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Dental Products Panel Meeting

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Ambassador Room
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PARTICIPANTS

Panel Members:

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Julianne Glowacki, Ph.D.
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Benjamin Gerson, D.D.S.
Mary J. Edwards, Industry Representative
Frederick A. Curro, D.M.D., Ph.D., Industry Representative
Jean Frazier, Ph.D., Consumer Representative

Consultants:

Charles Bertolami, D.D.S., D.M.Sc.
Sheila McGuire, D.D.S., D.M.Sc.

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PROCEEDINGS

DR. ROBERTSON: Welcome to the Dental Products Panel meeting. I am Paul Robertson, the Chairman, and I would like to introduce Dr. Carolyn Tylenda, the Executive Secretary.

DR. TYLENDA: Thank you, Dr. Robertson.

Welcome to the meeting of the Dental Products Panel. Anyone desiring a transcription or an executive summary of today's proceedings may obtain one. A handout is available at the reception desk providing information.

I request that everyone attending this meeting sign the attendance sheet. If you have not already done so, please stop by the registration desk.

I will now introduce the members of today's Panel. Starting at the far end of the table is Dr. Jean Frazier, our consumer representative. She is from Philomath, Oregon. There are two industry representatives for this two-day Panel meeting because we are discussing both dental device and dental drug issues. Miss Mary Edwards is from W.L. Gore & Associates, Flagstaff, Arizona. Dr. Frederick Curro is from Block Drug Co., Inc., Jersey City, New Jersey.

There are three consultants to the Panel present today. Dr. Sheila McGuire is a consultant to the Panel. She is on the faculty of the Harvard University School of Dental Medicine. Dr. Charles Bertolami is also a consultant. He is Professor and Chairman of the Section of Oral and Maxillo-facial Surgery, Center for the Health Sciences, University of California, Los Angeles. Dr. Carlos del Rio is Professor and Chairman, Department of Endodontics, University of Texas Health Science Center at San Antonio.

The remaining Panel members are voting members for today's meeting. Dr. Joel Sandak is a general dentist in practice in White Plains, New York. Dr. Burton Rosan is Professor of Microbiology, School of Dental Medicine, University of Pennsylvania. Dr. Benjamin Gerson is Professor of Pathology and Professor of Pharmacology and Experimental Therapeutics at Boston University, School of Medicine. Dr. Paul Robertson, the Panel Chairperson, is Dean of the School of Dentistry, University of Washington. Dr. Richard Norman is Professor of Restorative Dentistry at Southern Illinois University. Dr. Deborah Greenspan is Clinical Professor of Oral Medicine in the Department of Stomatology, School of Dentistry, University of California at San Francisco. Dr. Larz Spangberg is Professor and Chairman, Department of Restorative Dentistry and Endodontology, the School of Dental Medicine, University of Connecticut Health Center. Dr. Julianne Glowacki is senior investigator in the Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School.

On my right are Dr. David Kessler, Commissioner of the Food and Drug Administration; Dr. Paula Botstein, Acting Director, Division of Medical Imaging, Surgical and Dental Drug Products and Deputy Director, Office of Drug Evaluation I; Dr. Clarence Gilkes, senior reviewing dental officer, Division of Medical Imaging, Surgical and Dental Drug Products; and Dr. Ralph Harkin, group leader, Division of Biometrics.

Five of the voting members, Drs. Robertson, Greenspan, Glowacki, Norman and Rosan, each have a four-year term as a voting member of this Panel. Pursuant to the authority granted under the medical devices advisory committee charter, dated October 27, 1990, I appoint the following people as voting members for today's, February 12, 1993, meeting: Dr. Benjamin Gerson, Dr.

Larz Spangberg and Dr. Joel Sandak.

For the record, these people are special government employees and are either a consultant to this Panel or a consultant or voting member of another panel under the medical devices advisory committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at this meeting.

FDA is concerned about conflict of interest and I would like to read the following announcement which addresses the issue of conflicts of interest, and is made part of the record to preclude even the appearance of such at this meeting. The conflict of interest statutes prohibit federal executive branch employees, including special government employees, from participating in matters in which the employee, his or her spouse, minor child, partner, employer or employing institution has a financial interest. This includes any firm whose product is being reviewed or discussed by this panel or committee or any firms with which the employee is negotiating employment, grants, contracts, payments in kind or other gifts.

This also means the employee must not discuss competing products or competing technologies of other firms, or discuss generic or class action matters that affect the firm with which they or their employer are associated. However, waivers may be granted where the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved, or the interest is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from such employee. Therefore, waivers have been granted to the following special government employees: Dr. Paul Roberts, for his interest in the University of Washington; Dr. Deborah Greenspan, for her interest in the University of California at San Francisco; Dr. Julianne Glowacki, for her interest in the Brigham and Women's Hospital; Dr. Burton Rosan, for his interest in the University of Pennsylvania; Dr. Richard Norman, for his interest in Southern Illinois University; Dr. Larz Spangberg, for his interest in the University of Connecticut; Dr. Carlos del Rio, for his interest in the University of Texas; Dr. Benjamin Gerson, for his interest in Boston University; Dr. Jean Frazier, for her interest in the University of Minnesota; Dr. Charles Bertolami, for his interest in the University of California at Los Angeles, and Medchem Products, Inc; Dr. Sheila McGuire, for her interest in the Harvard School of Dental Medicine.

At this time, I am pleased to introduce Dr. David Kessler, Commissioner of the Food and Drug Administration, who would like to address the Panel. Dr. Kessler?

COMMENTS BY DR. DAVID KESSLER

DR. KESSLER: Good morning. I am here today for two reasons. First, I want to express my sincere appreciation to all the members of this Advisory Panel. I know that you all have very busy schedules and I appreciate, indeed, everyone at FDA appreciates your sharing your expertise with us.

My main reason for being here today is that I want to discuss how FDA can work more effectively with the dental community; how we can promote the type of information exchange that facilitates the practice of good dentistry and the availability of better drugs and devices. I am talking about better communications. We need to forge stronger communication links, the kind of communication that allows us to predict where potential problems may occur with dental products, and to address them before they become major health concerns for the dental clinician and the consumer; the kind of communications that allow us to resolve issues like dental handpiece sterilization, the use of dental lasers and the safety of TMJ implants before they become headlines. And we need to start now.

I believe that the first step may be as simple as making sure that the dental community understands the role of the FDA in the approval of drugs and devices used in the practice of dentistry. I am not fully convinced that practicing dentists know that the drugs and devices that they use to treat patients need to be approved and regulated by the FDA; that under the law it is FDA's responsibility to, one, determine the legality of products marketed for use in dentistry and, two, to help make sure that those products are safe and effective for their intended use.

In part, today's agenda shows the need for better communications. There is no better evidence than the fact that today you will be talking about a drug that this Advisory Committee will comment upon that has not been approved. Yet, some dentists have been using similar types of products for many years.

There are other examples that suggest that the dental community is not fully aware of FDA's mandate to help assure that dental products are safe and effective, as well as legally on the market. Furthermore, there is evidence that dental devices are being promoted for purposes beyond those for which they are approved. An example is the promotion of dental lasers for hard tissue applications.

Let me digress for a moment to say that some products are promoted and advertised in such a manner that a dentist may not be able to tell that they are not approved for their intended use, and that is a practice that we are now addressing.

We will be focusing on companies that make false advertisements and promotion for dental devices, and we will take appropriate regulatory action before they get too far on in making misleading claims to the dental community. But, again, this underscores the need for us to do a better job of communicating with the dental community at large, not just to tell dentists that FDA approves drugs and biologics and devices they use in their practice, but to let them know where they can get accurate information on the use of such products and, more importantly, to give them a meaningful understanding of the product approval process, the kind of scientific data that are required in our decision making, and why.

We need to enlist the dental community's assistance in evaluating new products, and to tell them why they should promptly report to us adverse events and medical device failures, and how to

report them.

One of the first messages to the dental community is for them to understand the basis on which we approve products and the importance of the dentist's role in assuring the integrity of those products. Simply put, to approve a drug or a new device for marketing, we need data collected on the performance of the new product in comparison with either an approved therapy or with a placebo, if appropriate. We need to know that the product works as intended, and we need a thorough analysis of its successes and its failures, its risk versus its benefit. We learn this information from looking at the scientific studies.

For drugs the law is clear. These data must come from adequate and well-controlled clinical trials. I want to emphasize those words—adequate and well-controlled. The trials should compare one group receiving the investigational therapy with a control group, and should report incidence of adverse reactions and assess effectiveness.

For devices requiring premarket approval, the law is slightly different but the general rule of valid scientific evidence still applies, including well-designed clinical trials when appropriate.

These requirements exist for new drugs and devices in all areas of medicine, not just dentistry. These are the rules that you will apply to the product under evaluation today. We want to hear your discussion of the scientific data in the NDA for this drug and your answers to the questions we have asked you about these data. Your recommendations will aid us in deciding whether the data are sufficient and whether the NDA should be approved.

I am not here to take any position on the application under consideration today. What I am committed to do is to bring this product, as well as all other dental products, into the Agency's regulatory purview and, further, into the realm of science. We need the dental community to be a part of this process. FDA needs to establish a closer relationship with the dental community, to have them involved at the outset in our scientific evaluation of products by being investigators in clinical trials, as well as serving on advisory committees.

We also need them involved throughout the process because often we do not find out about a problem, particularly with dental devices, unless the dental community provides that information to us. There are currently reporting requirements to dental device manufacturers, distributors and user facilities, such as hospitals and nursing homes. Most adverse events associated with dental devices, however, occur outside these facilities. As a result, FDA depends on dentists to voluntarily report problems with regulated products to us or we may not know of the problem in a timely manner.

Our medical device reporting records for dental products show that we need, all of us, to do more in this area. Really the need for this kind of data will increase with the development of new technologies that are becoming available in dentistry. We already are seeing an explosion with regard to dental technology, certainly with regard to endosteal implants and dental lasers. It is an

explosion that reinforces FDA's belief that clinicians cannot individually assess every technology with which they come into contact, or make certain that those products function both safely and effectively for their patients.

The Congress has assigned that role to the FDA so that clinicians can focus on providing patient care rather than assessing new products before using them. But it is absolutely critical that the dental community be willing to report to FDA the earliest information available on the performance of these devices and all dental products.

This is the second message that we need you to take to the dental community. The FDA needs to know about serious adverse experiences with drugs and devices. We need your colleagues to report them.

Let me say two things about the reporting process before I conclude. First, we hope that it will be a long-term collaborative effort between the practicing community and the Agency, and that will cover all products whether they are new or have been on the market for a long time. The shared responsibility has to be long range because problems can crop up years later.

Second, you need to know where to report problems, and today we will provide you with information that you can disseminate to assist dentists in the reporting of adverse events. I strongly encourage those of you who represent organizations to share this information with your membership and to enlist their participation in the program.

I recognize the many difficult professional issues that dentists have to confront in their offices every day. I am aware of the new OSHA regulations and the EPA guidelines. We are also aware that our Agency may also be seen as complicating the practice of dentistry. What we are now talking about is forging partnerships that will allow us both to do our jobs better.

FDA has traditionally had a strong relationship with the dental community through its cooperation with the American Dental Association and its many councils. We have worked together on many issues and we need to do even more. We need to deal with the consequences of new technologies head on.

The dental community needs to recognize that the law requires us, at the FDA, to regulate the safety and efficacy of dental products.

Once again, my thanks for your willingness to serve on this very important Panel. I look forward to the results of your deliberations and our continued working relationship.

Thank you.

DR. TYLENDA: Thank you, Dr. Kessler.

Each Panel member has been provided with materials on the product problem reporting program. There are some extra copies at the registration desk. Copies may also be obtained by calling 1-800-638-6725. Let me repeat that number, 1-800-638-6725.

Dr. Lee Joseph, from the Center for Devices and Radiological Health, FDA, will now make a presentation to the Panel.

PRESENTATION BY DR. LEE JOSEPH

DR. JOSEPH: Good morning. I spent half of the night trying to think of a line to say when you follow Dr. Kessler on a program, and I could not come up with anything other than behind every great man there is a great woman!

(Laughter)

But I would like to thank you for the opportunity to talk with you this morning and to discuss some of our recent activities in regard to dental amalgam restorative material.

It is your role as a conduit to your various representative organizations and to the FDA that provides us with a two-way communication channel, to which Dr. Kessler was referring, that assists us in making some informed decisions about the management of some of our dental products. So my presentation serves a couple of purposes:

(Transparency)

One, to update for the Panel our activities relative to dental amalgams since there does exist some recent history of the Panel's consideration of the safety of dental amalgams, and, two, to call your attention to the possibility that if we need to, we may confer with the Panel regarding some of the dental amalgam recommendations that we may implement in the future.

First of all before I continue, I want to acknowledge that the report, which I understand you have a copy of, took a cast of thousands to produce and there are several people in this room who worked very diligently on this. I would like to mention them. One is Dr. Carolyn Tylenda; Dr. Greg Singleton. Behind me we have Dr. Robert Collins, who is Chief Dental Officer in the Public Health Service, and Dr. Bill Kahn, who is with the National Institute for Dental Research. If I have missed anyone, hold up your hand.

It is instructive to describe the process, and you have a handout on that, by which this project was developed so that the recommendations contained in the Public Health Service interagency report, developed by the Committee to Coordinate Environmental Health and Related Programs—we will call it CCEHRP—can be placed in perspective. CCEHRP conducts its business through a variety of committees, such as those that were used to develop this final report.

In 1990, a "60 Minutes" report and various media stories led CCEHRP, chaired by the Assistant Secretary for Health, to undertake a review of dental amalgam safety.

(Slide)

The basic question faced by CCEHRP was do we have a problem with amalgam? Two subcommittees were charged to examine various aspects of dental amalgam. The first was the subcommittee on risk assessment, which as asked to assess the risk, obviously, associated with dental amalgam. The second was an ad hoc committee on the benefits of dental amalgam, which was chaired by Dr. Harold Loe of the National Institute for Dental Research. That committee was instructed to examine the benefits of dental amalgam and the benefits relative to alternative dental materials.

Also during 1991, an FDA Dental Products Advisory Panel, your predecessor, and a panel of experts convened at an NIH technology assessment conference and examined the risks posed by dental amalgam.

Both of these panels concluded that based on the scientific evidence available there was no demonstrated causal link between dental amalgam and health risk.

The risk assessment and benefit subcommittees took approximately a year to complete their charge, and concluded that the current research data do not demonstrate a health risk for the vast majority of individuals exposed to mercury vapor at levels commonly encountered from dental amalgam restorations.

Specifically, the risk assessment subcommittee acknowledged that amalgam restorations release small amounts of mercury vapor that can be absorbed by the body, but concluded that available data are not sufficient to indicate that health hazards can be identified in non-occupationally exposed persons— I am quoting—health hazards, however, cannot be dismissed.

The benefits subcommittee, noting that amalgam use has been on the decline with the decreasing incidence of dental caries and the availability of improved alternative materials, yet, noted that there are, and remain, substantial oral benefits that accrue to individuals and the population from the use of dental amalgam.

Each of these groups addressing the risks and the benefits questions recommended the need for additional research before the possibility of amalgam-caused and alternative-caused dental material risks can be dismissed.

Well, the reports of the risk assessment and the benefits subcommittees have been provided to the CCEHRP risk management subcommittee. That group was chaired by the Food and Drug Administration. Those two reports served as the basis for the recommendations and proposed

strategy for the management of dental amalgam.

The Assistant Secretary for Health charged the risk management subcommittee to develop a plan that addressed the research needs, the educational needs for the public and the health professions, and to identify options for increased regulatory oversight of this product.

(Slide)

The strategy developed by the risk management subcommittee was the use of three FDA-chaired inter-agency groups focused on research, education and regulation. Using all the materials available to the groups, those contained in the reports, the biotechnology assessment conference, proceedings from the dental panel, and two additional pieces of information which became available during their deliberations and that was the proceedings from a symposium by the Society for Toxicology, as well as proceedings from the Swedish Medical Council—using all those data, they developed recommendations that were incorporated into the strategy document.

That draft document was reviewed by a total of 60-70 people, including about a dozen dental and toxicology experts within the United States and abroad. Generally speaking, the reviews were very positive. Additional comments were made and were incorporated into the final report.

Moving on to the recommendations—there is a big board down here you can follow—the research work group recommended that the National Institutes of Health, in conjunction with the Centers for Disease Control and Prevention and the Food and Drug Administration, develop a research agenda targeted towards amalgam and non-amalgam restorative dental materials based on priority endpoints that were identified by the risk assessment and benefits subcommittee reports.

(Slide)

Some of the areas of research needs include the toxicological, the restorative, clinical decision-making criteria, new materials, other longevity data, as well as a commitment by the Public Health Service to undertake a research program that gathers data on endpoints in the neurological, the reproductive, the developmental and the metabolic areas.

Emphasis will be given to the important gaps in current knowledge about the possible effects of dental amalgam and alternative restorative materials on the body.

They also recommended—we are still at the research group—that the Office of the Assistant Secretary for Health monitor the progress of the research agenda through a tracking mechanism that would identify and evaluate amalgam research studies funded by the Public Health Service, other government agencies and the private sector. I have to add that this has not been done before. So it will be quite an undertaking to track all this.

The education work group emphasized that there is, indeed, a need to conduct a campaign to inform the public and health professionals about what is known and not known about amalgam risk, including the benefits and the controversy concerning the biological effects.

They recommended that the Centers for Disease Control and Prevention take the lead, working with the FDA and the NIH, in the development and implementation of that campaign.

Additionally, the education group recommended that NIH assume the lead on changing the practice behavior of health professionals so that they maximize the prevention of sound tooth structure, increase the use of preventive modalities and use dental amalgam and alternative materials in the appropriate situations.

Now I would like to address the recommendations that affect the FDA directly and our plans for implementing the recommendations by the regulatory work group.

First, instead of regulating the elemental mercury component, which is presently classified as Class I, and the alloy, now in Class II, separately, we would regulate both as a single Class II product. This recognizes the modern-day use of amalgam as a pre-mixed, encapsulated product. Such action also gives us broader regulatory options that you discussed yesterday, which would include guidelines, as well as postmarket studies.

To implement this recommendation, we plan to publish a notice in The Federal Register proposing the change in the classification of dental mercury. We hope to accomplish this by late spring, maybe. Naturally, if we need to, we will come back and confer with the Panel. But these are things you should be made aware of in case you get asked questions.

As another step in implementing this CCEHRP recommendation, FDA plans to send a letter to dentists and manufacturers informing them of our recommendation that the use of mercury in dental offices be confined to encapsulated forms. Dentists still using devices that titrate amalgam with free mercury will be strongly encouraged to switch to using amalgamators that accept the pre-encapsulated form.

The second recommendation had to do with the allergic sensitivity reaction to amalgam and other restorative materials that may occur, and that it would be helpful if dentists had information about the ingredients in a material.

FDA intends to issue a regulation requiring producers of all dental materials to disclose their product ingredients in labeling that lists the components in descending order of percent by weight composition, but without listing the actual percentage of each component.

Prior to this regulation, we will send a letter to all manufacturers of dental devices that are composed of metal alloys which are intended to remain in the oral cavity for an extended period of time, strongly recommending that they voluntarily place a list of ingredients in descending

order of percent composition in their label.

By taking this step, we would enable dentists to shift to a substitute material if a reaction occurs, or avoid a particular substance if a preexisting allergy condition is known.

The last recommendation by the regulation, as well as the education work groups, was that the Agency—and this is echoing what Dr. Kessler just said—be more proactive in encouraging health professionals and patients to report adverse effects from all dental restorative materials and devices. We intend to more actively publicize the problem reporting program through journal articles, presentations, correspondence and discussions with the professions and consumers. We will also try to undertake an effort to inform other government agencies about the program and the benefits of referring and reporting problem reports.

(Slide)

I would like to say that the report addresses three policy issues: Should amalgam use continue? The bottom line is yes.

Should existing amalgams be replaced? Not unless they need to. Presently, there are no data to compel a change by the Public Health Service in the current use of dental amalgam.

What are the cost implications? In a word, substantial. One estimate in the book using a model demonstrates that the use of alternative restorative materials in place of dental amalgam would increase the annual national expenditures by more than 12 million.

Lastly, what I would like to say is that during the two-year long process to develop this amalgam report, it was the thought of a colleague, Steve Corban who is on several of these committees as well, captures the goal of the Public Health Service regarding dental amalgam in specific and oral health in general. I think it is said quite well here.

(Slide)

I would commend you to read the report. It is a nice document containing everything in one place. If you have any questions, either myself or I will refer to my colleagues who will be glad to take them.

DR. ROBERTSON: Are there questions from the Panel?

(No response)

DR. JOSEPH: Terrific. Thank you.

DR. ROBERTSON: Well, I have one. Your remark about the necessity of replacing amalgams

was whenever they need to. Would you like to expand on what "whenever they need to" means?

DR. JOSEPH: The question was posed relative to some practices now of replacing the amalgam without it being defective because of the hope that it would alleviate certain conditions or disease states. There are no data to indicate at this moment that the removal of amalgam does, indeed, relieve those conditions or states. However, if you have a defective amalgam—margins are breaking down or it is cracked, or whatever—then it should be replaced. The choice of what to replace it with, naturally, will depend on that particular situation.

DR. ROBERTSON: Very good. Thank you.

DR. JOSEPH: Thank you.

DR. ROBERTSON: Today the Panel will consider a new drug application for a root canal filling material. We will begin with an open public hearing. A list of speakers for today's meeting has been provided at the registration desk. The first six speakers are persons who individually contacted FDA and expressed an interest in addressing the Panel. Each person has been given three minutes.

With the exception of the first speaker who has an important commitment elsewhere, the speakers will appear in alphabetical order.

The next five speakers represent organizations. Each has been given ten minutes to speak.

When each speaker approaches the microphone, we would ask that you give your name and your affiliation with any organization that has a known position related to products being discussed today, and any financial ties to the manufacturer of the product or products. This includes any payment for accommodation or travel to this meeting.

The timekeeper will maintain a time clock. When you have two minutes remaining the timer will show yellow; at one minute it will show red; and when you have run out of time it will be a blinking red. We would ask you to conclude your remarks at that point.

I would remind Panel members that it is important for all of us to speak into a microphone. I am told, however, that they have worked out the location of where we are and we do not have to precede our comments with our name today.

Because this is a large meeting, we are on a tight timetable. I would ask that any discussion or questions be recognized by the chair.

We will begin with Dr. Siegel. Dr. Siegel?

DR. TYLENDA: I believe that is Dr. Alan Siegel, from Tyson's Corner, Virginia.

DR. ROBERTSON: Welcome, Dr. Siegel. Would you give us your name, where you are from and what your affiliation is?

COMMENTS BY DR. SIEGEL

DR. SIEGEL: My name is Dr. Martin Siegel. I am a general practitioner, practicing in northern Virginia, in the McLean area. I am just here as an individual. I am not representing any group.

I would just like to give you a few minutes of my experience concerning the Sargenti technique. I graduated dental school in 1972 and I entered into private practice in 1973. Since that time, I have done approximately 3000 root canals utilizing the Sargenti technique.

I have found that I have had a success rate of over 95 percent and I have cases going back 20 years that I have postoperative x-rays on. I would like to just relate the following that I have found with the Sargenti technique:

I feel that it is a superior technique because, one, it eliminates a lot of postoperative pain and also eliminates a lot of pain in between visits of standard root canals.

It reduces chair time and, in many cases, allows for one visit completion of root canals.

It enables the practicing dentist to provide quality, good care at a reduced price because there is less chair time involved. I feel it is an excellent service to the public.

What are my criteria for success of root canals? First and foremost, I would feel it would be the elimination of pain. Secondly, if there is periapical lesion, I feel that the healing of the lesion should be able to be shown radiographically over a period of time.

The Sargenti technique accomplishes both of these criteria more effectively, in many cases, than standard gutta-percha. I have personally retreated a number of teeth that have been treated with the gutta-percha technique that were causing patients pain, and I found that by doing the Sargenti technique I have been able to eliminate this pain.

What are the causes of failure in the Sargenti technique? I feel they are much the same causes of failure as with any technique: incomplete instrumentation; incomplete debridement of the canals; overfilling of the canal. Any technique that is abused or is done incorrectly, I feel, will eventually fail. I do not care if this technique is standard gutta-percha paste, warm gutta-percha, whatever it is, if it is abused it will not work.

