system includes built-in redundancies to ensure patient safety.

### Stage 1: Screening for Patient Safety

Medical/social history evaluations are performed for every donor. This screening includes: family/next-of-kin interview, medical record evaluation/hospital record review, behavioral/lifestyle risk assessment, medical examiner/coroner's report (autopsy report, when available), and laboratory, pathology and radiology reports. RTI's medical director - a licensed physician - must approve each donor record.

### Stage 2: Testing for Patient Safety

Beyond donor screening, RTI performs an exhaustive panel of serological and microbiological tests that is significantly more comprehensive than required testing. These results are subject to stringent criteria in order to release the donor tissue to the processing stage. Additional microbiological testing and screening is used throughout the process to ensure the suitability of tissue for transplant.

#### Serological Testing

|                     | FDA | Florida | AATB | RTI |
|---------------------|-----|---------|------|-----|
| HCV Antibody        | ■   | ■       | ■    | ■   |
| HBV Surface Antigen | ■   | ■       | ■    | ■   |
| HIV 1&2 Antibody    | ■   | ■       | ■    | ■   |
| HBV Total Core      | ■   |         |      | ■   |
| HTLV I&II Antibody  |     | ■       | ■    | ■   |
| RPR for Syphilis    |     | ■       | ■    | ■   |
| HIV/NAT             |     |         | ■    | ■   |
| HCV/NAT             |     |         | ■    | ■   |

RTI is also working with the test manufacturer and the FDA to qualify NAT assays for WNV and HBV. Many of the tissues affected by the BTS recall were screened with this additional testing.

In addition to serological testing, microbiological testing is used throughout the process to screen for potential contamination and to provide confirmation of tissue suitability for distribution.

#### In-Process Microbiological Testing

- Pre-processing culturing: *Performed after serological testing, removes potentially unsuitable tissue from process*
- Sterility confirmation: *Performed pre-packaging, confirms sterility achieved during processing*
- Environmental controls: *Testing of processing environment and all processing reagents*

### Stage 3: Processing for Patient Safety

#### Sterilized through BioCleanse®:

##### Bone constructs, tendons and milled tissue

"The efficacy of the sterilization method (BioCleanse) is supported by the absence of reports of bacterial or viral allograft-associated infections in tissue processed by this method."

- *New England Journal of Medicine (June 2004)*

#### Sterilized through Demineralization Process:

##### Demineralized bone products

"The demineralization process inactivated infectious retrovirus in infected cortical bone, thereby preventing disease transmission."

- *Journal of Bone and Joint Surgery (February 2003)*

#### *Validated to Eliminate*

| Relevant and Model Viruses         | Spores                             | Vegetative Bacteria and Fungi     |                                    |
|------------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Human Immunodeficiency Virus (HIV) | <i>Clostridium sporogenes</i>      | <i>Staphylococcus aureus</i>      | <i>Enterococcus</i>                |
| Hepatitis B Virus (HBV)            | <i>Bacillus stearothermophilus</i> | <i>Escherichia coli</i>           | <i>Enterobacter cloacae</i>        |
| HCV Model (BVDV)                   |                                    | <i>Pseudomonas aeruginosa</i>     | <i>Citrobacter freundii</i>        |
| Syphilis                           |                                    | <i>Candida albicans</i>           | <i>Proteus vulgaris</i>            |
| Hepatitis A Virus (HAV)            |                                    | <i>Staphylococcus epidermidis</i> | <i>Acinetobacter calcoaceticus</i> |
| Parvovirus (PPV)                   |                                    |                                   |                                    |
| Herpes Virus Model (PrV)           |                                    |                                   |                                    |

Following processing, all grafts distributed by RTI undergo at least one of the following final steps to confirm safety.

#### Final Safety Assurance Steps

- Post-processing sterility culturing: *Grafts subject to sterility cultures before final release*
- Terminal sterilization through Sterrad®: *Grafts sterilized in final package to achieve 10<sup>-6</sup> sterility level*
- Low-temperature, low-dose gamma sterilization: *Grafts sterilized in final package to achieve 10<sup>-6</sup> sterility level*

### Delivering Patient Safety

RTI's primary goal is to ensure patient safety. To fulfill this goal, RTI employs stringent tissue testing combined with processes validated to eliminate potential disease transmission. These redundant safeguards provide the highest level of confidence that patients will receive safe, high quality tissue.