Meeting between FDA and AATB
Regarding Demineralized Bone Matrix Regulation

July 11, 1997

NIH, Building 29B, Conference Room C

Present:

FDA: CDRH: Susan Alpert, Claudia Gaffey, Celia Witten, Marie Schroeder, Eugene Berk, Peter Hudson; CBER: Emma Knight, Ruth Solomon, Phil Noguchi, Toni Stifano, Dan Murphy, Eric Flamm, John Bishop, Gerald Marti (Dr. Kathy Zoon joined at the end of the meeting)..

External (AATB): Jeanne Mowe, Executive Director, AATB; Jeffrey Sandler, Chair, Governmental Affairs Committee; Richard Russo, Vice Chair, Governmental Affairs Committee; Gail Javitts, Covington and Burling, liaison.

AATB presented FDA with three copies of a large bound folder containing copies of published articles on demineralized bone matrix (DBM). AATB distributed an agenda for the meeting. The objective of the meeting according to the AATB's agenda, was to exchange information and clarify views concerning demineralized bone matrix (DBM).

BRIEF RECAP OF FDA PROPOSALS

AATB began by reviewing the concept of homologous/non-homologous function. AATB stated that the function of DBM is bone grafting--therefore, this was a homologous function.

AATB also reviewed the definition of minimal manipulation/more-than-minimal manipulation, as it applies to structural tissue. A manipulation is more-than-minimal when it alters the original relevant characteristics of the tissue, i.e., its ability to perform its function. AATB stated that DBM is still bone, and has undergone minimal manipulation and proceeded to explain why.

OVERVIEW OF BONE TISSUE

Composition and Relevant Characteristics

AATB defined 3 terms: osteogenesis, osteoconduction, and osteoinduction. Osteogenesis is new bone formation, and requires cells. Since DBM is acellular, it cannot induce osteogenesis. Osteoinduction is the inducement of undifferentiated cells (connective tissue) to differentiate into bone, i.e., bone formation in the absence of osteogenesis and osteoconduction. DBM does this. Osteoconduction is the dead bone acting as a scaffold for the ingrowth of vessels, followed by the resorption of the implant and deposition of the new bone derived from the edges of the defect. DBM does this. Thus, DBM performs 2 out of the 3 functions of native bone, while a non-

demineralized bone allograft performs 1 out of the 3 functions (osteoconduction only).
Comments About Bone Processing

AATB described the manipulation of bone from the time it is procured. Exogenous substances such as blood and lipids, are removed by processing; endogenous substances, such as cells, are also removed by processing. A diagram was distributed which showed that bone is composed of a mineral phase (70%), and an organic phase (30%). The organic phase has cells (2%) and matrix (98%). With non-demineralized bone, cells are removed, leaving minerals and matrix. With demineralized bone, cells and minerals are removed, leaving matrix only.

Highlights of AATB Survey of DBM Processing

AATB did an informal survey of their membership who process DBM. There are 16 accredited tissue banks that process DBM, and all 16 replied (100% response). The conclusion from the survey was that all 16 banks had fairly consistent processing procedures. The steps included:

- donor screening;
- use of cortical (long) bones to produce DBM;
- total debridement;
- removal of blood (bone marrow) and lipids by ethanol soak,;
- hydrogen peroxide soak, wash with sterile water,;
- wash with sterile water;
- terminal sterilization with ethylene oxide or gamma irradiation (only a few did terminal sterilization);
- chipping and milling of the bone into powder. Particle size varies between about 100 to about 1000 microns (particle size determined by using commercially available sieve);
- Freeze-drying (lyophilization) occurred either before or after;
- Packaging.

Some banks did microbial culture. Cultures were taken at different stages of the processing (room, recovery, and final). Some banks measured residual moisture and residual calcium. The only label described was the one of the vial (ID#, how the tissue was tested, etc.). There were no claims for clinical properties of the DBM.

DISCUSSION

FDA asked if non-AATB-accredited tissue banks processed DBM. AATB replied that they thought that less than 20 did so, especially 2 large banks. AATB also indicated that a few of these banks were also surveyed, and they use the same processing procedures as described above. AATB said that in material submitted to CDRH by ——— it was mentioned that there were 13-15 steps involved in demineralization (in addition to the initial 6 steps). Mr. Russo responded that what had been provided to FDA was ——— procedure and some of these steps involved multiple washing..

the criteria of more-than minimal manipulation, as outlined in the February 28 Proposed Approach tissue document. FDA also asked if the osteoconduction/osteoinduction properties of DBM were inherent to the natural product or were induced/enhanced by the type of processing used to develop the product. AATB offered to send copies of articles where this point was discussed.

CONCLUSION

In conclusion, AATB reviewed what FDA expected AATB to do next:

1. Determine the scientific basis for AATB's proposal to regulate DBM as a tissue instead of a device.

2. Better characterize the manufacturing process.

3. Give examples of bone allograft products that AATB would consider more-than - minimally manipulated.

4. Attempt to develop standards for the demineralization process--the standards would not have to be static.