My experience and success with the Sargenti technique is that it is extremely operator sensitive. You cannot just pick up this technique overnight. It is a technique that has to be studied and it definitely has a learning curve to it. Great care must be taken in length determination,

debridement of canals, mixing the proper texture of the paste and, most importantly, introduction of the paste into the canals without extruding through the apical foramen.

In conclusion, after working with the Sargenti technique for 20 years, I feel very strongly that it would be a grave injustice to the public not to allow this technique to continue. Millions of teeth have been saved by this technique that otherwise might well have been extracted, thereby saving millions of dollars in reconstructive costs.

Certainly, in today's atmosphere of rapidly escalating health care costs, a technique such as the Sargenti technique that affords increased ease and access to endodontic treatment at a lower cost should certainly be considered.

Thank you very much.

DR. ROBERTSON: Thank you, Dr. Siegel.

Dr. John C. Baar. Welcome, Dr. Baar.

DR. BAAR: Thank you. I wish to demonstrate some slides.

DR. ROBERTSON: Certainly.

COMMENTS BY DR. JOHN C. BAAR

DR. BAAR: I am John C. Baar. I am a general dentist in practice here, in suburban Maryland. I graduated from the University of Maryland in 1966 and I have been using the Sargenti method of endodontics for approximately 20 years.

What I wanted to share with you today are several cases that I have had the opportunity to follow for a number of years, where the teeth were previously treated with other forms of endodontics. They were endodontically compromised. They had been treated many years prior to me treating the case. I have followed them after I originally examined the patients because the teeth were asymptomatic when I first saw the patient and I waited until they became symptomatic. When you see something that has been in place for 20 years, you do not disturb it if it seems to be working.

So I have brought some "before and after" slides and we will go over those right now. Is it possible to turn any more lights down?

(Slide)

I believe the first picture was taken in 1976; the second was taken in 1982. This patient came in with acute pain. We were working on the right central incisor, tooth number 8, that had

previously been filled with gutta-percha, draining fistula.

I retreated the case and the film on the right is six years postoperatively. We have a complete bony fill of the periapical granuloma.

(Slide)

This is one when I was retreating the case. There was a slight overfill. The tooth had been compromised, as I said, before I started treatment. My choice here was either endodontic surgery or removal of the tooth or trying to retreat the case using the paste filler.

(Slide)

There is the tooth in 1982—complete fill of the apical granuloma.

(Slide)

This patient presented with pain and swelling. This root canal was done over ten years previously. It was a support for a bridge. I was faced with the options of surgery, removal of the tooth or attempting to renegotiate the canals. I had the patient referred to a surgeon for a surgical opinion. His opinion was that surgery would be impractical because of potential complications. So my choice was further limited. I decided to treat the case if I could get through and renegotiate the canals with the Sargenti paste.

(Slide)

I managed to get through, and this is a year postoperatively. No more draining fistula. The tooth is stable and we essentially have a natural implant here to further rebuild the bite. I think we saved a considerable amount of money for this patients instead of having to go through an artificial implant.

(Slide)

The slide on the left demonstrates a granuloma that was present. This tooth had been root canaled 24 years previously. It had been asymptomatic since I first saw the patient ten years prior to this and finally became symptomatic. We renegotiated the canal, removed some of the gutta-percha and used the Sargenti paste in its place. I think that film was taken in 1992. It represents a six-year postoperative picture.

(Slide)

Overfill. Again, the tooth was compromised to begin with.

(Slide)

It also demonstrates how well tolerated this paste is.

DR. ROBERTSON: Dr. Baar, could you conclude, please?

DR. BAAR: Yes.

This is my last case. This patient had this root canal done in 1958. I saw him in 1977 and it was asymptomatic. I informed the patient there was a potential problem. What we did was observe it until it became symptomatic, roughly eight years later. I treated that case by renegotiating the canals. You can see we have bone filling out in an area where we had a granuloma for at least 13 years, possibly as long as 30 years.

(Slide)

That was the original granuloma.

(Slide)

I was working on the tooth.

(Slide)

We almost got complete bone fill after six years of time.

DR. ROBERTSON: Dr. Baar, thank you very much.

DR. BAAR: In conclusion, I would just like to say that I think the Sargenti paste formulation has saved many teeth that otherwise we would have had to extract.

DR. ROBERTSON: Thank you.

Dr. Benedict Kimmelman, please.

COMMENTS BY DR. BENEDICT B. KIMMELMAN

DR. KIMMELMAN: Good morning.

My name is Benedict B. Kimmelman. I am a member of the American Endodontic Society. I have been in general dental practice since graduation from dental school in 1936, except for five years on active military service. I have also carried out research in several areas of dentistry as a clinical associate professor of medicine at Harlem and Medical College, in Philadelphia, as an

attending and dental researcher in Einstein Medical Center, in Philadelphia, and a principal scientist and manager of dental sciences at the Franklin Institute, all in Philadelphia, over a period of 35 years.

I believe FDA approval of the N2 or Sargenti root canal filling material would be completely appropriate, as justified by the ample clinical evidence of its safety and effectiveness attendant on decades of use by thousands of United States dentists on literally millions of teeth and by supporting laboratory evidence.

My familiarity with the material, its extensive use on the issue surrounding its use, is based largely on research projects and administrative functions in which I participated, which were partially funded by the Society.

Several papers stemming from the work were published and refereed in dental journals of national scope. One research effort was directed at eliciting information on any and all cases of adverse health related sequelae to Sargenti root canal filling placement based on years long follow up.

A second was to monitor the 1982 multi-dentist study of 100 patients, as proposed by Dr. Mann of FDA. A third was to determine the existence or extent of formaldehyde health hazards entailed in the use of such sealer.

Each of these efforts addressed charges broadcast by respectable opponents of the Sargenti system. In project I, we located numbers of dentist participants who plowed through records and culled numerous patients, none reporting any ailments that could reasonably be attributed to their root canal treatment.

In project II, follow ups gave solid evidence of lasting effectiveness of the system. In project III, we showed that the formaldehyde "hazard" in a dental operatory was just over 1 percent of the most stringent requirements of just 1 parts per million established by NIASH.

These results showed that there were no bases for the charges made. I would also note that our formaldehyde paper, published in The Journal of Dentistry for Children, was awarded a prize for journalism in 1984.

I also served four years as chairman and reviewer of applications for the American Endodontic Society Fellowship status. Each applicant was required to submit records and x-ray films on a minimum of 20 teeth successfully treated with the Sargenti N2 paste, with favorable postop. evidence at intervals of up to at least 2 years, which are stiff standards and criteria. I reviewed records of about 4500 teeth, part of the 9500 records that were submitted in total to FDA.

What impressed me then and since then was the quantity and quality of work shown in these records and films. These dentists did not require any less demanding system. They were

obviously up to the most exacting requirements. That they elected to use the Sargenti system and material made the point.

The 10 following years of conferring Fellowship status reported by others amply reaffirms that point.

Thank you.

DR. ROBERTSON: Thank you very much, Dr. Kimmelman.

Dr. N.J. McDonald? Welcome, Dr. McDonald.

COMMENTS BY DR. N.J. MCDONALD

DR. MCDONALD: Good morning. I am Neil McDonald, an Assistant Professor of Endodontics at Baltimore College Dental Surgery, University of Maryland. I have no financial interest in any of these materials and I appear decrying approval by the FDA for paraformaldehyde containing root canal sealers.

Paraformaldehyde-containing paste originated in Europe in the 1890s. Gyisi was one of the first proponents of this technique. The technique using paraformaldehyde was popularized in the early 1970s by Sargenti, who produced the Sargenti compound, as well as other formaldehyde-containing formulations used in endodontics, such as N2 and RC2B.

Numerous research tests of paraformaldehyde have demonstrated that the material is extremely irritating and toxic. Cell culture studies have shown it to be toxic at one-hour intervals, and at 24 hours total cell lysis is present. Histologic reactions to N2, which contains paraformaldehyde in varying concentrations, show that it is surrounded by an initial sign of polymorphonuclear leukocytes, followed by sings of edema and necrosis.

Further evaluation of up to seven months by measuring chromium-51 release shows continual cytotoxicity. Evaluation of time or implanted specimens of animals shows a continuum of round cells and macrophages present. Macrophages will typically contain granules of the N2 material.

Evaluation of hard tissue reactions as a response to N2 placement shows initial acute inflammation that progresses to chronic inflammation with diffuse eosinophilia and loss of cellular detail. It leads to granuloma formation, bone loss and eventual root resorption. Ankylosis has also been shown to be present with inflammatory resorption.

The application of paraformaldehyde compounds directly onto pulp tissue shows that you initially get edema, distention of blood vessels, followed by tissue degeneration. This response will eventually progress to total pulpal necrosis which will be followed by chronic inflammation and necrosis of the adjacent hard tissue, severe root resorption and possibly osteomyelitis.

A number of cases of paresthesia have been reported as sequelae to endodontic overfilling with the paraformaldehyde type compounds. This event can happen even in the most skilled hands of placement of any obturation material.

It has been shown that when N2 comes into contact with nerve tissue, the neuronal tissue is irreversibly damaged.

Additionally, a number of case reports of Aspergillus infections have been attributed to the use of the N2 family of compounds.

Endodontically treated teeth are not a closed system. They have a vascular and neuronal supply from the periodontal ligament and when pulpal responses are absent, fluid exchange and immunological reactions occur due to chemical exchange through the dentinal tubules and any lateral or accessory canals that may be present.

Substantial body of scientific and clinical evidence shows that paraformaldehyde-containing materials are cytotoxic and cause irreversible damage to living systems. The institutional review board at the University of Maryland would not approve, based on current research data, any animal or human trials of these types of compounds.

It is well documented, and the research body of evidence is such that I cannot support the use of paraformaldehyde materials for FDA approval under these circumstances.

Thank you.

DR. ROBERTSON: Dr. Emanuel Ploumis?

COMMENTS BY DR. EMANUEL PLOUMIS

DR. PLOUMIS: Secretary Kessler, Secretary Tylenda, members of the Panel, ladies and gentlemen, I have been a member of the American Endodontic Society since 1972. As an active member of the Society, I have served as board member, first vice president and, since 1990, I have been Mastership chairman.

Our Mastership program was designed for the AES members who have demonstrated a proficiency in Sargenti endodontics and have a desire to achieve the highest level in the American Endodontic Society.

AES Mastership was designed to be a rigid demonstration of proficiency. In fact, to my knowledge, it is more rigid than the academic requirements for a specialist in endodontics.

To date, over 4420 cases have been submitted by 34 members of the American Endodontic

Society. Of the 34, all are members of organized dentistry or have participated in local, district, state and national dental organizations. All are required to write papers for publication. Articles have been printed in our AES newsletter and in The Journal of General Dentistry, as well as other publications.

Continuing education is also a requirement, with a minimum of 75 hours over a 3-year period.

The American Endodontic Society, its members, its followers and its masters are general practitioners who have demonstrated that endodontic therapy that follows the procedures of the Sargenti endodontics have demonstrated an unequalled success rate in millions of teeth that have root canal therapy.

Finally, I use Sargenti endodontics in my office, and have for over 20 years, and I am proud to have done so. The reason is that I have saved thousands of teeth at an economical cost to the patient, with predictable results and results that have not demonstrated any pulpal or other tissue necrosis from paraformaldehyde, or any other frightening statements by people other than the Sargenti endodontic group.

Thank you.

DR. ROBERTSON: Thank you very much.

DR. CURRO: Mr. Chairman, may I ask a question?

DR. ROBERTSON: Yes.

DR. CURRO: I have a question of Dr. Ploumis.

Do you view this as a drug or a device, the N2?

DR. PLOUMIS: I am familiar with devices. I am not familiar with the standards for drugs. If it is to be considered a drug, can someone give me a definition, their definition of a drug, and I will see if I accept it or reject it?

DR. TYLENDA: May I comment? The purpose of today's meeting is not to determine that this is a drug or a device. We are here to examine the material presented in the submission.

DR. PLOUMIS: Somebody asked me if I consider it a drug or a device.

DR. TYLENDA: And you may answer, but FDA is not here to state the reasons why this product is a drug or device. A decision is made within FDA.

DR. PLOUMIS: Who asked the question?

DR. CURRO: I did.

DR. ROBERTSON: Thank you. I think we will go on.

Dr. A. Joseph Venneri?

COMMENTS BY DR. A. JOSEPH VENNERI

DR. VENNERI: Good morning and thank you.

My name is A. Joseph Venneri. I am a practicing dentist. I represent myself, and I am reading a letter from Dr. Gordon Christensen. I practice in Hatboro with two of my children, Dr. Doreen and Dr. Joseph, and I present today in favor of approving the N2 product sealer, which has undergone years of research.

I would appreciate it if you would deliver on my behalf, the enclosed letter to be presented to the FDA Dental Products Panel meeting, on February 12, signed, Gordon J. Christensen, as written to Executive Secretary Dr. Carolyn Tylenda:

Dear Dr. Tylenda: I am sorry that I cannot attend the February 12, 1993 FDA Dental Products Panel meeting. I have requested that Dr. A. Joseph Venneri read this letter.

May I please express some views relative to the current arguments concerning the Sargenti technique and its use in the United States? For over 30 years I have lectured internationally on many subjects sin dentistry. Much of my information comes from research accomplished by 40 full-time researchers and 350 field evaluators of Clinical Research Associates, a non-profit oriented research organization that serves the worldwide profession. Our publication has a readership of 100,000 persons monthly and in several languages.

During my frequent encounters with the dentists of the world, the subject of endodontic therapy comes up often. I am a practicing prosthodontist, not an endodontist, and I must make very clear that I am not a proponent or opponent of the Sargenti technique. If anything, I am an ombudsman on this subject. I have observed thousands of root canals treated with the Sargenti technique in many countries of the world. Similarly, I have observed thousands of root canals treated with the standard gutta-percha techniques more popular in North America.

It would be difficult to ascertain the superiority or inferiority of either technique on this empirical observation basis. Also, it would be very difficult to state that one or the other technique has more failures or serious complications. Legal activities have been present with both techniques. If anything, the group of dentists supporting he Sargenti procedure is more enthusiastic about their success than the gutta-percha group.

Our group, Clinical Research Associates, is not political in nature and, for that reason, we have not engaged in research on the Sargenti technique. It was obvious to me many years ago that the subject was loaded with bias and political and organization confusion. I would only like to see justice done to the thousands of dentists using the Sargenti technique and the tens of thousands of persons they have treated successfully.

Yes, there are some potentially slightly toxic materials in the Sargenti formulation. However, many other medications, cements, pediatric dentistry pulpotomy agents, and other materials have significantly more toxic potential. Even some foods contain agents that are more dangerous.

Lets eliminate the political bias from this subject, accept the empirical and scientific research, and let the Sargenti group prove themselves over the next few years. Clinical success is the final research test. They have enjoyed clinical success for many years throughout the world.

I respect and acknowledge the fantastic positive advancements of traditional American endodontics, and in no way do I infer any problems with their beliefs or their methods of treatment. In fact, I work daily with traditional endodontists in my busy prosthodontics practice.

Thank you for your consideration, sincerely, Gordon J. Christensen, founder and senior consultant of Clinical Research Associates.

(Slide)

These are the clinical successes showing the area of rarefaction. I am not going to burden the Panel, but for those lay professionals, the area at the apex, the bottom of the tooth, shows that within two and a half years later healing has occurred. It confuses me, all the cellular trauma that was attributed to it a moment ago, but when put into the human body, the body accepts this product with such clinical success.

(Slide)

Young children with fistulas.

(Slide)

The area of treatment is on the left, the tooth with the opaque material going into the canals.

(Slide)

And this is no more than three weeks postoperatively, with the amalgam still in position prior to the treatment plan. I am going quickly.

(Slide)

On the bottom, you will see the dark circle. This is the body's response to some problem.

(Slide)

And this is the treatment plan with the material in the canal. Notice that healing has started to occur.

(Slide)

And this is in six months. I apologize for the speed, but look at the area of healing. Had all the things attributed a moment ago occurred, this human body would not have responded in that fashion.

(Slide)

Large circle opposite the central incisor—we do all the techniques taught in dental school, and there is the body again showing successful healing and accepting this product.

(Slide)

Our last slide, right over here, my dear colleagues and Panel members, is a young lady who still comes to us with her young child who is now four.

(Slide)

Four years later, showing the area of healing, we have a ten-year postoperative giving us at least another significant sign of longevity. I have been in practice for 40 years and certainly I have learned not to do anything that would not be there tomorrow morning or the next day.

DR. ROBERTSON: Thank you very much.

DR. VENNERI: Thank you. I apologize for the speed.

DR. ROBERTSON: Dr. Hudson? Dr. Hudson? We had a request this morning from a Dr. Hudson, from Cleveland, who wished to address the Panel.

Is Dr. Hudson here?

DR. RIGBY: That is me. My name is Dr. Rigby from Hudson.

(Laughter)

DR. ROBERTSON: I am sorry. Dr. Rigby, from Hudson. Welcome, Dr. Rigby.

DR. RIGBY: I apologize for the confusion.

DR. ROBERTSON: You have three minutes with us, please. The lights were not working for the last speaker so I will watch you.

COMMENTS BY DR. JOHN RIGBY

DR. RIGBY: Okay. My name is John Rigby, from Hudson, Ohio. I graduated from Case Western Reserve Dental School sixteen years ago where, as a senior in the dental school, I was given formal instruction in the Sargenti technique. This is the handout that you are welcome to have from the professor who taught it at Case Western University for over sixteen years.

We had a little tiff in Ohio 2 years ago, where some members of the board tried to propose a ban on the technique. At that state dental board hearing, 11 endodontists came and they favored a ban on the Sargenti technique; 22 general dentists came and they were all opposed to the ban. That gives you a little bit of a breakdown as to what is going on in our state.

There is currently no ban in the State of Ohio on the use of N2.

Now, the greatest research in the whole world is located in a dentist's file cabinet. This is the number of patients who have come into my office since the ADA meeting in October. I take postop. x-rays of everyone. I keep strict records of every single person who comes into my office.

I would like to just run through one case. In July of 1992, this young boy came in with a large draining fistula. I made the correct diagnosis that endodontic treatment was needed, and made a proper measurement wire x-ray.

Immediate postoperative x-ray of that tooth shows three lateral canals filled with the N2 material. Six months later there is total bone regeneration in the presence of N2.

This is something that I see every day, every single day. Norm Reckenbacker, is thirteen and a half years postop. Margaret O'Donnell, fourteen years postop. I do not know where the trauma is that these people are referring to. People come to me in pain and I get rid of their pain and I save their tooth, and I do it safely and efficiently.

I would like to give one more bit of information. I presented this information to the State Dental Board of Ohio at the time. In consult with oral surgeons in the area, I presented evidence of 100 years of oral surgeons in practice who had never seen a single person in any way harmed by this technique. So I do not know where these people are but they are not in Ohio.

Thank you very much.

DR. ROBERTSON: Thank you, Dr. Rigby, very much.

DR. RIGBY: Would you like these?

DR. ROBERTSON: You may leave them if you wish. Dr. Joseph D. Maggio, from the American Association of Endodontists. Dr. Maggio, you have ten minutes. I have lost confidence in the light system so I will wave at you when you have a minute of so left.

COMMENTS BY DR. JOSEPH D. MAGGIO

DR. MAGGIO: Thank you very much.

Good morning. I am Joseph Maggio. I am a past president of the American Association of Endodontists. I am here as a representative of the American Association of Endodontists. I have no commercial interest in any endodontic root canal filling material. My expenses are being reimbursed for travel only by the American Association of Endodontists.

The AAE, the American Association of Endodontists, is a not-for-profit organization that represents the discipline of endodontics for all dentists and the interests of practitioners and educators in the dental specialty of endodontics, one of only eight dental recognized dental specialties by the American Dental Association.

Endodontics is that branch of dentistry concerned with the diagnosis, prevention and treatment of diseases and injuries to the dental pulp and adjacent tissues. The practice of endodontics requires an understanding of the morphology, physiology and pathology of the human dental pulp and all associated dental structures, including the bone surrounding the teeth.

The objectives of the American Association of Endodontists includes the promotion and the dissemination of scientific, clinical and laboratory research to foster high standards for the practice and teaching of endodontics in the United States and, indeed, throughout the world. The American Association of Endodontics contributes to the establishment of endodontic standards and provides guidelines for both undergraduate and postgraduate endodontic curricula in all ADA accredited dental schools, and that would include all the dental schools within the United States.

Our Association is deeply concerned with the public's safety. Therefore, we oppose the approval of any new drug application for any root canal filling material that would contain paraformaldehyde, known as Sargenti N2, N2 Universal or RC2B. There is an overwhelming weight of scientific research that demonstrates that paraformaldehyde-containing root canal filling materials are, in fact, unsafe.

Sargenti pastes were introduced into the United States in the late 1950s and the early 1960s. The use of these materials has caused serious injuries to countless dental patients who, prior to receiving treatment, were unaware that very efficacious and safe alternative root canal filling materials were available.

In response to only 30 requests from attorneys, as well as neurosurgeons, oral surgeons and endodontists, who were subsequent treaters of these patients, we received 21 responses, and in those 21 responses we have copies of affidavits documenting more than 150 procedural accidents that resulted in serious patient injuries as a result of being treated with paraformaldehyde-containing root canal filling materials. Certainly, more exist and could be documented if only we expand our survey.

Extensive scientific research regarding paraformaldehyde-containing root canal filling materials has conclusively demonstrated that these materials are unsafe. Based on a survey of the literature, we have compiled, and made available to the FDA, a bibliography containing 141 articles, all from refereed scientific journals throughout the world that document the cytotoxic and neurotoxic effects of Sargenti or paraformaldehyde-containing root canal materials. These journals include the Journal of the American Dental Association, the British Dental Journal, Lancet, Oral Surgery, Oral Medicine and Oral Pathology, the Journal of Dental Research, Archives of Oral Biology, International Endodontic Journal, Journal of Endodontics, Archives of Otorhinolaryngology, and Journal of Periodontology.

This body of research demonstrates that Sargenti paraformaldehyde paste can cause irreversible damage to the tissues near the root canal system, such as the destruction of connective tissue, destruction of bone, intractable pain, paresthesia and dysthesia of the mandibular nerve, and chronic infections of the maxillary sinus. Moreover, the damage is not necessarily confined to the tissues near the root canal. Various ingredients in the formula for Sargenti materials have been found to travel throughout the body and have been shown to infiltrate the blood, lymph nodes, adrenal glands, kidney, spleen, liver and brain.

The body of published scientific research documenting the dangers of Sargenti paste is uncontested. However, we have found no research results published in any refereed journal that document the safety and the efficacy of the use of paraformaldehyde as a root canal filling material. Much anecdotal testimony exists but the scientific background for it is lacking.

Throughout the past thirty years, the formula for N2, Sargenti paste, or now N2 Universal, has been elusive and it has been ever changing. The original material contained as much as 11 percent lead tetroxide and phenylmercuric borate, heavy metals that lack any rationale for inclusion in any part of the human body. The one component, however, that has always remained is paraformaldehyde in a varying percentage, from as low as 4.5 to as high as 14 percent.

Paraformaldehyde is a hydrate of formaldehyde. It is a powder and in its powder form it contains somewhere between 91-99 percent formaldehyde. It is a basic ingredient in this particular

material.

In the past, Sargenti proponents have attempted to characterize their decision to use N2 as a reasonable selection from alternative filling materials about which there are well-founded professional differences of opinion. While there is a difference of professional opinion, it is certainly not well founded. The choice is between root canal filling materials that over time have proved to be safe and effective and those that have not proved to be safe at all.

If there were well-founded differences of professional opinion, the use of Sargenti type materials would be taught as an acceptable alternative at all ADA accredited dental schools. It is not. No accredited dental school is now, or has ever, taught or recommended the use of Sargenti material. It may, in fact, be covered in a seminar as a point of information but it has never been recommended by any dental school in the United States for use. We have copies of letters from leading dental schools stating that the use of Sargenti paste is not taught because the paste is toxic and unsafe.

Of course, virtually all dental materials and drugs involve some element of potential risk. However, in determining the appropriate procedures to be taught in dental schools, the judgment has been made that the risk inherent in the use of N2 or paraformaldehyde-containing paste is, in fact, unnecessary and is an unwarranted risk to patients because, certainly, safe alternatives are available, and those alternatives do not involve the same elements of risk. Damage from paraformaldehyde is, in fact, permanent when it occurs.

In addition, no branch of the military service nor the Department of Veterans Administration teaches or endorses the use of Sargenti type material.

Public health concerns and recent litigation have made the American Association of Endodontists aware of a significant number of patients who have suffered serious injury as a result of treatment with paraformaldehyde-containing root canal filling materials and sealers.

