DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

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Josephine M. Torrente
Association of Disposable Device Manufacturers
PO Box 344
1429 G Street, N.W.
Washington, DC 20005

RE: Docket No. 01P-0340

Dear Ms. Torrente,

This is in response to your petition filed by the Food and Drug Administration (FDA) on August 7, 2001 requesting that FDA regulate reprocessed single use devices as reusable medical devices. Because of the complexity of the issues presented by your petition and our workload, FDA is unable to issue a final response to your petition at this time. We will issue a final response as soon as possible.

If you have any questions about this interim response, please call Joseph M. Sheehan at (301) 827-2974.

Sincerely yours,

Linda S. Kahan

Linda S. Kahan
Deputy Director
Center for Devices and Radiological Health

01P-0340

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Docket No. 01P-0354

Dear Drs. Lurie, Wolfe and Jane:

You submitted a citizen petition on August 15, 2001, on behalf of Public Citizen, requesting that the Food and Drug Administration (FDA) ban human cadaveric dura mater as an unsafe medical device. You also requested that all unimplanted human cadaveric dura mater be recalled. You stated that sufficient information is available to support a ban on the sale of human cadaveric dura mater and a recall of all unimplanted human cadaveric dura mater. You base your requests on information you state demonstrates that: (1) there is evidence of harm; (2) there are safer alternatives available; and (3) there is an inadequacy of regulation to date. We have reviewed the information in your petition and we are denying the petition at this time for the reasons explained below.

I. Your Petition

Your petition presents information intended to demonstrate that human cadaveric dura mater should not remain on the market because of a risk to health associated with its clinical use, specifically the development of Creutzfeldt-Jakob disease (CJD). The information you rely on includes:

- The 1989 ban by the British government and the 1997 ban by the Japanese government on the use of human dura mater.

- The deaths of two patients in the United States (U.S.), one in 1987 and one in 1992, after implantation of Lyodura (Hannah et al., *Neurology*, 56: 1080-1083, 2001). Lyodura is a German product processed by B. Braun Melsungen AG.
- A third U.S. patient died in 1998 after implantation in 1992 of Tutoplast, which was another German product processed by Pfrimmer-Viggo GMBH & Co. (Hannah et al., 2001).[1]
- The cases of dura mater-associated CJD in New Zealand, Spain, and Japan, the vast majority of which involved the use of Lyodura.[2]
- The 1997 World Health Organization (WHO) recommendation concerning the use of human dura mater, which stated:

> Because over 50 cases of CJD have resulted from cadaveric dura mater grafts, it was strongly recommended that dura mater no longer be used, especially for neurosurgery, unless no other alternative is available. If, nevertheless, dura mater is to be used, only material should be considered that is from non-pooled sources originating from carefully screened donors and subjected to validated inactivation treatment.

Your petition also discusses the possible use of dura mater substitutes as "safer alternatives." These substitutes include synthetic material, animal tissue, and grafts from the patient's own tissue. You cite a randomized comparison published in 1990 that evaluated bovine pericardium and human dura mater. The petition states that the comparison found "[t]he cutting characteristics, suturability, and water tightness of the two materials . . . about equal." You note that the FDA has cleared nine dura substitutes.

Finally, the petition discusses your view that FDA's regulation of human dura mater has been inadequate. The petition notes that FDA "elected not to follow the WHO guidelines." The petition further states that FDA's 1999 guidance document, "Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater" (the 1999 guidance document) on the evaluation of risk factors and recommendations for manufacturing human dura mater is inadequate because compliance with the FDA guidance document is voluntary.

II. FDA Actions

FDA recognizes that information concerning CJD continues to emerge. Therefore, FDA is committed to monitoring new information related to human dura mater and appropriately updating its approach. Some recent examples of FDA's continued monitoring include: (1) a 2001 meeting with the TSEAC to discuss tissue donor

[1] As noted in your petition, the company recalled the product.
[2] Lyodura has never been cleared for use in the United States.

suitability criteria with regard to both CJD and variant CJD (vCJD);[3] (2) a 1999 Neurological Devices Panel meeting (the Panel) that discussed and reevaluated the safety of human dura mater, which included an updated Panel classification recommendation; (3) a 1999 revised guidance document for human dura mater premarket notification applications; (4) a 1998 TSEAC meeting to recommend revisions to the 1990 "Guide for 510(k) Review of Processed Human Dura Mater" (1990 guidance document); and (5) the issuance of the 1998 tracking order for human dura mater. These examples will be discussed in more detail below.

The information cited in your petition, with the exception of the 1998 patient death,[4] was known and fully discussed at an October 6 and 7, 1997, TSEAC meeting (1997 TSEAC meeting). Participants in this meeting included: representatives from FDA, the Centers for Disease Control and Prevention, the National Institutes of Health, dura mater providers, and the neurosurgical medical community.

