



# TUTOGEN

Tutogen Medical, U.S., Inc.

December 9, 2002

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane,  
Rm. 1061  
Rockville, MD 20852

RE: Docket No. 02D-0266, CBER 150. Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Availability. Pages 42789--42790 [FR Doc. 02-15898]

Tutogen Medical Inc. ("Tutogen") appreciates the opportunity to comment on the draft document issued by the FDA in June 2002 entitled: *"Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)"* In particular, we wish to use this venue to respond to your request for data assessing the impact of the recommendations contained therein to reduce the risk of CJD and vCJD on the availability of HCT/P.

***I. Demographic data about the HCT/P donor population:*** as an accredited member of the American Association of Tissue Banks (AATB), Tutogen along with other accredited tissue banks in the United States, provides extensive data to the AATB regarding the scope of its activities in tissue recovery, processing, and distribution. Since its founding in 1976, the AATB has existed as a scientific, not-for-profit, peer group organization with the mission to facilitate the provision of transplantable cells and tissues of uniform high quality [and safety] in quantities sufficient to meet national needs.<sup>1</sup> As a result, the data compiled by the AATB can be considered to be among the most comprehensive and reliable as it concerns HCT/P donor population.

**Annual Survey of Accredited Tissue Banks (for Year 2000)**

<b>1. # of Tissue Banks reporting</b>	63
<b>2. # of tissue donors recovered (HCT/P donor population)</b>	18,021
<b>3. # of Bone allografts distributed in U.S.</b>	675,370
<b>4. Volume of Skin grafts distributed in U.S.</b>	11,222 ft <sup>2</sup>

<sup>1</sup> Excerpt from "Background" statement contained in the *American Association of Tissue Banks Membership Directory 2001-2002*.

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**II. Impact of donor deferral upon the availability of HCT/Ps:** During the year 2001, Tutogen processed 3,500 donors recovered by our contract recovery agencies from various locations including Europe. In the 12 months from July 1, 2001 to June 30, 2002, Tutogen distributed a total of 21,639 musculoskeletal allograft products to patients in the U.S. Based upon the data above, this represents approximately 3% of the total number of bone allograft products distributed by AATB accredited Banks in the United States.

The implementation of the FDA's proposed guidance would immediately reduce the number of available HCT/P donors by approximately 10% in the U.S. due to country of origin exclusion. The direct impact to Tutogen would be an approximate 50% reduction in our donor base or approximately 10,820 musculoskeletal allograft products. Therefore, the impact of this proposal from the FDA upon Tutogen would be greater than upon any other U.S. based tissue bank.

Among the remaining 16,271 HCT/P donors (approximately) recovered by other AATB accredited organizations annually, a large percentage would be eliminated under the proposed FDA rule that would disqualify any donor who has visited a listed country for a cumulative period of 6-months or more. Not only would frequent travelers be considered *deferred donors*, but a large share of military veterans and their immediate family members due to being stationed overseas. Tutogen does not have verifiable data concerning these figures, however, it is not inconceivable that this would adversely impact the donor pool by at least an additional 6% or more, based on the blood bank industry experience, this would translated to a 976 HCT/P donors. The combination of Tutogen's and the rest of the tissue banks would total approximately 2,726 HCT/P donors. .

**III. Musculoskeletal allograft tissue has been scientifically classified as low risk for CJD/vCJD transmission.** As with other AATB certified organizations, Tutogen allograft products are used across a multitude of medical applications. Currently, none of Tutogen HCT/Ps in the United States are so-called high-risk tissue such as dura mater or corneas (refer to Appendix 1).

Not all tissue has the same infectivity risk. The HCT/Ps utilized by Tutogen in allograft products, distributed in the U.S, are classified as Category IV tissue (i.e., "No detectible (CJD-) infectivity") by the World Health Organization in its March 1997<sup>2</sup> study.

Tutogen has not processed or distributed in the United States high-risk Category II tissue such as dura mater since June 2000. Tutogen has never processed or distributed corneal tissue. Therefore the effect of any donor deferral ruling by the FDA on HCT/Ps limited to high-risk Category II tissue, will not have any effect upon Tutogen's ability to continue providing HCT/Ps in the United States as shown in the table above.

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<sup>2</sup> World Health Organization, *Emerging and other Communicable Diseases Report* of a WHO consultation on medicinal and other products in relation to human and animal transmissible Spongiform Encephalopathies.

***IV. Tutoplast safety claims are supported by a long-history (25 consecutive years) of successful allograft implants:***

Tutogen HCT/Ps are recovered following a very stringent donor selection criterion in accordance with AATB standards and FDA regulations. The current industry standard concerning CJD significantly reduces the risk of harvesting tissue from a potentially infected HCT/P donor.

