

1200 10:00 AM - 12:00 PM

**SUMMARY MINUTES**

**MEETING OF THE DENTAL PRODUCTS DEVICES ADVISORY PANEL**

**OPEN SESSION**

**May 22, 2003**

**Gaithersburg Holiday Inn  
Gaithersburg, MD**

395541

**Dental Products Devices Advisory Panel Meeting  
May 22, 2003**

**Attendees**

**Chairperson**

E. Dianne Rekow, D.D.S., Ph.D.  
New York University College of Dentistry

**Executive Secretary**

Michael E. Adjodha, M.ChE.  
Chemical Engineer  
Dental Devices Branch

**Voting Members**

David L. Cochran, D.D.S., Ph.D.  
University of Texas Health Sciences Center

Jon B. Suzuki, D.D.S., Ph.D.  
University of Pittsburgh School of Dentistry

**Consultants**

Richard G. Burton, D.D.S.  
University of Iowa

Julianne Glowacki, Ph.D.  
Brigham and Women's Hospital

Mark R. Patters, D.D.S., Ph.D.  
University of Tennessee College of  
Dentistry

**Consumer Representative**

Elizabeth S. Howe  
National Foundation for Ectodermal  
Dysplasias

**Industry Representative**

Daniel R. Schechter, J.D.  
Parkell, Inc.

**FDA Participants**

M. Susan Runner, D.D.S., M.A.  
Captain, USPHS  
Interim Division Director, DAGID

Kevin P. Mulry, D.D.S., M.P.H.  
Acting Chief, Dental Devices Branch

Robert S. Betz, D.D.S.  
Captain, USPHS  
Dental Officer, Dental Devices Branch

Marjorie Shulman  
Consumer Safety Officer  
Program Operations Staff

## **CALL TO ORDER**

**Panel Executive Secretary Michael E. Adjodha, M.ChE.**, called the meeting to order at 9:32 a.m. and introduced the panel members. He read the appointment to temporary voting status; Richard G. Burton, D.D.S., Edmond R. Hewlett, D.D.S., Julianne Glowacki, Ph.D., and Mark Patters, D.D.S., Ph.D., had been granted temporary voting status for the meeting. E. Dianne Rekow, D.D.S., Ph.D., had been appointed as temporary chairperson for the duration of the meeting. Mr. Adjodha then read the conflict of interest statement. Full waivers had been granted to David L. Cochran, D.D.S., Ph.D., and Julianne Glowacki, Ph.D., who reported past or current financial interests in firms at issue but in matters not related to the day's agenda.

**Katherine McComas, Ph.D., assistant professor, Department of Communication, University of Maryland**, invited the panel and the audience to participate in her survey on the public's understanding of the FDA's conflict of interest procedures.

Mr. Adjodha then turned the meeting over to **Panel Chair E. Dianne Rekow, D.D.S.**

## **FDA PRESENTATION**

**Kevin P. Mulry, D.D.S., M.P.H., acting chief, Dental Devices Branch**, noted that the purpose of the meeting was for the panel to provide a recommendation on a petition to reclassify beta tricalcium phosphate (bTCP) from Class III to Class II. He summarized the regulatory history of the material. The Agency has found one adverse event report for TCP, which was not associated with human use. FDA is asking the panel to provide input on a table that lists the risks generally associated with the use of TCP and to comment on recommended measures to mitigate the identified risks. Those risks and mitigations could be included in a guidance document to be developed by the Dental Branch if the panel makes a recommendation for reclassification.

TCP—tricalcium phosphate granules for dental bone repair—currently is regulated in the Dental Branch as a Class III device and is identified in the CFR as a device intended to be implanted into the upper or lower jaw to provide support for prosthetic devices. This classification includes all forms of TCP, and reclassification would likewise include all TCP forms. As with any new indication for use, if another form of TCP other than bTCP were submitted, appropriate data could be requested. By policy in the Dental Branch, bone void fillers that are less than 50 percent bTCP are unclassified devices and are reviewed under the premarket notification or 510(k) process.

The Agency has approved one PMA or premarket notification application for bTCP. In the Orthopedic and Restorative Branches within CDRH, TCP is an unclassified device. For those branches, the regulatory history is different. The Orthopedic and Rehabilitation Panel met in January 1998 and recommended that calcium sulfate bone void filler be classified into Class II; on February 7, 2002, a proposed rule was published in the *Federal Register* to classify the resorbable calcium salt bone void filler device into Class II. This classification included bTCP.