The Association of Trial Lawyers of America, in its Consumer Protection Program, called the ATLA Alert, published, in 1992, evidence of injuries and damages associated with the use of Sargenti paste. ATLA called on the FDA to ban the material and seize all identifiable supplies.

ATLA is committed to safeguarding victims; rights, promoting injury prevention and fostering the disclosure of information critical to public health and safety.

The issue is safety, and it is safety for the patients that we serve and that we treat. The American Dental Association estimates that 30 million endodontic procedures will be delivered annually by the year 2000. Based on records of third-party payers, endodontists deliver less than 20 percent of those endodontic services. Therefore, better than 80 percent are being delivered by general practitioners who have been well trained and are well qualified to deliver that type of treatment. This is not an issue of turf. It never has been a turf battle. It is purely an issue of safety.

Two recent independent surveys indicate that about five percent usage of Sargenti type materials occurs even though it has the unapproved status by the FDA.

If the FDA approves the new drug application, even more dental patients will continue to be exposed to the unnecessary risk of serious, often debilitating and, in some instances, life-threatening injuries. In order to protect the public, the FDA must reject this application and ban the use of all paraformaldehyde-containing root canal filling materials or sealers.

The FDA has already made substantial efforts to protect the public from unsafe drugs, especially this unsafe drug. For example, the FDA has repeatedly declared that these are unapproved prescription drugs that may not be distributed in interstate commerce. Although the quantities in which the Sargenti pastes are produced on the local level exceed the needs for single patient treatment, they are not produced in such large quantities or under such circumstances that regulatory efforts directed at interstate commerce will have a significant effect.

Individual state boards of dentistry, composed of both dental practitioners and members of the lay public, include in their objectives the protection of the public within their state. Several of these boards have recently addressed the safety of paraformaldehyde-containing root canal filling materials. The Ohio State Board of Dentistry, that was talked about before, voted unanimously to ban the material. The state legislature asked that it only be held until the FDA makes a ruling. Recently, Florida and Missouri have banned the use of the material in their states. The State of Maryland has prohibited its use for seven years.

On behalf of the American Association of Endodontists and, specifically the scientifically-based discipline of endodontics, I implore you as the advisory committee to recommend to the FDA that for the protection of the American public this unsafe root canal material not be used, and no permission for further research, and especially human studies, be granted.

Thank you.

DR. ROBERTSON: Thank you very much, Dr. Maggio.

DR. GLOWACKI: I have two questions.

DR. ROBERTSON: Yes, two questions.

DR. GLOWACKI: I have two quick questions for you. First, how many members are in the Association? Second, what did the Association do with the incident reports that you referred to in the beginning of your presentation? Did you pass those on to the ADA or the FDA?

DR. MAGGIO: First of all, there are just under 4000 active members of the American Association of Endodontists, representing mostly endodontists but we have a high percentage of

general practitioner members as well.

The affidavits that we have were given in a packet. You all should have had a copy of the packet. It was sent to Commissioner Kessler well over a year ago. I also have brought along copies of samples of those affidavits and I will be happy to leave them.

DR. ROBERTSON: Thank you.

The next speaker is Dr. William Fentress, from the American Association of Forensic Dentists. Dr. Fentress, you have ten minutes and I will give you a sign when you have a minute left.

COMMENTS BY DR. WILLIAM L. FENTRESS

DR. FENTRESS: Thank you.

I am Dr. William L. Fentress, a representative of the American Association of Forensic Dentists (AAFD), a group of approximately 3500 dentists and related scientists concerned with forensic dentistry.

The AAFD organization was formed in 1978 and has worldwide membership. The majority of our membership are practicing in the U.S. We are not affiliated with any other professional group, and this testimony is the official position of our independent organization.

We appreciate the opportunity to express our views and hope you, members of the Dental Products Panel, will share our belief that the use of the N2 Sargenti endodontic sealer, root canal filling material be approved by the FDA.

The AAFD is greatly concerned by the twenty-year battle between the general dental practitioners who mostly favor the use of N2 and the endodontists who officially oppose its use. We believe this situation has evolved over the years as an economic turf war issue, where the endodontists desire to eliminate the inexpensive, easily done and effective N2 endodontic technique so that more patients will be referred to their specialty.

This action has been seen in a systematic combination of the use of N2 in many dental schools, in textbooks, in pressure exerted on journal editors not to publish N2 research that is positive, the creation of malpractice hit teams who will testify against N2 treatments in civil cases, and in direct retaliation to endodontists who favor or are neutral to the use of N2.

This situation is unfortunate because valuable research supporting the safety and benefits of N2 is being diminished and the public is being discouraged from the benefits of this very effective material.

Several years ago the AAFD convened a special committee council, consisting of dental school

professors, clinical, endodontists specialists, general practitioners and dental material scientists, to review the data concerning N2 and related paraformaldehyde-containing sealers. After a lengthy and exhaustive study of hundreds of published reports and articles, discussing both merits and disadvantages of N2, material analysis and clinical interviews, the committee concluded that N2 is a safe, effective endodontic sealer material if used as directed.

The committee concluded that the majority of the negative N2 reports were caused by the misuse of the product, and not by any unique danger of the material by itself. N2 is no more dangerous than any of the other commercially available endodontic sealers and, in many cases, has been shown to be safer.

Not only is N2 a safe, effective and reliable endodontic sealer, but it allows dentists an opportunity to do endodontic treatment faster and more inexpensively than many other conventional endodontic treatments. This translates to a lower patient cost for endodontic treatment and, thus, increased retention of teeth which would have been otherwise lost due to patients' economic restraints.

The public considers endodontic therapy as a generally painful and traumatic process. Many people avoid endodontic therapy because of the frequency of pain and postoperative complications. This seriously affects their health.

In a unique AAFD-commissioned study, N2 treatment was shown to be significantly less painful and resulted in fewer incidents of postoperative swelling than other tested sealers.

In 1147 cases of endodontic treatment, 1.6 percent of patients reported swelling and 3.2 percent reported pain after N2 treatment. This was compared with the normal incidence of 10 percent swelling and 20 percent of the patients reporting pain after conventional endodontics.

Treatment with N2 appears to be less painful than any other tested sealers. This study is now in press. I believe there is an enclosure in your packet of a graph on this.

In conclusion, the AAFD endorses the safety, efficacy and humanly beneficial use of the N2 paraformaldehyde-containing root canal filling materials. This endorsement is based on sound scientific study and clinical experience. We urge the Panel members and FDA to approve its use.

Thank you.

DR. ROBERTSON: Thank you very much.

The next speaker will be Dr. Ken Burrell, from the American Dental Association.

COMMENTS BY DR. KEN BURRELL

DR. BURRELL: Thank you, Mr. Chairman. Thank you for the opportunity to speak before you today.

My name is Ken Burrell. I am Interim Assistant Executive Director of the American Dental Association's Division of Scientific Affairs. I am also Director of the Association's Council on Dental Therapeutics, and I continue to practice general dentistry.

By the way, I have no financial interest in any manufacturer of root canal filling materials.

The American Dental Association assumes that the new drug application for root canal filling material which the Panel plans to discuss is a root canal filling material containing paraformaldehyde.

Based on this assumption, the Association urges the Dental Products Panel and the Food and Drug Administration to process the new drug application as soon as possible. The availability of safe and effective products in this category continues to be an issue that is of great importance to the profession and to the public. The issue is of such concern that in 1991 the ADA's house of delegates passed a resolution providing that the American Dental Association continue its efforts to persuade the Food and Drug Administration to determine the safety of paraformaldehyde-containing root canal filling material.

In fact, the American Dental Association, through the offices of the Council on Dental Therapeutics, has requested on two occasions that an existing root canal filling material new drug application be processed as soon as possible. It is assumed that the application before the Panel today is the one to which the Association referred on those two occasions.

Before the evaluation is completed, however, I would like to apprise the Panel of the existence of documents the Association, through its Council on Dental Materials, Instruments and Equipment, helped to develop. These documents, Specification 57 and Document 41, can be useful in evaluating products used for root canal obturation.

Specification 57 outlines the physical characteristics a root canal filling material must possess. Document 41 allows for the biological evaluation of these dental materials. Meeting the requirements of both documents can assure the safety and effectiveness of root canal filling materials according to this Council.

In addition, the Council on Dental Therapeutics discussed the usefulness of paraformaldehyde-containing root canal filling materials at its April, 1992 meeting. Following testimony from the American Association of Endodontists and the American Endodontic Society, this Council issued the following resolution:

Resolved, that the Council on Dental Therapeutics encourages the manufacturer of paraformaldehyde-containing root canal filling materials to submit the product to the Council's

Acceptance Program for evaluation.

And be it further resolved that, in addition to the manufacturer satisfying all other applicable requirements of the Acceptance Program, the Council requests that the manufacturer provide complete quantitative and qualitative composition data; clearly define the therapeutic benefits offered by the product; state all promotional claims to be used for the product; and provide a minimum of two well-designed, prospective, independent, double-blind, clinical studies in order to support the promotional, safety and efficacy claims for the product.

Be it further resolved that the manufacturer satisfy the requirements of ANSI/ADA Specification 57 for endodontic filling materials, and ANSI/ADA Document 41 for recommended standard practices for biological evaluation of dental materials and 41a, addendum.

And be it further resolved that the manufacturer's examination of safety and morbidity include a review of all available information, including retrospective and prospective studies.

Therefore, the American Dental Association urges the Panel to recommend to the Food and Drug Administration that these existing Council on Dental Materials, Instruments and Equipment documents and, if necessary, the Council on Dental Therapeutics' position be employed when completing the evaluation of this new drug application.

Thank you.

DR. ROBERTSON: Thank you very much, Dr. Burrell.

We will next hear from Dr. Piacine, from the American Endodontic Society.

COMMENTS BY DR. MARK J. PIACINE

DR. PIACINE: Good morning, and thank you.

My name is Dr. Mark Piacine. I am the President of the American Endodontic Society. I have been practicing general dentistry in Pottstown, Pennsylvania for the past thirty years after graduating from the Temple Dental School in 1962.

I have no financial interest in the American Endodontic Society or in the N2 material.

At Temple I had excellent training in endodontics, 1961-62 state-of-the-arts endodontics, under the direction of Drs. Leonard Parris and Howard Seldon. I do not know if you, endodontists, remember those names. They were my instructors for whom I have the greatest admiration and respect. I also have the greatest admiration and respect for all the endodontists who have paved the way, in a scientific way, of saving teeth and human dentition.

My instruction was in 1962. Treatment modalities have changed since then. They have improved. About 1973, I had the extreme good fortune of being introduced to a new concept in endodontic treatment, called the Sargenti method, which included use of an innovative canal filling material called N2. It included a powerful but safe and actually therapeutic sterilizing agent, which more effectively and efficiently sterilizes the entire root canal system.

The exceptional antibiotic nature of the N2 is shown in the enclosed published scientific reports of Dr. Louis Grossman—I think I have handed those out—called "Antimicrobial Effect of Root Canal Cements," and another by Broisman, van Haute, Gron and Krakow, "Antimicrobial Effects of N2 in vitro." I think you have copies of those.

But there is more. Because of N2's exceptional sterilizing ability, most treatments can be completed in just one visit, and patients report little or no postoperative discomfort. Think of it, a no pain root canal treatment. N2 has taken the hocus-pocus out of root canal treatment. Sometimes we tend to make things more complicated than they really are when they could be simple.

I introduced this endodontic concept into my own practice about 1973, and have used it exclusively in my own root canal treatment since safely, successfully, treating approximately 2500 teeth in that time frame. I know of no deleterious effects that any of my patients have suffered from that treatment.

I am aware of only 8 cases in that time frame of 2500 that were not successful, and I do not attribute this to a fault of the material or technique but possibly, rather, to a split root, a blocked canal I could not negotiate; possibly a hidden canal or some other factor. In any event, I am very proud of that success rate which I attribute to be like 99.8 percent.

So convinced am I of this material's efficacy that I have, since 1973, had 7 of my own teeth in my dentition saved painlessly and efficiently with this root canal filling material, some of them as long as 15 and 20 years ago.

The philosophy of saving teeth directed me to the American Endodontics Society, an organization whose motto is "Dedicated to Saving Teeth" and which is devoted to promoting the N2 root canal filling material and the accompanying innovative technique. I am currently very proudly the president of that organization.

From 1980 to 1986 I was privileged to serve the AES national Fellowship chairman, a post which gave me the unique opportunity to personally evaluate more than 5500 individual teeth treated by the N2 material by 202 different dentists from all over the country, actually, from all over the world. They were candidates for the prestigious AES Fellowship award. I compiled these observations into a booklet, which was handed to you, called "A Six-Year, 5500 Tooth, Comprehensive Report Attesting to the Efficacy and Safety of the Simplified Endodontic Treatment Known as the Sargenti Method." The method utilizes the N2 filling material. That is

why we associate Sargenti's name with it. You all have a copy of that book. I think it was handed out.

The work has been dismissed by some as non-scientific, merely anecdotal. I submit that 5 or 10 cases might be considered anecdotal, but 5500 cases by 202 dentists all across the country, over a 6-year period? I hardly can consider that anecdotal.

Admittedly, it is not double-blind science. I do not know how you can perform double-blind science on endodontic root canal treatment. Every canal is different even within the same mouth. How can you do a bicuspid on one side of the mouth, and would you do one on the other side of the mouth whether it needs it or not, with a different material? Even the canal would be different.

I think the book itself makes a scientific statement and that is why I submit it for your consideration.

I would like to tell you just a few things about the book. Each of the 5500 cases has been independently completely submitted to the FDA some time ago as part of the 9000 cases that were submitted.

I know of no other dental material that possesses this kind of documentation.

The book is merely the condensation and evaluation of all of these cases. For example, page 5 depicts an example of a submission sheet filed for each of the 5500 cases. It shows the complete history of the case. It shows the medical history of the patient. It shows the dental case history, the pre- and minimum 2-year postop. x-rays. Many of these cases show 5, 10, 15, even 18-year postop. x-rays. The documentation is all of successful treatment.

The chart on page 8 compares year by year the 5520 cases in this report. For instance, mostly non-vital teeth sere submitted, 60 percent of them. One-third of all the teeth were multirooted teeth, therefore, probably molars or upper first bicuspids. And 4555 different patients are represented, 57 percent were females, 43 percent males; 6 percent were older than 65 years. The youngest patient was a 4-year-old boy; the oldest patient a 92-year-old man. N2 knows no age restrictions. Exactly 50 percent of the cases were treated in a single visit. Think about it!

The chart on page 9 visually shows which individual teeth in the human dentition were treated each year, and totally. The upper central incisors lead the list almost equally; followed by the lower right first molar, a multi-rooted tooth. Every tooth in the human dental arch is represented, even a considerable number of third molars. We do them all.

The map in the centerfold shows an example of where the dentists in my survey were located. The map depicts all the AES Fellows from 1976-1990. The red dots show the location of those 202 dentists involved in this study.

You will note that a broad cross-section of the country is represented. Bear in mind that this map shows only those AES members who have distinguished themselves by earning their fellowship and is a mere fraction of the estimated 30,000-plus dentists from all over the country who use this Sargenti N2 method.

My personal favorite pages are 22 through 25, which represent but a few of the many unsolicited comments by the participants in the study. All report the same positive phenomenal success of this material with virtually zero pain. It all reflects my own personal experience with N2.

You heard what Dr. Gordon Christensen, a noted author, lecturer and researcher, said about the material—clinical success is the final research test.

But despite the millions of teeth that have already been safely and painlessly saved by this method, despite the abundance of positive scientific evidence, there are those political factions who will inexplicably not like to see this root canal filler approved. They have clouded the air with innuendoes, half-truths and outright falsehoods about its use. One of the common misconceptions about N2 is that the therapeutic 5 percent paraformaldehyde sterilizing agent somehow leaks out of the tooth, enters the bloodstream and poisons the patient. How absurd!

N2, when placed into the tooth, becomes a solid filling material within an hour of placement. Any freshman dental student can tell you that once locked into the pulp chamber and canals, there is no way the material can get out into the body.

For the sake of argument, let's just suppose somehow it could leak out. Respected dental scientist Balint Orban, who studied and reported on the use of formaldehyde back in 1934, 60 years ago, established that 5 percent formaldehyde was a therapeutic concentration. Toxicity is a matter of dosage. Therefore, 5 percent is nowhere near the embalming fluid some of our critics would say we put in people's teeth. Embalming fluid is 40 percent formaldehyde.

An average N2 root canal filling would be about the size of a 5/8 inch long piece of thin toothpick, and 1/32 of an inch is the formaldehyde in there. That is only 2.5 mg. The Arizona Poison Control Information Center says that the mean lethal dose of formaldehyde is 30-60 ml, so the amount in this product is probably insignificant.

Formaldehyde is a very common product found in textiles, building products, cosmetics, even toothpastes and mouthwashes. It is a part of every living cell. So it is not foreign to the human body. Recognizing that an average N2 root canal filling contains a mere 2.5 mg of formaldehyde, consider the following: The World Health Organization states that an average pear contains approximately 13 mg of formaldehyde, which is ingested. An apple has about 7 mg of formaldehyde in it. That is ingested. A quarter pound pork chop has 4 mg. A quart of milk, 3 mg of formaldehyde. Remember, N2 is locked inside the tooth.

I am grossly offended and outraged by those who remotely suggest I perform less adequate,

sloppier endodontics or any dental treatment because I can do it quicker and/or cheaper. I and my colleagues in the American Endodontic Society use this material because it is better and it is less traumatic. N2 has given endodontics a better mousetrap and in the many years of its use all over the world there are no known deleterious effects.

I respectfully trust the FDA will maintain its objectivity in this matter in the interest of good dentistry. I strongly urge that you recommend approval of this outstanding material.

Thank you.

DR. ROBERTSON: Thank you very much.

Dr. Newell Yaple? Welcome, Dr. Yaple.

COMMENTS BY DR. NEWELL H. YAPLE

DR. YAPLE: Thank you very much. It is a pleasure to be with you this morning.

My name is Newell Yaple. I am a practicing oral maxillofacial surgeon, from Columbus, Ohio. I am here today representing the Ohio State Dental Board, of which I was a member since 1987-1992.

The Ohio State Dental Board is composed of five dentists, a hygienist and a lay member. Four of the five dentists, at the time this issue came before the Board were general practitioners.

I paid my own way here today because the State of Ohio is in bad financial straits and could not afford to send me. But I am, indeed, representing the board, and my statement is a statement of the board and not my statement personally.

In 1990, the Ohio State Dental Board became concerned about reports of patient injuries caused by paraformaldehyde-containing endodontic canal filling materials, such as N2 or Sargenti paste. Injuries included nerve paresthesia, acute maxillary sinusitis, swelling and pain, tissue death and slough and acute bone reaction, including osteomyelitis.

Investigation by the board revealed that the Food and Drug Administration and the American Dental Association Council on Dental Therapeutics had taken no direct action on the use of these drugs at that time. The Food and Drug Administration position stated that N2 or Sargenti paste could neither be manufactured nor distributed interstate. No further Food and Drug Administration action was taken because the application required for approval of the drug had not been received by the Food and Drug Administration.

Based on all information available to the Ohio State Dental Board at that time, the board proposed a rule barring the use of endodontic filling materials containing paraformaldehyde. A

public hearing on January 17, 1991, allowed for presentation of evidence relating to the use of the N2 materials.

Testimony, both anecdotal and scientific, was given both supporting and opposed to the use of these paraformaldehyde-containing materials. Overwhelmingly, the scientific information documented damage to viable tissue caused by the paraformaldehyde-containing substances.

Every dental school in the United States, without exception, indicated that the use of the paraformaldehyde-containing materials was neither condoned nor taught because of the possibility of patient injury.

I am including with my testimony this morning statements from every dental school in the United States based on this information that they neither condone nor teach the use of this material.

All the information collected by the Ohio State Dental Board relative to that hearing, including a videotape, has been forwarded to the Food and Drug Administration, and should be in your possession.

At the request of the Ohio State Legislature, final action on the proposed rule was postponed, pending establishment of national standards regulating the use of the compound, standards to be adopted by this body, the Food and Drug Administration. The Ohio State Dental Board is pleased to see that the Food and Drug Administration is considering a definitive statement on the use of these materials, and requests that the appropriate action be taken in this matter banning the use of these materials.

Thank you.

DR. ROBERTSON: Thank you very much.

I would like to thank all of the speakers so far this morning for being on time. I found it a very interesting morning. We will now have a coffee break. During the coffee break I, unfortunately, have to ask the Panel to stay seated for just a few minutes. But for everybody else, we will take a coffee break until 10:15.

(Brief recess)

DR. ROBERTSON: May we reconvene, please? We will now hear presentations by the N2 Universal manufacturers, N2 Products Corporation. The presentation will last an hour and the first speaker for the manufacturer will be Dr. Charles Raubicheck, followed by Dr. Alvin Arzt and then Dr. Ramon Werts. Dr. Raubicheck? We are told that the clock works but we will give it the benefit of the doubt and when you all get close to the end, I will wave.

PRESENTATION BY MR. CHARLES RAUBICHECK

MR. RAUBICHECK: Good morning, Dr. Robertson, Dr. Tylenda, members of the Panel. My name is Charles Raubicheck. I must correct the record though, I am not a doctor; I am just a lawyer. I represent N2 Products Corporation, the sponsor of the new drug application for N2 Universal, which is before you for a recommendation today.

I am a partner in the law firm of Piper & Marbury, in the New York office. This firm is headquartered in Baltimore, Maryland. I have no financial interests in the company, however, my expenses for coming here today will be covered by my client.

I have counseled N2 Products Corporation in connection with this company's NDA, or new drug application, for N2 Universal root canal filling material and sealer since the early 1980s.

My background briefly, I was associate chief counsel for enforcement at the FDA in their legal division for four years after I graduated from Georgetown Law School. I have been in private practice, specializing in FDA law, for the past seventeen years. Also for the past seventeen years, I have been adjunct professor of FDA law at New York University School of Law.

You have a statement that I prepared. I will give the Panel the statement which concerns the regulatory background involving this particular product. I will then comment on how the actual clinical data submitted in this application fulfill FDA's regulations governing new drug approval.

The reason that I have had to add remarks is that, unfortunately, my client did not get the FDA's reviews of the data until yesterday morning.

N2 Universal, the formulation that we are concerned with here, is composed of a powder constituent principally containing the ingredient zinc oxide, and a liquid constituent principally containing the ingredient eugenol. As such, this product is very similar to the many root canal filling formulations composed of zinc oxide and eugenol that have been used in endodontics for many years.

Indeed, the very panel that you are sitting on today, the FDA Dental Products Advisory Panel for devices, recommended to FDA in 1977 that zinc oxide-eugenol cements for root canal use be classified as Class I medical devices. A Class I medical device is a product that has been on the market and the FDA believes that the practical experience with the product has shown a reasonable assurance of the product's safety and effectiveness and, hence, there is no need for premarket approval data of any kind.

The FDA accepted this recommendation of your predecessor panel and, in a formal notice, issued in 1987, which is attached as Exhibit A to my statement, the FDA classified zinc oxideeugenol root canal cements as Class I devices.

Significantly, the FDA notice, in Exhibit A to my statement, reports that both the dental devices panel and the Agency did not base the decision regarding the safety and efficacy of zinc oxideeugenol cements on any clinical data, but solely on the fact that they have been used for a long period of time in dentistry without any safety problem.

The only compositional difference between these zinc oxideeugenol formulations and the material that is the subject of the application before you is that N2 Universal, this particular formulation, contains and additional small amount of paraformaldehyde, 6.5 percent of the powder component to be specific. Actually, when this 6.5 percent is mixed with the liquid which principally contains eugenol, the concentration of paraformaldehyde is reduced to about 4 percent.

The FDA, back in the 1970s, took a position that because this particular zinc oxide-eugenol formulation also contained paraformaldehyde, the product was thereby rendered a drug as opposed to a device because the paraformaldehyde ingredient achieves its disinfectant purpose through chemical action within the root canal.

In 1976, when Congress enacted the so-called Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, Congress made a distinction between the kinds of health care products that would be regulated by the FDA as drugs and those that would be regulated by the FDA as devices. If a healthcare product—and this is still the law today—achieves any of its principal intended purposes through chemical action within or on the body or metabolism within the body, then it is a drug. If it does not, it is a device. Hence, the zinc oxide-eugenol formulations which did not exert chemical activity continue to be regulated by the Agency as devices. But this particular formulation, solely because of the presence of the paraformaldehyde ingredient, was rendered a drug.

