

DOCKET NO. 2002P-0520
Tricalcium Phosphate Granules &
Other Bone Grafting Material for
Dental Bone Repair
REFERENCE NO. 3

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Dental Products Panel,
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May 22, 2003. *02P-0520*

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

MEETING OF THE

DENTAL PRODUCTS PANEL

THURSDAY, MAY 22, 2003

The meeting was held in the Walker/Whetstone Salons of the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland, at 9:30 a.m., E. Dianne Rekow, Chairperson, presiding.

PRESENT:

E. DIANNE REKOW, DDS, Ph.D.	Chair
MICHAEL E. ADJODHA, M.ChE.	Exec. Secretary
RICHARD G. BURTON, DDS	Panel Member
DAVID L. COCHRAN, DDS, Ph.D.	Panel Member
JULIANNE GLOWACKI, Ph.D.	Panel Member
ELIZABETH S. HOWE	Panel Member
MARK R. PATTERS, DDS, Ph.D.	Panel Member
DANIEL R. SCHECHTER, JD	Panel Member
JON B. SUZUKI, DDS, Ph.D.	Panel Member

FDA PARTICIPANTS:

M. SUSAN RUNNER, DDS, MA, Captain, USPHS
 KEVIN P. MULRY, DDS, MPH
 ROBERT S. BETZ, DDS, Captain, USPHS
 MARJORIE SHULMAN

SPONSOR PARTICIPANTS:

VINCENT J. MORGAN, DMD

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1 P-R-O-C-E-E-D-I-N-G-S

2 9:32 a.m.

3 SECRETARY ADJODHA: Good morning and
4 welcome to this meeting of the Dental Products Panel
5 of the CRH Medical Devices Advisory Committee. My
6 name is Michael Adjodha, executive secretary of this
7 Panel. This meeting is called to order.

8 Allow me to introduce the members of our
9 Panel. Please, raise your hand as I call your name.
10 Because of an illness, Dr. Leslie Heffez was unable to
11 attend this meeting. This meeting will be chaired by
12 Dr. Dianne Rekow. Chairwoman Rekow is the director of
13 Translational Research and professor in the Division
14 of Orthodontics at the New York University College of
15 Dentistry, New York, New York.

16 Joining her as voting members are Dr.
17 David Cochran, professor and chair of the Department
18 of Periodontics at the University of Texas, Health
19 Science Center, San Antonio, Texas, and Dr. Jon
20 Suzuki, professor at the University of Pittsburgh,
21 School of Dental Medicine, Pittsburgh, Pennsylvania.

22 Joining the voting members are the

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1 following consultants, who have been deputized to
2 vote: Dr. Richard Burton, graduate program director
3 of Oral and Maxillofacial Surgery at the University of
4 Iowa at the Department of Hospital Dentistry, Iowa
5 City, Iowa; Dr. Julianne Glowacki, senior investigator
6 at Brigham and Women's Hospital, Department of
7 Orthopedic Surgery, Boston, Massachusetts; and Dr.
8 Mark Patters, chairman of the University of Tennessee,
9 Department of Periodontology, Memphis, Tennessee. Dr.
10 Edmond Hewlett was invited, but was unable to attend,
11 because of an illness.

12 Also serving on this Panel as non-voting
13 members are industry representative Mr. Daniel
14 Schechter, general counsel for Parkell, Incorporated,
15 Farmingdale, New York, and Ms. Elizabeth Howe,
16 outreach coordinator for the National Foundation for
17 Ectodermal Dysplasias, Auburn, Washington.

18 Joining us at the table is Dr. Susan
19 Runner, interim director of FDA's Division of
20 Anesthesiology, Infection Control in General Hospital
21 and Dental Devices.

22 I will now read into the record a

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1 memorandum from our center director regarding the
2 building status of our Panel consultants. "Pursuant
3 to the authority granted unto the Medical Devices
4 Advisory Committee Charter, I appoint the following
5 consultants as voting members for the Dental Products
6 Panel for the meeting to be held on Thursday, May 22,
7 2003: Dr. Richard Burton, Dr. Edmond Hewlett, Dr.
8 Julianne Glowacki and Dr. Mark Patters.

9 For the record, these individuals are
10 special Government employees and are consultants to
11 this Panel under the Medical Advisory Committee. They
12 have undergone customary conflict of interest review.

13 They have reviewed the material to be considered for
14 this meeting.

15 In addition, I appoint Dr. Dianne Rekow to
16 act as temporary Chairperson for the duration on this
17 meeting. Signed, Dr. David Feigal, director of Center
18 for Devices and Radiological Health."

19 Next, I'll read into the record the
20 Conflict of Interest statement for this meeting. "The
21 following announcement addresses conflict of interest
22 issues associated with this meeting as made part of

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1 the record to preclude even the appearance of
2 impropriety.

3 The Conflict of Interest statutes prohibit
4 special Government employees from participating in
5 matters that could affect their or their employers'
6 financial interests. To determine if any conflict
7 existed, the Agency has reviewed the submitted agenda
8 for this meeting and all financial interests reported
9 by the committee participants.

10 The Agency has determined that no
11 conflicts exist. However, we would like to note for
12 the record that the Agency took into consideration
13 matters regarding Drs. David Cochran and Julianne
14 Glowacki. These panelists reported past and/or
15 current financial interests in firms at issue, but in
16 matters not related to today's agenda. The Agency has
17 determined, therefore, that they may participate fully
18 in today's deliberations.

19 In the event that the discussions involve
20 any other products or firms not already on the agenda,
21 for which FDA participant has a financial interest,
22 the participant should excuse him or herself from such

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1 involvement and the exclusion will be noted for the
2 record.

3 With respect to all other participants, we
4 ask in the interest of fairness that all persons
5 making statements or presentations disclose any
6 current or financial involvement with any firm whose
7 products they wish to comment upon."

8 On a related note, a Conflict of Interest
9 Survey is available for this meeting. This survey is
10 the result of an FDA University of Maryland
11 collaborative research effort. Dr. Katherine McComas,
12 assistant professor at the University of Maryland's
13 Department of Communication, is a sponsor of the
14 survey. I would like to ask Dr. McComas to come to
15 the microphone to say a few words about the survey
16 that's been handed out at this meeting.

17 DR. MCCOMAS: Thank you and good morning.

18 My name is Katherine McComas, and I'm a faculty
19 member at the University of Maryland, and I'm working
20 with the FDA on a study of public understanding and
21 knowledge of the Conflict of Interest Procedures that
22 the FDA uses to monitor and manage real or potential

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1 conflicts of interest of its Advisory Committee
2 members. This study is being conducted at multiple
3 Advisory Committee meetings across multiple centers at
4 the FDA, and I would like to ask for your assistance.

5 This is for non-FDA people to fill out.
6 I'm responsible for the questionnaires in your chairs.

7 It takes about 15 minutes to fill out. If you have a
8 chance today, there's a box at the registration desk
9 you can drop it in. Otherwise, there's a postage paid
10 envelope that you can drop it in and mail it back to
11 me. I also have distributed a separate questionnaire
12 for Advisory Committee members, and again I appreciate
13 your time in filling that out and getting that back to
14 me as soon as you can. The higher the number of
15 responses, the more reliable the results, and the
16 better we are able to make recommendations to the FDA
17 about ways that we might improve overall satisfaction
18 with the Advisory Committee process.

19 I will be here today to answer any
20 questions that you may have, and, as is in the letter,
21 which is included with the surveys, the results of
22 this will be freely disseminated to anybody who is

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1 interested. Thank you very much for your time.

2 SECRETARY ADJODHA: Thank you, Dr.
3 McComas. I'll now turn the meeting over to Chairwoman
4 Rekow.

5 CHAIR REKOW: Good morning. We have
6 before us, of course, the issue of reclassification of
7 the TCP for dental bone repair, and I believe that we
8 will begin with the presentation by Dr. Mulry, please.

9 DR. MULRY: Good morning and welcome to
10 the Dental Products Panel meeting. Today we are
11 asking you, the Panel, to provide a recommendation on
12 a petition to reclassify Beta Tricalcium Phosphate
13 from Class III to Class II. What I will be discussing
14 is the regulation of tricalcium phosphate beginning
15 with the current regulation, then looking at the
16 historical prospective and finally regulation in other
17 parts of CDRH.

18 Dr. Betz will present a review of the
19 petition and conclude with a risk and mitigation
20 table, which we will be requesting Panel input. With
21 regard to adverse events, the Agency has found one
22 report for tricalcium phosphate, which was not

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1 associated with human use. Dr. Betz will discuss this
2 adverse event in his presentation.

3 Today we will ask you, the Panel, to provide
4 input on a table which lists the risks to help
5 generally associated with the use of tricalcium
6 phosphate and to comment on recommended measures to
7 mitigate the identified risks. These risks and
8 mitigations could be included in a Guidance Document
9 to be developed by the Dental Branch if the Panel
10 makes a recommendation for reclassification.

11 Tricalcium phosphate currently is
12 regulated in the Dental Branch as a Class III device
13 under 21 Code of Federal Regulations 872.3930,
14 Tricalcium phosphate granules for dental bone repair,
15 and is identified in the CFR as a device intended to
16 be implanted into the upper or lower jaw to provide
17 support for prosthetic devices. This classification
18 regulation for tricalcium phosphate includes all forms
19 of tricalcium phosphate. A reclassification of this
20 regulation would include all forms of tricalcium
21 phosphate.

22 However, as with any new indication for

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1 use, if another form of tricalcium phosphate other
2 than Beta Tricalcium Phosphate were submitted,
3 appropriate data could be requested. By policy in the
4 Dental Branch, bone void fillers that are less than 50
5 percent of Beta Tricalcium Phosphate or unclassified
6 devices, and are reviewed under the pre-market
7 notification or 510(k) process.

8 So why this tricalcium phosphate
9 originally classified into Class III? At the time of
10 the enactment of the Medical Device Amendments in
11 1976, tricalcium phosphate for dental use was
12 regulated as a new drug requiring a new drug
13 application or NDA. Under the 1976 amendments,
14 Congress identified transitional devices, meaning
15 those devices previously regulated as new drugs into
16 Class III requiring a pre-market approval application
17 or PMA.

18 The transitional provisions were designed
19 to assure that devices formally considered as new
20 drugs continued to be subject to appropriate
21 regulatory controls. The final regulation for this
22 device was published on August 12, 1987 and classified

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1 tricalcium phosphate granules for dental bone repair
2 into Class III as a transitional device. The Agency
3 has approved one PMA or pre-market notification
4 application for Beta Tricalcium Phosphate.

5 So how is tricalcium phosphate regulated
6 in other branches in the Center for Devices and
7 Radiological Health or CDRH? In the Orthopedic and
8 Restorative Branches within CDRH, tricalcium phosphate
9 is an unclassified device. For these branches, the
10 regulatory history is different, in that tricalcium
11 phosphate was not identified as a new drug at the time
12 of the enactment of the Medical Device Amendments, and
13 thus was not automatically classified into Class III
14 as a transitional device. The transitional list was
15 specific for dental bone repair.

16 The Orthopedic and Rehabilitation Panel
17 met in January 1998 and recommended that calcium
18 sulfate bone void filler be classified into Class II,
19 and on February 7, 2002 a proposed rule was published
20 in the Federal Register proposing to classify the
21 resorbable calcium salt bone void filler device into
22 Class II. This included Beta Tricalcium Phosphate.

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1 Dr. Betz, who will present next, will
2 provide a review of the petition and present a table
3 outlining the risks and mitigations for your
4 consideration. Dr. Betz?

