



Question 1:

How are donors screened / qualified? How is the donor tissue processed? How reproducible is the process? Is the amniotic fluid concentrated?

When it comes to the donated tissue, NuTech is concerned about two things: gaining patient permission to use the "amniotic membrane" and the safety of the collected tissue. Patients are prescreened two weeks prior to surgery where they are asked more than 160 questions about themselves and their lifestyle. This screening process usually produces all the necessary information about the patient's behavior.

We obtain "informed consent" the day of surgery and, once this is received, the patient's chart, medical records, lab results, etc. are made available to our medical director who evaluates the information, making a final donor eligibility determination according to 21 CFR 1271.

An appropriately gowned and sterile OR Tech is present in the Operating Room when the birth occurs. At the time of procurement, a blood sample is drawn on the donor while the OR Tech collects the membrane, inspects it for any problems (cloudiness, etc.) and then performs a procurement culture on the tissue. The blood sample is sent to a CLIA certified lab and tested per FDA requirements in 21 CFR 1271 for Human Cell and Tissue Products.

The amniotic fluid that comprises NuCel is NOT concentrated; that is to say, we spin down a larger volume of liquid than what we prepare for the product. The washing, palletizing and re-suspension results in less volume of product than we had of fluid.

Question 2:

How have the cells in the material been characterized? Are there confirmed stem cells in this population? If so, how were they characterized?

To date there has been no characterization performed on this product.

Question 3:

How are adventitious agents extracted from the tissue? What are the adventitious agents that are removed? How is the removal verified?

The information regarding this is proprietary; as it is part of our intellectual property, we cannot reveal much about the process.

Question 4:

Is it correct to assume that the preparations cannot be pooled for processing, and that each donor placenta must be processed individually? If this is the case, how difficult will it be to "scale up" the process to meet future demands? Will the processing be similar to DBM where only one organ at a time can be processed and an entire clean up of the processing room is needed between organs?

In accordance with FDA regulations governing HCT/Ps, donors may not be pooled during manufacturing. Each donor tissue is processed separately and the controlled environment is disinfected between processing sessions.

There are an unlimited number of Caesarian sections performed at each major hospital in this country. As long as we continue to have contracts with hospitals to obtain the amniotic membrane, there should be no problems with maintaining a supply of tissue.

Each membrane must be processed individually. It is NOT necessary to "pool" two or three amniotic membranes together.

Question 5:

What is the release data for each preparation?

Donor testing must meet the following criteria:

1. *Serology Protocol:* All human cells and/or tissue intended for transplantation shall be recovered from donors who are tested and found to be negative for:
 - Antibodies to the human immunodeficiency virus type 1 and type 2 (anti-HIV-1 and anti-HIV-2)
 - HIV-1/Hepatitis C by Transcription Mediated Amplification
 - Hepatitis B surface antigen (HBsAg)
 - Hepatitis B total core antibody
 - Antibodies to the hepatitis C virus (anti-HCV)
 - Antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
 - Syphilis using FDA-licensed tests. If the blood sample to be used for syphilis screening is determined and documented to be unacceptable for the screening assay (e.g. hemolysis, sample testing time restriction) then an FDA-licensed treponemal-specific confirmatory assay may be performed instead (e.g. FTA-Abs).
2. *Other requirements:*
 - Results of microbiology cultures taken at time of C-Section
 - Donor with cultures testing positive for the following microorganisms shall be deferred:
 - Clostridium
 - Streptococcus pyogenes (group. A strep.)
 - Enterococcus

- Fungi (mold or yeast phase)
3. Testing laboratories: Infectious disease testing shall be performed only by laboratories maintaining current registration status with the FDA and currently registered under the Clinical Laboratories Improvement Act of 1988.

NuTech's goal for each release is the proper screening of patients, so that the material obtained is safe for use and free of disease. Unlike our competition that use material extracted from cadavers, these are living patients — no one can guarantee 100% effectiveness with each patient but this is what we strive for.

Question 6:

Please describe the cryopreservation procedure. Are viable cells quantified before and/or after adventitious agent removal and/or freezing at -140°C? What is the cell recovery / viability after cryopreservation? What storage conditions are used for the cryopreserved material? Has the material been stored at -80°C, and if so, for how long while retaining the viability of the cells?

NuCel is packed in a cell friendly solution containing a small amount of DMSO (approximately 10% v/v) and protein (20% v/v) with the balance being a buffer. The cell count is verified and recorded after the adventitious agents are removed, and the product is then frozen at a controlled rate to ensure the highest cell survival ratio. Each vial is stored at -140°C until it is shipped from the manufacturer. It is then packed in dry ice and delivered to the hospital in a portable carrier, all at a temperature of -80°C. In order to maintain the highest viability, the product must be stored at -80°C until it is used in surgery.

Question 7:

What growth factors, cytokines or other biologically active agents are present in the material? How long are they assayed? Are these agents present at reproducible concentrations across preparations?

While we know that there are a myriad of growth factors in each batch, we make no claims as such. Each batch is assayed and counted, similar to listing calories, following the FDA's 361 process for minimal manipulation.

The complexity of human biologics is well established as is the uniqueness and variability of human tissue. These same factors hold true for the material that comprises NuCel, so creating an absolute consistency of the product is a difficult task. NuTech has developed extensive production protocols and test methodologies that ensure that a minimum number of active cells and growth factors are present in the naturally prescribed ratio, ensuring a good patient response.

Question 8:

What evidence is there to show that NuCel is immune privileged? Is there pre-clinical and/or clinical data to support this assertion?

This information is proprietary; as it is part of our intellectual property we cannot reveal much about this assertion. However, our technical monograph will note clinical documentation that suggests that this is the case.

Question 9:

Please provide a table listing all of the pre-clinical and clinical studies in which this material has been used. What studies specifically related to spine and orthopedics have been completed? Please provide these study reports. Have there been any reports of adverse reactions resulting from the use of NuCel?

Our technical monograph will list a number of clinical studies in which amniotic fluid has been used in medicine, however there are no studies specifically related to the spine and/or orthopedics. The major use of amniotic fluid today is in ophthalmology. As of today there have been no reports of any adverse reactions to the material.

Question 10:

Could you please provide any regulatory opinions that have been obtained concerning the NuCel material? Additionally, please provide a summary of any FDA discussions that have been held concerning this product.

To date there have been NO regulatory opinions given about NuCel and NO discussions with the FDA regarding this product. NuTech has followed the regulatory guidelines supplied by the FDA in their 361 Tissue Document.

Question 11:

Have you encountered any informed consent issues with donors? Have you encountered any liability questions / issues in the use of these materials?

There have been NO issues in gaining informed consent from patients. Most patients are more than eager to sign of on the release of the amniotic membrane knowing it will be used for medical science.

Question 12:

What data do you have on the availability of donor tissue going forward?

Of the 4 million births in the United States each year, more than 30% are born via caesarian section. Thus there are approximately 1.2 million possible donors per year, making the material readily available.

For further information call Activize @ (610) 346-1992.