During the 1997 TSEAC meeting, the TSEAC considered the clinical benefit associated with human dura mater implantation during the last 40 years, i.e., providing mechanical support and protection of the brain, as well as reducing cerebrospinal fluid leakage after neurosurgical implantation, the risk to health associated with CJD transmission, and the clinical use of dura substitute products. Specifically, the TSEAC considered: 1) the methods for procuring and processing human dura mater, 2) the surgical use of human dura mater and dura substitutes, 3) an epidemiological assessment of CJD transmission related to human dura mater implantation, 4) experimental studies on decontamination procedures for human dura mater, and 5) the FDA regulatory controls for human dura mater.

After considering these issues, which are the same as those presented in your petition, the TSEAC voted in favor of urging neurosurgeons, whenever possible, to avoid the use of cadaveric dura mater allografts, but that the decision to use such products would be left to individual neurosurgeons. The TSEAC also recommended additional safety measures to minimize the risk of CJD transmission. The TSEAC and WHO recommendations are similar in that each recommended avoiding the use of human dura mater whenever possible. Both recommendations also included comments about the importance of carefully screening donors and using a validated method for inactivating CJD, in those situations when human dura mater is used.

Based on these 1997 TSEAC recommendations, the FDA sent letters on March 6, 1998, to providers of human dura mater and requested implementation of specific safety measures. The manufacturers' replies, which were discussed at the April 16, 1998 TSEAC meeting (the 1998 TSEAC meeting), included comments on the feasibility of the FDA recommendations. For example, manufacturers stated that requiring proteinase-resistant prion protein (PrP-RES) testing of tissues was not possible until a valid assay

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[3] Contrary to statements in your petition, FDA is concerned with both the transmission of vCJD and CJD. Given the recent emergence of vCJD, FDA requested input on potential revisions to donor selection criteria.

[4] Information concerning this patient's death was discussed at the June 1999 TSEAC meeting.

became available, full brain autopsy of every donor by a qualified neuropathologist may not be possible and could be prohibitively expensive, and archival of dura mater tissue for 50 years was overly burdensome. Based on these responses and additional FDA deliberations, FDA proposed revisions to the 1997 TSEAC recommendations for procuring and processing human dura mater at the 1998 TSEAC meeting.

After the 1998 TSEAC meeting, FDA revised the 1990 guidance document. The revised guidance document was issued in 1999 and supersedes the 1990 guidance document. The updated guidance document includes recommendations that PrP-RES testing be initiated when a suitable assay becomes available and that donor tissue be archived for ten years. FDA also issued a tracking order for human dura mater in 1998, as an additional method of protecting the public health. The tracking order requires each manufacturer to develop and implement a program that permits a manufacturer to locate patients implanted with human dura mater until device explantation or patient death.

On September 16 and 17, 1999, FDA asked the Panel to review its 1990 recommendation that human dura mater be classified into class II, because new information had become available since the Panel's 1990 recommendation. The Panel again recommended that human dura mater be classified into class II based on considerations of the medical benefits derived from dura mater implantation, the identified risks to health, and the possibility of implementing special controls that can control the cited risks to health. FDA is initiating rulemaking to classify human dura mater and revising the 1999 guidance document to be a class II special controls guidance document to support this classification. As a special control, the recommendations in the guidance document or an alternative providing equivalent safety should be followed.

As indicated in the final rule for "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue Based Products" issued in 2001, FDA intends to redesignate the regulation of human dura mater as a medical device to regulation as a human tissue (66 FR 5447, January 19, 2001). The regulations for human tissue are promulgated under the authority of Section 361 of the Public Health Service (PHS) Act and are intended to prevent the introduction, transmission, and spread of communicable disease. The date of this transfer is dependent upon finalization of the proposed rules addressing human tissue. These rules include: "Suitability Determination for Donors of Human Cellular and Tissue-Based Products; Proposed Rule" (64 FR 52696, September 30, 1999) and "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement: Proposed Rule" (proposed GTP rule) (66 FR 1508, January 8, 2001). Although the proposed GTP rule would not require individual recipients to be tracked indefinitely, it would put significant pre- and post-operative tracking requirements in place.[5]

[5] Proposed Sec. 1271.290(b) would require the establishment to establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from the donor to the recipient or final disposition and conversely from the recipient or final disposition to the donor. (Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement: Proposed Rule (66 FR 1508, 1556-57, January 8, 2001)).

If the transfer of human dura mater to regulation as a human tissue under section 361 of the PHS Act occurs before the classification is final, the proposed requirements of the rule governing tissue processing would be mandatory for all human dura mater manufacturers. Indeed, FDA has decided to move forward on both regulatory fronts (classification with a special control and transfer to jurisdiction under the tissue rules), in order to reduce the likelihood that appropriate regulation of this product will be delayed in any way.