5 DR. BETZ: Good morning. On November 12,
6 2002, Dr. Vincent Morgan submitted a petition for the
7 reclassification of Beta Tricalcium Phosphate or Beta
8 TCP. A revision of this petition dated April 5, 2002
9 was reviewed by the Dental Branch of the Office of
10 Device Evaluation. On 9 December 2002, the FDA
11 received a letter from Dr. Morgan requesting that the
12 petition be modified. The requested modification was
13 to change the final classification of Beta TCP in the
14 petition from unclassified to Class II.

15 The petition contains 11 sections,
16 including appendices. Section I is the Specifications
17 Section. This section describes Beta TCP, identifying
18 physical properties, such as formula weight density
19 and melting point, as well as identifying its Chemical
20 Abstract Service or CAS number as 7758-87-4.

21 Section II is the Statement of Action.
22 This is Dr. Morgan's request to reclassify the Beta

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1 TCP. Dr. Morgan's letter of December 9, 2002 modifies
2 this request changing the final classification to
3 Class II with special controls.

4 Section III is an FDA Supplemental Data
5 Sheet, FDA form 3247. Dr. Morgan identified the
6 indication for use as that of a bone substitute.
7 Risks identified included infection and pyrogenic
8 response. The information upon which the request for
9 reclassification is based are that Beta TCP has been
10 successfully used in medicine and dentistry for over
11 20 years, and that its properties are known to be
12 beneficial when used as a bone substitute.

13 Section IV is also Appendix II. This
14 section is the FDA General Device Classification
15 Questionnaire or FDA form 3429. This questionnaire
16 was not updated to reflect Dr. Morgan's December 9,
17 2002 request for a change in final classification.
18 Therefore, there is an inconsistency between the
19 letter and form 3429. This afternoon you will be
20 asked to complete this form as part of your discussion
21 and deliberation.

22 Section V is the Basis for Disagreement

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1 with the present classification. It includes the
2 following: Beta TCP has been successfully marketed
3 for over 20 years for dental purposes; Beta TCP is
4 presently a Class III device for dental indications
5 requiring a pre-market approval or PMA. However, it
6 has been cleared for market by pre-market notification
7 or 510(k) when used for other purposes, such as
8 orthopedic applications; and finally, no clinical
9 adverse events have been reported.

10 Section VI contains the Reasons for
11 Reclassification, which were a reiteration of
12 statements made in Section V. Appendix III includes
13 copies of published articles the petitioner submitted
14 to support claims of safety and effectiveness for Beta
15 TCP.

16 In Section VII, the petition states that
17 there are no known unfavorable clinical data.

18 FDA has found in its databases only one
19 reported adverse event related to calcium phosphate
20 compounds. When an unspecified calcium phosphate
21 compound was injected into the vein of a pig, blood
22 clots formed. This is the only adverse event within

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1 our database. In this report, a calcium phosphate
2 compound was injected intravascularly rather than
3 being placed in an intraosseous location.

4 The FDA believes that this report has
5 little or no relevance to the use of tricalcium
6 phosphate in periodontal or craniofacial applications,
7 especially when placed in humans. Again, there have
8 been no adverse events reported to FDA.

9 Section VIII is a Summary of New
10 Information, which is Appendix IV. This information
11 is from a Medline search of data three years old or
12 less.

13 In Section IX, Dr. Morgan indicated that
14 there were no source documents to be submitted
15 relevant to this petition. Appendices III and IV
16 contain information that would normally be included in
17 the section.

18 Section X was the Financial Certification/
19 Disclosure Statement, which stated that Dr. Morgan has
20 not received any compensation for any clinical studies
21 associated with the product. He also stated that he
22 will not have an equity interest in the product.

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1 Section XI contains the appendices, which
2 were included and reviewed as Section III, IV, VI and
3 VIII.

4 To summarize, Beta Tricalcium Phosphate is
5 a calcium phosphate salt that has the same intended
6 uses and is similar to legally marketed dental bone
7 void filler and grafting materials such as: Plaster
8 of Paris (like Capset); Hydroxyapatite (like Hapset);
9 Ceramics (like Bio Oss Ceramic). Beta TCP has been
10 successfully used in orthopedic applications without
11 reports of adverse events. Beta TCP is presently
12 unclassified for orthopedic and general restorative
13 purposes. It has been recommended for placement into
14 Class II by the Orthopedics Device Panel. Publication
15 of the Final Federal Register Notice to this effect is
16 pending. We hoped that would be done by the Panel
17 today so I didn't have to say that, but that's not
18 true.

19 Finally, Beta TCP has been cleared under
20 510(k) regulation for use in dentistry at
21 concentrations less than 50 percent for quite some
22 time, again without adverse events. FDA frequently

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1 uses guidance documents to communicate to sponsors and
2 the general public information that FDA believes is
3 important in their review of 510(k) submissions. The
4 headings above, on the screen, represent section
5 headings within guidance documents previously released
6 by FDA.

7 One of the sections of FDA's forthcoming
8 bone void filler bone grafting material guidance
9 document will be a table of risks encountered when
10 bone void filling or bone grafting materials are
11 placed in oral and craniofacial applications. Because
12 tricalcium phosphate bone void fillers are similar to
13 other bone void fillers, presently cleared under
14 510(k) regulations, the risk table that FDA is asking
15 you to review today may also be used within our
16 forthcoming bone void filler or bone grafting material
17 guidance document.

18 This table of risks is proposed for you to
19 discuss and consider in the decision making process to
20 place Beta tricalcium phosphate into another
21 classification. Identifying these risks should help
22 you determine whether general controls or special

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1 controls are needed to assure safe and effective use
2 of tricalcium phosphates or whether they should remain
3 in Class III.

4 In your deliberation, please, feel free to
5 add, delete and modify this risk table as you see fit.

6 Your recommendation, whatever it may be, should be
7 based in part on this risk table. The risks include,
8 and this is a two part table: Surgical risks; risks
9 related to bone or soft tissue infections; adverse
10 tissue reactions; problems associated with bone
11 formation; failure to osseointegrate; problems
12 associated with device migration or extrusion; and
13 weakness in newly formed bone.

14 On the right, you see the mitigations that
15 we propose for you to consider also to mitigate these
16 risks. This entire table will be displayed in its
17 entirety in one piece for your discussion. Now, we
18 get to the Panel questions.

19 Does the petition, as filed, adequately
20 describe the risks to health when using the device and
21 provide appropriate controls for these risks? If yes,
22 you're supposed to proceed to Question 3. If no, you

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1 proceed to Question 2.

2 Question 2 is what modifications would you
3 make to the risks to health presented by these
4 devices? The second part of Question 2 is what
5 controls for these risks would you recommend to
6 provide a reasonable assurance of safety and
7 effectiveness? And then you proceed onto 3.

8 Question 3 is, please, complete the
9 Classification Questionnaire and Supplemental Data
10 Sheet for the device. Completion of these forms will
11 provide a formal recommendation for the
12 reclassification of tricalcium phosphate granules for
13 dental bone repair. Again, 21 CFR 872.3930. And then
14 to Question 4.

15 Question 4, given your recommended
16 classification, what changes, if any, would you
17 recommend be made to the labeling? Your
18 recommendations could include directions for use,
19 indications for use and contraindications and anything
20 else that you feel appropriate. Thank you.

21 CHAIR REKOW: Does anyone have any
22 questions for Dr. Betz before he sits down?

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1 DR. GLOWACKI: I have a question for Dr.
2 Mulry.

3 CHAIR REKOW: Or for Dr. Mulry. Go ahead,
4 please.

5 DR. GLOWACKI: Mr. Mulry, do I have
6 control over turning this on?

7 CHAIR REKOW: No, I think it will take
8 care of it.

9 DR. GLOWACKI: It will come on
10 automatically? Can you set the stage for the Panel's
11 deliberation, because you've described the existing
12 reg as including all calcium phosphates, and I heard
13 you say for the support of dental implants and
14 materials having the composition of 50 percent of TCP
15 on one hand. And then the petition on the other hand
16 concerns Beta TCP for a specific application that is
17 distinct from the current regs. So can you set the
18 stage on how we're to do the reclassification, because
19 I thought I heard you say we're going to reclassify
20 the whole thing for dental implants, supporting the
21 dental implants and with the 50 percent, and that the
22 application, the petition, is much more confined.

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1 DR. MULRY: Okay. Let me see if I can
2 answer that. First of all, let's look at the
3 regulation, the current regulation 21 CFR 872.3930,
4 which is entitled "Tricalcium Phosphate Granules for
5 Dental Bone Repair." It's identified and the
6 definition is "A device intended to be implanted into
7 the upper or lower jaw to provide support for
8 prosthetic devices."

9 This discussion today, as to whether it is
10 reclassified from Class III to Class II, deals with
11 the total regulation, and that regulation includes all
12 forms of tricalcium phosphate, although, the petition
13 is entitled "Reclassification of Beta Tricalcium
14 Phosphate." So what you'll need to decide is in the
15 petition there is additional supporting information
16 about other forms of tricalcium phosphate, besides
17 Beta Tricalcium Phosphate. What you need to decide
18 today is is there sufficient information for you to
19 make a recommendation to either have the whole
20 regulation moved to Class II, meaning all forms of
21 tricalcium phosphate, or whether you want to separate
22 out Beta Tricalcium Phosphate alone to be reclassified

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1 into Class II.

2 DR. GLOWACKI: Does that also mean all
3 physical forms like granules, blocks?

4 DR. MULRY: Yes. It would include all
5 forms of tricalcium phosphate.

6 DR. GLOWACKI: Okay.

7 DR. MULRY: The other aspect of your
8 question was about the Dental Branch's policy decision
9 to regulate bone void fillers that are less than 50
10 percent Beta Tricalcium Phosphate as pre-market
11 notification or they are unclassified and also
12 reviewed under the 510(k) process. And that was a
13 policy in an administrative position that was made
14 looking at whether combining tricalcium phosphate with
15 other bone void fillers would present maybe different
16 questions or would be more appropriately put in with
17 the other bone void fillers, because this tricalcium
18 phosphate has been separated out only because of its
19 transitional device status. All the other bone void
20 fillers have been grouped together.

21 So I think the policy decision related to
22 looking at well, if it's less than 50 percent Beta

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1 Tricalcium Phosphate, then it may more appropriately
2 have been regulated with all the rest of the bone void
3 fillers. And, Dr. Runner, you may have a comment on
4 that.

5 DR. RUNNER: I don't know the history of
6 why that happened, but it happened and we have
7 multiple applications of products that have HA and
8 Beta TCP in less than 50 percent concentration.

9 DR. GLOWACKI: My understanding is that
10 those are biphasic materials not additives, not added
11 in, manufactured in a way to render them biphasic,
12 even a solid.

13 DR. RUNNER: I believe that's correct.

14 DR. MULRY: Yes.

15 DR. GLOWACKI: And I mean, that's very
16 helpful. This goes back to the slide that Dr. Betz
17 showed about does the petition as filed describe the
18 risks to the health? So in one hand we're being asked
19 questions that relate to the petition.

20 DR. MULRY: Yes.

21 DR. GLOWACKI: And yet we have to answer
22 questions related to the reg.

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1 DR. MULRY: Right.

2 DR. GLOWACKI: Am I understanding this
3 correctly?

4 DR. MULRY: Yes, you are. And I think in
5 looking at reclassifying the total reg, as I said in
6 my presentation, I think it needs to be remembered
7 that if a form of tricalcium phosphate other than Beta
8 Tricalcium Phosphate were to be submitted to the
9 Agency, we would have the option of asking for data,
10 supported data, to help us make a decision whether it
11 is Class II or Class III.

