

**Exhibit 1**

**USE OF ADVISORY COMMITTEES BY THE  
FOOD AND DRUG ADMINISTRATION  
(PART 3)**

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**HEARINGS  
BEFORE A  
SUBCOMMITTEE OF THE  
COMMITTEE ON  
GOVERNMENT OPERATIONS  
HOUSE OF REPRESENTATIVES  
NINETY-FOURTH CONGRESS  
FIRST SESSION**

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tion was available and would be submitted to the committee if requested.

If you have such documentation, the subcommittee would welcome it.

[As of December 24, 1975, no documentation was submitted to the subcommittee.]

Mr. FOUNTAIN. If the Food and Drug Administration continues to hold it to be a new drug, then of course, you will have to submit your scientific documentation to them if you apply for a new drug application.

Thank you very much, Dr. Werts. We appreciate your presence here.

FDA requested that the following written statement of J. Richard Crout, M.D., be inserted in the hearing record in lieu of the further appearance of FDA witnesses on this matter. This statement represents FDA's position on its use of an advisory committee in the regulation of N2-type drugs.

[The statement referred to follows:]

PREPARED STATEMENT OF J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS,  
FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE

Mr. Chairman: My colleagues and I are pleased to appear at your request to discuss the past and present regulatory status of dental root canal sealers and the preparation known as N-2 and related products. I will also explain our proposed review of these products before our Dental Drug Products Advisory Committee. Our present posture must be assessed in the context of current controversy over root-canal procedures within the dental profession.

Root-canal therapy, which involves removal of the pulp inside a decayed tooth, is a widely used conservative and restorative treatment in dentistry today. Successful root-canal therapy makes extraction and replacement with a false tooth unnecessary. Conventional root-canal therapy or endodontics is a specialized dental discipline which requires two years of special training and experience for board certification.

Over the past 25 to 30 years a controversy has evolved in dentistry over an alternative approach to root-canal therapy known as the Sargenti technique after its leading proponent Angelo Sargenti, D.M.D., of Switzerland. To our knowledge there are two main groups involved in this controversy. They are the American Association of Endodontists (AAE, board qualified and certified), which, according to their estimates, number approximately 2,000, and the American Endodontic Society (AES, general practitioners who have attended one-day seminars on the Sargenti technique). Of the approximately 120,000 dentists in the United States today, the AES states that 9,000 are considered members of the society. We do not know how many of these actually practice the Sargenti technique.

The Sargenti method of root-canal treatment may involve the use of motorized devices instead of the hand-held instruments usually used in the traditional method to remove the root canal pulp. After the root canal is cleaned, it is filled with a special paste which may contain several chemicals including compounds of lead and mercury, zinc oxide and eugenol, steroid hormones and paraformaldehyde. This material, which is purported to seal, sterilize and protect the root canal, is known as N-2 or RC2B. It should be noted that several of the ingredients used in the Sargenti method are also employed in the more conventional approaches to root-canal therapy.

The N-2 preparation is one of a number of dental materials which are widely used in the practice of dentistry but which have not been specifically approved as new drugs by the Food and Drug Administration (FDA). ~~In accordance with congressional understanding, we have been cautious in applying the powers of the Federal Food, Drug, and Cosmetic Act to interfere directly with the practice of dentistry, medicine or pharmacy.~~ As you know, a dentist or physician may, as part of his practice, write a prescription for a mixture of ingredients or compound such a mixture and use it in his practice. N-2 and related products are mixtures

like this which can be compounded readily by a pharmacist for a dentist as part of his professional activities.

The only new drug application (NDA) ever submitted to the FDA for an N-2 type preparation was for a Swiss product called AGSA Root Canal Sealer No. 2. It was submitted to the FDA in June 1962. The application did not include adequate information to permit review and approval. In particular it failed to provide evidence of safety and effectiveness in the form of adequate and well-controlled studies; consequently, the application was eventually withdrawn by the company in July 1967. FDA regulatory activity over the subsequent years restricted importation of the product, but did not deal with local compounding by pharmacies. More recently, the FDA has received complaints from segments of the dental profession alleging that the N-2 formulation or variations of it are being promoted on a nationwide basis. In response to these complaints, we initiated field investigations to determine if regulatory action was indicated. In addition, Dr. Howard Martin, D.M.D., an endodontist from Silver Spring, Maryland, was particularly active in providing FDA with useful information early this year.

Our investigations and Dr. Martin's information indicated that N-2 and related preparations are indeed being promoted at seminars which are conducted to teach a one-visit, root-canal-filling technique that utilizes this material. Dentists attending the seminars are provided with preprinted "prescription" blanks. These blanks have the N-2 type formulation printed on them. The dentist fills in his name, the amount needed, and mails the preaddressed card to one of several compounders and/or distributors of the product whose name appears on the card. The distributor in turn sends the preparation to the requesting dentist.

