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December 28, 1999

Jane E. Henney, MD
Commissioner
c/o Docket Management Branch
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Attention: Docket No. 97N-484S

Dear Commissioner Henney:

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), representing over 4,500 neurological surgeons in the United States, offer the following comments regarding the regulation of human tissue as proposed in the September 30, 1999 *Federal Register*. In particular, our comments are directed to three areas.

First and foremost, towards the criteria of minimally manipulated (*proposed §1271.3*), in particular the proposed change in its definition and its effect on the use of human tissue for the production of pre-shaped bone products such as tricortical and threaded cylindrical dowels, blocks and rings. A copy of our recent position paper regarding the use of human dowels is attached for further information and clarification on this issue.

We also offer comments on the questions posed in the rule regarding clarifying or modifying the term "systemic effect" in order to encompass neurons used to replace or supplement brain neurons. Finally, we support the proposed donor testing and screening requirements regarding dura mater.

I. The AANS and CNS strongly believe that human bone dowels fall within the definition of "minimally processed tissue" and therefore clearly meet the standing criteria for regulation as "tissue".

The May 14, 1998 *Federal Register* notice states, "procedures that would be considered minimal manipulation include: cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cryopreservation; and freezing." Such examples are clearly indicative of bone dowel production. We are concerned that the changes made to the definition of minimally manipulated in the proposed rule are overly broad and blur or eliminate this clear application for bone products.

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In the FDA's May 14, 1998 *Federal Register* notice to create unified registration for tissue processors (63 FR 26744), several issues impact upon the requirement for premarket approval in tissues used for transplantation:

... premarket approval would generally be required for...tissues that are processed extensively, are combined with noncellular or nontissue components, are labeled or promoted for purposes other than their normal functions, or have a systemic effect.

Standard bone dowels are also not generally combined with noncellular or nontissue components, hence FDA restrictions against combining with noncellular or nontissue components are not violated. The notice goes on to cite bone allograft obtained from a long bone but labeled for use in a vertebra as an example of homologous tissue. Vertebral fusion of human bone dowels clearly points to a FDA defined homologous use. Finally, retrospective review of over 50 years of peer reviewed publications clearly demonstrates no systemic effect of bone dowels for vertebral fusion, thus meeting the FDA restrictions in this area.

The FDA has previously stated that the primary goal of registration of human tissue-based products is **"improved protection of the public health without the imposition of unnecessary restrictions on research, development, or the availability of new products."** Any effort to reclassify human bone dowels from "tissue" to "medical devices" would appear to be contrary to this intent.

A. Use of human bone products (processed and pre-shaped) for spine surgery has a long history of documented safety and efficacy.

It can safely be stated that use of allograft fusion material is part of every practicing neurosurgeon, orthopedic surgeon, and spine surgeon's technical armamentarium. It is certainly considered acceptable standard for many surgical procedures. Transplantation of human allograft bone has a long and successful history in medicine. Because of its demonstrated safety and efficacy, it is estimated that over 250,000 allograft procedures are performed per year. There are literally hundreds of peer-reviewed medical publications reporting excellent results with low complication rates in spinal fusion procedures using human allograft bone.

B. Adequate standards and regulations for tissue processing already exist.

In 1947, Dr. L.F. Bush proposed donor acceptance criteria, and described methods for proper storage of tissue.¹ In addition to the numerous antiseptic and sterile practices long documented for these types of procedures, the American Association of Tissue Banks (AATB) provided guidelines for tissue banks covering all issues relevant to tissue procurement, preparation and storage in 1995. The FDA has also consistently sought to regulate tissue since the early 1990s. On December 14, 1993, the FDA issued its proposed regulation on Human Tissue Intended for Transplantation, which was ultimately finalized in July 1997 and incorporated many of AATB's standards.

C. The use of processed and pre-shaped bone products has been clinically proven to enhance patient care and improve outcomes.

¹ Bush LF. The use of homogenous bone grafts. *The Journal of bone and joint surgery.* 1947 (29A) 620-628.

The newest spinal fusion procedure using human allograft bone tissue was developed in large part to provide a natural biological product in lieu of metal instrumentation. A patient's operative time is decreased substantially with these products, thus decreasing patient morbidity. This procedure greatly simplifies back surgery. Surgical time is shortened and blood loss is reduced resulting in corresponding reductions in patient hospital stay. On average, the patients having anterior lumbar interbody fusion using human bone dowels are discharged within two-three days versus longer stays associated with other techniques. Use of processed and pre-shaped bone products also improves allograft to patient "surface to surface" contact, thereby improving probability of achieving successful fusion and improved outcome. Furthermore, such biological implants provide for better radiographic examination and are easier to adjust or revise if needed.