12 DR. BETZ: I would also like to make a
13 comment as a periodontist. It would also include bone
14 grafting materials, as well as bone void fillers, used
15 in periodontal indications.

16 DR. GLOWACKI: Even though --

17 DR. BETZ: Craniofacial defects,
18 periodontal defects and in general.

19 DR. RUNNER: Well, I think you're talking,
20 you're discussion indications and we're talking about
21 the regulation of the product itself. Each individual
22 application comes in with an indication for use, and

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1 then we are charged with looking at that indication to
2 see if it requires additional clinical data, etcetera.

3 So the indications need to be --

4 DR. GLOWACKI: So just the title of the
5 reg saying that it's for support.

6 DR. RUNNER: Right.

7 DR. GLOWACKI: Prosthetic devices.

8 DR. MULRY: Right.

9 DR. GLOWACKI: -- is not something that we
10 take hard and fast.

11 DR. RUNNER: Right, exactly.

12 DR. GLOWACKI: We're talking about other
13 indications?

14 DR. RUNNER: Correct.

15 DR. MULRY: It was a generic term or
16 definition from 1976. We're a little bit more
17 sophisticated now, I hope.

18 DR. GLOWACKI: That's very helpful. Thank
19 you.

20 CHAIR REKOW: Because I was about to make
21 the same mistake, we need to help for the people that
22 are doing the transcription when we begin to speak, to

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1 identify who we are. So this is Dr. Rekow. And I
2 have a question for Susan or either of you gentlemen.

3 Something that you said was the petition is the Beta
4 TCP, we could talk about all TCPs. Are we talking
5 about all calcium salts of all genres? Are we going
6 to stick to the TCP?

7 DR. MULRY: No, specifically, TCP.

8 CHAIR REKOW: Okay.

9 DR. MULRY: This is regulation, because
10 this was separated out as the only bone void filler in
11 the dental arena that was regulated as a new drug
12 prior to the 1976 amendments.

13 CHAIR REKOW: Right.

14 DR. MULRY: We need to limit this
15 discussion today just to the regulation of tricalcium
16 phosphate, as defined in the CFR.

17 CHAIR REKOW: Thank you.

18 DR. MULRY: You're welcome.

19 CHAIR REKOW: Are there other questions
20 from the Panel? Okay. I believe we then go on to the
21 presentation by the sponsors. Dr. Morgan, are you
22 taking responsibility?

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1 DR. MORGAN: If you wish.

2 CHAIR REKOW: I suspect you probably are
3 the best person to represent them.

4 DR. MORGAN: Well, I will define that. My
5 name is Vincent Morgan, and we brought this petition
6 because we deemed the current classification to be an
7 oversight of the Agency, and I believe logical
8 scientific thought would agree with that process.
9 Because of the fact that it's just inconsistent to
10 think that an orthopedic surgeon has the capability of
11 placing tricalcium phosphate or a maxillofacial
12 surgeon could not, to me, osteoblast and osteocyte, so
13 the regulation is inconsistent with the reality of
14 biology.

15 So to that end, there's also evidence,
16 historical evidence, that I shall not go into it, I
17 spoke to Susan about, and that's my position. Just to
18 have you look at it as an oversight on the
19 regulations. Thomas Driskell is here to follow this
20 discussion, who, in fact, is the person who developed
21 this product in the 1970s and is the person who wrote
22 initially a PMA and subsequently a 510(k) for the

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1 Miter Corporation, so he can speak to the history of
2 it better than all of us. And then Dr. John Long will
3 be producing the product or has produced it and can
4 address the scientific aspects of the chemistry.

5 In addition to the financial statement,
6 since you made this announcement public, I have been
7 contacted by two parties. One is representing a Dr.
8 Lynch in Tennessee who wanted to be included in our
9 presentation in support of this. I declined. The
10 other I was contacted by the Curasan Corporation, a
11 German corporation, and they wanted me to drop my
12 petition or to consider dropping it, and if I were to
13 drop this petition, they would offer me the sole
14 distributorship of their product in the United States.

15 So I declined that, as well. If there's any
16 questions, I would be happy to answer.

17 CHAIR REKOW: Yes, Dr. Patters?

18 DR. PATTERS: Mark Patters. Dr. Morgan,
19 perhaps you could clear up a discrepancy here in my
20 papers. It lists you as president of Bicon,
21 Incorporated.

22 DR. MORGAN: That's true.

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1 DR. PATTERS: Somewhere else it says you
2 have no financial interest in this product.

3 DR. MORGAN: That's true.

4 DR. PATTERS: Are both those statements
5 correct?

6 DR. MORGAN: That's true.

7 DR. PATTERS: I think that requires some
8 explanation. How can you be the president of the
9 company, but no financial interest?

10 DR. MORGAN: I think you'll find the
11 question is do I have any equity interest in the
12 company, and the answer is no.

13 DR. PATTERS: So you're just a paid
14 employee of the company?

15 DR. MORGAN: True.

16 DR. PATTERS: Okay. I would say that's a
17 financial interest.

18 DR. MORGAN: I think the question was
19 equity interest there.

20 DR. PATTERS: Thank you.

21 DR. MORGAN: I would be happy to tell you,
22 I have no equity interest. Equity is a shareholder.

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1 You could be an employee of IBM and not own a share of
2 it. I do not own a share of Bicon, so to clarify
3 that.

4 DR. PATTERS: I know. But I'm asked as a
5 Panel member do I have any financial interest that if
6 your petition was granted, that I would benefit from.
7 That doesn't require that I be an equity holder.

8 DR. MORGAN: Well, I won't debate other
9 than the fact that we answered the question as stated.
10 So if you want to know, I've so disclosed. But I
11 have no equity interest in Bicon.

12 CHAIR REKOW: Dr. Rekow again. You are a
13 paid employee and you stated that clearly.

14 DR. MORGAN: Yes, yes, I have no argument
15 about that.

16 CHAIR REKOW: Okay.

17 DR. BURTON: Dr. Burton. Does Bicon then
18 intend -- because it's still sort of unclear. I think
19 what we're all getting at is what the benefit of doing
20 this, but is Bicon then intending to market a product
21 of this type?

22 DR. MORGAN: If it were, yes.

1 DR. BURTON: If it was reclassified, it
2 would be offering a product. And I guess the question
3 that I would assume Dr. Patters was getting at that as
4 president of the company, the product would have some
5 -- whether you had an equity stake in the company or
6 not, it would still provide some financial incentive
7 to you to have that approved and come to market in
8 whatever classification.

9 DR. MORGAN: Oh, yes. It would to Bicon.

10 But to me personally, I believe the question, I
11 believe I answered it correctly, but if you want me to
12 state that Bicon hopes to have an financial interest,
13 absolutely, but I believe the question that was posed
14 by the FDA is do I have an equity interest. And I
15 think a distinction was made on your behalf today that
16 some of you represent other dental implant
17 manufacturers, other dental implants, but for this
18 particular product you don't. So if you were to
19 represent a competitor of Bicon in any fashion, I
20 would also suggest to you that that's a conflict of
21 interest.

22 However, if you can distinguish between

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1 having representing or your school representing, you
2 may not have an interest, but your school may receive
3 a significant grant, as many do. You don't receive it
4 directly, but your department receives significant
5 funding, then it may be in your best interest to vote
6 against Bicon. So the truth is the truth. The
7 question should be specific.

8 DR. RUNNER: I think that we've developed
9 the answer to the question, so I don't think we need
10 to continue. You know that Dr. Morgan is financially
11 enumerated by the company for which the product will
12 be marketed.

13 CHAIR REKOW: Thank you.

14 DR. MORGAN: Thank you.

15 CHAIR REKOW: So, Mr. Driskell, you have a
16 presentation, please? And would you, please, sir, and
17 the rest of you as you present, would you disclose
18 whatever financial, if you have a financial,
19 investment in the company just for clarity, please.

20 MR. DRISKELL: Okay. I didn't want to
21 show you any pictures particularly, so I don't need
22 that. My name is Tom Driskell. I did invent this

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1 material back in the very early '70s. Regarding my
2 association with Bicon, I have no equity interest. I
3 have no salary from them. I do receive a royalty,
4 because they market products to which I've designed
5 and have patents on, so I do get royalty from them,
6 which I appreciate very much. I'm not paid in any way
7 for what I do. It's just that when it goes on the
8 market, if it makes money, maybe I make some money.
9 Then I appreciate that, because I'm supposed to be
10 retired.

11 I will make this very concise, but I will
12 be happy to answer questions if you wish. Materials
13 oriented research ultimately leading to the
14 development of calcium phosphate structural and void
15 filling materials, bone implant materials I should
16 say, began at Battelle Memorial Institute's Columbus
17 Laboratories in 1968. I was principal investigator of
18 the project. Disappointed with the results of earlier
19 research and development of bio-inert ceramics, which
20 the materials and coatings which began in 1967
21 stimulated this departure into bio-active materials
22 development. I think that was a new term at the time,

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1 but that's what they are is bio-active.

2 In fact, I even came up with a term for
3 it, so it's not osteogenic and it is osteoconductive,
4 but it also will allow bone to grow beyond its normal
5 bounds if you use it as an augmentation material. So
6 I came up with the term osteophilic, which bone likes
7 it and it does. In 1971, three high purity calcium
8 phosphate compounds were selected for in vivo
9 evaluation in rats and rabbits. The three compounds
10 were monocalcium phosphate, dicalcium phosphate and
11 Beta Tricalcium Phosphate.

12 Initial in vivo studies were conducted at
13 the U.S. Army Institute of Dental Research at Walter
14 Reed Army Medical Center. Beta Tricalcium Phosphate
15 proved to be the most promising compound. It was
16 found to demonstrate excellent bio-compatibility
17 reserved resorbed while being displaced by rapid bone
18 ingrowth and as was discovered later in our research
19 could be sintered into a relatively strong structural
20 form.

21 Our original concept was to develop a
22 resorbable bone porous block grafting material for use

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1 as a gap filler in large bony defects and a resorbable
2 particulate form for smaller contained defects. We
3 were successful in developing these concepts in 1971.

4 In vivo research in various laboratories continued
5 and the results have been presented and published over
6 the years. Coatings of these materials were applied
7 to dental implants and successfully implanted in
8 Rhesus monkeys in 1972. There is a joke that goes
9 along with that, but I'll dispense with it for now.

10 These studies and subsequent work by
11 Hubbard, Jarcho, Kay and numerous other researchers
12 resulted in the development of additional variations
13 of calcium phosphate materials and coatings. The
14 substance of this research is the foundation upon
15 which the field of calcium phosphate materials
16 technology and hydroxyapatite coatings has developed.

17 Thank you. Any questions?

18 CHAIR REKOW: I suspect there will be some
19 questions.

20 MR. DRISKELL: All right.

21 CHAIR REKOW: Do you want to stay for just
22 a minute, please?

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1 DR. GLOWACKI: I'm not a chemist, so
2 forgive me if I don't ask the question, this is Dr.
3 Glowacki, if I don't pose the question in the precise
4 terms that you are used to. We know that the Beta
5 Tricalcium Phosphate, at least what we read in the
6 books, is resorbable material and that the
7 hydroxyapatites are dense ceramics with the different
8 type of crystallinity and are far less resorbable.

9 My question is whether there is control
10 over the degree of resorption in the class that we're
11 calling the Beta Tricalcium Phosphates? What I
12 understand is that after preparing the material that
13 there's an amount of compression and sintering in
14 order to make it into the granular form, small
15 granules, large granules or blocks. Do those
16 processes give you a consistent rate of resorption an
17 how dependent is the rate of resorption on compression
18 and temperature of sintering?