Under ordinary circumstances, FDA would not contest the practitioner's prerogative to write a prescription. However, a strong argument can be made—though it has not been tested in court—that distribution of the N-2 products in this matter does not constitute dispensing under a prescription in the traditional sense. On this theory, the shipping procedure would not be an exempt pharmacy operation but rather would constitute the marketing of a drug by or on behalf of a manufacturer.

For several reasons, immediate regulatory action was not considered the best course of action in dealing with the N-2 product. A number of factors could diminish the prospects of sustaining in court the position FDA has stated that the product is a new drug. First, N-2 is a combination of active ingredients which are individually well established and widely used in dental practice. The combination itself is viewed with considerable confidence by many dentists, though the Sargentl treatment is highly controversial. Moreover, although N-2 has been in use for a number of years, we have not until very recently received reports indicating that the material may pose a potential hazard.

We are dealing, therefore, with a combination of accepted ingredients that is used in connection with a mode of dental practice that has numerous proponents as well as critics. At the very least, these factors suggest that correction of the problem—if there is a problem—will require more than simple removal of the product from the market. We are, of course, prepared to apply the new drug procedures of the Act to marketed drug products, including dental sealers, especially if there is some evidence of a significant hazard to the public health. We are reluctant, however, to apply these procedures selectively to one group of such products in the absence of information that these products present hazards different from those used in "conventional" therapy.

The hazards that are said to be associated with the Sargentl approach and its associated sealer agents are those which arise from inadequate sterilization of the root canal and from excessive local tissue reaction and/or infection. Such reactions can be severe and jeopardize the tooth and the integrity of the oral cavity tissues. If indeed these hazards are verified and clearly associated with the N-2 and related formulations, the public health would dictate that they should be removed from the market and required to demonstrate their safety and effectiveness through the usual IND procedures.

This entire matter thus requires that a number of questions be resolved before additional regulatory activity is taken by the Food and Drug Administration. It appears to us at the present time that the essential feature of the professional controversy involved is not the availability or regulatory status of the products in question. Rather the basic controversy is over who is qualified to perform root-canal dentistry and what technique is required. Proponents of the Sargentl method claim that the technique can be easily learned and widely practiced, that

It is much less costly, requires fewer visits, and can be made available to a larger population than the "conventional" technique. The endodontists allege, on the other hand, that all of these claimed advantages can only be obtained at the cost of an unacceptable incidence of failures and adverse effects. We have seen little data on either side of this controversy. For example, we do not know whether the alleged adverse outcomes are due to the filling and sealing materials, to the motorized drills employed, or are, in fact, more frequent than may be expected with conventional methods. In the past, when FDA has been confronted with such controversial and complex issues, particularly issues relating to medical or dental practice, we have often consulted with our scientific advisory committees. These committees are composed of experts in the medical, dental and scientific communities, and such consultation has been very useful and often essential.

As an example, we recently sought such consultation on the safety and effectiveness of topical fluoride preparations for reducing the incidence of dental caries. From time-to-time controversy and questions have arisen regarding the safety and efficacy of these preparations, which have been on the market for a number of years. None of these preparations was the subject of a new drug application, but after careful consideration of the data at hand, including recommendations from our Dental Drug Products Advisory Committee, the FDA concluded that these products could continue to be marketed without NDA approval on the basis that they are generally recognized as safe and effective. This determination was announced in the *Federal Register* of May 14, 1974, a copy of which will be submitted for the record.<sup>1</sup>

In line with this general approach and other precedents, we have decided to seek the advice of the Dental Drug Products Advisory Committee before making a final Agency decision in regard to N-2 and related products. This approach is consistent with past Agency practice, and with a policy we believe to be sound. Proposed regulations governing FDA Administrative Practices and Procedures, published in the *Federal Register* on September 3, 1975, specifically point out that a public advisory committee "shall be utilized to conduct public hearings on matters of importance that come before the FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner on such matters." Our Dental Drug Products Advisory Committee, in particular, was established to review and evaluate ". . . available data concerning safety and effectiveness of marketed and investigational prescription drugs for use in the practice of dentistry." Such committees are established to advise the Commissioner specifically ". . . on any particular matter involving a human prescription drug pending before the FDA, including whether the available data and information are adequate to support a determination that: . . . A particular drug meets the statutory standard for proof of safety and effectiveness necessary for approval or continued approval for marketing. [and] A particular drug is properly classified as a new drug, an old drug, or a banned drug." Thus, "Any matter involving a human prescription drug under review within the Agency may, in the discretion of the Commissioner, be the subject of a public hearing . . . High priority for such hearing and review by the appropriate standing technical advisory committee for human prescription drugs shall be given to . . . : Marketed drugs . . . which pose newly discovered safety hazards, or which are the subject of major scientific or public controversy, or which may be subject to important regulatory actions such as withdrawal of approval for marketing . . . ."