D. Any change in the classification of human bone dowels from its current status of "tissues" to "medical device" would decrease availability of these products to physicians and their patients. Reclassification consideration will have significant patient care ramifications

One of the major concerns regarding the use of any allograft tissue is whether or not there is a consistent supply. There are numerous reports of delays in obtaining suitable tissue when needed. Those delays are clearly due to a limited number of donors and a limited amount of bone being available for processing each year. FDA requirements for premarket approval (PMA) or 510(k) would immediately decrease use and delay widespread use of this product for a minimum of three to five years. Since many of the suppliers of these products are small companies who could not afford the cost of PMA or 510(k) review, it is likely that many would stop production of these products altogether. Reclassification and its associated increase in record keeping and documentation would duplicate work and make an already cumbersome record keeping system even more overwhelming.

Furthermore, the overall effect of reclassification of these products from human tissues to medical devices could have dramatic and unpredictable implications on utilization of all other human tissues, with widespread negative impact on patient care.

In summary the AANS and CNS therefore believe that:

- 1) Bone products for spine fusion have a long history of safety and efficacy,
- 2) Appropriate regulations for the harvesting, preparation, storage and use of these bone products already exists and has been adequately tested,
- 3) Availability of pre-shaped bone products results in decreased patient surgical time, surgical trauma, and morbidity,
- 4) Use of pre-shaped bone products results in improved surface to surface contact and, therefore, potentially improved outcome,
- 5) Patient access and availability of these products could be seriously harmed by an overly burdensome regulatory classification,
- 6) Current documentation system requirements already adequately protect patient safety. Further requirements are unlikely to increase such benefits and could in fact cause extreme hardship for some tissue facilities.
- 7) Reclassification could have profound implications on all human tissue product availability, and
- 8) Current FDA rules regarding "tissues" clearly place bone dowels within the definition of "tissues" and, therefore, not in the classification scheme of "medical devices".

The AANS and CNS therefore strongly believe that reclassification of bone dowels from "tissues" to "medical devices" has no logical basis or medical justification. Furthermore, it has a high probability of harming, rather than helping, patient care. We strongly recommend that such tissue remain in its current classification structure and be clearly defined as minimally manipulated. The FDA's stated intentions declare that the reorganization and clarification of this section is not meant to change the previous application of the section. We believe that in fact if the proposed definition changes for minimally manipulated, it will have precisely that effect.

II. The proposed rule (pg. 52699) also discusses possibly changing the definition of "systemic effect" to include such biological products such as neurons used to replace or supplement brain neurons.

We appreciate the opportunity to discuss this issue with the FDA. Currently, there is little or no evidence that supports regenerated neurons having any systemic effect. Unfortunately, the intent of your proposed changes is quite vague and it would be difficult to understand what possible ramifications it might engender. We would warn, however, that the research and development of such neural tissue is currently occurring at its earliest stages and in only a few clinical trials. It is too early to warrant bringing heavy regulatory requirements on to this important work, which holds such promise for neurological diseases such as Parkinson's, epilepsy and multiple sclerosis. We hope that further input and discussion of this issue can occur between the FDA and all interested stakeholders before further action is taken.

III. The AANS and CNS support the recommendations as approved by both the Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC) and by the FDA Neurological Devices Advisory Panel regarding the changes for testing and screening of dura mater donors (proposed §1271.85(e) and 1271.75(a)(4)).

In light of current scientific evidence regarding prion diseases, the precautions of a full brain autopsy in addition to donor screening and medical history, are a necessary step until such time that there is a fully approved screening test. Once a validated FDA-approved test is available, the requirement of a brain autopsy should be eliminated. We would also offer any necessary assistance regarding development of protocols for dura mater procurement.

The AANS and CNS appreciate the opportunity to offer these comments regarding the proposed tissue-based product rule. If you have any questions or need further information, please contact us.