19 MR. DRISKELL: Okay. Well, I think it
20 probably does have quite an effect. The denser it is,
21 the more material that's there. It obviously is going
22 to take longer to resorb. The largest factor is quite

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1 possibly the particular proclivities of the patient.
2 For example, if you have a person that is not
3 particularly hale or hearty, I hate to say it but
4 post-menopausal women, people who have some sort of an
5 ongoing illness or something that affects their
6 health, the resorption would probably be slower. That
7 is one of the inconsistencies of it as you really are
8 not sure how long it will take.

9 But I can tell you that in a healthy
10 patient, it heals pretty quickly, anywhere from within
11 six months to a year. And as the material does
12 resorb, it is immediately replaced by bone in those
13 areas, because actually osteocytic -- well, the
14 osteocytes seem to osteoblast, I'm sorry.
15 Osteoclastic activity seems to be the major cause of
16 resorption of the material. And it is resorbed and
17 broken down into calcium phosphorous, which is already
18 in the body, which I think accounts for the lack of
19 side effects. It's a material that is basically
20 already there.

21 DR. GLOWACKI: So there is patient to
22 patient variability. But let's talk about animal

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1 studies where there may be more consistency with
2 respect to the recipient.

3 MR. DRISKELL: Yes.

4 DR. GLOWACKI: If you put material that
5 came from one batch of preparation of a Beta
6 Tricalcium Phosphate compared to another batch in
7 similar types of animals, is there a wide range of
8 resorbability on the basis of the manufacturing
9 process?

10 MR. DRISKELL: Well, presuming that you
11 have adequate controls over the manufacturer, there
12 shouldn't be any appreciable differences. Again, with
13 the exception of the relative hale and heartiness of
14 the critter that you're putting it in. But really,
15 you have to have a good manufacturing process. It is
16 not a simple material to make, and we have been very
17 careful over the years in making it and being
18 consistent in the process, because things like that
19 can affect the resorption. No doubt about it.

20 DR. GLOWACKI: And -- I'm sorry.

21 MR. DRISKELL: Well, as I say, it can vary
22 from patient to patient. But the thing to keep in

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1 mind is that the structural integrity is still there
2 to a fair degree, because the bone actually does bond
3 to the material. It is not just a resorption as the
4 material disappears the bone just fills in. The bone
5 has already bonded to it. I have scanning electron
6 microscopy that shows that very nicely.

7 DR. GLOWACKI: So with respect to the
8 careful manufacturing steps then, are there tests that
9 are done at the end of the manufacturing to say, you
10 know, this is a batch that's going to have the same
11 physical properties as the previous batch?

12 MR. DRISKELL: Well, actually, the way it
13 is made pretty well controls what it is going to be.
14 And if you follow the parameters of how it should be
15 made, of course the chemistry of it you can do with x-
16 ray faction patterns and that sort of thing, but
17 frankly over the years of personally making it, I
18 never really found any discrepancy, because of the way
19 that we ran the materials. We sieve them. And we
20 have the same particulate size that's used all
21 throughout the whole process. So the variations in
22 the manufacturing process are very, very slight,

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1 because we just are very careful with what we do.

2 CHAIR REKOW: Can I perhaps ask the
3 question with a slightly different spin?

4 MR. DRISKELL: Okay.

5 CHAIR REKOW: For a fixed manufacturing
6 and sintering regime, can you give us some sense of
7 the range and variation you would expect in the
8 important parameters?

9 MR. DRISKELL: I think I'll let our
10 chemist answer that.

11 CHAIR REKOW: Okay.

12 MR. DRISKELL: I think that might be the
13 person.

14 CHAIR REKOW: We'll put that question on
15 hold.

16 MR. DRISKELL: If you don't mind?

17 CHAIR REKOW: No.

18 DR. GLOWACKI: That's fine. I just wanted
19 to give you, you know, coming from the questions, I
20 can't quite picture in the manufacturing how you get
21 granules of different sizes.

22 MR. DRISKELL: Oh.

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1 DR. GLOWACKI: You applied just now that
2 you just sort of pressed them and crushed them and
3 sinter them, and then you sieve them to separate them.

4 MR. DRISKELL: Well, we do do that, and we
5 sieve them so that we have a certain particle size,
6 both plus and minus, so that we have a certain
7 particulate that we use, and that is pretty
8 consistent.

9 DR. GLOWACKI: Thank you.

10 MR. DRISKELL: So we don't have a problem
11 with that.

12 CHAIR REKOW: Jon, did you have a
13 question? Jon first and then you David, please.

14 DR. COCHRAN: Okay.

15 DR. SUZUKI: Okay. Jon Suzuki, FDA Panel
16 member. You used the word osteophilic to describe and
17 relate to your product.

18 MR. DRISKELL: Yes.

19 DR. SUZUKI: And could you just
20 differentiate osteophilic versus osteoconductive and
21 make that definition?

22 MR. DRISKELL: Well, the osteophilic

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1 materials are always osteoconductive, but
2 osteoconductive is more of a passive term.
3 Osteophilic means that it seems to have -- by the way,
4 we don't claim that. But we have noticed and I'll
5 give you an example. In some of our orthopedic
6 studies in earlier years, we put some block form
7 material, this was porous block form, in the femurs of
8 dogs and these were fairly large. I can't remember
9 the exact size, but they were probably 25 millimeters
10 or 30 millimeters in length, maybe even longer than
11 that come to think of it.

12 But they stuck above the bone by 10
13 millimeters, and so only the lower part of that
14 implant was actually implanted in a cut, a defect that
15 was created in the bone, and we got bone all the way
16 to the top. So that's 10 millimeters beyond the
17 normal bounds of a long bone. So I think there is
18 something in there, but it does not -- we do not claim
19 anything as far as being osteogenic or anything. I
20 don't think it is. But osteophilic it does seem to be
21 from the standpoint that it will cause bone to grow
22 into an area that it wouldn't normally be expected to

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1 grow into. Now, whether that bone would stay over a
2 long period of time, I doubt it, because there's no
3 reason for it being there. But it does grow in there.

4 DR. SUZUKI: Jon Suzuki again. Just one
5 follow-up question. Then osteophilic to me, at least,
6 implies there is no adverse reactions like immune
7 rejection or anything like that, but you're not making
8 that claim?

9 MR. DRISKELL: Well, actually, I have
10 never seen any immune rejection. Honestly, I have
11 never known anything like that. The only thing that
12 we have ever seen was an occasional infection, and
13 those are going to happen I don't care what you use,
14 but that's all I can say. That this never has any
15 sort of an immune response or anything like that.

16 CHAIR REKOW: Dr. Cochran?

17 DR. COCHRAN: David Cochran. My question
18 centers around the indications for this material. As
19 you have alluded to, when you put in a bony site you
20 see osteoclastic resorption, macrophage resorbate, but
21 in many of the indications in the oral cavity that we
22 use today, and especially the particulate material,

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1 sometime it gets fibrous and capsulated. There's
2 fibrous tissue that will encapsulate the particles.
3 Can you tell us how that might be resorbed and is that
4 a slower process or how is that turned over?

5 MR. DRISKELL: It would be, but I would
6 like to know precisely what you're talking about,
7 because I know, for example, the hydroxyapatite that's
8 not uncommon. But if it is actually in contact with
9 fresh bleeding bone, and you know, to a reasonable
10 degree, I mean, I'm not sure I want to give you the
11 total definition of that, but if it's just sitting on
12 top of some abraded bone, it might or might not fill.

13 I do have histology, though, on say a ridge
14 augmentation which has, as you know, become a very
15 equivocal thing as to whether you really ought to do
16 that. But I can show you absolutely gorgeous bone in
17 a year, and there's very little of the tricalcium
18 phosphate left. It's just solid bone. So again, it
19 has to be in contact with fresh bleeding bone to make
20 it work.

21 CHAIR REKOW: Are there any other
22 questions? Thank you, sir.

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1 MR. DRISKELL: You're welcome.

2 CHAIR REKOW: Dr. Long, would you, please,
3 again identify yourself and your potential conflict of
4 interest?

5 DR. LONG: My name is John Long. I'm the
6 director of technology at GFS Chemicals in Columbus,
7 Ohio. I have no equity, financial or other personal
8 interest, other than as a supplier, of tricalcium
9 phosphate to Bicon. We are a private company. We
10 have been in the same location in Columbus since 1928.

11 We're in the third generation of family management.
12 The letters in the company name GFS come from the
13 professor of analytical chemistry, who founded the
14 company. He was at the University of Illinois. And
15 over the years he developed many analytical reasons
16 that his colleagues were interested in and eventually
17 formed the company with his brothers, because he and
18 his graduate students could not keep up with the
19 bucks.

20 We had specialized in high purity and
21 materials for analytical markets over the years,
22 branched off into some other things as well. In the

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1 1960s when the Apollo Program was in full force and
2 NASA was looking for high purity acids to use in the
3 analysis of lunar samples, our company was contacted
4 to produce high purity perchloric acid for the
5 digestion of those samples. So we have a long history
6 of working with very high purity materials.

7 The Beta Tricalcium Phosphate is made in a
8 dedicated room in our facility. We've got about 15
9 buildings on our plant site in Columbus, Ohio. Within
10 one of those buildings there is a room dedicated to
11 its production as well as dedicated equipment, ovens,
12 various other parts of the operation are confined to
13 that one room. We are ISO-9000 certified, which means
14 we have the traceability and accountability with our
15 computer system to govern the batches of the material
16 that are produced and to provide whatever information
17 might be needed to look at vendor data, vendor lot
18 information, our lot information, finished goods
19 information, analytical information that are connected
20 to a given batch.

21 The material is qualified by a number of
22 things. It requires a very particular calcium

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1 phosphorous ratio that is governed in the
2 manufacturing steps. It also can be confirmed by
3 analytical methods after it is made. The primary
4 analytical method is x-ray diffraction. It allows you
5 to determine that the proper phase, the Beta phase of
6 tricalcium phosphate is present, usually to the
7 exclusion of all other phases. We have made this
8 material a couple of times.

9 We have been visited by a Cincinnati
10 representative of the FDA, who came and discussed with
11 us what our process was. He looked at our facility.
12 He looked at our equipment. And as we get into the
13 further production of this material, he will be
14 available to oversee its operation, so we have been in
15 contact with a gentleman named Jeffrey Sincek at the
16 Cincinnati Office of the EPA. So we are in the
17 position to produce this material in significant
18 quantities and are pleased to be able to support Bicon
19 in this petition. I'll be happy to answer any
20 questions that you might have.

21 DR. GLOWACKI: I'll ask you a question
22 then. This is Dr. Glowacki. Good morning, Dr. Long.

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1 Can you paint a picture then of the differences in
2 the actual crystal structure as one varies the
3 formulations? I'm talking about making granules
4 versus, can I use the word, casting a larger block
5 with a particular shape?

6 DR. LONG: Sure.

7 DR. GLOWACKI: Does the casting or does
8 the, I'm calling it compression, you'll give me the
9 correct technical words, compression and sintering to
10 make different forms of it give you materials with 100
11 percent similar x-ray diffractions or is there some
12 modification due to the preparation of different
13 forms?

14 DR. LONG: The x-ray part of diffraction
15 defines the microscopic property of the material.
16 It's based upon the repeating array of unit cells in
17 the solid. This could occur with particles of various
18 sizes. It's not a function of particle size, but you
19 do have to grind the material to get a powder to be
20 able to do the x-ray effectively. So if you have
21 carried out your synthetic process properly,
22 regardless of the number of times or the nature of the

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1 compression of the material, when you grind it to get
2 the x-ray powder pattern, it will tell you whether you
3 have the Beta phase or if you have mixed phases.