All of the criteria established by the Federal Advisory Committee Act and by Agency regulations for committee review are met by the matter in question. After receiving the committee's views, FDA will be in a stronger position to determine the soundest course of action to follow. Consultation with the advisory committee will strengthen the scientific basis for whatever regulatory action FDA may take. Moreover, participation by the scientific community enhances the credibility of Agency decisions, and is particularly important in a sensitive matter which cuts deeply into the practice of dentistry and the cost and availability of health care. Any regulatory decision is more readily accepted if it has the endorsement of leaders in the medical, academic, and scientific communities.

Consultation with a standing advisory committee with expertise in the precise area of concern helps establish a full administrative record and affords fair treatment to all affected parties. We have placed the N-2 matter on the agenda for the next meeting of the Dental Drug Products Advisory Committee, which

<sup>1</sup> As of Dec. 24, 1975, the subcommittee was not provided with this material.

is scheduled for November 12, 1975, and have invited both the opponents and proponents of these drugs to present their views before this committee. A memorandum setting out the questions on which we are seeking the advice of the committee is submitted here for the record.

You may be assured that we are anxious to resolve this matter as rapidly as possible. However, our first responsibility is to assure that the ultimate decision is legally and scientifically correct and in the best interests of the public health. We, therefore, believe it is appropriate to take the time necessary to accomplish this. We will be happy to keep you abreast of our actions as they occur.

My colleagues and I will be pleased to answer any questions you may have.

Mr. FOUNTAIN. I am placing into the record pertinent documents from the files of the Food and Drug Administration.

[The documents follow:]

MEMORANDUM OF CONFERENCE

(September 21, 1971, 9 a.m. to 9:45 a.m.)

Between: Dr. Angelo Sargenti, D.M.D., Locarno, Switzerland and William J. Gyarfas, M.D., Director, DSDDP; Frederick J. Grigsby, M.D., Deputy Director, DSDDP; George W. Wade, D.D.S., Dental Officer, DSDDP; Clarence C. Gilkes, D.D.S., Dental Officer, DSDDP; Joseph M. Renna, D.D.S., Dental Officer, DSDDP; Clarence M. Nealey, Food and Drug Officer, DSDDP; John R. Carr, D.D.S., DESI; Donald Plumb, Food and Drug Officer, Office of Compliance.

Subject: N-2 root canal sealer.

Dr. Sargenti thanked us for the opportunity to meet. He mentioned that he has just completed a tour during which he had lectured on his technique on the use of N-2. (Some of the places mentioned were Chicago, Philadelphia, Delaware, Boston, California.)

Dr. Sargenti then spent approximately 5 minutes shuffling papers (and reprints) on to Dr. Gyarfas' desk, on surrounding chairs and on the floor.

He then proceeded to read portions of letters from dental organizations and from individual dentists across the country.

He said that he realized that this could be considered as mere testimony but added that this country (U.S.A.) is a "dentally underdeveloped nation" in the treatment of root canal problems when compared to Switzerland.

He proceeded to give a lengthy dissertation on the need (as he saw it) to correct the problems (as he saw them) and proceeded to quote figures relating to the large number of edentulous people in the U.S.A. as contrasted to the few in Switzerland where his product is widely used.

He proceeded to give a long-winded (and somewhat irrational) criticism of the present state of Root Canal Therapy in the U.S. Some of the statements made by Dr. Sargenti were:

His material is for the obliteration of the root canal and is a hard material. (He passed around a sample of a hard pink substance in a plastic sac.)

That he has a solution for all our problems in root canal work.

That approximately 25 different formulations had been used and that they had all produced the same good results. He said that these were basically zinc oxide and that some date back to about 6 years ago.

FDA is influenced by falsified information.

That he has other connections.

He then asked if there were any questions.

Dr. Gyarfas gave him copies of the pertinent sections of the Food, Drug and Cosmetic Act and the Federal Regulations.

Dr. Sargenti showed some knowledge of the Food, Drug and Cosmetic Act and stated that he knows most of it from memory. He expressed the idea that we are denying the dentists in this country the use of a "new Product" (by these regulations).

Since Dr. Sargenti said that the N-2 stayed within the root canal, Dr. Wade asked what purpose the formaldehyde served. Dr. Sargenti's answer was evasive and he could not be pinned down.

Dr. Gyarfas explained that we are not denying anything to dentists or to dentistry—that our purpose is to protect the public—that no clinical evidence was

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