Your petition notes the deaths of three U.S. patients who had been implanted with human dura mater. The first two U.S. patient deaths were associated with the implantation of Lyodura, which FDA never cleared for marketing. In April 1987, FDA issued a safety alert that warned of the potential risk of transmitting CJD to surgical patients through use of contaminated Lyodura. In June of 1987, FDA issued an import alert to prevent Lyodura from entering the U.S. This import alert is still in effect.

The publication by Hannah et al. states that Lyodura was commingled and inactivated with 0.1 N sodium hydroxide (NaOH). Concerning NaOH inactivation of human dura mater, we note and agree with the comment in your petition that even treatment with 1.0 N NaOH may not totally eliminate the presence of the CJD causative agent. However, it is generally accepted that such a treatment can significantly reduce the level of this agent in biological material. It is for this reason that the 1999 guidance document recommends that manufacturers use several steps to reduce the potential infectivity of human dura mater grafts. These steps include appropriate donor screening, gross and histological examination of each potential donor's brain, product manufacturing steps that exclude pooling of donor tissue and include the use of a generally accepted disinfection technique for the CJD-causative agent.

The third U.S. patient death occurred in 1998, after the 1992 implantation of a Tutoplast dura mater graft, which was processed in Germany by Pfrimmer-Viggo GMBH & Co., (a company subsequently acquired by Biodynamics International (US), Inc. and then Tutogen Medical U.S., Inc.). The donor of this graft had a suspicious history of dysarthria, ataxia, and behavioral changes of an unknown origin. Because of concerns about the manufacturer's lack of compliance with Good Manufacturing Practices, including donor selection, component handling, environmental controls, record keeping, and processing controls, FDA issued an import alert in May 1994 for Tutoplast.

You also noted that FDA did not adopt the 1997 WHO recommendation concerning the surgical use of human dura mater. At the time of the WHO's recommendation, FDA had already issued a safety alert and an import alert for Lyodura, as well as the 1990 guidance document related to human dura mater production. The basic principles articulated in the 1990 guidance document included appropriate donor screening and specific manufacturing methods that precluded commingling of dura mater from different donors. These recommendations were revised and updated in the 1999 guidance document. Thus, as stated above, the 1997 WHO and FDA conclusions are consistent in their recommendations to avoid the use of human dura mater whenever possible. Both the

WHO and FDA recommendations also identify important measures for selecting potential human dura mater donors and processing the subsequent tissue.

Your petition also states that a ban on the sale of human cadaveric dura mater and a recall of all unimplanted human cadaveric dura mater from hospitals and all other channels of commerce is justified, because "safer alternatives" are available, including synthetic dura mater grafts, bovine pericardium grafts, and autologous fascia lata.

The concerns associated with the implantation of various types of dura mater substitutes were also discussed during the 1997 TSEAC and the 1999 Panel meetings. The identified risks to health associated with the use of alternate products include hemorrhage, infection, re-exposure of the brain when reopening a craniotomy site, formation of thick connective tissue capsules or hematoma, and possible neurological deficit. Because these complications may also result from neurosurgery and because large scale studies comparing the incidence of these complications after implantation with either human dura mater or a dura mater substitute have not been done, the true complication rates associated with the use of dura substitute products remain unknown. Concerns expressed about the implantation of autologous fascia lata included the requirement for an additional operative procedure, a low risk of prolonged postoperative pain and infection, and potential cosmetic implications.

Although your petition asserts that FDA regulation is inadequate, you provide no new types of information on which to base a change in FDA's current regulatory initiatives in this area. FDA believes that the information provided in your petition does provide the most current enumeration of the deaths associated with human dura mater transplantation, but does not identify any new issues beyond those discussed at the 1997 TSEAC meeting. As stated above, the TSEAC, which is composed of many of the most knowledgeable neurological researchers, neurologists and neurosurgeons, voted in favor of urging neurosurgeons, whenever possible, to avoid the use of dura mater allografts, but that the decision to use such products should be left to individual neurosurgeons. FDA continues to believe that this is currently an appropriate approach for the regulation of this medical device as the Agency proceeds with rulemaking.

In considering the safety of human dura mater grafts, your petition cites the loss of 114 lives, including three U.S. patients from CJD infection after human dura mater implantation. It should be noted that the majority of these deaths occurred after implantation of Lyodura, which was never cleared in the U.S. and for which an import alert remains in effect. It should also be noted that none of the three patients who died in the U.S. were implanted with a medical device cleared for commercial distribution in the U.S. Further, these two human dura mater products were not procured and processed in accordance with the 1999 guidance document. The three U.S. deaths reflect a total U.S. patient population in which

[6] Contrary to statements in your petition, FDA is concerned with both the transmission of vCJD and CJD. Given the recent emergence of vCJD, FDA requested input on potential revisions to donor selection criteria.

the device has been used for over 40 years[7] and in which approximately 4,000 patients per year are currently implanted.