Sincerely,

Martin H. Weiss, MD
President
American Association of Neurological Surgeons

Daniel A. Barrow, MD
President
Congress of Neurological Surgeons

Jane E. Henney, MD
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Enclosure: The Use of Bone Dowels from "Human Tissue"



AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS CONGRESS OF NEUROLOGICAL SURGEONS

Position Paper on The Use of Bone Dowels from “Human Tissue”

Introductory Statement

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), representing over 4,500 neurological surgeons in the United States offer the following position regarding the use of human tissue for the production of bone dowels:

- 1) **Use of human bone products (processed and pre-shaped) for spine surgery has a long history of documented safety and efficacy.**
- 2) **Appropriate regulations for infectious disease testing, donor screening and record keeping already exist.**
- 3) **The use of processed and pre-shaped bone products has been clinically proven to enhance patient care and improve outcomes.**
- 4) **Any change in the classification of human bone dowels from its current status of tissues to that of a medical device would decrease availability of these products to physicians and their patients.**
- 5) **The overall effect of any reclassification of these products from human tissues to medical devices could have dramatic and unpredictable implications on utilization of all other human tissues, with widespread negative impact on patient care.**

Furthermore, it is the position of the AANS and the CNS that human bone dowels currently fall within the definition of “minimally processed tissue” and therefore meets the proposed criteria for regulation as “tissue”.

Finally, any effort to reclassify human bone dowels from “tissue” to “medical devices” would appear to be contrary to the previously stated intent of the Federal Register notice regarding registration of human tissue-based products (63 FR 26744, May 14, 1998) in which it was stated that a primary goal of registration was “improved protection of the public health **without the imposition of unnecessary restrictions on research, development, or the availability of new products**”.

BACKGROUND AND HISTORY

- **Use of human bone products (processed and pre-shaped) for spine surgery has a long history of documented safety and efficacy.**

Transplantation of human allograft bone has a long and successful history in medicine. Because of its demonstrated safety and efficacy, it is estimated that over 250,000 allograft procedures are performed per year.

The first successful reported case of allograft transplantation was reported as early as 1878. The successful use of "xenograft" bone to fill an osseous defect in both tibia and femur was reported by Dr. Senn in 1889. After these successful reports, allograft tissue became more widespread and attention focused not only on its use, but also on the technique of insuring preservation and antisepsis. Continuing reports on the techniques of preservation and antisepsis date back as early as 1912 and are frequent throughout the early to mid-1900s.

The first reported use of allograft in spine fusion surgery was in 1929 by Dr. S.F. Albee.¹ For the next twenty-five years many additional reports followed, particularly emphasizing interbody fusion procedures. Today there are literally hundreds of peer-reviewed medical publications reporting excellent results with low complication rates in spinal fusion procedures using human allograft bone. It can safely be stated that use of allograft fusion material is part of every practicing neurosurgeon, orthopedic surgeon, and spine surgeon's technical armamentarium. It is certainly considered acceptable standard for many surgical procedures.

Shaped bone products also have a long history of use in human spinal surgery. Drs. Briggs and Milligan first reported using bone in the shape of a "peg" in *the Journal of Bone and Joint Surgery* in 1944.² The same journal reported the use of a block of bone 4 mm X 10 mm X 16 mm by Dr. Jaslow in 1946.³ Drs. G. Smith and R. Robinson also reported on the use of this type of block of bone in 1958, a procedure that is the most frequently used method of anterior spine fusion to date.⁴ Since then, many shaped bone products have become commonly used products. These include: tricortical and threaded cylindrical dowels, blocks, and rings.

These references represent only a small sampling of the many peer-reviewed publications available to support the observation that allograft bone has been long utilized in a safe and efficacious manner. Today there are literally hundreds of peer-reviewed medical publications reporting excellent results with low complication rates in spinal fusion procedures using human allograft bone. It can safely be stated that use of allograft fusion material is part of every practicing neurosurgeon, orthopedic surgeon, and spine surgeon's technical armamentarium. It is certainly considered acceptable standard for many surgical procedures.

¹ Albee FH, Spondylolisthesis. *The Journal of bone and joint surgery.* 1927(9) 427-446

² Briggs H., Milligan PR. Chip Fusion of the low back following exploration of the spinal canal. *The Journal of bone and joint surgery.* 1944 (26) 125-130.

³ Jaslow IA. Intercorporal bone graft in spinal fusion after disc removal. *Surgery Gynecology and Obstetrics.* 1946 (82) 215-218.

⁴ Smith GW and Robinson RA. The treatment of Certain Cervical Spine Disorders by Anterior removal of the Intervertebral Disc and Interbody Fusion. *The Journal of bone and joint surgery.* 1958(40A) 607-624.

History and Review of Tissue Regulation Relating to Human Bone Dowels

- **Adequate standards and regulations for tissue processing are already in existence:**

In 1947, Dr. L.F. Bush proposed donor acceptance criteria, and described methods for proper storage of tissue.⁵ In addition to the numerous antiseptics and sterile practices long documented for these types of procedures, the American Association of Tissue Banks (AATB) provided guidelines for tissue banks covering all issues relevant to tissue procurement, preparation and storage in 1995. The Food and Drug Administration has also consistently sought to regulate tissue since the early 1990s. On December 14, 1993, the FDA issued its proposed regulation on Human Tissue Intended for Transplantation which was ultimately finalized in July 1997 and incorporated many of AATB's standards.