**Robert S. Betz, D.D.S., Dental Officer, Dental Devices Branch,** summarized the history of the reclassification petition. Risks identified in the application include infection and pyrogenic response. The reclassification is based on the fact that bTCP has been successfully used in medicine and dentistry for more than 20 years and that its properties are known to be beneficial when used as a bone substitute. bTCP is presently a Class III device for dental indications and requires a PMA; however, it has been cleared for market by premarket notification or 510(k) when used for other purposes, such as orthopedic applications.

FDA has found in its databases only one reported adverse event related to calcium phosphate compounds: When an unspecified calcium phosphate compound was injected into the

vein of a pig, blood clots formed. FDA believes that this report has little or no relevance to the use of TCP in periodontal or craniofacial applications, especially when placed in humans.

bTCP is a calcium phosphate salt that has the same intended uses and is similar to legally marketed dental bone void filler and grafting materials such as plaster of Paris (like Capset); hydroxyapatite (like Hapset); and ceramics (like Bio Oss Ceramic). It has been successfully used in orthopedic applications without reports of adverse events and is presently unclassified for orthopedic and general restorative purposes.

One of the sections of FDA's forthcoming bone void filler or bone grafting material guidance document will be a table of risks encountered when bone void filling or bone grafting materials are placed in oral and craniofacial applications. Because TCP bone void fillers are similar to other bone void fillers presently cleared under 510(k) regulations, the risk table that FDA is asking the panel to review may also be used within the forthcoming bone void filler or bone grafting material guidance document. This table of risks is proposed for the panel to discuss and consider in its decision-making process. The panel should feel free to modify the table as it sees fit.

Dr. Betz then reviewed the panel questions.

## **SPONSOR PRESENTATION**

**Vincent J. Morgan, D.M.D., president, Bicon, Inc., Boston, Mass.,** said that he initiated the reclassification petition because the current classification is inconsistent. Why can an orthopedic surgeon, but not a maxillofacial surgeon, place TCP? He introduced the sponsor presenters and noted that Curasan AG, a German corporation, had asked him to drop his petition in exchange for the sole distributorship of its product in the United States; he declined the offer.

**Thomas Driskell, inventor, Westerville, Ohio,** summarized the history of bTCP development. bTCP is not osteogenic or osteoconductive, but *osteophilic*.

Dr. Glowacki asked several questions about factors that could affect the rate of resorption, such as compression, sintering temperature, and manufacturing processes. Mr. Driskell said that resorption time is directly related to the amount of material that is implanted. The most important factor, however, is likely the health of the patient. In people with poor health, resorption is probably slower. As the material resorbs, it is immediately replaced by bone. Assuming adequate controls over manufacture, there should not be any appreciable differences between batches. The variations in the manufacturing process are slight.

Dr. Suzuki asked Mr. Driskell to clarify the difference between osteophilic and osteoconductive material. He replied that the term osteophilic refers to causing bone to grow in an area into which it would not normally be expected to grow. Dr. Suzuki noted that osteophilic implies that there are no adverse reactions, such as immune rejection; Mr. Driskell replied that the only problem he has seen is an occasional infection.

Dr. Cochran asked for clarification on the mechanism of the resorption process. Mr. Driskell noted that the bTCP has to be in contact with fresh bleeding bone to work.

**John R. Long, Ph.D., director of technology, GFS Chemicals, Columbus, Ohio,** stated that his company supplies TCP to Bicon. bTCP is made in a room dedicated to its production; dedicated equipment, ovens, various other parts of the operation are confined to that one room. GFS is ISO-9000 certified, which means that the company can trace batches of the material and provide whatever information might be needed on vendors, lots, finished goods, and other data. The material requires a particular calcium-to-phosphorous ratio, which is governed in the manufacturing steps. The composition can be confirmed by analytical methods, primarily x-ray diffraction.

Dr. Glowacki asked whether the compression and sintering to make different forms of TCP results in materials with 100 percent similar x-ray diffractions. Dr. Long replied that x-ray

diffraction defines the microscopic property of the material; it could occur with particles of various sizes. TCP form is not a function of particle size, but the material must be ground to a certain powder in order to do the x-ray effectively. Achieving the beta phase requires a specific temperature; if that temperature is not achieved, the x-ray will show the presence of impurities. Dr. Glowacki asked additional questions concerning the effects of granule size on the product effectiveness, which Dr. Long answered to her satisfaction.

Panel members asked questions concerning the differences between beta and the other forms of TCP, manufacturing tolerances, and sterility. Dr. Long said that the purity of the material is very high and that sterile product is not provided. Specifications cover aspects including density, particle size, and calcium-to-phosphorous ratio.