4 It requires a very particular temperature
5 in order to achieve the Beta phase. If you miss that
6 temperature, the x-ray will show you that you have
7 impurities present and the product is not properly
8 qualified. This is done after all the processing,
9 after the compression, after the grinding, so in that
10 sense the x-ray testing is independent of all of that
11 until you get it ground and you can put it on the
12 machine and look at it.

13 DR. GLOWACKI: Thank you. Now, with
14 respect to the point about the rate of resorption,
15 because people are always asking in journal articles
16 and reviewing articles in presentations, you know,
17 what about the rate of resorption? In your view, does
18 the rate of resorption in an animal model where there
19 is consistency in the recipient tissue, are there
20 differences in the rates that are due to casting the
21 blocks or making or getting granules that have been
22 ground up to greater or lesser degrees that can

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1 influence the rate of resorption because of something
2 that can be measured, because of some physical
3 property?

4 DR. LONG: My opinion, which is not
5 necessarily an expert opinion in your area, but my
6 opinion is that you're talking about a microscopic
7 property, especially the ability of blood to flow
8 through the microcrystalline structure of the
9 material. And do me, that is independent of most
10 aspects of the processing that we do. Once the
11 material is cast and there is pressure applied, you
12 produce a bulk material and you grind that material
13 into the final form.

14 Once you produce that material, you have
15 created a microcrystalline property that is
16 identifiable by x-ray in the Beta form, which
17 according to what Mr. Driskell says in all the studies
18 that have been done, allow this porosity, blood flow,
19 this clinical action that enables it to perform as it
20 does. I don't see that variations leading up to the
21 final step would significantly change the property of
22 the material, as long as you fire it to the right

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1 temperature and get the Beta phase, that's the key
2 aspect. If you have different phases in there, the
3 microcrystalline property is changed and it will
4 effect the blood flow in the resorbability of the
5 material.

6 DR. GLOWACKI: Thank you.

7 CHAIR REKOW: Okay.

8 DR. BURTON: You spoke of your plant in
9 Columbus. Do you currently manufacture this product
10 for other companies, other than Bicon? You know, you
11 said you had a dedicated facility for this. I mean,
12 it must be going somewhere.

13 DR. LONG: We have only manufactured this
14 up to this time for Bicon. We have had discussions
15 with a couple of other companies about calcium
16 phosphates of various types. We are interested in the
17 Beta phase and we have had contact with other
18 companies about the Alpha phase and about
19 hydroxyapatite. To this point, we have not made any
20 of those phases. We have made no commitment with any
21 other companies about any of those materials. We have
22 only made the Beta phase for Bicon.

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1 DR. BURTON: Okay. So we've mentioned the
2 fact that there are dental products that contain less
3 than 50 percent, and those are manufactured by some
4 other companies then?

5 DR. LONG: To my knowledge, yes. The
6 material that we have produced has shown well over 95
7 percent Beta phase. In fact, the x-ray that we have
8 seen has shown no contamination. It would lead me to
9 believe it's 98 to 99 percent. The more pure it is,
10 the more efficient it is going to be in its function.

11 DR. BURTON: Yes.

12 DR. LONG: I think it would still function
13 below 95 percent, but the specification will be a
14 very, very clean x-ray.

15 DR. BURTON: Okay.

16 CHAIR REKOW: Jon?

17 DR. SUZUKI: Jon Suzuki, Panel member.
18 Just for my own edification, I'm not a chemist. Can
19 you just highlight the differences between Beta and
20 the other forms of TCP?

21 DR. LONG: Okay. Hydroxyapatite is not a
22 strictly a calcium phosphate. You're looking at a

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1 formula of CA3 PO4 taken twice for tricalcium
2 phosphate. The hydroxyapatite has hydroxyl groups on
3 it, as the name applies, and it is not a pure phase,
4 single phase TCP. The Alpha and the Beta forms are
5 distinguished simply by the difference in temperature
6 to which they are taken in their final step.

7 A few dozen degrees too high or too low in
8 this step, you will not have pure Beta phase. You
9 will either have a mixture of Alpha and Beta or you
10 could revert to Alpha, and that simply represents the
11 three dimensional array in which all the phosphates
12 and all the calciums align themselves. They can be
13 aligned in more than one way. And the temperature
14 allows you to fix the way in which all the elements
15 that are present are aligned. So that's the primary
16 difference between the two is the temperature to which
17 it is taken and its final sintering step.

18 DR. SUZUKI: Thank you.

19 CHAIR REKOW: Can I ask one more? Dianne
20 Rekow, I'm sorry. Can I ask one more question? You
21 have some quality assurance specifications. Can you
22 give us some sense of the percentage of tolerance

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1 control you are able to get? I don't think you need
2 to disclose what you are measuring, but are you
3 holding things to 1 percent, 20 percent, you know, 200
4 percent? I'm being facetious clearly.

5 DR. LONG: We would be very comfortable
6 talking about a percent purity in the high 90s. Now,
7 you're talking -- there's various ways of defining
8 chemical purity.

9 CHAIR REKOW: Let me interrupt.

10 DR. LONG: Yes.

11 CHAIR REKOW: I'm asking more about any
12 physical properties you might measure, rather than the
13 purities.

14 DR. LONG: There are density
15 specifications. There is a particle science
16 specification. There is a calcium phosphorous ratio,
17 which can be a specification, and that can be managed
18 by careful blending of the starting materials. Then
19 there is the x-ray, which is the primary
20 specification. We use an independent laboratory to
21 provide that information.

22 CHAIR REKOW: Okay.

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1 DR. LONG: The other testing we can do on
2 site. We do not have x-ray diffraction on our site,
3 so we usually use the Ohio State facility in Columbus.
4 So there is a distinct set of parameters that are set
5 up in our computer for qualifying the material.

6 CHAIR REKOW: Okay.

7 DR. LONG: And we also qualify starting
8 materials, as well.

9 CHAIR REKOW: Okay. Susan?

10 DR. RUNNER: Just a comment that when we
11 do get applications on these types of materials that
12 is the sort of information that we request.

13 CHAIR REKOW: Okay. Thanks.

14 DR. GLOWACKI: I have one question, too.

15 CHAIR REKOW: Yes?

16 DR. GLOWACKI: This is Dr. Glowacki. Do
17 you provide sterile product to Bicon?

18 DR. LONG: Which product, ma'am?

19 DR. GLOWACKI: Sterile.

20 DR. LONG: Sterile products, no. At this
21 point, the product that we provide was not sterile.
22 We can develop those capabilities if that turns out to

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1 be part of what Bicon would desire. To this point, we
2 have not.

3 DR. GLOWACKI: Thank you.

4 CHAIR REKOW: Thank you.

5 DR. LONG: Yes.

6 CHAIR REKOW: Are there other questions
7 for any of the three company representatives? I'm
8 told that Dr. Morgan has to leave by noon, so perhaps
9 we can continue if there's no more questions right
10 this minute, but keep in mind that we have a time
11 issue that we'll need to make sure that we pick his
12 brain sufficiently before he disappears.

13 Shall we take a five minute break, maybe
14 six minutes?

15 (Whereupon, at 10:38 a.m. off the record
16 until 10:50 a.m.)

17 CHAIR REKOW: If we could, please,
18 reconvene? I understand that Dr. Boyan is unable to
19 attend today. She was going to make a presentation on
20 behalf of the American Academy of Dental Research.
21 The next speaker who has agreed to provide some
22 information is Dr. Mark Reynolds, who is speaking on

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1 behalf of the American Academy of Periodontology and I
2 will let him introduce his academic credentials and
3 his potential conflicts of interest. Please, Mark,
4 good morning.

5 DR. REYNOLDS: Good morning. Thank you
6 very much for this opportunity to address the Panel.
7 I am an associate professor and director of the Post-
8 Doctoral Residency and Periodontist at the University
9 of Maryland. To my knowledge, I have no conflicts of
10 interest or vested interest in Bicon or any other
11 manufacturers related to this issue.

12 On behalf of the American Academy of
13 Periodontology, I would like to make several
14 statements regarding the position of the academy with
15 respect to this issue of reclassification. Following
16 this presentation, at the request of the Panel, the
17 AAP will be delighted to provide additional and
18 specific scientific documentation to support any of
19 the points that I raise this morning.

20 We speak in support of the
21 reclassification of Beta Tricalcium Phosphate as a
22 Class II device based on both scientific and clinical

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1 considerations. Clearly there are numerous
2 publications that document both the clinical
3 effectiveness and safety of Beta TCP granules that we
4 use as a bone substitute in periodontal applications.

5 Moreover, there is emerging literature
6 from outside the United States that continues to
7 provide additional information on the safety and
8 clinical efficacy in use of Beta Tricalcium Phosphate
9 and other applications including sinus augmentation.
10 These observations and documentation coupled with
11 similarities and clinical and safety profiles that
12 have already been established for other legally
13 marketed ceramic bone grafting materials argue
14 strongly for reconsideration of the current
15 classification of tricalcium phosphate.

16 We feel that the reclassification of TCP
17 should result in greater public access to this bone
18 replacement material. Although there are other
19 materials such as allogeneic bone replacement grafts,
20 there are considerations that limit their use and
21 acceptance by the public. Furthermore, the clinical
22 characteristics of other alloplastic and grafting

1 materials also place limitations on the clinical
2 indication and use within the community.

3 Although Beta Tricalcium Phosphate shares
4 similar physical and chemical characteristics and
5 properties with other marketed dental grafting
6 materials, we feel that the inherent properties, both
7 handling and otherwise, may afford clinicians with a
8 broader range of bone replacement materials for use in
9 clinical practice. It appears that in the axis of a
10 510(k) mechanism, cost-benefit considerations will
11 continue to deter manufacturers from bringing this
12 device to market, ultimately impairing practitioner
13 and patient accessibility to this technology.

14 Finally, there is increasing recognition
15 that future advances and repair to medicine including
16 periodontal and alveolar regeneration will require the
17 adjunctive use of biologic mediators. Beta Tricalcium
18 Phosphate offers great potential as a graft material
19 for the delivery of such adjunctive mediators. These
20 include platelet-rich plasma. The adjunctive biologic
21 mediator such as platelet-rich plasma are already
22 cleared for market via 510(k), and as such the

1 reclassification of TCP will recognize the current
2 clinical practice and bring about a consistency in
3 this regulation. Thank you.

4 CHAIR REKOW: Does the Panel have any
5 questions for Dr. Reynolds? Yes, Elizabeth?

6 MS. HOWE: Elizabeth Howe, consumer
7 representative. I have a question about the
8 comparison of using this product in orthopedic versus
9 oral implication, and I'm wondering about the
10 reference that it's soluble in mineral acids and how
11 that would differ in using this product for oral
12 implications?

13 DR. REYNOLDS: If I may ask, please, a
14 question?

15 MS. HOWE: In using this product for oral
16 use, the fact that it is soluble in mineral acids,
17 would that be different because of infection in the
18 mouth that might be present? Is there some indication
19 that we need to be aware of?

20 DR. REYNOLDS: If I understand your
21 question correctly, would there be clinical
22 characteristics of the wound orally that would make

1 the material behave differently? For example, the
2 presence of acid secondary bacterial colonization?