Now, in 1977 at the time, the FDA had a dental drugs advisory panel, similar to the Dental Devices Panel that they had at the time and that you now sit on today. At that time, this Panel was presented with N2 and concluded that further clinical investigation was appropriate but recommended to the FDA that the material be allowed to be on the market at the same time.

For regulatory reasons, the FDA disagreed with that Panel recommendation insofar as allowing the commercial availability of the material was concerned. In other words, the FDA said, "look, we are a federal regulatory agency. We do not regulate the practice of medicine or dentistry. Hence, practitioners, if you want to continue using this type of formulation for root canal therapy, you can do so on prescription only. You have to get it from a pharmacy."

But any commercial use, namely, manufacturing of the material in bulk and distributing it nationwide through dental supply houses, for example, would be considered commercial distribution of the material and, because the product was deemed a drug, it was automatically deemed a new drug by the FDA, requiring approval of a new drug application before the material could be sold in interstate commerce on a widespread basis. However, the material still remained

available. That is why you heard evidence of practical clinical experience with the material being available on prescription only.

My client, a small business located in Levittown, Pennsylvania, has applied to the FDA for approval of a new drug application, which is the FDA legal standard involved, in order to obtain the right to distribute the material commercially to make it more widely available throughout the country.

Now, this new drug application procedure, as I am sure you will hear from the FDA representatives this afternoon, requires the submission of clinical data demonstrating the safety and effectiveness of the material. It also requires manufacturing controls, chemical tests and the like. The company, N2 Products Corporation, was principally formed in order to create and prosecute through the FDA this new drug application for N2 Universal.

Now, there has been some observation in some of the FDA reviews, and you have heard some remarks this morning, that this formulation has changed many times over the years. In fact, it has not changed that many times. The critical fact for you to understand is that the FDA, in 1977, when it received the recommendations of the dental drugs advisory panel, came to N2 Products Corporation and said, "if you want to file an NDA, this is the formulation you should use, the powder to contain 72.5 percent zinc oxide; the powder also to contain 6.5 percent paraformaldehyde; and the liquid to contain 80 percent eugenol."

That is the product that has been studied by my client. That is the product that has been evaluated in the clinical data we have submitted to the FDA in this new drug application, and which you are being asked to evaluate and give a recommendation on.

Now, if this NDA is approved, my client will not be manufacturing it. My client will be marketing it and distributing it. The manufacturer will be a company called Moyco Industries, which is a well-known dental supply producer, in Philadelphia.

The following things had to be done in order to get approval for this NDA: Moyco had to develop manufacturing methods and controls to assure that this drug product would be consistently and safely manufactured. In other words, the raw material coming in from various suppliers would be incorporated into the powder and the liquid in accordance with so-called Good Manufacturing Practice regulations that the FDA maintains in place for pharmaceutical manufacturers.

Toward this end, my client was also required, in conjunction with Moyco, to do something that has never before been done for any root canal filling material of any type, and that is to develop identity tests and chemical assays for the zinc oxide and eugenol and paraformaldehyde components of the material. This was done. Two identity tests were developed for each ingredient. One assay was developed for each ingredient. Pilot lots were run and the material passed.

Then stability data had to be developed. The finished product had to be put in containers that will be used for marketing, and a shelf-life had to be determined for expiration dating purposes. This also was done.

Furthermore, the manufacturing methods and the analytical methods that are described had to be validated according to FDA procedures. This too was done.

Finally, while all this was going on, the company was generating the clinical data necessary for approval. It is the clinical part of the NDA that you will be asked to give a recommendation on today.

Now, regarding the clinical data, Dr. James P. Mann, who was the Director of the FDA's Surgical-Dental Drug Products Division in the early '80s, at a meeting with my client, on April 12, 1982, recommended a protocol for the clinical portion of this NDA. That protocol consisted of two things: Number one, a clinical investigation that would encompass approximately 100 patients. You may find the protocol in Tab D of the meeting package that I was asked to prepare on behalf of the sponsor for you, and which you should have in your possession. That protocol is dated April 19, 1982 in Tab D because that is the date when Dr. Mann signed off on it and sent it to the applicant.

This protocol will be more fully described for you by Dr. Arzt in his following presentation.

This protocol called not only for a 100-patient clinical investigation, but it also called for confirmatory data consisting of the submission of case histories from the American Endodontic Society Fellowship Program that you have heard about today. Dr. Mann represented to the applicant at the time that if these data were submitted pursuant to this protocol, and the data showed that the material was safe and effective, they would constitute substantial evidence of effectiveness and adequate evidence of safety for NDA approval purposes.

So the company proceeded to conduct the protocol. Essentially, in the 100-person study, an effectiveness or success rate of 94.5 percent was achieved and reported. The clinical case histories showed an approximately 99 percent success rate. The adverse reactions, principally consisting of postoperative pain and normal sequelae that are treatment-emergent signs and symptoms that are expected with endodontic therapy, such as postoperative tenderness. Sensitivity, a little bit of inflammation and the like, were the other side effects that were experienced and reported.

The applicant then submitted these data to the FDA. By the way, the case histories—originally there were about 375 of them. In September of 1991, Dr. Botstein, of the FDA, who is now the Division Director, Dr. Mann's successor, asked for any additional case histories we had. Ultimately, the total number was 9514, and they are reported on in the meeting package that you have.

In the FDA dental reviews that we received yesterday morning, it becomes apparent that the senior reviewing dental officer, Dr. Clarence Gilkes, who reviewed the clinical part of the FDA concurred with the sponsor that these data constitute data sufficient for approval of this application. Dr. Gilkes has two reviews that are pertinent. I have been informed that you also have these reviews. The first one is dated July 31, 1986. The second one is dated September 15, 1992.

The July 31, 1986 review is a review of the clinical investigation. The September 15, 1992 review is his review of the clinical case histories. When I say his review of the data, I also mean his review of the sponsor's evaluation of the data.

The first Gilkes review, which I will Gilkes I, is entitled, "Dental Officer's Review of NDA Amendment." That similar title appears on Gilkes II.

Now, the conclusion of Dr. Gilkes is set forth at page 18 of the Gilkes I document. Recommendation: It is recommended that this new drug application be approved and final printed labeling requested. That recommendation is based on the first sense of Dr. Gilkes' summary and conclusions which you will find at the bottom of page 17 of Gilkes I. It states: The sponsor has adequately demonstrated safety and efficacy for N2 Universal root canal filling material and sealant.

Dr. Gilkes' review was signed off on by his superiors at the FDA. Upon information and belief, the supervisory dental reviewing officer, John Kanilee (phonetic), signed off on this review on August 18, 1986. The Deputy Director of the Surgical-Dental Drug Products Division, Dr. Philip G. Walters, signed off on this review on August 29, 1986. The interim Director of the Surgical-Dental Drug Products Division—and when I say interim, I mean Dr. Mann had retired; now Dr. Botstein is the Acting Director, but in the meantime there was another Director, Dr. Patricia Russell who, unfortunately is not with us today because she passed away some years ago, but in 1986, on August 21, the Division Director signed off on this approval.

The FDA felt that with the submission of the additional clinical case histories, the 9500 cases, it ought to get an independent evaluation of the data, not only of the case histories but also of the Gilkes I review of the clinical study. So it turned to Dr. Sheila McGuire, of the Harvard University School of Dental Medicine, who reviewed the entire data package. Her review is in your materials. It is entitled, "Expert Reviewer's Review," completed January 4, 1993. Dr. McGuire concludes, on the last page which should be page 10: Recommendation: I recommend approval of N2 Universal after revisions to the label and with monitoring of Phase IV activities. Those are issues which you will, obviously, be discussing later on today. My talk will focus solely on the data.

I may also add that the sponsor is certainly willing to make appropriate amendments to its labeling to reflect any concerns that the FDA or the committee may have in that regard.

Dr. McGuire's recommendation was based upon her conclusion that you will see above on the same page. Conclusions: When used properly, N2 Universal is a safe and effective material for the treatment of a tooth requiring endodontic therapy.

Based on these reviews, one would expect and hope that the FDA would concur and approve this NDA. However, among the materials that you have received is a document entitled, "Division Director's Memorandum," dated February 2, 1993, which is a document that looks like this. It appears to be a review of the NDA file, including these data, by Dr. Paula Botstein, who is the current Acting Director of the Surgical-Dental Drug Products Division.

This review, upon evaluating it, appears to be a marked departure from all the reviews that have gone before. In essence, Dr. Botstein is recommending to this Panel that the database is deficient, and has submitted to the Panel a series of questions which her Division wants the Panel to answer in formulating its recommendation.

Since this is the only opportunity we will get to give our view on how you ought to answer these questions, I will proceed to do so.

At the outset, let me remark that while Dr. Botstein obviously has eminent qualifications as a physician, she is not a dentist. She is also the lone dissenting voice within the FDA on the approvability of this NDA, apparently from what we have been allowed to see.

Her memorandum contradicts Dr. Mann's recommended protocol that the sponsor was asked to follow, back in 1982, in terms of the study design. It contradicts the analysis and conclusions regarding the data in both of Dr. Gilkes' reviews. It contradicts the analysis of the data and the conclusions in Dr. McGuire's review.

A close and careful reading of Dr. Botstein's memo indicates that it appears to be based on an approach that is typically required by FDA for new chemical entities that are intended to be marketed for pharmaceutical use, either orally or by injection. Typically, when a pharmaceutical house—the Merck's and the Lily's and the Upjohn's of the world—come out with a new drug product, it is a new drug and they have to go through NDA approval.

Whether you are talking about an oncology drug, or cardiovascular pharmaceutical, the FDA has these regulations and, typically, the Agency requires, as you will hear this afternoon, adequate and well-controlled clinical studies demonstrating the safety and efficacy of the drug product involved. Typically, the control that the FDA requests is a placebo control or an active-treatment control.

But we, at N2 Products Corporation, submit to you that this is not the classic pharmaceutical product. This is basically a dental material which, other than the 6.5 percent paraformaldehyde in it, would be a Class I medical device, regulated just like all other zinc oxide-eugenol cements.

Yet, because of the paraformaldehyde, it has been requested to undergo the drug regulatory approval process.

We have no quarrel with this. We have gone through it. We have spent twelve years going through it. We have submitted many amendments to the NDA. And we believe we have a clinical database that warrants approval.

The questions that Dr. Botstein has put to you essentially have already been answered by Dr. Gilkes and Dr. McGuire. The data show that the FDA's regulations have been fulfilled.

I will now proceed to go through the questions with you and indicate how they have already been answered by the Agency's own dental reviewers.

If you turn to the questions which are appended to Dr. Botstein's memorandum, which is entitled, "Questions for the Dental Products Panel of the Medical Devices Advisory Committee," you will see that there are a series of questions. I am only going to have time to focus on about the first page and a half but that is appropriate because those are the ones that I am knowledgeable about since I am particularly knowledgeable about the clinical database here. The other issues are additional things that you, all, can discuss in the due course of the meeting.

The ultimate two questions that are being asked of you are set forth as I.a., II. and III.a. Number I. says, is this study—referring now to the 100-patient clinical investigation which, actually, turned out to be 109 because more patients showed up than were originally anticipated—is this study adequate and well-controlled, which is the legal and scientific standard for drug approval?

The second question that is being asked of you, on page two, regarding the case histories, asks whether they are controlled data and whether they provide useful information.

Question III.a. asks do the data presented demonstrate effectiveness and safety of N2 Universal?

We submit that they have. We submit that Dr. McGuire and Dr. Gilkes have already concluded that they have. So let's go through what leads up to these conclusions because are those are the interim questions that are listed here.

First of all, in question I.b. regarding effectiveness, you are asked is a historical control adequate for effectiveness of a root canal filling and sealing material?

Well, the answer is yes for the following reasons: Number one, a historical control is authorized by the FDA's regulations setting forth criteria for what constitutes an adequate and well-controlled clinical investigation. You can find this, and I have it if you want to look at it, in 21 CFR Section 314.126(b)(2)(v). The regulations here provide for four different types of controls. The FDA will accept a placebo control, an active-treatment control, a no-treatment control or a historical control.

As Dr. Mann recognized, for reasons articulated better than I could do by Dr. McGuire and Dr. Gilkes, a placebo or active-treatment control or a no-treatment control would be inappropriate in this context. First of all, you have your ethical problem, and I say first and that is paramount. Giving somebody a placebo, an inert substance, for root canal treatment is obviously not in the best interest of the patient. The same goes for a no-treatment control because with either of those controls the tooth will be lost, to the patient's detriment.

The active-treatment control is impractical. How are you going to select a patient population only consisting of people who have two canals that have to be treated in the same mouth, canals with the same configuration? As a practical matter, that cannot be done.

Indeed, if you turn to page 17 of Dr. Gilkes' first review, what I have called Gilkes I, you will see this articulated. Dr. Gilkes states, on page 17 in the second full paragraph, under the heading "discussion:" Historical controls are acceptable for an indication of this type. Use of a placebo would result in additional pathology associated with the affected tooth. Therefore, to use a placebo would be unethical.

Similarly, if you turn to Dr. McGuire's review, at page 6 under the heading "clinical studies," she states as follows: Only one clinical study during the mid-1980s was conducted with no randomization of treatment, per suggestion of Dr. Mann of the FDA, because of the ethical difficulties with a placebo control and the practical difficulties with an active control.

Now, one might look at that statement and say, "well, all she's doing is saying what Dr. Mann said." Well, obviously she is doing more. She is from Harvard Dental School. She has been brought in as the expert reviewer. If Dr. McGuire felt that a historical control was inappropriate, I am sure she would have said so.

So a historical control is not only appropriate because it fulfills the regulations, but it is appropriate because FDA's dental reviewers have agreed that it is.

Now, if you go to the next question, I.c., you will see that it asks has a historical control for this study for effectiveness been adequately characterized and described by the sponsor? Identify the historical control.

Well, if you turn to pages 14 and 15 of the meeting package you have, where we have summarized what is in the NDA in terms of the historical control, you will see that there is a discussion of success rates, i.e., efficacy rates using conventional root canal filling materials that appear in the relevant scientific literature within the last 10-15 years. These are reports by Ashkanaz, Saunderson and Martinoff, Wine and Grossman (names phonetic). You will find the actual articles in Tab L of your meeting package.

We submit that these are adequately characterized historical controls and that they have been

appropriately identified.

The next question asks, I.d., are the criteria for effectiveness clearly defined in the study and in the historical control?

Well, the criteria for effectiveness constitute endodontic success rates. These endodontic success rates are essentially the clinical judgment of the investigator as to whether or not the root canal treatment has proven to be effective both upon physical examination and radiographic evidence. In terms of criteria, these criteria were accepted by Dr. Mann in his protocol. They were articulated by Dr. Kimmelman, the monitor of this study, whom you heard from this morning, in his evaluation of the data. That is also in your meeting package. They were currently articulated by the authors of these articles that were published texts and peer-review journals on success rates using conventional materials.

The next questions asks, in I.e., are data on effectiveness endpoints adequately collected and analyzed in this study?

Well, the effectiveness endpoint was whether or not there would be effective root canal therapy, with no undue degree of postoperative pain and return to function, These, again, are all in your materials as identified by Dr. Kimmelman in his monitoring report on this study, and well-known throughout the profession of endodontics as the traditional means by which effective endodontic therapy is assessed.

So the endpoints were adequately defined. Were they adequately collected? Well, the sponsor thought so and Dr. Gilkes agreed because, if you turn to the Gilkes I review at pages 5-16, you sill find Dr. Gilkes' personal analysis of each and every case in the 109 patients studied. By looking at the case report forms and the x-rays, Dr. Gilkes made his own independent judgment as to the collection of the effectiveness endpoints, and Dr. McGuire concurred in her review of the data.

Now, whether these effectiveness endpoints were adequately analyzed seems to bring in a statistical issue. Well, if you are using a historical control, essentially you are comparing the success rate in root canal treatment that you find in the data at hand with the success rate that is reported in the literature. We have seen here, and essentially this answers question I.f., that the effectiveness rate in the clinical study of 109 patients was 94.5 percent. As the literature references in Tab L of your meeting package state, the efficacy or success rates using conventional materials have ranged between 83 and 97.8 percent. So 94.5 is squarely within the range. Indeed, it is at the high end of that range.

The FDA materials that have been sent to you include a statistician's report, apparently by a doctor named Harkin, who took a look at these data and his conclusions appear on the last page. This document is entitled, "Statistical Review and Evaluation." If you look there at the end, you will see the following paragraph: If the 94.5 success rate quoted by the sponsor is a valid

population success rate when antiseptic paste filler/sealers, meaning conventional materials, are used, and if the success rates reported for studies 1 and 2, meaning the clinical investigation and the case histories submitted in the NDA, are really representative of success rates one can expect when the N2 formulation for which approval is being sought is used, then the success rates reported are not statistically lower than 94.5 percent.

We agree. Obviously, the literature shows that the antiseptic paste fillers/sealers achieve a success rate between 83 and 97 percent. Both the FDA and Dr. Gilkes and Dr. McGuire have made a judgment—when I say the FDA, I mean Dr. Mann and his originally recommended protocol—that the results from the study and the case histories would be really representative of what you would see in real life.

Back again to the questions, we are into safety now. Actually, before I leave the efficacy, I want to mention two other things. There were questions in Dr. Botstein's memorandum about the case report forms and the length of the follow up. These case report forms were approved by Dr. Mann when he approved the protocol. So the FDA had already made the judgment that the case report form was adequate. You will see a typical case report form used in the study and the case histories when Dr. Arzt presents after me. In your meeting package you also have all 109 case report forms from the clinical study so you can judge for yourself.

As far as the follow up is concerned, we had 3- and 6-month radiographs and clinical examinations. As Dr. Gilkes reports in his first review, down at the bottom of page 17, there were follow-up radiographs submitted for 3 months, 6 months and, in some cases, up to 14 months. Dr. Hoffman successfully treated 18, all with follow ups of 10-12 months. Dr. Siebert successfully treated 17, all with follow ups of 9-14 months. Routine follow-up radiographs for the conventional technique are usually at 2 months. The Agency agreed that the 3-month and 6-month follow-up radiographs would satisfy our requirements for safety end efficacy.

Dr. Botstein asks in her memo did they really do evaluations at both 3 and 6 months? What does this success represent? Well, the investigators were instructed to do so and it is presumed that they did, but beyond that, both Dr. Gilkes and Dr. McGuire took a look at the 3-month x-ray and the 6-month x-ray and obviously concluded that the vast majority, if not all, the cases that were rated successful by the investigators and the monitor were also rated successful by themselves.

Moving on to efficacy, and we are back to questions again, I.g. asks is a historical control adequate for safety of a root canal filling and sealing material?

The answer is yes for the reasons I have already given in talking about efficacy.

I.h., has a historical control for this study for safety been adequately characterized and described by the sponsor? Identify that historical control.

If you turn to pages 9-12 of the meeting package, you will see a summary of the comparison of

results of adverse events in both the clinical study and the case histories with the historical control of adverse events for root canal therapy with conventional materials reported in the literature. That literature can be found in Tab A of your material.

So we submit that it has been adequately identified.

In question I.i. we are talking about collection an characterization and analysis of adverse events. Are they adequately carried out in this study and this historical control?

Well, again, in Gilkes I, pages 5-16, Dr. Gilkes reports on his evaluation of the adverse events in the clinical study. If you turn to Gilkes II, Dr. Gilkes personally went further than the sponsor. The sponsor listed the adverse events by number and Dr. Gilkes went further, on pages 3 and 4 of his second review, and computed the percent-ages based upon the 9514 patients in the study. In sum, the sponsor believes that the adverse events were adequately collected and characterized and analyzed.

As far as the historical control is concerned, I would refer you again to Tab K where you have texts with references from peer-review journals which report on adverse effects occurring with conventional materials, and the comparisons, as we reported in our summary, are very favorable.

For example, the most commonly seen postoperative sequelae to endodontic therapy is pain or discomfort. The literature, and I am talking about Grossman, Seltzer and well-recognized people in the field, report an average of about 33 percent incidence of postoperative pain with conventional root canal materials and technique. In these data in the NDA, there were 5.49 percent adverse events in the clinical study and 4.7 percent adverse events in the clinical case history. As you will see from the list of the other adverse events down in the case histories, the list by Dr. Gilkes, none of them are serious or life-threatening or permanent in nature.

If you go to the top of page 2, you will see question I.j. which asks what are the rates of adverse events in this study? I have just told you what they were reported to be. So you do not have to look them up for yourselves.

I.k. talks about follow up. We have already talked about that, 3 and 6 months being adequate.

Question II asks whether the clinical case histories provide controlled data. It is obvious that they do not provide controlled data. It is a loaded question. The clinical case histories are just that, clinical case histories. But the FDA determined, back in 1982 when Dr. Mann wrote the protocol that you will find in Tab D of your meeting package, that clinical case histories of a substantial enough number were adequate confirmatory data to confirm the clinical study.

This is in accordance with FDA regulations. 21 CFR Section 314.126(c) says that the FDA is authorized to waive any of the criteria for NDA approval in the appropriate circumstances. Indeed, the Agency has frequently done so in recent years for other pharmaceuticals. There is a

normal 2-study requirement but some drugs have been approved on the basis of 1 study. This is a matter of public record.

So the FDA told the sponsor 12 years ago you need this clinical study and you need these case histories. That is what we have given the Agency, and you have the data before you today.

So the useful information provided by the case histories, asked by question II, is that there is a 99 percent success rate in those case histories and an adverse reaction rate of 4.77 percent.

In conclusion, in answer to question III.a., the sponsor respectfully submits that the data presented do demonstrate the safety and effectiveness of N2 Universal root canal filling material and sealer for its intended use.

Thank you very much. I will take any questions now or later.

DR. ROBERTSON: Maybe we can save the questions until the other two presentations are over.

MR. RAUBICHECK: Thank you.

DR. ROBERTSON: Thank you very much for a very clear presentation.

Dr. Arzt, you have about 15 minutes.

PRESENTATION BY DR. ALVIN H. ARZT

DR. ARZT: I am going to try to go very rapidly so that my colleague, Dr. Werts, can also make a presentation.

I am Dr. Alvin Arzt, a general practitioner from Levittown, Pennsylvania. I am an officer and member of the board of the N2 Products corporation. I do not receive any salary but my expenses will be paid today.

N2 Products Corporation is the sponsor of the new drug application for N2 Universal. My presentation today—I had hoped to go through a description of the Sargenti root canal method and the similarity to conventional root canal methods; a description of the formulation and an explanation of the clinical case histories submitted to the NDA. So I will go very quickly.

(Slide)

As we know today, 25 million Americans are totally edentulous. Why is this happening? It is because, from a recent survey and an article from the Journal of Endodontics, there are to enough dentists doing root canal, plus the fact that 50 percent of our population do not even go to the dentist and the delay in getting root canal therapy, especially if they have to be referred, means

that the tooth will eventually be lost.

(Slide)

This is the number of totally edentulous people in the world. As you can see very quickly, the United States has the greatest number of persons with the most loss of teeth, yet, we have a country with the best medical and dental schools and procedures that we could possibly have, yet, we have the most people with the most loss of teeth.

The purpose of endodontics is to save a damaged or abscessed tooth by removing pulp tissue from the tooth's root canal system and by filling and sealing the canal to prevent infection.

(Slide)

Dr. Sargenti, over 40 years ago, of Locarno, Switzerland, realized that a precise, rational root canal method needed to e developed to stem the loss of abscessed teeth in the general population.

(Slide)

He developed all these procedures and he even introduced an instrument program that would permit the general practitioner to have a precise technique to be able to save teeth without doing some random treatments on his own. He set about to create an endodontic method that could be used safely, effectively and most efficiently by the general dental practitioners who are most available to most patients.

(Slide)

We are able to realize that with our technique and our material, N2 Universal, we are now able to do root canals in majority of patients in one visit as compared to multiple visits.

(Slide)

It has been shown through electrochemical microleakage studies that N2 is the best root canal [method] and produces the least amount of leakage. I will not dwell on that but this is what the canals look like. We have to go in and fill all this anatomy; remove all the debris and be able to prevent reinfection.

(Slide)

So we developed the technique of cleaning and shaping canals. This technique is not a haphazard technique; it is a very precise technique.

(Slide)

As you will see, we developed a technique to use engine preparation so the dentist himself, especially the general practitioner who knows who to use an engine, as you all well know. He now has been able to adapt it for use in root canal. This is known as a giromatic. It is one of the first engine instruments that was used to clean out a canal. Now it is traveling forward to the point where we use sonics and ultrasonics to clean out the canals.