## **OPEN PUBLIC HEARING**

Dr. Rekow noted that Dr. Barbara Boyan, who had planned to speak on behalf of the American Academy of Dental Research, was unable to attend.

**Mark Reynolds, associate professor and director of the postdoctoral residency and periodontist at the University of Maryland,** spoke on behalf of the American Academy of Periodontology. AAP supports the reclassification of bTCP as a Class II device based on both scientific and clinical considerations. Numerous publications document both the clinical effectiveness and safety of bTCP granules that used as a bone substitute in periodontal applications. Emerging literature from outside the United States continues to provide additional information on the safety and clinical efficacy in use of bTCP and other applications, including sinus augmentation. Reclassification of TCP should result in greater public access to this bone replacement material. Although bTCP shares similar physical and chemical characteristics and properties with other

marketed dental grafting materials, its inherent properties may afford clinicians with a broader range of bone replacement materials for use in clinical practice. In the absence of a 510(k) mechanism, cost-benefit considerations will continue to deter manufacturers from bringing this device to market, ultimately impairing practitioner and patient accessibility to this technology. Adjunctive biologic mediators, such as platelet-rich plasma, are already cleared for market via 510(k); the reclassification of TCP will recognize the current clinical practice and bring about a consistency in the regulation.

Ms. Howe asked whether the product's solubility in mineral acids should be a consideration, given that infection in the mouth might be present. Dr. Reynolds replied that he would anticipate no difference in clinical practice from any other bone replacement material.

Panel members asked clarifying questions about the material's indications and contraindications. Dr. Glowacki asked Dr. Reynolds whether sufficient experience exists in the use of bTCP and periodontal disorders for replacement of cortical bone; he replied that that use depends in large measure on the form of the TCP and its placement and whether other mechanisms are provided to stabilize and support the graft material. Dr. Glowacki noted that one of the comments in the orthopedic directives suggested avoiding use of bTCP in patients who have problems with calcium homeostasis; Dr. Reynolds noted that he is not aware of any experience in the periodontal field using this material inside patients. Indications could include intrabony defects and furcation defects associated with dentition implants, and likely will include other augmentation as well as sinus augmentation. Scant literature exists on the latter applications.

**Gunter Uhr, head of Clinical Research, Curasan AG,** noted that Curasan purchased the PMA for bTCP from Miter and intended to bring the product to market in the United States. The company opposes reclassifying the material to Class II. Bone and wound healing of the skull differ

from that in the skeletal system. To be safe and effective, the material must be more than 99 percent pure and must have specific characteristics with regard to shape, size, and porosity. He described the bone formation and healing process and presented slides demonstrating that skull bone differs from skeletal bone. He noted that injury to skull is more likely to result from infection, whereas it is more likely to be systemic in skeletal bone.

bTCP has been on the market in Europe since 1970; it disappeared in from the market in the 1980s because it disintegrates rapidly into particles that can be found in the neighboring lymph nodes. Impurities impair the results and process and are less resorbable than bTCP. Particle size and microporosity are important because a certain amount of intragranular space is needed for the invasion of blood vessels. Particles that are too large can damage tissue. If the material is not well sintered and stable, the particles will be phagocytized.

Panel members asked for clarification as to why Curasan opposes the downclassification. Dr. Uhr expressed concerns about the purity of the material. Dr. Patters noted that the purity issue can be covered in the guidance document with special controls if bTCP is reclassified.

**Tom Arrowsmith-Lowe, a regulatory consultant for Curasan,** noted that he is a retired public health service captain and served in the FDA until his retirement. He was a deputy office director in the Center for Devices and was director of the Human Tissue Program in the Center for Biologics. Curasan AG opposes the proposal to reclassify bTCP for two reasons. First, skeletal bone and maxillofacial bone differ in many ways. The histogenesis of the two types of bones is different. In addition, the maxillofacial bone exists for support of dentition for use in mastication and other uses; skeletal bone is for musculoskeletal support. Periodic stresses are applied to bone for dentition; more constant stresses are applied to the musculoskeletal system bone. The healing process of the two bones differ when bTCP is used for treatment of a defect; the postoperative healing process is

longer in the maxillofacial bone. The main etiology for defects that develop in musculoskeletal bone tend to be systemic, whereas the main etiology for defects that occur in the bone supporting the dentition is primarily of an infectious origin.

Second, bTCP was unavailable for a period of approximately 10 years for dental use in Europe, primarily because the TCP that was being marketed in the 1970s had problems of purity that affected the safety and effectiveness of that product. The clinical community stopped purchasing the product, and the manufacturer removed it from the market.