3 MS. HOWE: Right.

4 DR. REYNOLDS: I would argue that there
5 probably are instances in which oral wounds do differ
6 from orthopedic applications. However, all of these
7 environments become contaminated in the surgical
8 process. What makes some applications, particularly
9 periodontal applications, different is that we have a
10 delay in closure of the wound. However, there is a
11 long history of use of bone replacement materials in
12 that environment and almost, you know, uniformly
13 meet with varying degrees of success. So I don't know
14 if that answers your question directly.

15 MS. HOWE: Would there be a concern then
16 in closing the wound directives that would be given on
17 problems for follow-up that they need to be aware of?

18 DR. REYNOLDS: I would anticipate that
19 there would be no difference in clinical practice from
20 use of any other bone replacement material, and those
21 would include appropriate patient management and post-
22 operative follow-up. One should not, based on

1 material, anticipate any difference in clinical
2 behavior. In fact, if anything, there is properties
3 that might suggest that it may behave more favorably.

4 MS. HOWE: Thank you.

5 DR. GLOWACKI: This is Dr. Glowacki. One
6 of the comments in the orthopedic directives mentioned
7 a voidance of its use, Beta TCP, in patients who have
8 problems with calcium homeostasis. Are you aware of
9 any experience in the periodontal field using this
10 material inside patients? For example, what type of
11 calcium malignancy or patients with renal diseases?

12 DR. REYNOLDS: No, I'm not. If I might
13 add, though, when we look at periodontal applications
14 versus orthopedic indications, there are a
15 considerable difference in the volumes of material
16 that are used generally, and I would suspect that that
17 would also be a consideration and concerns regarding
18 that. There may be potential issues in the patient
19 populations.

20 DR. GLOWACKI: And you talked about your
21 constituency use in periodontal and alveolar
22 reconstruction, and it's my understanding that in the

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1 orthopedic applications use is restricted to
2 metaphyseal defects. In other words, not in cortical
3 bone or bone that is really supporting structure. But
4 with respect to the alveolar ideas and possibly an
5 association with dental implants, do you have an
6 opinion about whether there is sufficient experience
7 in the use of Beta TCP and periodontal disorders for
8 construction of -- for replacement of cortical bone?
9 Let me put it that way.

10 DR. REYNOLDS: Excellent question, and I
11 can only offer my opinion, and that is to say that I
12 believe it will depend in large measure on the form of
13 the TCP on its placement and whether other mechanisms
14 are provided to stabilize and support the graft
15 material. Particular material tends to move and
16 that's a dilemma that we're confronted with with,
17 essentially, all the material, particularly bone
18 replacement materials that we use in those types of
19 applications. But we don't have any in general
20 indications that would require structural support.
21 More often than not it's all tissue support to the
22 wound healing process.

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1 DR. GLOWACKI: Thank you.

2 CHAIR REKOW: Mark?

3 DR. PATTERS: Mark Patters. Dr. Reynolds,
4 in your opinion, given the existing data, what
5 indications do you think that this product should be
6 labeled for in treatment of periodontal defects?

7 DR. REYNOLDS: Well, at this time,
8 recognizing that there is variability in clinical
9 outcome in this material, but others of similar
10 characteristics, currently intrabonal defects,
11 furcation defects, both associated with dentition and
12 for bonal defects associated with implants and very
13 likely there will be other augmentation as well as
14 sinus augmentation. There's very scant literature
15 though currently on the latter applications, and so
16 there's no reason that I would expect that the
17 clinical outcome or histologic outcome would differ
18 appreciably from the use of other ceramics.

19 DR. PATTERS: Do you believe that there is
20 existing data to support the use of furcation defects?

21 DR. REYNOLDS: Point well taken. I would
22 argue that currently the literature suggests that

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1 there is no single modality that is appropriate for
2 this successful management and predictable management
3 furcations if we taken a spaced approach. In fact, we
4 probably should revisit a number of materials and
5 approach it that way.

6 DR. PATTERS: Thank you.

7 DR. BURTON: Richard Burton. Two
8 questions. You had said that, you know, reclassifying
9 this product would expand. My understanding was that
10 there are some products of lower percentage on the
11 market. Is there not one that is currently a 3, but
12 that are not marketed now? Is that correct or not? I
13 mean, what's available right now in the periodontal
14 area in terms of existing products?

15 DR. REYNOLDS: Well, in terms of alveolar?

16 DR. BURTON: No, of this particular
17 material, the other one.

18 DR. REYNOLDS: To my knowledge right now,
19 there is no currently marketed TCP.

20 DR. BURTON: Okay.

21 DR. REYNOLDS: A centigraph was available.
22 I believe that is no longer available in the United

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1 States. Please, correct me if I'm wrong.

2 DR. BURTON: No, you alluded earlier that
3 there was some things on the horizon as well. I would
4 assume you are planning that this would have the
5 potential then to act as some kind of a scaffold. You
6 mentioned PRP as one alternative, but also obviously
7 plans looking at potentially BMP as a delivery system
8 for that as well.

9 DR. REYNOLDS: I would say yes. I did not
10 mention I served frequently as a reviewer on OPM II
11 and on Reparative Study Section, an area of keen
12 interest. Clearly, the use of biologic mediators will
13 be in our future and are here now to one extent.
14 Scaffolding remains the one frontier, too, that we
15 need to address. So opportunities to identify
16 material that might need specific clinical indications
17 are extremely important.

18 DR. BURTON: Yes, thank you.

19 CHAIR REKOW: This is Dianne Rekow again.
20 I'm assuming you people of the FDA, please, confirm
21 or correct me, that we're talking about this in its
22 pure form not in its mixture with all the primordial

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1 soup options, right? We're not talking about the BMPs
2 and the gross factors and the various other stuff that
3 could be added?

4 DR. RUNNER: That's correct. Any addition
5 of those types of factors would push that into a PMA
6 Class III type of device.

7 CHAIR REKOW: I share your enthusiasm for
8 that, but I just want to be clear that what we're
9 addressing here is simply the material as a material.

10 DR. REYNOLDS: Yes.

11 DR. RUNNER: And I also wanted to make the
12 comment that there were a lot of specific questions
13 from the Panel about the manufacturing of this
14 particular company of the product. You should be
15 thinking of it as a broad reclassification not of the
16 specific company.

17 CHAIR REKOW: Thank you. Are there any
18 other questions for Dr. Reynolds?

19 DR. REYNOLDS: Thank you very much.

20 CHAIR REKOW: Thank you. Both Dr. Gunter
21 Uhr and Dr. Thomas Arrowsmith-Lowe from Curasan, if
22 that's not the proper pronunciation, I'm sorry, are

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1 here. How would you gentlemen like to proceed, and
2 would you, please, identify yourselves and your
3 interests?

4 DR. UHR: Thank you. Thank you very much.

5 CHAIR REKOW: Can you use the microphone,
6 please, because it needs to be public information?

7 DR. UHR: Okay. Thank you.

8 CHAIR REKOW: We need as a society to come
9 up with some comfortable segway from getting computers
10 up and running. You know, there's got to be something
11 we have to learn to do to take care of that pause.

12 DR. UHR: Okay. Thank you for the
13 possibility that I'm here, and that I have you to give
14 me the chance to make a small presentation. My
15 person, I'm Gunter Uhr from the Curasan. I'm the head
16 of the Clinic of Research, and the Curasan also
17 purchased the PMA from Miter and intended to bring the
18 product here in America on the market.

19 My intention is to show you that we not
20 agree with reclassification from III to Class II.
21 Why? You see on the left side is the skeleton.
22 You'll see the skull, and what I intend to show is

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1 that we have two bones. Bone is not bone. And bone
2 and wound healing of the skull differ from those in
3 the skeletal system. This concerns the histogenesis.

4 This concerns the function and the healing process.
5 And the etiology of maxillofacial defects is also
6 different.

7 And to take an inference on the wound
8 healing, for example, and therefore we need material
9 which has a special feature. We need a material
10 that's as pure, that means more than 99 percent, and
11 you must have a special shape of the material, the
12 granule form, the size and the porosity, because all
13 these four features will affect safety and the
14 effectiveness.

15 Now, I structured this presentation in two
16 parts. One part is a biological one and the second is
17 material. Now, at first to the histogenesis. The
18 skull we have an intramembranous bone formation. What
19 does it mean? We have small cells, that's this one,
20 this aggregate, the mesenchymal stem cells, you know,
21 and they differ into osteoblast and they form at
22 different location simultaneously bone. That's

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1 typical for the skull, especially, you see here the
2 child at nine weeks, and you see the maxillar
3 mandibula and the frontal bone is formed at nine
4 weeks.

5 The blue color it's cartilage. This is
6 typical for the skull. The next bone is enchondral
7 bone formation, and this is a typical bone formation
8 for the skeleton. And what is the difference? Here
9 the green color it's cartilage, and cartilage is
10 replaced to bone, and this is here shown. And what is
11 the function? Both bone types have different
12 function. Here the skeleton has to carry the load,
13 has to bear the weight, and the function probably here
14 of the mandible or the maxilla is to carry this, and
15 the load is periodically, not continuously. And also,
16 the bone quality is different. The modeling, for
17 example, you have a higher remodeling rate in this
18 skeleton system than here in the skull.

19 Now, we come to the etiology of the bone
20 defects, and most of the bone defects in the skeleton
21 have a systemic origin. There are no contaminations
22 with microorganisms, bacteria, viruses, and each

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1 orthopedic surgeon fears the bacteria invasion. Then
2 you got problems in bone. If you have a bacteria
3 invasion, you know, the osteomyelitis. This occurs in
4 long bones. What is the situation, the region of the
5 mouth?

6 Now, we are speaking about, you know, the
7 periodontosis. The periodontosis is a chronicle
8 infection with bacteria. It's a completely different
9 situation. And, for example, the apicoectomy, you get
10 an invasion of bacterial through the root canal in the
11 apex. Here we have an invasion with bacteria. The
12 next point, filling of tooth sockets. You extract the
13 tooth not just for fun. And it burns when you have an
14 invasion there of bacteria, and also if you make a
15 sinus for elevation or augmentation, lateral or
16 horizontal augmentation, you are working in the field
17 of contamination with bacteria and microorganisms.
18 And also, in large defects, for example, in tumors.
19 If you have contact with vestibulum, you have the
20 problem of the infection.

21 And now, we look at the time frame. This
22 infection also has an effect on the time of healing.

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1 Here we have typical defects, for example, in long
2 bone. We take this from the hand, because here we
3 have comparable volumes to defects in the mouth
4 region. Here we have a broken finger. You see the
5 surgery. You see the osteosynthesis, microplate to
6 stabilize the bone, and you see here the Beta
7 Tricalcium Phosphate. It's completely resolved at six
8 months. It's a marvelous result.

9 Here below, that's the young girl. Of
10 course, we have influences on bone regeneration. You
11 know the age is important, also if their system make
12 diseases. But here, we see it was a horse bite. The
13 joint was destroyed. And the surgeon made a
14 chiroplasty and filled it with Cerasorb. You see at
15 two and a half months you take a biopsy to look what
16 has happened in the defect. And this is a biopsy, and
17 we can enlarge it, and what you see is that the
18 Cerasorb, the granules were totally disappeared. They
19 are dissolved. And we have a very smooth, smooth
20 transition from the cartilage here, the joint to the
21 bone. If you use a higher magnification, you will see
22 some rests here of Cerasorb, but only some rests.

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1 Cerasorb is the better TCP.

2 Now, what will happen in our maxillofacial
3 region and the dental region? Here we have the Beta
4 TCP in the sinus for elevation situation. And what
5 you see is, at first, we have separated the
6 regeneration phase into -- we have separated the
7 regeneration into four phases. The first phase is the
8 stability of the bone regeneration material during the
9 acute inflammatory reaction. That's the first phase
10 in wound healing, and it's very important. Just a
11 minute ago here there was a question about the
12 acidity, the pH and I will speak a little bit later
13 and come to this point. It's very important for the
14 material.