(Slide)

This engine does a quarter turn. It simulates finger action. In the hands of a general practitioner who is adapt at using the engine, he adapts very quickly. Perhaps the specialist who is so adapt at hand instrumentation has problems using an engine. He does n to use it as frequently as we, general practitioners.

(Slide)

The technique means local anesthesia, opening the pulp chamber, instrumenting to the physiologic foramen. This is the anatomy of the tooth. This is what the canals are made up of. There is the physiologic foramen. That is where the pulp tissue meets the periapical tissue. We have anatomical foramen and we have the radiographic foramen. That is what we see on the x-ray.

(Slide)

So we learn—and this is what has been adapted even in conventional root canal techniques—that we must be finishing our technique and our instrumentation to within 1-3 mm from the apical portion of the tooth, as you see it on an x-ray.

(Slide)

So we are in the canal in the vicinity of the apex. Instrumentation is very, very important in our technique. I have taught this technique at Case Western, Chicago Dental School, Einstein Dental School in New York. They say it is not taught in dental school, but our technique is taught in every dental school because the Sargenti technique is not a unique technique. It is a basic technique. It is the basic technique of instrumentation, enlarging and shaping the canals. Every dental student learns it from his first introduction to endodonture in dental school.

(Slide)

The ingredients, as has been talked about, are zinc oxide, a small amount of paraformaldehyde, 6.5 percent, and eugenol.

(Slide)

N2 is meant to be placed within the canals. We take careful x-rays and we measure.

(Slide)

This is what is done and taught in our technique which we adapted and called the Sargenti root canal technique but it is conventional root canal.

(Slide)

We now use the lentulo spiral, which is also on an engine, to put the sealer into the canal.

(Slide)

The sealer technique is up and down without the engine running. Then as you turn on the engine, slow-turning engine, the lentulo can put the sealer into the canal. The material can be used in conjunction with gutta-percha. There are many dentists who use gutta-percha in conjunction with the sealer.

(Slide)

The formulation, which is very difficult to read here but I believe is in your package, has not changed in all the years that this technique has been out. The Sargenti material has been 6.5 percent paraformaldehyde, zinc oxide and eugenol. Some of the incipients, barium and bismuth, have varied in order to get more radiopacity. But the main ingredients have never changed.

(Slide)

The missing of formula is very much as we would do for any dental cement. It is put on a slab. The powder is mixed with the liquid. It is made into a very fine creamy consistency and it makes it very easy for the dentist to seal the canal.

(Slide)

The criteria in judging successful endodontic treatment are the criteria for any root canal technique out today.

(Slide)

Absence of pain or swelling.

(Slide)

Disappearance of a fistula. No loss of function.

(Slide)

No evidence of tissue destruction.

(Slide)

Roentgenographic evidence of eliminated or arrested area of rarefaction after post-treatment at 2 months or 6 years. Those are the criteria for successful root canal whether you are doing Sargenti or traditional.

(Slide)

Regardless of the roentgenographic interpretation, endodontically treated teeth which are functioning adequately, and without adverse clinical symptoms should be regarded as successfully treated.

(Slide)

This is what we get in our typical N2 treatment. This is immediately postop.

(Slide)

Here we are at 6 months.

(Slide)

Here we are approximately a year later. As you can see, the area is regenerating to a normal situation. This is what happens in over 95 percent of our cases.

(Slide)

Preop. x-ray.

(Slide)

Postop.

(Slide)

And here we are, 1983, and you can see how the area has returned to normal anatomy.

(Slide)

Another tooth.

(Slide)

Filled with sealant, showing you how the material helps seal that canal; prevent reinfection and the tooth has returned to normal.

(Slide)

A large area done with the N2 Universal. Here we have a 2-year follow up and we have a 7-year follow up, showing you the normal healing procedure that takes place with this technique.

(Slide)

The American Endodontic Society has had a survey with the dentists who do Sargenti root canal, and over the past 10 years over 26 million teeth have been saved in the United States just using this technique. Do we need to go back to animal studies? These have been done on the human animal and I think that speaks for itself.

(Slide)

Histology—we have done histology. To go quickly through it, this is from Dr. Marguerita Marouzabel (phonetic), from the University of Argentina. She submitted these slides to us personally, and she worked on 25,000 rats. We do not have that many in our office. But she proceeded to show that after 30 days the inflammatory cells disappeared. Normal anatomy returned.

(Slide)

Within 90 days, we found that the osteoblasts start producing normal, healthy cells.

(Slide)

This is what was in the report at the Fifth International Conference of Endodonture, 1973.

So to conclude, and I am going very quickly to give my colleague time to go through this, 109 teeth were completed on 91 patients in our NDA by 19 participating dentists. The dental investigators themselves rated 106 successful cases and 3 cases questionable. The monitor of the study, Dr. Benedict Kimmelman of the Franklin Institute Research Center, in Philadelphia, rated 104 cases successful, 3 cases unsuccessful and 2 cases questionable. The combination of 3 unsuccessful and 2 questionable, if all 5 are considered unsuccessful, still yielded 104 successful

cases, which represents a success rate of 95.4 percent.

These data in the NDA are submitted for your review, showing that N2 Universal is a safe and effective root canal sealer. Approval of the application will provide general dental practitioners across America with the material necessary to provide safe, effective and cost-efficient endodontic treatment to millions of our citizens.

Thanks for your time. I am sorry I went so quickly.

DR. ROBERTSON: Thank you, Dr. Arzt.

We have one question for you from Dr. Greenspan.

DR. ARZT: Sure.

DR. GREENSPAN: You referred to the giromatic handpiece. Is this technique recommended to be used with a handpiece? Is that an integral part of the use of N2?

DR. ARZT: No, it is not. But, you see, the fact is that by introducing the engine instrumentation, for those who had not done root canal, it became more efficient for them. Those who were still adapt at hand instrumentation continued to do so. So it can be a combination. But in our teachings, we teach how to use the giromatic. Now we even teach how to use the sonic and ultrasonic.

DR. GREENSPAN: Fine. Can you tell me, is the giromatic handpiece autoclavable?

DR. ARTZ: Yes, it is.

DR. GREENSPAN: Thank you.

DR. ROBERTSON: Thank you.

Dr. Werts? To be fair, would you be about five minutes?

PRESENTATION BY DR. RAMON A. WERTS

DR. WERTS: I certainly will. I appreciate that. I think we only have 30 seconds and I appreciate the 5 minutes.

My name is Ramon Werts. I am a general practitioner in Fullerton, California. I am here as a consultant to N2 Products Corporation, which has filed this NDA. I have no financial interest, nor does any member of my family have any financial interest in the N2 Products Corporation, and I am not affiliated in any other way, other than acting as a consultant. I am the Executive

Director of the American Endodontic Society.

In the five minutes I have, I would only refer you to the prepared statement that was submitted to each of you previously, I believe, and would ask that you review it. The first portion of it is further commentary on the controls, very similar to what Mr. Raubicheck told you; the reasons why some of the more traditional controls cannot be used and why we chose, with FDA approval, to use the historical control in the clinical study.

The next section discusses the safety and efficacy, and how we have compared, and have those statistics for you. All of that, again, is a reiteration of what you already have in your meeting package.

As far as the clinical case histories are concerned, I think we have covered adequately how that fulfills the requirement.

I think, however, the one comment I would refer you to in my presentation is the fact that we have been repeatedly assured by FDA that when a decision is made on this NDA, that it will be made on the scientific data presented, and not upon political innuendo and so on.

However, you have heard some things today that I would like to briefly mention. Again, the idea that the formula is changing—the fact is that it has changed several times, but only because of improvements in working time, setting time and that sort of thing. The specific change that was made for the formulation here was specifically done to eliminate the lead component, which we have done.

The comment that several states have banned the use of N2 is a half-truth. There is no state in which an effective ban is now in effective. Yes, Florida passed a resolution that would ban it, but that is being legally challenged. It is not in effect.

Other state boards have considered this issue also, specifically California. Since I happen to be from there, I can comment on it, and I was present at the meeting of the California Board of Dental Examiners when they discussed the use of the Sargenti N2 in the State of California. They concluded, and the formal position of the California board is that they neither approve nor disapprove of the Sargenti material.

A comment has been made about lawsuits. There has been an analysis made of lawsuits from a very respected publication, called, "Medical Malpractice." We surveyed cases which were listed by them for a period of six years and only four-tenths of one percent of the dental malpractice cases had anything to do with the Sargenti technique.

The fact that endodontists set the practice of care in dentistry is not true either. The position of the American Dental Association itself, according to their general counsel, is that ADA does not establish standards of care, nor does it recognize other dental organizations as responsible for

setting standards of care.

Dr. Burrell, from the Council on Dental Therapeutics, made a very nice plea for your prompt action on this. I would comment, however, that he also has said in a letter: I wish to point out that the Council on Dental Therapeutics has never stated that any Sargenti root canal filling materials is not safe and effective.

The literature has many articles regarding endodontic procedures. Dr. Maggio referred to the bibliography that AAE prepared. I would like to comment, and this has been submitted to you also, that our Society prepared a correction to that bibliography, which goes through each of those same 141 articles, and we can tell you that many of the conclusions that they list in their bibliography are vastly different from the content of the actual article. This has been presented to the FDA but I will present it and leave it here for anyone to look at, and if there are any questions about any of these articles, we have every one of them on file.

So the bibliography is flawed. The bibliography was submitted by AAE to the FDA, along with a request that the FDA issue a ban on N2.

FDA Commissioner Kessler wrote back to AAE that the bibliography was an inadequate basis for which to prohibit the use of root canal materials.

So you can read through my statement as to why and how this bibliography is flawed and here are our corrections to that.

In conclusion, I would simply say the other thing that this shows is that virtually every endodontic material can be toxic, can cause inflammation, can do all the things that supposedly are bad. Abuses of technique really are the problems in root canal therapy, not just abuses of the use of N2 but abuses of any endodontic material.

I would like to conclude by reminding the Panel that your predecessor committee that was alluded to previously, in 1975, chaired by Dr. Robert Shira, said that they recommended further studies, which we have now done. They believed that the potential risk of these materials is such that they should not be removed from the market. So even in 1975, you predecessor panel could not find dangers from this material.

The situation that you are looking at is really fairly comparable to the amalgam situation in that, yes, mercury is a poison. Similarly, we acknowledge that para-formaldehyde is a toxic material. But, again, it relates to the dosage. There is no more paraformaldehyde in one root canal than there is in a quart of milk, and I think most of us drink more milk in a lifetime than one root canal.

Thank you very much.

DR. ROBERTSON: Thank you very much.

Are there any questions from the Panel at this time of the representatives who presented here this morning for N2 Products Corporation?

(No response)

Hearing none, I would like to thank the three presenters. I will declare us adjourned for lunch. We will reconvene back here at one o'clock.

(Whereupon, at 11:35 a.m., the Panel recessed for to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:00 p.m.)

DR. ROBERTSON: Can we reconvene the meeting?

The Panel will now hear presentations from the FDA. Dr. Paul Botstein is Acting Director, Division of Medial Imaging, Surgical and Dental Drug Products, as well as Deputy Director of the Office of Drug Evaluation I. Dr. Botstein?

PRESENTATION BY DR. PAULA BOTSTEIN

DR. BOTSTEIN: Thank you.

I would like to thank the Center for Devices and Rad. Health and members of the committee for letting us, from the Center for Drugs, use your expertise for discussion of the drug today.

Our policy in the Center for Drugs is to take new drugs to advisory committees. We are using the Dental Devices Advisory Panel because we do not have a dental drugs advisory committee. Here, today, are various people from the Center for Drugs: Included the speakers listed, Dr. Gilkes, the reviewing dental officer, who has decided to make some remarks; Dr. Cheever, one of our dentists; Miss Rhee, a consumer safety officer, and a set of other people. We are here to answer questions and give information. So if something does not make sense, please do ask us about it.

You have the list of questions which we will ask you to vote on. A discussion by an advisory committee is very valuable to us. We need to hear your reasoning and the data you use for your conclusions, and we would like a formal vote on each question by each member.

We usually follow the recommendations of the committee but not always. Sometimes a recommendation is not backed by specifics, or it conflicts with our regulations or our laws, or we

get more information after a meeting that sheds a new light on the matter. For instance, there may be a follow-up study that gives different results from the studies that we saw before, or unexpected results from a new analysis that is done after a meeting.

Today, we are bringing for evaluation of clinical data in this NDA for N2. Other aspects of the application may still need resolution but we are not planning to discuss those in the public session today.

The items that typically may not be done at the time of an advisory committee are an inspection of the manufacturing facility, or of the clinical records kept by investigators. For product with multiple ingredients, it is necessary to have a fair amount of information about the source and the manufacture of each ingredient.

A decision by the FDA on the approvability of a drug product for marketing must rest on the data that are actually in the application, and not on the material about the drug that is available to committee members or reviewing staff from other sources, including personal experience or knowledge.

A decision on approvability has to rest on the science and on the regulations on drug approval, and not on considerations like economics. The law provides no ability to use economics in our decisions whatsoever.

We are not asking you to judge N2 itself. We are not asking you what you think of the method or what you think of the drug. We are asking you to evaluate the adequacy of the database that is in the NDA, and those may be very different things.

The time since the NDA was originally submitted does not relieve the sponsor of the need to present good scientific data. The NDA has received multiple non-approval letters in the past because of inadequacies in the science and in presentation of the data. And we want your view of the data as they are right now.

I might just say here that the Center for Drugs is an intellectually lively place. We argue among each other, and we debate, and we discuss quite a lot and that is the way it should be. We disagree with each other sometimes. Although, in this case, there are reviews and reviewers who recommended approval of the application in the past, that is not the overall action the Agency has decided on, and we have sent a series of non-approval letters to the sponsor, and that is codified as our official overall conclusions about the drug.

The database submitted is basically of two items. One is a clinical study of 109 teeth in 91 patients, with a historical control group that is taken from the literature.

Secondly, there are case histories, 9514 case histories which are from a training program of a professional organization, and these case histories were not consecutive and were apparently

selected for successful outcome.

The list of questions that you have captures the clinical issues with the database for this drug. They are in these areas: One is the design of the clinical study and its historical control, and the adequacy of that design.

Secondly, adequacy of the data collected in the study. Adequacy of the analysis of the data; results of the study; the role of data from other sources; further data or study needed and, finally, the labeling.

Now, take the questions about a historical control. Question I.b. asks if you think a historical control is reasonable for a root canal sealant. That is a theoretical question. FDA staff have told the sponsor in the past that a historical control is okay. You can tell us that you agree with that or you do not agree with that. You can say that the historical control is okay for this application but future root canal sealants should use a concurrent control—whatever you think on this issue.

There are other questions that ask about the adequacy of the data on the historical control actually submitted in the NDA. The Agency can never make a commitment in advance that a historical control is okay, no matter what that control consists of. It depends on whether the control is scientifically good and well described when it comes in, in the application.

Central in looking at this study is the issue of whether it is adequate and well-controlled. The historical control comes in as literature citations. The case report form for this study consisted of one page and evidently contained all the data that were collected on each patient, including x-rays of the relevant teeth. The reports of readings of the x-rays are not provided by the sponsor in the NDA.

The sponsor states in the protocol that the overall outcome was to be graded as satisfactory or unsatisfactory and that clinical findings, and I am quoting from the protocol, shall assess maintenance of function, absence of pain and absence of increased mobility of the tooth. So it is talking about function, absence of pain and absence of increased mobility. On the case report form, the investigator is not asked to grade the outcome as successful or unsuccessful. The case report form does not ask explicitly whether there was maintenance of function, etc. The case report form does not ask for information on adverse events. In some way that is not specified, the information that is on the case report forms and the x-rays have been translated into successful or unsuccessful.

We have no listing of how each case report form was graded or what criteria were used for the grading. We do not know if the same criteria were used for the evaluation of each case.

The absence of information on the case report form, for instance, the lack of mention of pain, is taken in the most favorable light. If pain is not mentioned, then the assumption is that there is absence of pain. That is certainly not the usual way for collecting this kind of information, which

is usually fairly systematically collected and the explicit questions are asked.

The historical controls cited from the literature references contain numbers for outcome from conventional therapy but do not give any data to back up the numbers.

So the outcome data collected on the case report forms are sketchy and not very much analyzed. The readings are not provided on the x-rays. Adverse reaction information was not asked for in the case report form, or collected systematically in any other way. The historical control for the clinical study is not well characterized.

We know that the database for this NDA is not the usual concurrently controlled clinical trial data that is collected systematically and analyzed rigorously. Partly what we are asking you is whether there are special reasons that have to do with root canal fillings that make the database more convincing than it looks on the surface.

For instance, is effectiveness obvious if the tooth was preserved? Is that enough?

Thank you very much.

I am here to answer questions.

DR. ROBERTSON: Questions from the Panel?

(No response)

Thank you very much, Dr. Botstein.

We will now hear from Dr. Clarence Gilkes, who is senior reviewing dental officer for the Center for Drug Evaluation and Research, Division of Medical Imaging, Surgical and Dental Products. Dr. Gilkes?

PRESENTATION BY DR. CLARENCE GILKES

DR. GILKES: Good afternoon. I would like to add that for the past 25 years I have also served as assistant professor in oral surgery at the College of Dentistry—and I must be careful in enunciating—Howard University. I do not want to get that confused with Harvard University.

(Laughter)

I joined the Agency as a reviewing dental officer in June of 1966. I was first exposed to a forerunner of this dental drug product in March of 1967 when I reviewed a related document.

The members of the Dental Drugs Product have three of my reviews before them. The review

dated February 3, 1984 evaluated the submission which was dated December 14, 1983. The Agency requested, as a result of that review, submission of all patient radiographs. These x-rays were to be preop., immediately postop., 3- and 6-month follow ups. All x-rays were to be dated.

The review dated July 31, 1986 evaluated each and every single radiograph which had been submitted by the sponsor on February 13, 1986.

I might add that in the more than 26 years that I have been employed as a dental reviewer, no other sponsor has ever submitted dental x-rays.

These radiographs were of paramount importance to me in my evaluation of the safety and efficacy of this product. However, you, the Panel, do not have benefit of these more than 400 individual periapical radiographs to assist you in your evaluation of safety and efficacy. They have been lost by the Agency.

Thank you for the opportunity to address you, and I will do my best to answer any questions that you might have now or later.

DR. ROBERTSON: Any questions for Dr. Gilkes?

DR. SPANGBERG: Were you the only reviewer of the x-rays to assess success or failure?

DR. GILKES: My supervisor looked at them.

DR. SPANGBERG: Did you calibrate each other?

DR. GILKES: No. He was a physician and I merely showed him how to be certain that one x-ray and then a postop. and a follow up would be of the same patient, and showed him how I came to the conclusion that in some instances the preop. was not the same as the final film 6 months later. That is about the extent of the calibration or standardization of our review.

DR. SPANGBERG: So you only verified that the x-rays really were there? You did not assess the outcome?

DR. GILKES: I assessed the outcome based on radiographs inasmuch as they indicated that no more tissue was lost; areas of rarefaction had healed; and I could ascertain this by looking at the preop. and the 6-month follow up.

On the case report forms there is an indication as to what the final restoration was and what date. All of us dentists are well aware that we do not usually embark on full coverage of a tooth until we feel the pathology has been resolved. That was there, as well as a comment on the patient report form of prognosis.

DR. SPANGBERG: The reason I am asking is because the presentation of the individual cases really do not give the outcome of the cases. They talk about prognosis but not really the outcome. Since it is very difficult to assess outcome of endodontic treatment, normally two evaluators are required and calibration is required. That was not done in your case, obviously.

DR. GILKES: Well, we did not ask the sponsor to have a radiologist evaluate the radiographs independently prior to the submission because when I was consulted by my then division director, I felt I had more confidence in my own evaluation than that of a radiologist evaluating it.

DR. ROBERTSON: Further questions for Dr. Gilkes from anyone on the Panel? Dr. Gerson?

DR. GERSON: I want to pick up on a comment that you made in responding to the last question. Is there a problem, or is there a question about the identity of some of the x-rays?

DR. GILKES: One or two on the six-month follow up. It is in your handout. If you look at the review dated February 3, 1984, there seemed to be some misunderstanding as to whether or not that table was presented by the sponsor. That table was not presented by the sponsor. Hence, you do not have it in the prepared book that was sent to you by the sponsor. I did that table. I listed the investigators by name. In keeping with the code of federal regulations, I merely identified the patients by initial. Consistency among the investigators led me to think that for one or two the x-rays were mixed up or it was just a matter of a simple error, and not an indication that the practitioner was trying to in any way mislead the Agency's conclusions. Is that what you were asking?

DR. GERSON: Yes, that is the question I was asking. I got a very clear answer. Thank you.

Just to clarify, did the sponsor, in fact, submit everything to you that they were supposed to? I am reading your second paragraph.

DR. GILKES: Yes.

DR. GERSON: They did everything that you think they were asked to do?

DR. GILKES: Yes. In the first review that you have, in what we call the clinical portion of the letter to the sponsor, we said we wanted pre-, immediate postop., 3- and 6-month radiographs. My superiors felt that those kind of data would satisfy them. We also wanted the radiographs dated. They submitted it and I tabulated it for you. I could cited it for you. I can go over it and call out the pages that involve my interpretations.

DR. GERSON: I was just looking for a more general response. As far as you recall, they did exactly what they were supposed to do?

DR. GILKES: They did exactly what we asked them to do.

DR. GERSON: Thank you.

DR. ROBERTSON: A follow up to that, Dr. Gilkes, in what you asked the investigators to do, did you ask them in any way to include all cases they had treated so that they were all consecutive cases, and/or did you insist that they include all failures as well as successes?

DR. GILKES: We asked that they select about 20. I was present, of course, at the meeting we had with the sponsor. Then, of course, the letter that went out, went out over the division director's signature. We asked 20 investigators to do about 5 teeth each and submit their results. This was the extent of the instruction. We did not say just your successfully-treated teeth. But, as many of you are aware, when board certification is a matter to come before a group, they indicate successfully treated. In other words, a board certified person in endodontics would not get his/her certification if they submitted 5 unsuccessful cases and that was all. They know they will not get certification. So it is the verbiage and it is the context that may have been taken. We did not mean, and they did not take it that way. I feel confident they did not—"don't give us the bad ones." You know the Agency would never put themselves in that position. We wanted them to get 20 investigators and each one of them to do about 5.

If you would look in the review, I think it is called Gilkes I, you will see that they are geographically spread out, and it was not just a little nest of practitioners doing the study that the Agency requested.

DR. DEL RIO: Dr. Gilkes, did you by any chance request the amount of time that this x-ray should be? Right here, in your statement you say a follow up postop., a follow up of 3 months and 6 months. Did you specify the amount of time at which these x-rays should be taken, and what para-meters did you use to suggest that it was 3 months and 6 months?

DR. GILKES: We stated it in no uncertain terms, pre-, immediate postop., and 3 and 6 months. Then if you notice the tabulation, supposedly that was within the frame that we requested. In other words, if I put a date down under 6 months, I had figured back to the preop. film and it was 6 months. Am I interpreting what you are asking correctly?

DR. DEL RIO: Yes, you answered part of the question. What parameters did you follow or what studies did you follow to specify 3 months and 6 months, and not 3 months, 6 months, 1 year and 2 years, for example? Do you have any basis to just limit it to 3 months

DR. GILKES: Some of the historical controls that we referred to, the follow ups, were within that time frame, and these are historical controls

DR. DEL RIO: What historical controls then did you follow? Can you cite for me

DR. GILKES: No, I cannot cite them. They are articles that existed, indicating that the board certified endodontics would follow up within that time frame and shortly after that restorations were placed.

DR. ROBERTSON: Thank you.

Are there other questions from the Panel?

Yes, Dr. Glowacki?

DR. GLOWACKI: I have a question about the original study design. I am looking at page 7 of the material submitted by the sponsor. I understood, in terms of the study design and the patient recruitment, that the patients were to be among 20 participating investigators in each of 5 randomly presenting consecutive patients who required such treatment. What I have been hearing so far makes me a little bit unclear about whether there was documentation that they were randomized, in a sense, by being consecutive patients who required this treatment.

DR. GILKES: Nothing more than you have before you. The only thing that you are missing in that book—they are the patient record forms. All of them usually were only of one page. Hence, there was no indication then that they were randomized per se.