All Tutogen HCT/Ps are processed using a proprietary system known as the *Tutoplast®* process. Tutogen's single donor tissue processing methods (no pooling of donors) have been shown to ensure viral/bacterial inactivation in controlled studies. The *Tutoplast®* process has been validated, specifically for the inactivation of prions and other transmissible agents. Two independent studies have confirmed that the *Tutoplast®* process is capable of removing infectious prion agents from soft tissue as a result of treating soft tissue with sodium hydroxide.<sup>3/4</sup>

**Recommendations:**

Tutogen recognizes that the spread of bovine spongiform encephalopathy, or mad cow disease, has prompted debate concerning the possible modification of recent deferral criteria. Tutogen urges the FDA to continue inviting scientists, physicians and patient groups to participate in this policy discussion. Physicians must be given accurate information about the benefits and risks, both real and theoretical associated with HCT/P transplantation so that they can effectively educate every patient when an HCT/P transplant is needed.

While Tutogen also recognizes that studies about the potential for transmission of TSEs in animal models continue, however, evidence is still lacking of such transmission among patients who have received human tissues, blood transfusions and clotting factor concentrates. Tutogen respectfully requests that the Food and Drug Administration, before any final ruling, address issues cited herein, by limiting its definition of *deferred donor* to those cases where high-risk Category II tissue is being implanted (e.g., dura mater, corneas), and/or to those cases where tissue recovery and processing methods being used pose additional risks.

**Conclusion:**

The very low incidence of human CJD/vCJD and our current screening criterion already poses a low risk that an infected donor may enter the process. The Centers for Disease Control and Prevention reports that the incidence of CJD is one case per million people each year.

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<sup>3</sup>Robert Koch Institut in Berlin (Department of the German Federal Institute of Health) Diringer H, Braig H, Infectivity of unconventional viruses in dura mater, *The Lancet*, February 25, 1989

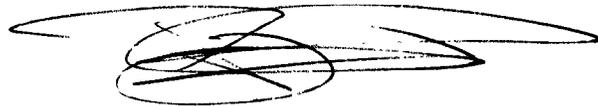
<sup>4</sup> Laboratories of RBM, Ivrea, Italy and expert opinion by Dr. Masullo (Nurosurgeon) Masullo, 1994, Estimate of the theoretical risk of transmission of Creutzfeld-Jacob Disease by human dura mater grafts manufactured by the Tutoplast process. RBM, Studienbericht, 1994, Determination of the clearance factor for unconventional slow viruses during the processing of dura mater.

Based upon the track record of safety, quality, and clinical efficacy of *Tutoplast*® and the product approval protocols adhered to by Tutogen, and already audited by the FDA, relating to the import of HCT/Ps into the U.S. from Europe, we do not believe that there is any additional risk associated with HCT/Ps recovered and processed by Tutogen. Given the scientific data available today, Tutogen does not believe that a blanket ruling to defer HCT/P donors from specific countries would reduce CJD and vCJD risk in cases where a validated recovery and processing procedure is being used. Indeed, the impact of a deferred donor ruling as presently proposed would significantly reduce the availability of HCT/Ps in the United States (up to 20% or more based upon the data contained herein) without a commensurate and measurable risk reduction in CJD and vCJD transmission.

Very truly yours,



Wade S. Tetsuka  
Tutogen Medical U.S., Inc.  
General Manager



P.J. Pardo  
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Director,  
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Appendix 1: Tutoplast® Processed Allografts Distributed

<i>Field of Use / Distribution Partner</i>	<i>Procedures</i>	<i>Tissue Utilized</i>	<i>Approximate number of Allografts distributed in the last 12 months in the United States</i>
<b><i>Spinal / Trauma</i></b> <i>Sulzer SpineTech, Minneapolis MN</i>	Spinal Fusion, ACL, Rotator Cuff repair	Femur, Ulna, Radius, Humurous with cuff, anterior cruciate ligament.	4,000 grafts
<b><i>Ophthalmology</i></b> <i>IOP, Inc., Costa Mesa ,CA</i>	Glaucoma patch, eye- brow slings, enucleation wraps, posterior segment, eyelid spacers	Sclera, Pericardium, Fascia Lata	8,000 grafts
<b><i>ENT</i></b>	Tympanoplasty, Cholesteoma Resection	Sclera, Pericardium, Fascia Temporalis	2,000 grafts
<b><i>Urology</i></b> <i>Mentor Corp., Santa Barbara, CA</i>	Pelvic Floor repair, urinary incontinence	Fascia Lata, Pericardium, Dermis	9,000 grafts
<b><i>Dental</i></b> <i>Sulzer Dental, Carlsbad, CA</i>	Peridental implants	Cancellous bone chips from femur, ulna, radius	17,000 grafts