Other issues are that variations in the product's purity, porosity, and particle shape and size can affect the product itself and make it less safe and less effective. The most appropriate way to assess whether the product is truly safe and effective is to look at how purity, porosity, particle shape and particle size actually affect the performance of the product in a clinical setting. Actual review of data is required.

The petition has not adequately established that the two types of bone are similar and that the product actually has had no problems associated with it throughout its period of use. However, if reclassification were to occur, Curasan would like to make two recommendations to the Panel and to the Agency about how they would make a determination of substantial equivalence using a 510(k) process. First, the predicate product, to which substantial equivalence would need to be established, has to be a current generation bTCP, a purer product than the sort of product that was initially manufactured when the first PMA was cleared. Curasan AG now is the owner of the original PMA; as the Panel may be aware, Curasan AG has submitted a supplement to that original PMA to change the product into a purer form; the supplement addresses issues having to do with the size of the particles and also with porosity and with particle shape as well. Second, the 510(k)

process would need to include a determination of substantial equivalence looking at particle size, porosity, and shape and looking at the purity of the product.

Dr. Cochran asked Dr. Arrowsmith-Lowe whether he could provide any data that would suggest a difference in performance at some cutoff value of each of the four characteristics he mentioned. He replied that the basic science data presented already goes to establishing the significance of determining each of those. When purity dropped to a 95 or 96 percent range, the healing process changed. The presence of impurities also can affect particle size. Dr. Cochran indicated that more data are needed to demonstrate a cutoff.

Dr. Burton asked whether Curasan represents or currently markets a competing product, and Dr. Arrowsmith-Lowe replied that the company markets bTCP in Europe and for orthopedic, nondental use in the United States. They are the holder of what was originally Miter's PMA. They could market the product that was described in the original PMA. Dr. Burton noted that the Curasan representative had argued that that was an inferior product.

Dr. Suzuki asked whether Dr. Uhr was implying that smaller particles were harmful because of a potential foreign body reaction or that the macrophage is interfered with in terms of molecular quarterbacking. Dr. Uhr replied that the phagocytosis process is a stimulation of the activity of the macrophage. If the resorbable material is phagocytized, it will disappear. If it is an impure material, hydroxyapatite, it will not be resorbable. Dr. Arrowsmith-Lowe added that if the particle size is too small, the bTCP cannot do its intended job because the particles are phagocytized. Dr. Uhr noted that T lymphocytes stimulate the fever of the fiber and release interleukines. There is an interconnection between the T lymphocytes and the macrophage.

Dr. Suzuki noted that T lymphocytes are frequently associated with a delayed hypersensitivity or allergic type or rejection reactions and asked whether Dr. Uhr was suggesting that the panel needs to consider that parameter, too. Dr. Uhr said that was possible.

Mr. Schechter noted that the parameters could be spelled out in special controls in a Class II product. Dr. Arrowsmith-Lowe replied that if the reclassification occurs, it is essential that the parameters be assessed as a part of a determination of substantial equivalents. Curasan supports a higher acceptable level of purity than the ASTM standard. Clinically negative occurrences can result from particle shape.

Dr. Rekow asked whether scientific data support upper and lower thresholds for each of the four parameters (purity, size, shape, and porosity). Dr. Arrowsmith-Lowe replied that data are available. Some of it is company data, and some is published European literature.

Dr. Runner asked whether Curasan's proposed standard of care is accepted in the clinical community or is something that is proprietary to Curasan. Would the company be setting the standard? Is it something that FDA or the panel could recommend, or is it just the company's opinion? Dr. Arrowsmith-Lowe replied that it was the latter. In response to a question from Dr. Rekow, he clarified that the material was removed from the marketplace because of market pressures, not regulatory actions. His opinion has been informed by an analysis of the guidance document that was generated out of the orthopedic proposal to reclassify it to Class II.

Dr. Morgan pointed out that less than 100 percent pure bTCP has been successfully used in dental products in the United States for more than 20 years without a single adverse report. If Curasan's argument is that the bone of the skull is different from other bone, the FDA should restrict the use of the product by any plastic surgeon or orthopedic surgeon.

## **PANEL PRESENTATIONS AND DISCUSSION**

**Jon B. Suzuki, D.D.S., Ph.D.**, reviewed the panel questions. In his opinion, the petition does not adequately describe the risks to health of the device and provide for appropriate controls for those risks. Other guidelines need to be spelled out, particularly with regard to the indications for use, sterility, and degradation of the product. The risk of infection needs to be identified, and more information is needed on the sterility of product and its use in infected sites, especially periodontal sites. Form, shape, size, and other parameters need to be further defined. Dr. Suzuki reiterated the importance of considering infections and the acidity of the site and their role in degradation and solubility of the product.