15 The next point is, at first, we have the
16 fibrin network, coming from blood, and this fibrin
17 network is replaced by the collagenous fibers network
18 and then at about three months, here at this side, the
19 woven bone formation begins into the inter-granular
20 spaces, and at about six or eight months here, we have
21 the transition of the maturation into lamellar bone at
22 eight months. And finally, we need 12 to 24 months

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1 for the remodeling, the remodeling starts and the
2 total appears in the material. This is longer than in
3 long bones.

4 Now, we go into detail. What happened?
5 What has occurred in the wound? Probably have a
6 broken bone here. What you see is that's the bone
7 line, the osteoblast. We have at the broken side, we
8 have to relieve the growth factors, BMPs, for example.

9 We have the clotted blood vessels here in the bone
10 marrow. Now, the space here is filled with blood and
11 you put in some granules, Beta TCP granules. The
12 activation of platelets occurs immediately. They
13 release growth factors, and then we see here the
14 fibrin network and the cell tied, but first which come
15 in from the clotted blood vessel, this is the granule
16 side. Here clears the region, but at 12 to 48 hours,
17 they will disappear. They will disappear, but will be
18 phagocytized. They make their drop and then they
19 disappear.

20 And now the next cell come on the plan and
21 this is a macrophage. And a macrophage is as a
22 central role in this period. It organizes the whole

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1 wound healing process. The macrophage and we have
2 seen, here on the top, we had a pH of 4 to 6 until the
3 fibroblast formed the collagenous fibrin network.
4 They replace the fibrin network, and then the blood
5 vessels move in. And this is a point that the pH now
6 goes to a normal physiological level of 7.4.

7 But here we have two important functions
8 concentrated in the macrophage, and the macrophage
9 will attack, at first, now that's a biological
10 principle, you know. At first the antigen, the
11 bacteria, they will clean the region. Also they
12 phagocytize the microorganisms, and they do it
13 together with the T lymphocytes. And when this
14 process comes to an end, then the regeneration begins.

15 So if there is a stimulation for the
16 macrophages, the phase of defense will extend, and
17 they phagocytize not only the bacteria, but they
18 phagocytize everything which is smaller than 10 H to
19 10 microns. So if you have a material here, the Beta
20 TCP granules, which are not stable and they
21 disintegrate, you know, we have an acid situation.
22 And if this acid situation links to disintegration of

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1 a particle, then this particle below 10 microns will
2 phagocytize by the macrophages. And it comes to a
3 shrinkage of the defect, of the filling of the defect.

4 CHAIR REKOW: Can I interrupt for just one
5 second, please?

6 DR. UHR: Yes.

7 CHAIR REKOW: These are fascinating
8 slides. There's no question about it, but I need to
9 remind you that almost everyone in this Panel is a
10 clinician and trained in dentistry and bone
11 regeneration, so maybe we could have a slightly
12 shorter version of some of the basic concepts.

13 DR. UHR: Okay.

14 CHAIR REKOW: I don't want you to miss
15 your main points, by any stretch of the imagination.

16 DR. UHR: Okay.

17 CHAIR REKOW: Thank you.

18 DR. UHR: Now, to the material, and the
19 material, here we have four features, which are
20 necessary, which are very important. It's purity, the
21 shape, the size and the porosity. This effects the
22 safety and effectiveness. Now, a very important point

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1 is that the Beta Tricalcium Phosphate in Europe was on
2 the market since 1970, and we see here some
3 publications, also here from the U.S. And this
4 material disappeared in 1980, roundabout in the '80s,
5 from the market, because no one wants to use any more
6 the Beta TCP.

7 Why? They got here from Holland published
8 that Beta TCP disintegrates very rapidly into
9 particles that can be found in the neighboring lymph
10 nodes. And that means the end for this product. And
11 then this guy here, this Dr. Heide, he was convinced
12 that Beta TCP is a good material. But he says it is
13 good if it is pure and is pure higher than 99 percent.

14 And here we have a lot of publications which show
15 that this material works.

16 Now, I will show you what happens in the
17 body if you have an impure material. It's a
18 competitive material in Germany. It comes on the
19 market and it disappears very rapidly, because you see
20 here it corrects, it's covered by an impure phase and
21 it is very instable material. And if you test or will
22 test -- if a material is, I'm looking for it, suitable

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1 for the defect to use it, you can move it between your
2 fingers. And if you use this granule and move between
3 your fingers, and you put it back, and you blow, you
4 have no abrasion, and also you can also eat them,
5 because there is just like to drink a glass of milk.

6 But we go back to impure material and I
7 can show you what will happen. These are all
8 immunohistological figures and this is a result. And
9 what you see is after 11 months, you'll see the
10 persistence of lymphoid cells together with
11 macrophages. And you will see like stars in the night
12 sky, you'll see the small particles of this Beta TCP
13 distributed in the tissue. And up to now, there is no
14 regeneration of material of bone.

15 So to sum up, impurities impair the
16 results and process. Impurities less resorbable than
17 Beta TCP. These particles migrate to lymph nodes, De
18 Groot. Especially, we have talked also about the
19 Alpha TCP, and it is know that Alpha TCP converts into
20 hydroxyapatite in the biological system. And the
21 impurity is more soluble than Beta TCP. You have
22 retarded bone formation.

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1 Now, important for the material is the
2 size, the size and the micro-porosity. Here we see
3 the movie and the spherical shape is important,
4 because you need the intragranular spaces. We have
5 spoken about osteoconductivity. You need the
6 intragranular spaces for the invasion of blood
7 vessels. And additionally, the spherical size is
8 necessary. Most of these indications where you can
9 use this material in dental field is to fill the
10 sinus. You have to push the Schneider's membrane.
11 Then you have to put these granules below. If you
12 have a material which is broken and has edges, there
13 is a danger to hurt this membrane. Especially, if you
14 use the Summers method.

15 The next point, you need a well-defined
16 micro-porous structure, because we don't -- we also
17 need the movement of blood vessels and fibrins. It's
18 a street for the cells. The first streets and
19 highways for the cells into the granule. And so we
20 have a porosity of 1 to 20 microns, and it's a lower
21 limit for small blood vessels are, you know, 5
22 microns.

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1 The next point is you need a product which
2 is very strong sintered. With this table, you'll see
3 here the cubic sugar. This will happen with a
4 material, which is not stable. And you will get
5 particles which will be phagocytized. What you need
6 is a solvent from the surface, a continuous solvent
7 from the surface, and this prevents the particle
8 decomposition and genus solubility, we call it
9 halisteresis. And there is no degradation by
10 osteoblast that came there, and the question is the
11 degradation by the osteoblast plausible?

12 We know that for the degradation of
13 osteoblast you need two informations. We need the
14 bio-contact with osteoblast and we need the membrane
15 of the osteoblast, we need bio-receptors information
16 from the bone matrix proteins. So in a acidic
17 material we never have this information.

18 And finally, this granule is built up of
19 particles, of primary particles, and these have a size
20 of 50 percent larger than 10 microns, that's another
21 point. So I want to summary it. Bone and wound
22 healing, I think, I have shown it in a very short

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1 time, so it differs. We have a different
2 histogenesis. We have a different function. We have
3 a different healing process. And the etiology of the
4 maxillofacial defects differs from the skeletal
5 defects.

6 Therefore, you need a material which --
7 and this is a point, the human body sets the limits
8 not the material, and therefore we need a purity, a
9 shape, a size and a special porosity. Thank you.
10 That's the end.

11 CHAIR REKOW: Thank you. Are there
12 questions for Dr. Uhr? Yes, Mark?

13 DR. PATTERS: Mark Patters. Dr. Uhr, it's
14 a very pretty presentation, but what I didn't get from
15 it was why you oppose the petition? The petition says
16 nothing about purity, only reclassification of not
17 just their product, but all tricalcium phosphates that
18 are intended for use in oral cavity, so why do you
19 oppose that?

20 DR. UHR: As a purity.

21 DR. PATTERS: The petition, as I read it,
22 does not address purity.

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1 DR. UHR: Yes, but may I explain why it is
2 important that you have such a high purity? For
3 example, these granules consist of primary particles,
4 batch primary particles and during a sintering
5 process, these particles are recrystallized, and you
6 get -- between these particles you get sintering next
7 that means from both primary particles the crystals
8 move to each other, they bridge, and the impureness,
9 for example, hydroxyapatite, for example, calcium
10 phosphate, other phosphates move in front.

11 Now, this material gets contact. At this
12 bridge you have the impureness, and if it is more
13 soluble, the material breaks down. Especially in the
14 acid condition, in the acute inflammatory reaction.
15 And then there's a possibility that these particles
16 below 10 are phagocytized by the macrophage. Then you
17 will stimulate the new reaction.

18 DR. PATTERS: Now, I understand that, but
19 the purity issue can be covered in the guidance
20 document with special controls if this is
21 reclassified. Are you saying that highly purified
22 Beta TCPs should be reclassified, but impure ones

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1 should not be?

2 DR. UHR: Yes, I think it's -- so I'm a
3 scientist. I would say the purer the material is, if
4 you have a high pure material, it is -- whether it is
5 to control, you want to control the purity. Of course
6 you can make batch controls. You can make batch
7 controls with diffracture meters, yes?

8 DR. PATTERS: Maybe the FDA process is not
9 completely clear to you. I've been on the panel for
10 more than 10 years and it's not completely clear to
11 me. But my understanding, however, is that the
12 guidance documents and the special controls can deal
13 with issues of purity. What we're looking at, the
14 Panel is being asked to look at a much more generic
15 issue.

16 CHAIR REKOW: Thank you. Dr. Arrowsmith?

17 DR. ARROWSMITH-LOWE: Yes, I think I'll be
18 addressing more of the regulatory aspect of this.

19 DR. UHR: Yes, okay.

20 CHAIR REKOW: Could you introduce
21 yourself, please?

22 DR. ARROWSMITH-LOWE: Yes, I'm Tom

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1 Arrowsmith-Lowe. I'm a regulatory consultant, Curasan
2 AG is one of my clients. I am compensated by Curasan
3 AG for consulting services that I provide to them,
4 including my presentation. I am a retired FDAer. I'm
5 a retired public health service captain and served in
6 the FDA until my retirement. I was a deputy office
7 director in the Center for Devices and was director of
8 the Human Tissue Program in the Center for Biologics
9 prior to my retirement from the Agency, and hopefully
10 I can work this.

11 CHAIR REKOW: Just for the record, Dr.
12 Uhr, I'm sure, will have some more questions for you,
13 but perhaps we can finish the other presentations and
14 then combine them.

15 DR. ARROWSMITH-LOWE: As has previously
16 been stated Curasan AG is speaking in opposition to
17 the proposal to reclassify Beta TCP from Class III to
18 Class II. As we reviewed the reclassification
19 petition it distilled down essentially in making two
20 points. One that there was no difference between
21 skeletal and maxillofacial bone, essentially saying
22 that the use is the same whether it is used

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1 maxillofacially a Beta TCP for an implant or whether
2 it is used in skeletal bone, and the second point
3 being that there were no reported problems.

4 We would like to respond to those two
5 statements. Dr. Uhr has fairly clearly shown that
6 there are some differences between the two bones, that
7 bone is not just bone, that there is a difference
8 between skeletal bone and maxillofacial bone. He has
9 pointed out that the origin of the bones, the
10 histogenesis of the two types of bones is different.
11 He has also shown a difference in function with the
12 maxillofacial bone existing for support of the
13 dentition for use in mastication and other uses
14 speaking as well, and has also shown in that that the
15 pressures that are generated in the function of the
16 two different types of bone are different as well.
17 That there's a different function, one being for
18 skeletal musculoskeletal support and the other for
19 support of dentition.