In the Food and Drug Administration's May 14, 1998 Federal Register notice to create unified registration for tissue processors (63 FR 26744), several issues impact upon the requirement for premarket approval in tissues used for transplantation:

"...premarket approval would generally be required for...tissues that are processed extensively, are combined with noncellular or nontissue components, are labeled or promoted for purposes other than their normal functions, or have a systemic effect."

Standard bone dowels are also not generally combined with noncellular or nontissue components hence FDA restriction against combining with noncellular or nontissue components are not violated. The notice goes on to cite bone allograft obtained from a long bone but labeled for use in a vertebra as an example of homologous tissue. Vertebral fusion of human bone dowels clearly points to a FDA defined homologous use. Finally, retrospective review of over 50 years of peer reviewed publications clearly demonstrates no systemic effect of bone dowels for vertebral fusion. The use of human bone dowels has clearly demonstrated they meet the FDA restrictions of no systemic effect.

Additionally, the May 14, 1998 Federal Register notice states, "procedures that would be considered minimal manipulation include: cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cryopreservation; and freezing." Again, such examples are clearly indicative of bone dowel production and clearly meet the FDA definition of minimally processed tissues.

Clinical Safety and Efficacy

- **The use of processed and pre-shaped bone products has been clinically proven to enhance patient care and improve outcomes.**

The newest spinal fusion procedure using human allograft bone tissue was developed in large part to provide a natural biological product in lieu of metal instrumentation. A patient's operative time is decreased substantially with these products, thus decreasing patient morbidity. This procedure greatly simplifies back surgery. Surgical time is shortened and blood loss is reduced resulting in corresponding reductions in patient hospital stay. On average, the patients having anterior lumbar interbody fusion using human bone dowels are discharged within two-three days versus longer stays associated with previous techniques. Use of processed and pre-shaped bone products also improves allograft to patient "surface to surface" contact, thereby improving

⁵ Bush LF. The use of homogenous bone grafts. The Journal of bone and joint surgery. 1947 (29A) 620-628.

probability of achieving successful fusion and improved outcome. Furthermore, such biological implants provide for better radiographic examination and are easier to adjust or revise if needed.

Reclassification Consideration will have Significant Patient Care Ramifications

- **Any change in the classification of human bone dowels from its current status of tissues to that of a medical device would decrease availability of these products to physicians and their patients.**

One of the major concerns regarding the use of any allograft tissue is whether or not there is a consistent supply. There are numerous reports of delays in obtaining suitable tissue when needed. Those delays are clearly due to a limited number of donors and a limited amount of bone being available for processing each year. FDA requirements for premarket approval (PPMA) or 510(k) would immediately decrease use and delay widespread use of this product for a minimum of three to five years. Since many of the suppliers of these products are small companies who could not afford the cost of PMA or 510(k) review, it is likely that many would stop production of these products altogether. Reclassification and its associated increase in record keeping and documentation would duplicate work and make an already cumbersome record keeping system even more overwhelming.

SUMMARY

- **The overall effect of reclassification of these products from human tissues to medical devices could have dramatic and unpredictable implications on utilization of all other human tissues, with widespread negative impact on patient care.**

In summary the AANS and CNS believe that:

- 1) Bone products for spine fusion have a long history of safety and efficacy,
- 2) Appropriate regulations for the harvesting, preparation, storage and use of these bone products already exist and have been adequately tested,
- 3) Availability of pre-shaped bone products results in decreased patient surgical time, surgical trauma, and morbidity,
- 4) Use of pre-shaped bone products results in improved surface to surface contact and, therefore, potentially improved outcome,
- 5) Patient access and availability of these products could be seriously harmed by an overburdensome regulatory classification,
- 6) Current documentation system requirements very adequately protect patient safety. Further requirements are unlikely to increase such benefits and could in fact cause extreme hardship for some tissue facilities.
- 7) Reclassification could have profound implications on all human tissue product availability, and
- 8) Current FDA rules regarding "tissues" clearly place bone dowels within the definition of "tissues" and, therefore, not in the classification scheme of "medical devices".

Therefore, it is the opinion of the AANS and CNS that reclassification of bone dowels from "tissues" to "medical devices" has no logical basis or medical justification. Furthermore, it has a high probability of harming, rather than helping, patient care. We strongly recommend that such tissue remain in its current classification structure.