I might add that at that time, the state-of-the-art of what the Agency requested did not call upon statisticians to give input, as we do now, when we make certain demands of a sponsor for pivotal studies or NDA studies. At the time, Dr. Mann and Dr. Walters, who was the deputy director, did not feel that it was necessary to have the input of a statistician. He came to the conclusion that after 374 cases were presented to us in a fashion that we gave them a not-approvable letter, that they would have to go back and do it the way he had requested. I daresay it was an arbitrary figure of 100 patients, but if 374 humans had been tested but not properly reported, Dr. Mann and the rest of the division did not feel it necessary to ask for additional animal studies. They felt safety was adequately demonstrated.

DR. GLOWACKI: My question was whether you think there was any misunderstanding about the nature of presenting consecutive patients.

DR. GILKES: No, I do not think there was any misunderstanding.

DR. GLOWACKI: Thank you.

MS. EDWARDS: I have a point of confusion. It gets back to the basic drug-device separation. Since this discussion may have a little bit broader implications than just this device, I would like to take a second and go backwards.

When I look at the formulation and the testimony from the attorney for the case, if this device

were just zinc oxide and eugenol, it would be regarded as a filler material and the evaluation would be before this group as to whether it was an effective filler material. In this case, the addition of the active ingredient of paraformaldehyde was included for its antimicrobial properties to prevent infection within the canal, which is a typical drug claim, which is where the Drug Center will become involved.

Then later on in this document it talks about the duration of the drug being from 7-10 days.

It seems to me that we can get very confused here. I really want to have some help from FDA on what this Panel is supposed to be looking at, and if there are two separate issues here. Are they supposed to be looking at was the antimicrobial treatment effective for the 7-10 days? Does the benefit of that antimicrobial treatment outweigh any potential of cell toxicity? Is the cell toxicity for 7-10 days? As a device group, are we supposed to be looking at is this an adequate filler material, as other filler materials made of zinc oxide and eugenol are?

It seems to me that there are two separate, distinct issues going on here if you look at the way the other drug-device groups are being looked at. Since this is part of the federal record, I would like some clarification on that issue as it would relate to other industry and manufacturers. I think it also helps when you are trying to look at the data and get away a little bit from whether it is the method or not, and what are the issues at hand. I am confused about what the issues are at hand.

DR. ROBERTSON: Is this a question for Dr. Gilkes or is this a general question to the FDA?

MS. EDWARDS: I think it is a general question to the FDA.

DR. ROBERTSON: Do you have any questions for Dr. Gilkes?

MS. EDWARDS: No, sir.

DR. GILKES: I might answer one point of the issue you raised there. We did not evaluate the labeling because we felt it had to be complete in other areas. There were some manufacturing controls needed, information on manufacturing controls. Hence, the letter read that we reserve comment on final printed labeling until the document has met the other deficiencies.

The other point I want to make before I leave is that at the time of the submission, when I evaluated it, we did not deal with microbiology. Had we done so, we have many microbiologists in our division, to say nothing of having them down in another division, that we would have called upon had we hung our hats on microbiological claims. At the time of the submission they were not making any. Hence, we did not ask them any microbiology data.

DR. ROBERTSON: Thank you, Dr. Gilkes.

Could we have some response to Miss Edwards' question?

DR. BOTSTEIN: Very good questions, and it is a complicated issue. Because the paraformaldehyde is in there and because the sponsor's draft labeling talks about disinfectant, this is regarded as a drug. Now it has an application as a drug and it is in-house.

So once we have it to evaluate, we can decide that the substance does nothing more than the already approved root canal fillers that are devices. Okay? It depends on what the information is in the application and how convincing it is that any more is done by the application. Does that make sense?

MS. EDWARDS: I think so. If I heard what you said correctly, you have narrowed your review to the adequacy

DR. BOTSTEIN: No, we did not, but once the decision is made, as it was for this application years ago, that this is a drug, it comes in with whatever labeling and package information the sponsor submits, and we do not go back again and decide whether this is really a device after all, and whether it should be in the category of the other substances. We could have but we did not. The sponsor could ask us to and we would always do that again.

But you can make a perfectly reasonable argument that if the labeling for this talks about disinfectant or preventing infection or whatever, that that is something that needs to be shown in the clinical database for the product.

DR. GILKES: May I add to that comment? The document that we received had the trade name of N2 Universal root canal filling material and sealant. The indication at that time was to fill and seal the canals and chamber of the tooth after the nerves and blood vessels had been removed. That was the framework that I used in my evaluation. At the time they did not make any claims in the indications to kill bacteria, and I daresay that would be quite a task, to demonstrate the same.

DR. ROBERTSON: The next presenter is Dr. Sheila McGuire, a consultant to the Panel, who has been a primary reviewer of this submission. Dr. McGuire?

PRESENTATION BY DR. SHEILA MCGUIRE

DR. MCGUIRE: The clinical data sources I reviewed for the NDA included the clinical study involving the 19 dentists who treated the 91 patients, with at least 1 tooth requiring endodontic therapy.

Additionally, the sponsor submitted case reports from the American Endodontic Society of 9514 treated patients.

Only one clinical study during the mid-1980s was conducted with no randomization of treatment,

per suggestion of Dr. Mann, of the FDA, because of, as he stated, the ethical difficulties with a placebo control and the practical difficulties with an active control.

Nineteen dentists performed the 119 endodontic procedures using the Sargenti method with N2 Universal as a root canal filling material of choice. The patients ranged from age 15-74, with 60 percent of the population male.

It is my understanding that we are considering the N2 Universal today as a drug because the sponsor wants to make the drug claim that N2 disinfects.

In the clinical study, the duration of exposure to the active ingredient, paraformaldehyde, was reported to be 7-10 days. However, blood samples were not drawn to document this estimation. Additionally, dose ranges were estimated to be between 32.6 and 51.7 mg although, again, no documentation from the 19 dentists was found on this point. At least, it was not included in the materials I reviewed.

Periapical radiographs were taken immediately postop. in 114 cases and, as we have discussed, 3- and 6-month postop. visit in 112 cases. I did not view the radiographs myself. They were not available to me, as Dr. Gilkes has explained. I took what they had estimated as the decision of whether the case was satisfactory or not.

My overview of efficacy: Acceptable ranges of ages and gender were represented in the study that Dr. Mann, in 1982, ordered. Seven dentists had not used the Sargenti method on molars. Only 25 molars were included in the rest of the population. The majority of the teeth undergoing the Sargenti method were incisors and canines.

The success rate in the clinical study was over 90 percent, thus, similar to the results of the conventional endodontic method, as reported in historical control populations.

Sufficient efficacy has been demonstrated in the study, that is, in accordance with 21 CFR 314.90, set forth by Dr. Mann from the FDA.

The case reports submitted by the sponsor and the American Endodontic Society were considered in determining the efficacy of the N2 Universal. Notably, the Society only requests case reports on teeth that have been treated safely and effectively from its Fellows. That is a quote from the NDA submission.

The accumulated results from these case reports, therefore, are certainly biased. However, the evidence from over 9000 patients must be considered, I feel, during the process of determined efficacy. The success rate was over 90 percent.

Overview of safety: From the materials I reviewed, I find insufficient evidence of significant risk from the proper use of N2 Universal. It is the sequelae of improper use that I find troubling. With

any endodontic method iatrogenic complications can occur. These complications include inadequate biomedical instrumentation; perforation of a root caused by instrumentation; or extrusion of the filling material out of the apex.

In the conventional method, hand-held reamers are the instruments used to prepare the canals. In the Sargenti method, the potential for iatrogenic problems to occur is greatly enhanced, I feel, due to the use of the power-driven instruments.

In my review of NDA materials, power-driven instruments are recommended with the use of the N2 Universal material.

A root fracture can develop following perforation. The likelihood and extent of perforation is less likely with the controlled, hand-held reamer versus a mechanized or power-driven instrument.

Paresthesia of the inferior alveolar branch of the second or third division of the trigeminal nerve has occurred because of the overfilling of roots. The N2 paste can be mechanically forced through an apex much more easily in the Sargenti method than with a hand-held instrument in gutta-percha with lateral condensation.

Another instrument suggested for use by the Sargenti method is the fistulator, a motor-powered rotating drill. Not used in the standard method, the drill is particularly dangerous in the areas of the mental foramen or inferior alveolar canal, as we saw, as an example, in the clinical study.

The literature review since 1985 on the N2 accidents highlights the danger of the incorrect use of this product. The preponderance of adverse clinical events reported in the literature were associated with the use of N2 Universal-like materials in the treatment of molars.

While the Sargenti method does not recommend overfilling, the difficulty in achieving a successful root canal treatment of the molar most likely was not reflected in the clinical study because of the small number of molars involved. Control during the placement of N2 is difficult.

In summary, the drug product, when used properly, I find to be safe. However, the potential for gross abuse of the endodontic technique must be addressed by this committee. Disclosure of the information relating to ease with which the N2 paste and technique can cause long-lasting damage to the patient must be provided to the dentist and to the patient.

My labeling review: The averse clinical events associated with overfilling and the use of the fistulator are not mentioned. The proper technique includes the use of power-driven instruments. Therefore, the label should report, in my view, the documented adverse reactions caused by their use.

In its current state, the label does not provide the dentist and the patient with sufficient

explanation of the negative sequelae associated with the technique that can easily and unintentionally be mishandled.

My conclusions: When used properly, when kept within the canal, the study of the 91 patients in which N2 was used showed it to be a safe and effective material in the treatment of a tooth requiring endodontic therapy. However, the claim of duration of exposure of 7-10 days was undocumented, as was the claim of dose range. These facts, plus the issues of, one, the adverse reactions associated with overfilling and fistulation and, two, the ease with which unintentional abuse of the technique can occur, I feel must be addressed by this committee.

Are there any questions?

DR. ROBERTSON: Any questions from the Panel for Dr. McGuire?

DR. BERTOLAMI: I am obviously not an endodontist, but I still have a couple of basic questions that have confused me through this morning's discussion and which I think Dr. McGuire is probably the best competent to address.

The first, in relation to the study done under the questionnaire headed by the American Endodontic Society, I still have some difficulty in ascribing this to anything other than a testimonial account. It would seem that having a person evaluate radiographs, who is one and the same individual who actually performed the case, in some sense, disqualifies them. Was there any systematic reason why a separate individual could not have, in a non-biased manner, been able to assess radiographs, rather than the statements that the prognosis is very good when that individual was the treating practitioner? That is the first point.

The second thing that has confused me is the statement that valid controls somehow are not applicable to endodontic treatment. It would seem that having the same or other practitioners use conventional endodontic techniques, not necessarily in the same patient but in a relatively large population of other patients, would have qualified as an adequate control.

So I guess the basic question is are we really dealing with a system that is not amenable to valid control, number one? Number two, wouldn't there have been a convenient way of eliminating the bias even when using radiographs of this sort? Those two things confuse me.

DR. MCGUIRE: Well, first of all, Dr. Kimmelman did independently review the radiographs only and made an assessment, as did Dr. Gilkes.

Two other points that I know I followed when I was reviewing this, I followed an took as I thought was an edict how Dr. Mann put forth the protocol was how the sponsor responded. While, in 1993 I would have designed the study differently, I felt I had to review this in light of how an FDA official told them to do it in 1982. I do not know if that is a correct standard or not for this Advisory Panel to follow, but that is what I followed.

Thirdly, I think the state-of-the-art of how clinical studies were done in 1982—we have to remember that. While now we are held to a higher standard in designs, again, I think we have to think back to what they knew and what the status quo was in 1982.

Does that answer your questions?

DR. BERTOLAMI: Yes, thank you.

DR. ROBERTSON: Other questions from the Panel?

DR. SPANGBERG: I think I would like to correct the last statement. I think even back in the 1950s and 1960s very well-controlled endodontic prognosis studies were done, and they were not used as reference in this material.

The other thing which bothers me with this material is that whoever wrote that these were supposed to be consecutive cases in a randomized sample, looking through the material which is presented here, the 100-plus cases, you find that the study, for instance, was supposed to be done in a 6-month period. It actually took 18 months to do the study.

In addition to that, I have difficulties believing that it would take a practitioner up to 6 months to collect 5 cases in their offices.

So I would like to be assured that these are consecutive cases and were not selected either up front or at the end. Missing in this study are any kind of up-front selection criteria. There are no such criteria. At the same time, for example, I see no endpoint evaluation and I am very disappointed in FDA for not doing an endpoint evaluation. I think that is very unsatisfactory.

DR. MCGUIRE: Well, I concur. I do not have independent confirmation that they were 5 consecutive endodontic teeth that walked into their offices.

DR. ROBERTSON: Other questions from the Panel for Dr. Mcguire?

(No response)

Thank you, Dr. McGuire.

Finally, a presentation from Dr. Ralph Harkin, who is group leader in the Division of Biometrics at FDA.

PRESENTATION BY DR. RALPH HARKIN

DR. HARKIN: While we are getting set up with the transparencies, I have not been involved in

any dental study since graduate school, in 1964. This division was assigned to me on December 28, a month or so ago.

(Transparency)

The criterion I follow in doing a review is to look at what has been told a sponsor to do. If they have been told to do things that I do not agree with, then I try to figure out how to salvage the data generated, if there is any way to salvage them.

In this particular study, it seems that the sponsor was told to do certain things and, at that time, as Dr. Gilkes said, there were no statisticians. I think there was a total of 5 statisticians in the Center at the time. We are still short but that is another story.

The objective was to clearly demonstrate safety and efficacy of N2 filler/sealer. I had 3 choices for a comparator success rate: those given in the text; that from the 10,000-plus subjects that were submitted; and then that contained in the 91-subject study that was submitted.

(Transparency)

I will try to go over each of these. They list 5 points to determine whether or not each tooth filled was a success or not. Yet, in the forms provided me, they did not list all 5 of those points. It may be that some of those are so transparent that if you mark down that there is minimal or no pain or swelling, then, number 3, return of tooth to function naturally follows and you do not have to record it. I do not know.

A second thing that was puzzling is that they recorded minimal or no pain and swelling. In some of the subjects they recorded as failures, the pain and swelling was recorded as having disappeared at the end of 3 days. When I have a dentist working on my jaw bone and it hurts for about 3 days sometimes. I do not know if that is truly a failure or not but, by the same token, the other subjects in the study did n to report or record the absence of pain either. I do not know if they failed to record the absence of pain because it was not asked, or there truly was no pain later.

So I had a lot of problems in making sure for myself that they had followed all 5 of their criteria for determining success.

(Transparency)

Key to any statistical procedure is the proper randomization of subjects to the drug or therapy that is being evaluated. In this particular case, as has been pointed out by the Panel and by the various presenters, there is some question as to whether or not the subjects were truly randomized, picked at random, from the people who presented to the 19 clinicians who participated in this study.

At the same time, as Dr. McGuire pointed out, the number of molars treated seems to be somewhat low compared to non-molars when you look at the literature submitted by the sponsor. This would possibly indicate that a lack of randomization was followed also.

Secondly, when they got into the preparation of the molars, they did not use the engine-driven tool entirely. I do not really fault the dentists for that. In fact, I would rather congratulate them if they feel that the instrument is not going to work, clearly, they should move to something that will work and not harm the patient. But it confounds the effect of the tool being used with the effect of the N2 sealer being used, and I cannot separate the two out in my analysis.

That covers the root canal preparation. We have engine-driven tools. Some switched to a hand preparation and some went with the combination of the two.

(Transparency)

Dr. Mann had mentioned the choice of a historical control group. A historical control group normally consists of subjects who had the same indication that you are treating but they received some other approved therapy. In this case, they should have been picking 100 subjects who had received gutta-percha, or something similar to that, winnowed from case report forms of subjects who needed root canal work. What we received is a success rate from literature which is more in the nature of a population figure. We have no real handle on how it was arrived at. If you go to one source of literature, it is as low as 80 percent; another, it is 97 percent. We do not know exactly what we are hanging our hat on, but they did report 94.5.

In the law it says we can weigh the criteria of a historical control group based on ethical reasons, clinical reasons or scientific reasons. I find no reason in what was presented in any of these 3 to warrant waiver of obtaining a true historical control group.

Secondly, Dr. Mann ruled out the use of a parallel group. A parallel group could have clearly been used as an active control in this where the gutta-percha or a similar, approved filler had been used.

(Transparency)

What I did do, in an effort to compare these results to the results of the 91-subject trial, and you have it in my review, is look at the number of fistulations and other observed events that occurred to these people to see if they are comparable between the 2 groups. I find that they are not statistically comparable, which indicates that the 2 groups probably are, not only in the obvious way of being requested to submit those that were successful, different in other ways also.

But if the 91 subjects that are in the one study do meet some valid criterion in the endodontic community, then the lower confidence limit of the success rate is around 82 percent, which means that you can expect 80 percent or better of the people treated within N2 to have a successful outcome if, in fact, the data we used are valid.

I am open to questions.

DR. ROBERTSON: Does the Panel have questions for Dr. Harkin? Yes, Dr. Sandak?

DR. SANDAK: In the review where it is mentioned that in 3 days pain and swelling is reduced, was there any indication that antibiotic therapy was afforded to the patient, as is most times customary in root therapy for a patient with a conventional procedure?

DR. HARKIN: There is a separate listing in there of those who received concomitant therapy, and some of them did, yes.

DR. SANDAK: The other question, from the root therapy that I am familiar with I have always found that if periapical lesions are present prior to treatment, that a 1-year radiograph is far more effective than a 3- and 6-month radiograph for continuing to restore the tooth.

DR. HARKIN: I will let Dr. Gilkes answer that.

DR. GILKES: In order to help the Panel arrive at their conclusions, I might first address the fact that the format for the protocol came from what we, at that time, identified as the "review of drugs manual." That came right out of manual 123.

The other point that I might make regarding the succession of cases is that the individual investigators did not state that they did them consecutively. They did n to say they did; they did not say they did not. However, if you follow each investigator, his sequence of presentation of preop. x-rays indicated, on page 5—10/18/82, 10/26/82, 11/10/82, 11/16/82—that would indicate to me that he did take them consecutively. He is a general practitioner and not doing oral endodontics every day.

So the Agency, at the time, had no reason to doubt this if he presented the data in the fashion he did, and then supported it.

DR. BOTSTEIN: Some of these questions you may consider asking the sponsor. They are factual questions about how the database was derived at.

DR. GILKES: I do not think I have answered your question. I do not think I have adequately answered it.

DR. SANDAK: The second question relates to the 1-year periapical filling.

DR. GILKES: That the dates that the permanent restorations were placed, as well as dates in studies that I cannot at this moment cite from the literature, indicate that the minute you proceed with a permanent restoration, be it to fill it with amalgam or put a full crown on it, would indicate to you that this has been successfully treated. I would yield to the board-qualified endodontists to address that as to when they suggest to their patients they go back to the general practitioner for permanent restoration.

DR. ROBERTSON: On the other hand, it seems to me that it was made clear by the industry sponsors who spoke this morning, and has been confirmed on several occasions by Dr. Gilkes, that the instructions to the investigators limited, rightly or wrongly, the films to 3 and 6 months. I think it is a separate question as to whether, in 1992, you might ask different sorts of things. But the rationale for doing those studies on the part of the investigators seemed to be well confirmed.

I would like to explore for just a minute this concept of historical control in the context of this study. We have had some unanswered questions about whether these cases in the "experimental group" represent either randomly selected or consecutively selected cases, and if not, then were they selected for a success bias?

Do you have any sense that that might also be true in the historical controls that are used to match the experimental group?

DR. HARKIN: Yes, you can clearly select historical controls which will clearly favor your product.

DR. ROBERTSON: I did not ask whether you could. I asked whether the historical controls from which you drew population numbers for success or failure rates were historical controls in which you know that the cases are either randomly selected or consecutively selected? Or, do the historical controls that they were comparing against have the same difficulties that the experimental group had?

DR. HARKIN: I do not feel that there is a true historical group in this NDA. That is my position. One set of figures are those reported in textbooks and journal articles, and they are simply a number of successes. It ranges from around 80 percent up to 96, 97 percent. They have a 94.5 percent figure that they hang their hat on.

The other, the 9000 set, is probably not a good set because they only asked for those who were successfully and safely treated.

DR. ROBERTSON: Thank you.

Dr. Curro?

DR. CURRO: Do you get a sense from the data, if you broke it out into the combination of the hand-held instruments and the machine, that there is a bias of the technique? That is, does the technique alter the safety, since we are talking about the safety of the paraformaldehyde here? If you use the machine only, is it safer? Is it safer if you use the combination, or is it safer if you use the hand-held? Was there any sense in the data?

DR. HARKIN: I got a sense that I would like to see more information on that. I felt that there may be something there but there is not enough hard evidence to make me go one way or the other. It raised doubt in my mind associated with using the instrument all by itself versus using the instrument and finishing up the fine detail by hand versus doing it by hand. But, again, the effects are confounded with the N2 filler/sealer and I do not have the information or the design to break those out.

DR. ROBERTSON: Can I follow up just with a point of information? Does that mean that you could not identify the cells in order to either modeling or multivariate analysis? You simply could not define those cells in order to see what contributed to the variance?

DR. HARKIN: There were not enough of them.

DR. ROBERTSON: There were no t enough of them?

DR. HARKIN: Right.

DR. CURRO: I just want to follow up on that. If you were to design the study as it is now, with the criteria that were given by Dr. Gilkes, how large of a population would you need to create a power of 80 percent?

DR. HARKIN: Eighty percent power or 5 percent alpha level?

DR. CURRO: Right.

DR. HARKIN: You would probably need somewhere in the neighborhood of 80-90 subjects in each of the arms, and I was looking at a 4-arm trial to separate out the effect of the filler/sealer from the effect of the various tooth preparation mechanisms used versus a control, whether it is the gutta-percha or whatever in the control arm.

DR. CURRO: But if I wanted to have, say, a double-blind and a placebo with that, a placebo being a similar formulation without the paraformaldehyde, would you create a study that would be, say, 6 arms?

DR. HARKIN: I would use the gutta-percha without the antibiotic.

DR. ROBERTSON: Any more questions for Dr. Harkin?

DR. DEL RIO: I have a problem. Maybe you will be able to solve it for me. When I went over the study, I found out that I was evaluating two studies. I was evaluating one study for 109 cases and I was evaluating another study for 9000 cases. Did you have any problem having to evaluate two cases at the same time?

DR. HARKIN: Two different samples sizes?

DR. DEL RIO: Two different sample sizes.

DR. HARKIN: That is not a problem in evaluations for me. No.

DR. SPANGBERG: Just an additional question, do you think this clinical study evaluated the efficacy and safety of paraformaldehyde?

DR. HARKIN: I do not think so. I do not think they followed up on the blood data and everything else required to do that.

DR. ROBERTSON: Thank you very much, Dr. Harkin.

Dr. McGuire is going to summarize for us with some slides, and then we will move into the discussion.

DR. MCGUIRE: It is not exactly a summary but, for the non-dentists on the Panel, I just want to make show the sequelae of improper technique.

(Transparency)

We did see an example of how it can be extruded out the apex by a dentist who does not handle it properly.

That is all.

DR. BERTOLAMI: May I ask a question? What anatomical structure is that material residing in? Can we tell? Is that in the inferior alveolar nerve canal?

DR. MCGUIRE: Yes, I was told that it was, and there is paresthesia because of it.

DR. BERTOLAMI: Thank you.

MS. EDWARDS: Dr. McGuire, is this particular to this device, or is it an understood phenomenon of devices of this type?

DR. MCGUIRE: Back to your original question of whether this is a drug or a device, I am just saying that I think the committee should consider the sequelae that can occur when not used properly. I do not know how to factor that in, how we are supposed to be factoring that in. But I just wanted to demonstrate it.

DR. ROBERTSON: There may be more questions here. I guess I have one also as a non-endodontist. If, by whatever means, I force zing oxide and eugenol, not containing paraformaldehyde, into whatever anatomical space that is, am I more likely or less likely to get paresthesia from having done so?

DR. MCGUIRE: I do not know how to determine that.

DR. ROBERTSON: So the answer is that you do not know?

DR. MCGUIRE: Correct. But since the N2 Universal was presented to us with directions on using the power-driven instruments, this is why I feel we should know it exists.

DR. ROBERTSON: I understand. Dr. Spangberg?

DR. SPANGBERG: As an addition to that, I think this kind of accident can probably happen with many sealers. The only problem is that with formaldehyde-containing sealers you get permanent nerve damage which cannot be reconstituted. With other kind of materials you can surgically remove the excess of material and be left with no permanent nerve injury. These cases are very clearly experienced by many endodontists and surgeons.

DR. MCGUIRE: I would like to ask you a question, Dr. Spangberg. With simply hand-held instruments, can this much material be forced out the apex?