**Julianne Glowacki, Ph.D.**, emphasized that her comments are not from a clinician's point of view. With regard to panel question 1, the panel should be reclassifying bTCP. A more precise description of the device needs to be provided, particularly with regard to characteristics such as composition and form. Pure TCP performs better than other forms. The panel needs more clarity on the intended use and indications; intraosseous applications seem more appropriate. The orthopedic literature indicates that the material does not provide physical properties of cortical bone; stability is an issue. Clinicians should not be led to believe that they can use the material in discontinuity defects.

In the labeling, precautions are needed against use in infected sites, against overfilling, and against use in discontinuity defects; information should be provided on how to remove excess. Clinicians need to know whether the material can be cut to fit. Some materials are brittle and provide debris that is difficult to get rid of. In addition, the labeling needs to include precautions against concurrent use with implants as well as information concerning the suitability of mixing TCP with other materials. The precautions should include avoidance of soft

tissue, nerves, pulp, and so forth; the material should not enter the bloodstream. In summary, bTCP can be reclassified, but it needs special controls.

Panel members noted the dearth of scientific data, observing that the papers presented in the petition are case reports and uncontrolled studies. However, clinicians have considerable experience with the material and regard it as safe, even though that has not been proven through trials. Although efficacy may not have been established, the material seems safe.

Ms. Howe said that although having an inexpensive, less invasive product available would be of benefit, is concerned about having a standard of quality, certification for those providing treatment, and contraindications for patients with special needs because of disease processes or other factors.

Mr. Schechter said that from an industry standpoint, he is interested in seeing the fewest obstacles. He supports downclassification. He asked whether, given the general sentiment that there is a dearth of scientific evidence, it would be appropriate for panel to reclassify with special controls, and then leave it up to FDA to state those controls more specifically?

Dr. Runner noted that the agency takes into account all panel comments. The panel is voting on indications as stated in the present regulations. Any additional indications must be supported with appropriate data. The PMA is cleared for periodontal alveolar bone defects, fresh tooth extraction sockets, additional stability, and to fill bony voids. The Dental Branch has interpreted the regulation to exclude endosseous implants.

## **PANEL RECOMMENDATIONS AND CLASSIFICATION**

**Marjorie Shulman, consumer safety officer, CDRH**, helped the panel complete the General Device Classification Questionnaire and the Supplemental Data Sheet. The panel agreed to

reclassify TCP granules for dental bone repair from Class III to Class II. Special controls are to be provided in a guidance document. The device is to be restricted to use only upon the written or oral authorization of a practitioner licensed by law to administer or use the device.

In completing the Supplemental Data Sheet, the panel recommended that the indications for use be those stated in the approved PMA. The panel concurred that because no data were available to evaluate their concerns related to pediatric and periodontal use and the treatment of tri- and bifurcations, they would rely on FDA to handle those issues in reviewing 510(k)s.

The panel agreed that the risks to health presented by the device were accurately reflected in the risk table provided by FDA. Panel members recommended editing the table as follows:

- Items 1-3: no modifications
- Item 4: change “lack” to “inadequate”
- Item 5: change wording to “failure to support osseointegration of endosseous implants”
- Item 6: no change
- Item 7: delete.

The panel recommended that FDA place high priority on making a final decision on the reclassification.

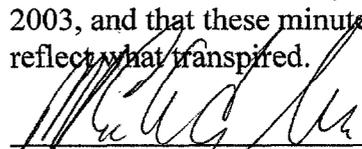
#### **VOTE**

The panel voted unanimously to reclassify the device as Class II and to accept the forms as completed in the panel session.

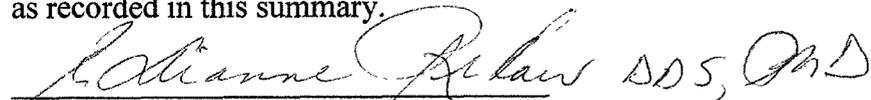
**ADJOURNMENT**

Dr. Rekow thanked the participants and adjourned the meeting at 3:04 p.m.

I certify that I attended this meeting of the Dental Products Advisory Panel on May 22, 2003, and that these minutes accurately reflect what transpired.

  
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Michael E. Adjedha, M.ChE.  
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

  
\_\_\_\_\_  
E. Dianne Rekow, D.D.S., Ph.D.  
Chairperson

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