III. Request to Ban and to Recall

Banning

The petition requests that FDA ban all human cadaveric dura mater. FDA's authority to ban a device comes from section 516 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C.A. 360f). Subsection (a) of that section sets forth the criteria for banning a device as follows:

> Whenever the Secretary finds, on the basis of all available data and information, that –
>
> (1) a device intended for human use presents substantial deception or an unreasonable and substantial risk of illness or injury; and
>
> (2) in the case of substantial deception or an unreasonable and substantial risk of illness or injury which the Secretary determined could be corrected or eliminated by labeling or change in labeling and with respect to which the Secretary provided written notice to the manufacturer specifying the deception or risk of illness or injury, the labeling or change in labeling to correct the deception or eliminate or reduce such risk, and the period within which such labeling or change in labeling was to be done, such labeling or change in labeling was not done within such period;
>
> he may initiate a proceeding to promulgate a regulation to make such device a banned device.

FDA regulations implementing this provision and listing devices that have been banned are found in 21 C.F.R. Part 895.[8]

In order to initiate a proceeding to ban a device, the Commissioner must find "that the device presents substantial deception or an unreasonable and substantial risk of illness or injury that. . . cannot be, or has not been, corrected or eliminated by labeling or by a change in labeling." See 21 C.F.R. § 895.20. The Commissioner must consider whether "the deception or risk posed by continued marketing . . . is important, material, or

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[7] Gresham, R.B., "Freeze-drying of human tissue for clinical use," *Cryobiology*, 1: 150-156, 1964.

[8] The Secretary has delegated the authorities to ban and recall devices to the Commissioner. See 21 C.F.R. § 5.10(a)(1).

significant in relation to the benefit of the public health from its continued marketing." 21 C.F.R. § 895.21(a)(1).

As discussed above, FDA has previously considered the information you cite and has undertaken several actions based upon the information. Among other things, FDA has issued a tracking order for human dura mater, updated its 1990 guidance document, inspected human dura mater manufacturers, is initiating rulemaking to make its recommendations a special control under the Act, and has proposed rules that would apply to human dura mater when it is redesignated to regulation as a human tissue. At this time, FDA believes the actions that it has undertaken are an appropriate response to the current information and exhibit an appropriate balance of the risks and benefits posed by human dura mater.

As new information becomes available, FDA will continue to assess the situation and determine whether additional actions are necessary. FDA does not believe that the information you provided and that has previously been considered supports a conclusion that this device presents a substantial deception or an unreasonable and substantial risk of illness or injury within the meaning of section 516.

Recalls

The petition also requests that FDA recall all unimplanted dura mater. FDA' s authority to recall a device comes from section 518(e)(1) of the Act (21 U.S.C.A. 360h(e)(1)). Subsection (e)(1) of that section sets forth the criteria for recalling a device:

> If the Secretary finds that there is a reasonable probability that a device intended for human use would cause serious adverse health consequences or death, the Secretary shall issue an order requiring the appropriate person (including the manufacturers, importers, distributors, or retailers of the device)-
>
> (A) to immediately cease distribution of such device, and
>
> (B) to immediately notify health professionals and device user facilities of the order and to instruct such professionals and facilities to cease use of such device.

FDA regulations implementing this provision are found in 21 C.F.R. Part 810. Section 810.2(h) defines reasonable probability as meaning, "it is more likely than not that an event will occur."

The evidence you provided in support of your request that the FDA recall all human cadaveric dura mater from "channels of commerce" is the same as that submitted in support of your request to ban human cadaveric dura mater. FDA finds that a recall is not supported by the information you submitted for the reasons already explained above,

including a lack of information establishing that it is more likely than not that the device will cause serious adverse health consequences or death.

IV. Conclusion

For the reasons stated above, FDA finds that the citizen petition to ban and to recall human cadaveric dura mater has not met the statutory requirements for banning human dura mater and recalling unimplanted human dura mater. In the event that you develop new information in the future that may trigger use of these statutory requirements, you may submit a new petition for FDA consideration. If you have any questions regarding this response, please contact Charles N. Durfor, Ph.D., Division of General, Restorative, and Neurological Devices, Office of Device Evaluation, Center for Devices and Radiological Health at (301) 594-3090.

Sincerely yours,

Linda S. Kahan

Linda S. Kahan
Deputy Director
Center for Devices
and Radiological Health