20 And has then also shown that there is a
21 difference between the stresses that are applied to
22 the two bones with periodic stresses being the case

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1 for the bone that is supported of dentition with much
2 more constant stresses being applied to the
3 musculoskeletal system bone. In addition, he pointed
4 out that there is a difference in the healing process
5 between the two bones when Beta TCP is used for
6 treatment of a defect, that the post-operative healing
7 process is a longer process in the maxillofacial bone
8 than the process that occurs in long bone.

9 As well, he has also pointed out a
10 difference in the etiology of the bony defects in the
11 two types of bones, pointing out that principally the
12 main etiology for defects that develop in
13 musculoskeletal bone tend to be defects that are
14 systemic defects. Whereas, the main etiology for
15 defects that occur in the bone supporting the
16 dentition is primarily of an infectious origin.

17 And so we do support the idea that there
18 really are differences between the two bones. There
19 are differences not only in how those bones function,
20 but also differences in their origin and differences
21 in the etiology of the defects that occur in those
22 bones. So I think the point can be made that we

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1 really can't say that bone is bone in this case. That
2 there are differences that are easily demonstrated
3 here.

4 In addition to that, the second point that
5 was made in the petition is a point about,
6 essentially, there have been no problems reported.
7 One of the points that Dr. Uhr mentioned having to do
8 with the growth article that was published in the
9 1980s was that there actually was a product removal
10 that occurred and Beta TCP was unavailable for a
11 period of approximately 10 years for dental use in
12 Europe, and that really primarily related to the fact
13 that the TCP that was being marketed initially in the
14 1970s had problems of purity that very definitely
15 effected the safety and effectiveness of that product.

16 And so the clinical community stopped purchasing the
17 product, and the product, essentially, was removed
18 from the market by the manufacturer of that product.

19 Dr. --

20 CHAIR REKOW: Could I --

21 DR. ARROWSMITH-LOWE: Yes.

22 CHAIR REKOW: Oh, I'm sorry. Actually,

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1 I'll wait.

2 DR. ARROWSMITH-LOWE: Okay.

3 CHAIR REKOW: Sorry.

4 DR. ARROWSMITH-LOWE: Dr. Uhr also talked
5 about other issues that we feel are fairly essential
6 parts of making a determination of safety and
7 effectiveness. That variations in the purity of the
8 product, variations in porosity and particle shape and
9 in particle size can very definitely have an effect on
10 the product itself and make that product less safe and
11 less effective. This is an issue that is of concern
12 to us, and we feel it should be a concern to the Panel
13 and to the clinical community as well.

14 Because it is our feeling that the most
15 appropriate way to try to make an assessment that a
16 product truly is safe and effective and to include in
17 that determination of safety and effectiveness is
18 looking at how purity, porosity, particle shape and
19 particle size actually affect the performance of that
20 product in a clinical setting. So actual review of
21 data as opposed to just making a comparison between
22 two products, looking at physical properties, such as

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1 purity, porosity, particle shape and particle size.

2 And so our recommendation is against
3 reclassification as I have already said, and for
4 reasons that we feel that the petition has not
5 adequately established those two primary points about
6 the similarity of bone being bone, and the point that
7 the product actually has had no problems associated
8 with it throughout its period of use. And so as I
9 said, we're recommending against reclassification.
10 If, however, reclassification were to occur, we would
11 like to make two recommendations to the Panel and to
12 the Agency about how they would make a determination
13 of substantial equivalence using a 510(k) process.

14 One, we feel that a predicate product, to
15 which substantial equivalence would need to be
16 established, has to be a current generation Beta TCP.

17 A purer product than the sort of product that was
18 initially manufactured back at the point when the
19 first PMA was cleared for Beta TCP. As was mentioned,
20 Curasan AG now is the owner of the original PMA and,
21 as the Panel may be aware, there is a submission that
22 has come in from Curasan AG, a supplement, to that

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1 original PMA to, essentially, change the product into
2 a form that is a purer product form that addresses
3 issues having to do with the size of the particles and
4 also with porosity and with particle shape as well.

5 And so we feel that to have an adequate
6 determination of substantial equivalence if the 510(k)
7 process is used, that there really must be a
8 comparison made and a determination that the product
9 that has submitted to pre-market notification does
10 favorably compare with the current generation of Beta
11 TCP when looking at a product or particle size,
12 particle porosity, looking at particle shape and
13 looking at the overall purity of the product. And we
14 feel that if the 510(k) process were applied, that it
15 would need to include a determination of substantial
16 equivalence looking at these factors. Thank you.

17 CHAIR REKOW: Thank you. Dr. Patters,
18 does that answer your question or would you like to
19 restate it?

20 DR. PATTERS: Well, Mark Patters. My
21 understanding is then that you feel that this product
22 should come to market through the PMA route, and you

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1 already have a PMA, which I was unaware. I think the
2 Panel is not aware.

3 DR. ARROWSMITH-LOWE: Okay.

4 DR. PATTERS: As you thought they were.
5 We're not.

6 DR. ARROWSMITH-LOWE: Oh, okay. I thought
7 the Panel was aware. Yes, we feel that --

8 DR. PATTERS: PMAs are a closely guarded
9 secret, I believe, by FDA and they do not share that.

10 DR. ARROWSMITH-LOWE: Well, we feel that
11 the PMA process provides a better opportunity for
12 making a determination of the safety and effectiveness
13 of the product, rather than just making a comparison
14 with a predicate product. One of the things that we
15 want to make certain of is that given the advancement
16 of this product over the last several decades, and
17 given the improvement in clinical utility and the
18 decrease in incidences with the purer product and with
19 a product that addresses some of the other issues as
20 well, that we do have a level of safety now and a
21 level of product effectiveness.

22 That is really a standard with the newer

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1 Beta TCP. And it would be a concern that we would
2 have that using a comparison method in establishing
3 substantial equivalent might not necessarily provide
4 sufficient information to really make a determination
5 that this implantable product really is safe and
6 effective.

7 DR. PATTERS: So if I could summarize then
8 what I understand you to be saying is you do not
9 believe that, at the present time, there is adequate
10 data in the literature to support reclassification?
11 And you believe that new clinical trials and new --
12 not just clinical trials, but new data need to be
13 presented?

14 DR. ARROWSMITH-LOWE: Well, I believe that
15 the presentation of new data would go toward
16 establishing safety and effectiveness of any new
17 product that would come on the market, as opposed to
18 just merely doing a comparison to a predicate product,
19 yes.

20 DR. PATTERS: Thank you.

21 CHAIR REKOW: Dr. Cochran?

22 DR. COCHRAN: David Cochran. You

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1 mentioned four different aspects: The purity,
2 porosity, shape and size, and you are implying that
3 one would receive one set of outcomes in testing if
4 you reach some point. Say purity was 99 percent, I
5 think you mentioned, but maybe at 96 percent it would
6 not. In other words, for each of these issues, these
7 four issues, that you've mentioned here, you are
8 implying that there is data to say that there is going
9 to be a difference in performance at some cutoff
10 value. Can you provide any data that would suggest
11 that that's true?

12 DR. ARROWSMITH-LOWE: Well, part of the
13 reason some of the data, the basic science data, that
14 was presented already goes to establishing the
15 significance of determining each of those.

16 DR. COCHRAN: Well, that was one study or
17 publication.

18 DR. ARROWSMITH-LOWE: Well, no. Actually,
19 the De Groot study basically was looking at what was
20 wrong, why the product was, essentially, not being an
21 effective product, and the dental community turned
22 against the use of the product. And principally, that

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1 was really looking at only one of these issues,
2 looking at the purity issue. Because what was
3 determined was that when you had purities that were,
4 say only at a 95 or 96 percent range, that you were
5 going to get a change in the healing process.

6 What we've further found beyond that was
7 some of the work that Dr. Uhr was talking about is the
8 presence of impurities also can effect particle size,
9 because the success of the sintering, which brings the
10 impurities to the surface when two of the primary
11 particles join in the sintering process, because the
12 impurities are brought to the surface through the
13 heating process, the point of juncture actually is the
14 point of impurity between those two primary particles,
15 and that increases the likelihood of that particle,
16 primary particles, that have been sintered and joined
17 of those breaking apart.

18 Then what is more likely to happen when
19 you have those smaller particles is that you are going
20 to get a greater likelihood of having a response on
21 the part of the body that the macrophages will come in
22 and will consume the smaller particles and you are

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1 actually going to have a slowing of the overall
2 healing process, because you are having particle
3 disintegration occurring more rapidly.

4 DR. COCHRAN: Yes, but what I'm asking for
5 is do you have data that says that 96 is not good, but
6 98 is good or you think 99 is good? I mean, if you're
7 going to make this recommendation, it would be nice to
8 see data that suggests that there is a cutoff area.

9 DR. ARROWSMITH-LOWE: Yes.

10 DR. COCHRAN: Or that one is better or
11 not. Otherwise, we're doing the same thing, because
12 the Panel has got to make decisions as to what it
13 would recommend.

14 DR. ARROWSMITH-LOWE: Right.

15 DR. COCHRAN: Without the data to support
16 it, it's tough for us to do that.

17 DR. UHR: Sorry, I can answer. We, in our
18 company, tested -- our company tested not for its own,
19 but we test the material. We give it to a nurturer
20 institute, another university, sorry, and there we
21 tested the material. And so you can see in a
22 different meter whether there is impure or not

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1 impureness.

2 CHAIR REKOW: Has that been published yet?

3 DR. UHR: It will be published, yes, but
4 not by us, of course.

5 CHAIR REKOW: Yes.

6 DR. UHR: It's not in press, but it will
7 come soon. Another point is we have publications,
8 especially also of Alpha TCP, that's a material which
9 converts probably into hydroxyapatite and you can see
10 it in the animal model. You can see in the lymph
11 nodes the particles, the hydroxyapatite. And I think
12 it is not the target to use a material which normally
13 it has to be solved and it should be replaced totally
14 by bone. So we will not find any particles anywhere.
15 This should be the target.

16 CHAIR REKOW: Yes, Dr. Burton?

17 DR. BURTON: Richard Burton. Does your
18 company represent currently market a competing product
19 or is this product that you have now currently
20 marketed?

21 DR. ARROWSMITH-LOWE: Curasan AG markets
22 Beta TCP in Europe and markets Beta TCP in the United

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1 States for orthopedic, for non-dental use in the
2 United States. As I also mentioned, they are the
3 holder of what was originally Miter's PMA and have
4 intentions if the --

5 DR. BURTON: And I assume then it's under
6 that PMA without a reclassification they could market
7 it?

8 DR. ARROWSMITH-LOWE: They could basically
9 market under that PMA the product that was described
10 in the original PMA.

11 DR. BURTON: Which was inferior product.

12 DR. ARROWSMITH-LOWE: Which is a product
13 that does not meet Miter standards of production, yes.

14 DR. BURTON: Okay.

15 CHAIR REKOW: Jon?

16 DR. SUZUKI: Jon Suzuki, Panel member.
17 Just this is a question to Dr. Gunter Uhr.

18 DR. UHR: Yes.

19 DR. SUZUKI: It's a point and then a
20 question. First, you mentioned that neutrophilic PMM
21 leukocytes both disappear from the scene and that's
22 not exactly true. They are always indeciduous and

NEAL R. GROSS

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