DR. SPANGBERG: You would have to be very clumsy to do that. It could be done if you really worked at it but normally it would not happen.

DR. ROBERTSON: Thank you.

Dr. Curro?

DR. CURRO: Just a point of clarification, when you reviewed this, how did you define the paraformaldehyde? Is it an antimicrobial? Is it a disinfectant? Or is it a sterilant?

DR. MCGUIRE: I took it purely as an endpoint designation that was set forth by Dr. Mann.

DR. CURRO: And what was that?

DR. MCGUIRE: It was satisfactory/unsatisfactory.

DR. CURRO: Yes, but, for example, if you interpret it as an antimicrobial

DR. MCGUIRE: As I said in my review, there was no documentation of duration or dose.

DR. CURRO: So that remains an open question then.

DR. BERTOLAMI: Just one last question, apart from its antimicrobial properties—and I have no knowledge of paraformaldehyde, but I know that formaldehyde is a fixative and the question I would have is would the effects in that slide—and I have never seen a slide like that before—would the effects of a formaldehyde derivative on the inferior alveolar nerve be any different from the effects of a fixative on residual pulp tissue?

DR. MCGUIRE: Well, except that you want the residual pulp tissue to be destroyed or inactivated.

DR. BERTOLAMI: But would, for example, an intact healthy inferior alveolar nerve be any more resistant to the fixative properties of the agent than, say, the desirable fixative properties that would be applied to the dental pulp? This may be a concentration-dependent phenomenon and I generally do not know the answer.

DR. MCGUIRE: Nor do I.

DR. ROBERTSON: Thank you.

We will now move into beginning our discussion for the afternoon amongst the Panel members. We have tried to give everyone in the audience time this morning to make their presentations and present concerns to the committee. We certainly will allow response of members of the audience to questions directed to them by the Panel members, but we would appreciate allowing the Panel members to have their discussions without unsolicited comments from the audience.

In that vein, Dr. Glowacki has some questions of the AAE representative.

DR. GLOWACKI: Yes. In light of the questions about finding whether there are appropriate historical controls, in the documentation provided by the sponsor there was, at best, second-hand citations from review articles and book chapters. I wondered if anyone in the audience, perhaps the representative from the American Association of Endodontists, might be able to clarify that. Dr. Maggio?

DR. ROBERTSON: Would you introduce yourself?

DR. MAGGIO: I am Dr. Joseph Maggio, from the American Association of Endodontists.

Would you repeat the question? Are you asking it from a sponsoring

DR. GLOWACKI: No, no, no. I am asking it just in terms of the literature because, in preparing for this, I had informal conversations with friends who are endodontists and the impression that I got was that there is information out there in rigorous controlled studies about more conventional endodontic treatments. That would seem to be what we are looking for in a historical control.

DR. MAGGIO: Now I understand. Absolutely. The bibliography that I alluded to this morning of 141 articles was simply in response to the question of whether there is enough scientific information available at this particular point to decide one way or the other in favor of the use of paraformaldehyde or not. That bibliography has no mention of the historical significance of success in conventionally treated cases.

Since I do not know what articles were used in developing what the sponsor put out, it would be very difficult for me to tell you whether that 3-month, 6-month period was, in fact, long enough. I can tell you that in the American Association of Endodontists for board certification it is a minimum of a 1-year follow up.

The success/failure study that comes to mind that was even shown on a slide here by the members of the AES was one done by Seltzer, where he set a minimum 6-month and 1-year follow up.

As the statistician, Dr. Harkin, alluded to, those success and failure studies run the gamut from somewhere around 80 percent as high as 98 and 99 percent. You would have to go back and search the literature. But I can only assure you that there is a tremendous number of articles that have appeared in refereed scientific journals that all address it. So it would not be hard to come up with something that would be statistically significant and also historical.

DR. ROBERTSON: Is there other discussion that the Panel needs in order to prepare yourselves to address the questions we have been asked to address this afternoon?

DR. ROSAN: Yes, I just want to know from the sponsors, I guess, whether there are any other studies about the antimicrobial effects except the two quoted, the one from Grossman and the Von Haute study on the organisms? There was some mention earlier of Bacteroides infection of sinuses and I do not see any data on the effects on those anaerobes. So do you have any information?

DR. WERTS: Dr. Ramon Werts. With respect to that comment regarding the specific bacteria, the articles that were alluded to, the actual conclusion—and I cannot find the quotation right now but we will find it—implied that there was no proof that it could be one or another of the materials that did it. It was not specific to the effect that this was involved with N2 in any way whatsoever.

As to other specific antimicrobial studies, in all honesty, no, there really have not been. I will look for that reference and pass it on to you later.

DR. MCGUIRE: I have a question for you. What would you say the probability of a dentist mishandling this material after, let's say, an experience of 40 teeth would be?

DR. WERTS: Very small. Very small of mishandling it. I think one of the things that I would like to mention in that respect is that the same ill effects that have been alluded to regarding N2 have been shown in the literature to occur with virtually every other material. One of the most commonly used endodontic sealers today, is used in my university where I graduate from, is AH26. In the literature there is evidence that AH26 gives off formaldehyde. Yet, AH26 has never applied for a new drug status.

So when you look at the literature, you find the very same things occurring from anything.

Now, the implication has been that mechanical instrumentation can cause it more readily. I think it also should be pointed out that many endodontists today are using mechanical instrumentation. They are using the giromatic handpiece. They are using the sonic instrumentation. So the implication has been that all endodontists only use hand instruments and all Sargenti people only use engine-driven instruments. That is simply not true.

DR. MCGUIRE: They use power-driven for instrumentation but not for placement of the filler? Is that correct?

DR. WERTS: There are endodontists who use the spiral filler for placing the sealer and then placing the gutta-percha by hand or now some of the newer gutta-percha materials.

DR. MCGUIRE: So that is the distinction then? Some endodontists are using it primarily for instrumentation and a few are using it with sealers, versus the N2 technique used in the clinical study where they used power-driven to use everything, instrumentation and filling?

DR. WERTS: No, not necessarily, and I think it has been analyzed. There were some that used hand instrumentation with N2, yes.

DR. ROBERTSON: Thank you, Dr. Werts.

DR. WERTS: Thank you.

DR. NORMAN: I have a question I would like to ask Dr. Kimmelman, please.

DR. KIMMELMAN: Yes?

DR. NORMAN: You were the monitor of this project, were you not?

DR. KIMMELMAN: Yes, sir.

DR. NORMAN: What were the specific duties that you felt you needed to do as monitor?

DR. KIMMELMAN: I had to address the candidates who would submit cases and make sure that they followed the general rule, which I do want to say something about in a minute, and give them a time limit and keep after them. We went back and forth on the phone with them more than we were by letters. I think 1/20 or so failed to comply. I do not know whether that was illness. It has been over 10 years now. I think maybe one of them died.

But I did want to say something, if I might, about this very question

DR. ROBERTSON: Is it responsive to the question?

DR. KIMMELMAN: It does refer to the question, yes, I think so.

All the participants were instructed to take the patients in sequence, in other words, not to select from among their patients but to take the next 5 patients on whom they would normally do endo. and to record those patients according to the rules that we were laying down to acquire the data by the Mann protocol.

DR. ROBERTSON: And do you have evidence that they, in fact, did that?

DR. KIMMELMAN: The evidence I have, sir—again, this goes back ten or eleven years—is that we were attentive to how this material came in. I do not have the papers with me but I know they were on record. And it was not at all casual but each of these participants was required to justify the selection, the procedures, and even his judgment on success or failure.

DR. NORMAN: Did you visit each of these offices?

DR. KIMMELMAN: Not a bit, sir. No, I do not believe I visited any of them personally.

DR. NORMAN: So you have no evidence of looking at any records.

DR. KIMMELMAN: I looked at all the records, sir.

DR. NORMAN: No, you have no evidence of looking at patient records in any of the offices to see that they were sequential.

DR. KIMMELMAN: The patient records I saw were those that were sent in. That is all. I might just say about those same people, all of them were people interested in participating in this.

DR. NORMAN: I notice that a great number of the case forms are not signed, which is like sending in something that has no data on it at all. Why were they accepted in a form where signatures were not required?

DR. KIMMELMAN: I do not remember specifically, except that what would sometimes happen is that a submission would be accompanied by a letter that would be signed.

DR. NORMAN: The case report forms are not signed in a majority of the submissions.

DR. KIMMELMAN: I cannot answer that, not remembering whether we were concerned about it or not. I do not remember that.

DR. ROBERTSON: And you then worked with Dr. Gilkes to arrive at the outcome decision of successful or not successful?

DR. KIMMELMAN: No, sir. I have met Dr. Gilkes before but when the papers were completed, as they were collected they were turned over to either Dr. Arzt or one of his associates at the time. It was with Dr. Arzt that I did the project. I met Dr. Gilkes.

DR. ROBERTSON: So the definition of success was made by the person who did he endodontic procedure?

DR. KIMMELMAN: He could record success or not but he was obligated to send on those cases that he had under-taken, the first five.

DR. ROBERTSON: But you did n to evaluate any of those?

DR. KIMMELMAN: Yes, I did. In other words, no matter what he said, we made our independent judgment on those.

DR. ROBERTSON: So you did look at all of those?

DR. KIMMELMAN: All of those, yes, sir.

DR. ROBERTSON: And you made an independent judgment of success or failure?

DR. KIMMELMAN: Yes, sir.

DR. NORMAN: Where are those data?

DR. KIMMELMAN: All those data were turned over to Dr. Artz and the AES, and turned over then to the FDA. All those data were turned over to the FDA.

DR. ROBERTSON: Thank you.

DR. BERTOLAMI: One more question. It is relevant to this point.

How were you able to confirm success based on a paper review of case report forms if these forms did not have a place for the practitioner to record the five endpoints that had originally been mentioned; only success of not success? What criteria could you use to confirm that as being a correct conclusion?

DR. KIMMELMAN: As I said, I have not seen the data for years but, if I remember correctly, the main data were the x-rays, which had to legible and clear, and information as to dates and procedure. That was all on the form. Whether or not they were signed or initialled, I really do not remember. Actually, the report of absence of pain or return to function, and all the rest, were, as far as I remember, either in the covering letter or in each case history. Every one of them was assumed to be judged by the practitioner.

DR. BERTOLAMI: So with those five endpoints, was some form generated in some way that then came back to you so that you could make an independent assessment?

DR KIMMELMAN: I saw all of them periodically, and sometimes we would keep after a dentist.

DR. BERTOLAMI: Okay, so where now are those forms, apart from the case report forms?

DR. KIMMELMAN: Everything that was in there was turned in. We did not keep any individual records. We turned them in to the AES, which turned them in to the FDA.

DR. BERTOLAMI: I guess there is a point I am unclear on. Is there a separate data report form, apart from other one that we have here in the document, the American Endodontic Society investigation study—is there some form, some place, that has these five endpoints that would allow an objective reviewer a more independent capacity to assess --?

DR. KIMMELMAN: You mean each case with five endpoints?

DR. BERTOLAMI: Yes.

DR. KIMMELMAN: It is possible that it exists, and I am sure if they were collected, if they were not turned over, that they do exist. But my recollection is that we, at Franklin Institute, did not keep duplicates of them. We turned over the originals.

DR. BERTOLAMI: Okay, but, you see, I am still not getting to the heart of the matter, which is, as the monitor of the study, you ought to be able to tell us if they ever existed.

DR. KIMMELMAN: Oh, they all existed. Are you asking me whether I saw them all?

DR. BERTOLAMI: No, I am asking is there a form some place which lists five endpoints, which could now be looked at in order to permit an objective reviewer to confirm the statement of an excellent result, as we see in what we have before us? Did that ever exist?

DR. KIMMELMAN: Yes, sir. It existed at one point. Sure. I had to make a final report. I made a final report to the AES.

DR. MCGUIRE: I have a question for clarification. So at 6 months you did something more than look at the radiograph?

DR. KIMMELMAN: I had a written report. That is what else I had. In other words, I had a written report. It was not just radiographs. It was a report form. I thought all of them were signed or initialled by the dentist. Sometimes five would come at a time. You know, somebody would be remiss and you would phone them and so he would send a batch of them. Maybe he would be a month late. Nonetheless, we certainly in every instance had a written form, a case history submitted by each participating dentist for each patient, yes.

DR. ROSAN: Is that the form we are looking at now?

DR. KIMMELMAN: I have n to seen what you have there, Dr. Rosan. So I do not know.

DR. ROSAN: Dentist's report—is that the report?

DR. KIMMELMAN: That would be right.

DR. ROSAN: That is the one you are talking about?

DR. KIMMELMAN; Yes, it is.

DR. ROSAN: I think the point is that in many of these reports the documentation for what the patient experienced is not there. As Dr. Bertolami says, it says "excellent" and we have no further information.

DR. KIMMELMAN: I see. You mean there would be a judgment and not details as to why. Is that what you are saying? But that is not because it was careless. It was because sometimes you would phone and ask what the situation is and there were copious notes, and everything else, and they were turned over.

DR. ROBERTSON: Thank you very much.

DR. KIMMELMAN: Thank you.

DR. GILKES: Dr. Robertson, in the review you have, there was a table submitted to the Agency. The review is dated February 3, 1984. There was a table submitted by the sponsor where they gave the investigators as A through U, on page 3 of that review. They indicated the number of teeth, the number of patients and the investigators' ratings as satisfactory, unsatisfactory or questionable. They did not address the endpoints. But that is one table that came to us originally. If you look on the last page, you will see the recommendation, based on that single one-page table, the application is not approvable. That is when we requested the information that Dr. Mann set forth. If you have not found that one-page table, this is what it looks like.

Based on that, they got a not-approvable letter. Now, when these patient consent forms came in, along with the record forms, each one is signed. True, the individual patient record form was not signed but this informed consent is signed by the dentist. In the second paragraph he acknowledges: I understand that the material is similar to the material that he would normally use, and this is part of a continuing study in order to gain approval of the U.S. Food and Drug Administration.

I do not know if that answers your question, Dr. Norman, as to a signature.

DR. NORMAN: No. These forms are not signed. That is not sufficient.

DR. GILKES: Very well.

DR. BOTSTEIN: I wonder if these forms were actually filled out by the dentists. In a couple of cases, behind this typed form is a handwritten form with the same information and it is signed by the dentist. Can we ask the sponsor whether the sponsor has made up these case report forms or whether individual dentists did?

MR. RAUBICHECK: I can say without equivocation that the individual dentist did. Let me clarify something; maybe I can clear some of this up for you. We followed the Mann protocol in Tab D of the meeting package. The Mann protocol did not say that on the case report forms we had to list the five individual criteria of return to function, absence of pain, etc. It just said what it said. It said submit the radiographs.

What happened was that the individual investigators, per instructions from Dr. Kimmelman, used those five criteria in assessing the patient, in assessing the radiograph, and then made the judgment of successful or unsuccessful. Dr. Kimmelman, using those five criteria mentally, looking at the case report forms and looking at the individual radiographs, made his own independent judgment.

That was sent in to the FDA. Dr. Gilkes did the same thing. So that is how the sequence occurred. You have the material in front of you. I do not recall whether dentists signed each individual case report form. The dentists signed the informed consent forms that were attached to

them and they signed the cover letter that went in with the five cases. I do not believe that the FDA had a regulatory requirement at that time that each case report form be individually signed, but I am not sure about that.

DR. GILKES: You stand corrected. In our letter we state that the investigator's signature, not initials—in our letter that Dr. Mann wrote, on page two, at the very end of page two, we requested this.

MR. RAUBICHECK: Well, you got it on the consent form.

DR. GILKES: Yes, we noted that we had it on the consent form and that is why I answered Dr. Norman as I did. But, yes, we did tell them on page two, Tab D of Dr. Mann's letter. That is why I replied to Dr. Norman in the manner I did because I knew it was in there but I also knew that the informed consent form was signed, which implied NDA involvement.

MR. RAUBICHECK: We did not do anything with those case report forms, other than look at them and send them in.

DR. ROBERTSON: I think the primary question is how do the data get derived.

MR. RAUBICHECK: Does that help a little bit?

DR. ROBERTSON: Dr. Spangberg, do you have another question?

DR. SPANGBERG: Yes, I would like to ask a question of Dr. Piacine. You participated in this study. You submitted eight cases. Is that true?

DR. PIACINE: Which study?

DR. SPANGBERG: These 109 cases.

DR. PIACINE: Not specifically, unless my name is on there.

DR. SPANGBERG: Yes

DR. PIACINE: Is that right? Perhaps I did. It is over twelve years. I do not remember.

DR. SPANGBERG: Can you remember how you selected those cases?

DR. PIACINE: I do not recall at all.

DR. SPANGBERG: Because it brings up the issue of how cases were selected. In you presentation this morning you told us that you had done at least 2500 teeth.

DR. PIACINE: That is an estimate, yes.

DR. SPANGBERG: Kind of rapidly, that comes out to about half a tooth a day. And to get eight patients, it took you eight months in this study. Can you explain that?

DR. PIACINE: To get me eight patients?

DR. SPANGBERG: Yes. The first patient you had was dated October 14. The last patient you saw in this study was June 22, the following year.

DR. PIACINE: I do not even recall. I just do not recall.

DR. SPANGBERG: But you understand why I am curious.

DR. PIACINE: I do understand, except I do not understand my involvement.

DR. SPANGBERG: Because you must have been busier than that in your office.

DR. PIACINE: I presume so but I do not know. I cannot answer that because I do not recall.

DR. GILKES: Doctor, on page 10 and 11 of my review it indicates under preop. that they were sequential, and only when you get to 6-month postop.—if we are looking at the same material, page 10, patient D.A.L., 10/2/82; another tooth done 12/6/82; then we go to patient J.O., 10/14/82; patient M.S., 11/10/82. Then on page 11, patient J.M.I., 11/5/82; patient G.H., 12/3/82; and then 12/3/82 another tooth was done. Then finally, patient W.C.E was done on 10/20/82. Other than that one being out of sequential order, all the others were in sequential order to our satisfaction at the time.

DR. SPANGBERG: Not to my satisfaction though at this time because I have a concise record of this and it started October 14, 1982; the next case is October 18; then November 10; one, December 16; one, January 21; one, February 8; one, March 17; and one, June 22. Those are the starting dates. Sorry to debate this.

DR. ROBERTSON: Thank you.

Are there any other questions that the Panel wishes to ask, or discussion that the Panel wishes to have before we move into addressing the questions that have been provided?

(No response)

Would you like to take a coffee break before we start that process?

(Several Panel members nod in agreement)

Then we are adjourned for 15 minutes to take a coffee break, and we will begin the answers to the questions at 3:00.

(Brief recess)

DR. ROBERTSON: Can we reconvene the meeting, please? We are going to go through the questions for which we have been asked to provide advice. That is our role here, simply, to the best of ability, to provide the FDA with advice. We are not making a definitive statement on acceptability or unacceptability, and I think we have actually provided considerable information to the FDA through the day's proceedings.

I would like to ask Dr. Botstein to give us some context in which we should address these questions, particularly as it relates to the context of what the investigators were told initially to do versus considerations of today.

DR. BOTSTEIN: Thank you.

I do not want to give too facile an answer because it is quite a difficult issue, and it arises whenever there is a gap between the time a clinical study was actually done and the data are evaluated here because of science advances and the state of clinical trials advances. And we get smarter. We learn more about medicine.

Nonetheless, there are certain scientific medical-dental standards, and I am not convinced that the standards were as different ten years ago as they may have been portrayed in some of the discussion today. I think, in any case, we have to evaluate the data before us today because we are here today. When the Agency has looked at the product in the past, the action has been to not approve it. So even in light of whatever standards were in people's minds some years ago, the application was not approved at that time.

Dr. Mann was the division director, and you can see from the letter that he wrote to the company, he enumerated some items that had to be in the case report form. Putting those items in the case report form certainly seemed sensible. It is predominantly identifying information—patients' initials, age, and so forth.

What is absolutely missing from that letter is a discussion of what information needs to be recorded on the case report form about outcome, and how you would measure success, etc. I have no idea why it is not there, but the fact that it does not there does not mean that the company had no obligation to look at outcome because, clearly, that was the main purpose of the study.

So I guess my message is use the standard scientific standards of today. We would be willing to

apply some flexibility to those, as we always do, but it is today's standards.

MR. RAUBICHECK: May the sponsor be heard on that issue, Mr. Chairman?

DR. ROBERTSON: Briefly.

MR. RAUBICHECK: Thank you.

This issue has not been definitively addressed by the courts. However, it is our position, and would be the position of any NDA applicant before the Food and Drug Administration, that to deny approval of an NDA because of shifting standards would essentially be to change the rules in the middle of the game, and would constitute arbitrary and capricious Agency action, in violation of the Administrative Procedure Act, and a violation of the due process clause of the Fifth Amendment to the Constitution.

As a lawyer, practicing in the field, I feel strongly that the Agency should adhere to the standards that it has set for the applicant.

I might also add that Dr. Gilkes and his superiors, including Dr. Botstein's predecessor, did, indeed, approve the clinical study in 1986. The reason for the delay is because the sponsor had to develop special manufacturing and chemistry information through another entity of the manufacturer, the drug product.

On September 30, 1991, a meeting was had in Dr. Botstein's office. That was almost a year and a half ago. At that time, we discussed the approvability of the NDA. We discussed the issue of study design. We discussed Dr. Mann's protocol. We took the position with Dr. Botstein that we would be glad to provide any additional information beyond what the Agency had then that would warrant approval. Her response was not your design is deficient. Her response was not go out and do another study. Her response was submit the clinical case histories from other AES Fellowship Program from 1984 to the present, which we did.

So we feel that we have met the legal standard and the regulatory standard, and if this body is to be guided, it should not be guided by an arbitrary principle where the FDA, ten to twelve years later, comes in and says we have different standards, therefore, you lose.

As a matter of fact, there have been no different standards that have been articulated today, other than those in the regulations. As Dr. Botstein correctly points out, those are the same. There is nothing in the regulations about case report forms, etc.

I would just like to add one final point, just to clear up some confusion that the Panel might be having about this antimicrobial issue. There is no antimicrobial claim in the proposed labeling for this product. The only language in the proposed labeling that relates to the activity of the paraformaldehyde component is the word "disinfects." If that poses a problem, as we said, we

would be glad to alter the labeling. But antimicrobial data, blood data in terms of extent of activity in the bloodstream—that is not in the labeling. That was put in the application because the FDA asked us to put that in the application, and there are data, which we did submit, which show that the N2 material has a 710-day life within the root canal. But that is not part of the labeling. It was not part of the data that you are looking at today. You are looking simply at clinical data pursuant to the protocol that Dr. Mann recommended.

Thank you.

DR. ROBERTSON: Thank you.

Is the Panel ready to consider the questions?

This will be limited to the voting members of the Panel, and I will go back and forth so we do not have the same person start. In some cases, there are two questions per question and I will try and keep those separate. We I can have yes, or no, or an I do not know among the choices and then a very brief statement of why you feel the way you do.

I., one clinical study of 109 teeth in 91 patients is provided to support the use of N2 Universal. The control group for this study is historical from the published literature.

Question I.a. is, is this study adequate and well-controlled, which is the legal an scientific standard for drug approval? Dr. Glowacki?

DR. GLOWACKI: I am going to modify study by making it clear that we are not talking about the study design in this, but that we are talking about the documentation and the execution of the study. For that, I would say I have lingering problems based upon the package of materials that was sent by the sponsor, that does not document adherence to an adequate and well-controlled study. So the answer is no.

DR. ROBERTSON: Thank you.

Dr. Spangberg?

DR. SPANGBERG: My answer is also no.

DR. ROBERTSON: Some comment?

DR. SPANGBERG: Yes, I have a similar problem as Dr. Glowacki. I think especially in the submission of the report, there is a fairly detailed outline of the study that was intended to be done, and that study protocol has not been followed.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. If we assume that the 1982 protocol is acceptable, it is evident by the data supplied by the sponsor that the clinical study is unacceptable. This is based on the fact that only 8/109 cases were signed by the investigator; certain criteria were not given; and 3 other requirements stated by Dr. Mann were not followed by the trialists.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No.

DR. ROBERTSON: Comments?

DR. GERSON: Well, I arrived at that because I do not feel that the control was adequately characterized. So I am forced to say no.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: No. I have trouble with the controls and with the lack of information in the study itself.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: My answer is no. I feel there is inadequate data supplied and the documentation does not seem to be proper.

DR. ROBERTSON: And my answer is no, with many of the same concerns, and concerns with the bias in the selection of the cases.

I.b., under effectiveness—so we are talking about effectiveness in the context of this clinical study: Is a historical control adequate for effectiveness of a root canal filling and sealing material? So it is asking a generic question here, is a historic control adequate to evaluate the effectiveness of a root canal filling and sealing material? Dr. Sandak?

DR. SANDAK: I would say no because I think what we have learned before is that there were many instances where the research has not proved itself to be true.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: I would also say no. I think today you certainly could carry out a controlled study, with the arms that were explained before. So I think if we were limited and we could not get that kind of information, then I would say a historical control is adequate. But I think we can get real, solid information.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: My answer is no.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. There are opportunities to provide adequate controls and they should be taken.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: My answer is no, based no a number of factors. First, if you are using historical controls, you could either go back through the literature, or you could go back and pull similar cases, which has already historically been done. In that case, I think it is also very important to underscore that if you do historical controls through material, you really have to match diagnosis especially because diagnosis of the case you start to treat has an enormous effect on the outcome of the treatment. If you match necrotic cases, for example, with vital cases in historical controls you are going to get unacceptable comparisons. So I think that is very important.

Unfortunately, initially the observation period was prescribed for the applicant to be 6 months. In general though, I think 6 months is an absolutely inadequate period of observation. It may be satisfactory for a case which has a periapical rarefaction when you start when you could observe healing, or at least slow healing of a periapical lesion. I take that as a sign of success. When you are dealing with a vital case which has no periapical lesion when you start, it is going to take a year of more before a periapical lesion is going to develop. So you cannot observe your failures in a clinical observation like that.

I will say for future references that any study like this should have an observation period of at least two years-plus to be able to be adequate for this purpose.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: Well, I would say that it would be possible to come up with a historical control that was well-matched for the site of the lesions an well-matched for a longer follow up. However, I think there is nothing inherent in evaluating the efficacy of this type of material that would preclude using a simultaneous control. So my answer is no.

DR. ROBERTSON: I agree with Dr. Glowacki to some extent. In the context of the original directives given to these investigators, I might accept a historical control under conditions where the historical control then did not have selection bias, and I had some sense that the cases were either random or consecutive. But I was not provided with any evidence that that was done. So I would have to say for that time no; for the present time, I think I agree that there is no reason

why you could not start with reasonable controls.

I.c. has kind of two parts: One, has a historical control for this study for effectiveness been adequately characterized and described by the sponsor? If it has, identify the historical control. But I think the bottomline question, and we have just addressed some of it, is has a historical control for this study for effectiveness been adequately characterized an described by the sponsor? Dr. Sandak?

DR. SANDAK: I would say no to the first part, a historical control for this study, and I cannot identify the historical control.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: I would also say no. The character of the population is very difficult to determine, I mean who the people were, and the people who carried out the control were evidently not unbiased. So I am concerned about this as a historical control.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No.

DR. ROBERTSON: I agree, no, simply because I had great difficulty in going through the material, trying to characterize all of the information from the controls. Some of the papers that made up the historical control were accessible an I could go and get them and read them. Some of the other material was from textbooks and it was unclear to me whether it was a combination of cases or where the cases came from.

Dr. Norman?

DR. NORMAN: No. The historical controls given were not the best source, I do not believe, and contained material that would not be considered modern.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: No, and I would like to refer to the excellent review on this issue by Dr. Harkin earlier this afternoon.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No. In the material provided there was not an adequate description of the historical control for comparison.

DR. ROBERTSON: I.d., under effectiveness, are the criteria for effectiveness clearly defined in

the study an in the historical control? Are the criteria for effectiveness clearly defined in the study—an if you wish to separate them, you can—an in the historical control? Dr. Glowacki?

DR. GLOWACKI: No for both. I think the problems in terms of the efficacy in this study have been summarized as a problem in the specific patient reports. The way that that page is set up, it does not have an item by item identification of the outcome effects to be evaluated by the examining physician or of the monitoring physician.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: The answer is no here too. I would like to divide it up into two answers. I think that in regard to the experimental material which was submitted, there is not sufficient information to jude this. If we you had such information, you could then look at the historical controls and see if you had adequate comparative material in the historical control. So lacking the first, I cannot answer the second.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. The evidence for effectiveness could not be obtained from the forms used, an I would agree with Dr. Spangberg that the historical control would have to be in combination with the criteria for the effectiveness of the submitted material.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: I suspect that I am in agreement with what has been said but my full response is that I do not know. I think the unifying theme here, at least in my response, is a problem with the documentation. I think it is very clear that the sponsors feel they did what they were supposed to do. I am just having trouble culling that out from the documentation that we have, and that is all we are really supposed to be considering.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: Yes, I feel similar to Dr. Gerson. I think, no, we do not know what criteria were used for the individual cases beyond the fact that they were judged successful.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: No, for reasons already stated.

DR. ROBERTSON: I join the "I don't know." I do not claim expertise here. I simply do not know, given the documentation I saw, whether the investigators, in fact, clearly defined effectiveness.

We are on question I.e., are data on effectiveness endpoints adequately collected and analyzed in this study? And, if you wish to separate it, in the historical control? Are data on effectiveness endpoints adequately collected and analyzed in this study and in the historical control?

Dr. Sandak?

DR. SANDAK: I would say I am not sure of that. So I will say I do not know for the first part, and in the historical study it was not very clear at that time.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: I would say no, really. It was difficult to pick out the endpoints. They seemed to vary in many cases. As far as the historical control goes, I do not know what the endpoints are.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: Again, no for the study and, since I do not recognize the control, it would be no.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. The effective endpoints are not adequate because successful an unsuccessful at six months is not adequate.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: No, because of lack of information with regard to the endpoint, both the definition of the endpoint and the collected material. In regard to the historical control, once again, I think the historical control which was used may be adequate but if you do not know exactly what kind of material you are using in your experimental group, it is difficult to say if the historical control is adequate or not.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No. My concern is that because the criteria for efficacy were not spelled out in the forms, the evidence that was accumulated was very sketchy and poorly documented. Similarly, because the historical control was not rigorously identified, the answer for that would be no.

DR. ROBERTSON: And I would say no for the study, and for the historical control I do not know.

We move to I.f., what is the effectiveness rate in the study? I guess I will turn this around, with your permission, and I will say do we truly know the effectiveness rate in the study? And do we

know the effectiveness rate in the control, given the way the study was done? Do you know, yes, no or I do not know, what the effectiveness rate is in the study and in the historical control? Dr. Glowacki?

DR. GLOWACKI: From the documentation that was provided by the sponsor, I do not know either.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: The answer to the study is no. With regard to the historical control, I think that is more a matter of scientific debate, whether that study is good or not. But I think it is maybe.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: I cannot give a figure but it would be low from the data presented.

DR. ROBERTSON: Do you think you know the effectiveness rate based on the study?

DR. NORMAN: No.

DR. ROBERTSON: You would think that the effectiveness rate based on the study is low?

DR. NORMAN: First of all, the data are not acceptable. So the rate has to be low.

DR. ROBERTSON: Okay. Dr. Gerson?

DR. GERSON: I do not know what the effectiveness rate is. In fact, it was one of the things I was listening for and trying to pull out from the events of today.

DR. ROSAN: I have to go back a little to what Dr. Harkin said about the calculations in which he was not sure what either the numerator or denominator was in either study. So I really do not know in terms of a rate here.

DR. SANDAK: My answer to the first part is that I do not know, and my answer to the second part is that I do not know.

DR. ROBERTSON: In terms of this particular study and the effectiveness rate of this study, I would have to agree that I do not know. In terms of historical controls, for some of the studies that are used, it would appear that the effectiveness rate of endodontic procedures in general is fairly high but I could not give it an exact number. For the particular historical controls as a collection used for this study, I would agree, I would have to say I do not know.

We have moved on to I.g., and we are under safety. Is a historical control adequate for safety of a root canal filling and sealing material? Is a historical control adequate to determine the safety of a root canal filling material? Dr. Sandak?

DR. SANDAK: When listening to Dr. McGuire, when she said depending upon how the operator handles the material, or if handled very well, I would have to say that I am not sure.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: Well, this is a generic question on historical controls in general. I suppose it really would depend upon knowing all the conditions of the historical control, as Dr. Harkin outlined. If we have all the information, it is probably possible to construct a control that would be reasonably successful, but I do not see any reason for that if we can do a simultaneous control.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: Because of the way it is worded generically, I am going to say yes.

DR. ROBERTSON: Yes, I would agree. I would say that, yes, you can use material over many years knowing very carefully what was done to each of those and retrospectively look at those, particularly in a procedure that has sequelae over decades, an be able, indeed, to determine from those kinds of carefully done retrospective studies what the risk of a particular procedure or agent is, and I think that is a good idea. So my answer is yes. Dr. Norman?

DR. NORMAN: I would agree that yes is the answer, but there is absolutely no reason today to use a historical control for this type of study.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: The answer is yes. I think that if the historical material is well classified an documented, I think there are several historical material which are published that may not be that adequately characterized so they can be used as historical controls, but if the material is well characterized, I do not see any reason why you could not use it.

DR. ROBERTSON: I assume that well characterized there means all of the cases done under a particular condition and not selected out for success.

DR. SPANGBERG: Exactly, that you know exactly what has been done in the various cases and what the selection criteria were for the outcome.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: Well, I think I have to go back to the way I thought about it before, that it is

possible to develop a historical control for safety, but there does not seem to be any reason for this type of product to use one.

DR. ROBERTSON: Okay. We will move on to I.h., has a historical control for this study—for this study—for safety been adequately characterized and described by the sponsor? So we have addressed the question generically and now we want to concentrate on this particular study. Has the historical control used for this particular study been adequately characterized and described? Dr. Glowacki?

DR. GLOWACKI: I think there was no documentation of an adequate historical control for safety, no.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: The answer is no. The historical controls which have been used are generalized reports of endodontic treatment and you cannot draw the information which you need to have for a historical control when you compare it to the clinical data for this.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. The safety, I do not believe, was addressed adequately in any of the historical data given.

DR. ROBERTSON: I agree for the particular study and the use of the historical control. Dr. Gerson?

DR. GERSON: No. I think that is a matter of documentation.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: No, again, for the same reasons already mentioned.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: No, insufficient documentation.

DR. ROBERTSON: We move on to question I.i., under safety, are adverse events—again, dealing with the clinical study of 109 teeth in 91 patients—adequately collected, characterized and analyzed in this study and in the historical control? It is a kind of two-part question. Are adverse events adequately collected, characterized and analyzed in this study, and are they adequately collected, characterized and analyzed in the historical control? Dr. Sandak?

DR. SANDAK: In answer to the first part, I would say no. But in the historical control, I would

say that they were fairly well represented.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: For the first part I would say no. For the second part, it is just hard to know. I really do not know because it is more anecdotal.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No.

DR. ROBERTSON: No and?

DR. GERSON: No and no.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No and no.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: No on the first part of the question. I think it has to do with the fact that information in the material is very sketchy. I think they could have collected the data but they did not. For the historical control, I would like to reiterate what was mentioned before, most of the historical controls have more an anecdotal, summary report of things happening but not detailed information.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No, because in this study the data sheets that the clinicians used to collect the information, I think, were very sketchy and inadequate. As far as the historical control is concerned, I vote no because it has not been identified.

DR. ROBERTSON: And I would have to say no for the study, and depending upon which control maybe for the historical controls.

We have moved on to I.j., and we are still dealing with this study of 109 teeth, and I will turn the question around a little bit again and make it read do we know the rates of adverse events in this study? Adverse events? And do we know the rates of adverse events in the historical control? It is a very similar question to I.j. Dr. Sandak?

DR. SANDAK: I think the answer would be no to both parts of that question.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: Yes, my answer is no. We have total rates but we have no way of really judging it because there are no data, and the same for the historical control really.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: With the rewording, my response goes from I do not know to no.

DR. ROBERTSON: Would you like me to change the wording back? Are you happy with that wording?

DR. TYLENDA: Yes.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No to both.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: I do not think we have adequate information from a rigorous study. We have some compilation made by the FDA but I am not really convinced that the original data are clearly analyzed.

DR. ROBERTSON: And for the historical control?

DR. SPANGBERG: No.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: Well, we do not know what the rates of adverse events are in this study, n or in a defined, appropriate historical control. Again, I think it is because the data collection forms expected the physician to put a note in if there were an adverse response. So, in the absence of the data, it was assumed that there was none.

DR. ROBERTSON: For me, in terms of classical adverse rate calculations, I have no historical perspective. I have used only what I am required to do now for recording adverse events. I have to say no and no.

We move on to I.k., and that has to do with follow up. Is follow up of patients in the study and in the historical control long enough? This is independent of what the investigators were asked to do. We fully understand that the investigators were given a protocol and we have discussed the extent that they followed the protocol, but certainly in terms of the 3- to 6-month follow up, they

followed it. But this question is more generic and it simply asks in today's context is follow up of patients for endodontic studies, particularly studies of these materials of 3 to 6 months long enough? Dr. Spangberg?

DR. SPANGBERG: No. As I mentioned before, I think that an absolute minimum would be two years and preferably four years for this type of cases.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No. Although I am not a clinician and I am certainly not an endodontist, I was able to do some background reading on this and my understanding of these clinical problems is that perhaps in the pediatric population one can come to complete healing of lesions by six months, but in other populations it takes much longer to be comfortable with the long-term success.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No. I would prefer that a four-year study be run, but some data could be collected at two years.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: I do not know.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: No, and I caution that in all dental treatment longevity is an attribute.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: No, at least one to two years.

DR. ROBERTSON: I have to say I do not know how long one would need to follow endodontically treated teeth. I think it would depend, for me, on the kind of questions we were asking. But if you were looking for long-term efficacy, I think six months is probably too short so I would say no.

We are on II., the sponsor has submitted 9514 case histories from 1978-1991 from a training program of a professional organization. These case histories were not consecutive and were apparently selected for successful outcome.

The question is, does the sponsor's summary of these case histories provide controlled data on the effectiveness or safety of N2 Universal? Maybe we can just go through and answer that

question yes, no or don't know.

Does the summary of these case histories that we have reviewed provide controlled data on the effectiveness or safety of N2 Universal? Dr. Norman?

DR. NORMAN: No. To have such data, one would have to know the unsuccessful cases and that is not provided.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: No, I would characterize these as 9514 incidental reports.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No. These are not controlled data.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: No, these are not controlled data.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: No.

DR. ROBERTSON: And I agree, no.

We move to III.a., adequacy of the data, dealing now with these 9514 case histories, do the data presented in these case histories demonstrate effectiveness and safety of N2 Universal? Do the data presented demonstrate effectiveness and safety? Dr. Sandak?

DR. BOTSTEIN: Excuse me, this question was intended to be aimed at both, the case histories and the clinical study.

DR. ROBERTSON: I am sorry. Based on both sets of studies then. That is an important point. We may have actually been through it once before but we will go through it again. For both studies, both the study of 109 teeth in the 91 patients compared to the historical control and the 9514 case histories—do the data presented in those 2 studies demonstrate effectiveness and safety of the N2 Universal? Dr. Sandak?

DR. SANDAK: In the first part, the effectiveness, I would say yes. But as far as safety, I would say no.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: Well, I think what they suggest is the successfulness of endodontic treatment generally. I am not sure whether we can then extrapolate that to either the effectiveness of this material or to the safety of it.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: Yes, effectiveness has been demonstrated. Safety has not been demonstrated yet.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: Without the accompanying evidence of unsuccessful treatments, effectiveness cannot be determined and the safety cannot be determined. So I would say no.

DR. ROBERTSON: Dr. Spangberg?

DR. SPANGBERG: Subsequent to what I said before, the answer to this question is no because the material is not adequate to demonstrate effectiveness or safety.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: The answer is no because of the inadequacy of the data that were presented.

DR. ROBERTSON: And I concur with Dr. Glowacki.

III.b., I assume still dealing with all of the data that we have, should the present data set, the study and the case histories, be supplemented with additional information? I guess the question is, and I will seek advice here, are there things that we can do to this present data set to make it acceptable in making the determinations of effective use and safety? Is that the thrust of the question?

DR. BOTSTEIN: In light of all the discussion and the previous answers, it is obviously not the best question. It was intended to mean what further studies, but it would be helpful to answer it the way you phrase it also: is there anything that could be done to the present data set, more analyses or whatever that would help? If not, what do you recommend for the product?

DR. ROBERTSON: Maybe we can deal with the question this way, are there things that could be done with the present data set to make it acceptable in determining safety and efficacy? That is, add-ons or reanalysis or some additional fill-in studies, those kinds of questions. So can we use

what we have and supplement it to make it acceptable to us? Dr. Spangberg?

DR. SPANGBERG: My answer is no, I do not think there is any way to save this material, especially as it is very difficult to retrieve anything from this. I do not think there is any way to look at it.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No, I think the data would have to be regenerated with very careful on-site monitoring and a proto-col that more adequately addresses the issues.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: No, it is not possible to go back to the 3-month an 6-month evaluation times and give scores on these outcome measures that have been defined for the study.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No, and I am going to agree with Dr. Glowacki.

DR. ROBERTSON: Dr. Rosan?

DR. ROSAN: No, I do not think there is any way to retrieve this.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: I do not know. I think that certain information can be added to improve it.

DR. ROBERTSON: Well, regretfully, I am going to have to say no. In the absence of knowing that these are either random or consecutive cases in both the study and the historical controls so that there is not a selection bias which simply selected the successful versus the nonsuccessful cases, in the absence of the ability to do that, I guess regretfully, because it was a great deal of work, I would have to say no.

IV.a., labeling and use, considering the data available on multi-root versus single-root cases in the application and the generally accepted difficulty of molar endodontics, should labeling recommend that this product not be used, or be used with cautions in molar endodontics?

So considering what we know about molars versus incisors, should something be included in the labeling to caution use of the N2 device in molar endodontics? Dr. Spangberg?

DR. SPANGBERG: I am sorry to inform you that the statement in the question is not correct. It happens to be that if you look at molar roots, the success rate is higher than in incisor roots. So I

do not think there is any reason to label it for specific teeth. When you get to molars, especially mandibular molars, you are dealing with a problem which is indicated in question c.

DR. ROBERTSON: I guess the problem, Lars, was that there was some concern that the data we have here did not have enough molar cases in there.

DR. SPANGBERG: No, that is correct but, as far as I am concerned, I would not feel that you could use it on any of the roots. So from that point of view, I think the statistical analysis of the material is such that I could not say that it was more or less successful in incisors or molars.

DR. ROBERTSON: So your answer to the question is no, you do not need special labeling.

DR. SPANGBERG: No.

DR. BOTSTEIN: You know, I am not at all sure that we need the answers to the rest of the questions. If you would like to tell us the answers, we would be happy to receive them but it has to do with labeling.

DR. ROBERTSON: I think you will get no argument from the Panel. We are here solely to provide you with information and advice that you need. If we have given you sufficient information and advice that you need, we are happy.

That being the case, we will stop here. Is there further information or advice with these kinds of questions that you need from us?

DR. BOTSTEIN: I do not think so.

DR. ROBERTSON: That being the case

DR. FRAZIER: Mr. Chairman?

DR. ROBERTSON: Yes?

DR. FRAZIER: I would like to make a brief statement. As consumer representative, having listened very intently to the entire day's conversation, one of the things that consumers expect, I think, is that their dental professional provider will do no harm, similar to a physician. The patient consumer needs to expect not to be harmed.

I think that consumers who are in pain or in need of procedures such as endodontics can be vulnerable to harm because they might be more likely to go ahead and give informed consent without really, clearly hearing any detailed description of a particular procedure. So I see a problem in perhaps the informed consent procedures that could be utilized with this type of thing.

A second kind of comment that I would make is that, regardless of how old a supposed protocol might have been, the research clearly does not meet scientific standards of today and consumer responses to being harmed are not going to care whether such a protocol of eight years ago, ten years ago, twenty years ago was followed.

So I feel very strongly that this material has not met the scientific standards that consumer groups would want to believe that their health care providers would use to judge efficacy and safety of a given product.

DR. ROBERTSON: Thank you.

I will go around the Panel and ask quickly for any further comments.

Miss Edwards?

MS. EDWARDS: I do have one comment.

I think there is a concern that is a level playing field, once again, that if this device was not associated with a controversial technique and with a controversial agent, then some of these decisions might be different. So I think that for the manufacturers in their talking with FDA, there might be some constructive comments on how to perhaps keep the submission a little bit cleaner, with some things on issues that are strictly having to do with the device.

As I said earlier, for me, I had to keep in mind the fact that the other zinc oxide-eugenol materials would be Class I devices and would require none of this information. So I do have a concern there.

The concerns about the technique and the instrumentation are legitimate, plus the fact that there is an additional component. I did go back through and look at our classification proposal, issued in 1987, and did notice that zinc oxide and eugenol materials that had chloroform added to them were specifically regarded by the panel at that time as requiring PMAs, not new drug applications, and specifically called out additional carcinogenicity testing and testing that might look specifically at the safety of that additional material.

So I am wondering once again, to make it consistent with other devices that are used, if there is maybe not an opportunity for the manufacturer to kind of fall back ten yards and try and find out if there is a more constructive way to move this material through.

DR. ROBERTSON: Dr. Curro?

DR. CURRO: Yes, I would like to offer a proposal should this material have to undergo further studies, that the case histories from the 109 people, if they can be retrieved and used as safety. I

feel that four years out is kind of a long time. Even in practice you do not wait four years. If you get healing, you can see that relatively quickly, within six months to a year. A year, I think, would be adequate for this. But if the manufacturer could retrieve the case histories of the 109 subjects and show that safety is not an issue, maybe that could be some grounds for conciliation in this.

DR. ROBERTSON: We will take that as advice. Dr. McGuire?

DR. MCGUIRE: No comment.

DR. ROBERTSON: Dr. Bertolami?

DR. BERTOLAMI: I have no comment.

DR. ROBERTSON: Dr. del Rio?

DR. DEL RIO: No comment.

DR. ROBERTSON: Dr. Sandak?

DR. SANDAK: No further comment.

DR. ROSAN: None.

DR. ROBERTSON: Dr. Gerson?

DR. GERSON: No, thank you.

DR. ROBERTSON: Dr. Norman?

DR. NORMAN: No.

DR. ROBERTSON: We regret that Dr. Greenspan became ill and had to go home early.

Dr. Spangberg?

DR. SPANGBERG: I would like to address an issue here which has not really been discussed very much when we discussed N2, and that is really the content of formaldehyde. We have been circling around it and I do not think the clinical study was specifically oriented towards formaldehyde either. The N2 presentation this morning made some note of the fact that pears and fruit have much higher formaldehyde content than N2 has.

I think that is a misunderstanding of what the problem with formaldehyde is. Formaldehyde

exists in our environment to quite some extent in small amounts. The problem with the formaldehyde in N2 is the fact that it causes a local necrosis where it is applied, and that local necrosis needs to be reorganized or it will be reinfected with a later breakdown. That is one of the problems when we are using formaldehyde for other type of tissue necrotizing agents—the observation period has to be rather long, especially if you are treating vital cases.

I think the formaldehyde content here is a very specific issue and has to be looked at as very separate. So for future applications, I think the content of formaldehyde should be carefully evaluated and I would recommend, as the representative from ADA this morning mentioned, there are accepted, by the American National Standards Institute, protocols for how to test biological dental materials, and I think that is a good starting point for future evaluation of materials.

DR. ROBERTSON: Dr. Glowacki?

DR. GLOWACKI: I want to say that in my voting today I do not challenge the sincerity or the integrity of the clinicians in trying to give good care to their patients and have chosen to use N2. I think, clearly, the testimonials offered show that many of them have the skill to do so. What I have been focusing on is whether there is rigorous scientific information to support the widespread use of this material, and I am disappointed that in the study that was offered today we do not find that evidence.

DR. ROBERTSON: Thank you.

DR. BOTSTEIN: May I add something?

It seems to me, from the discussion of Panel members and from I have seen in the NDA, that the problem is more that the scientific data that have been presented are not enough to establish safety and effectiveness for this product, rather than a concern that it is absolutely unsafe or it is absolutely ineffective. I would hope that proponents of this product would go ahead and do some other studies, do some better studies and get better evidence about its safety and effectiveness.

DR. ROBERTSON: Thank you.

I would like to thank all of the members of the Panel, as well as all the members of the audience. It has been a difficult situation and I thought the N2 Products representatives acted professionally and constructively. Finally, my sincere thanks on behalf of the Panel to Dr. Tylenda, who organized a very well-organized meeting and made our lives a lot easier.

With that, I declare this meeting adjourned.

(Whereupon, at 4:05 p.m., the Panel was adjourned.)