UNITED STATEMENT OF AMERICA

+ + + + +

DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

JOINT MEETING OF DENTAL PRODUCTS PANEL AND

CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

+ + + + +

WEDNESDAY, SEPTEMBER 6, 2006

+ + + + +

The meeting was held in the Grand Ballroom, Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, at 8:00 a.m., Richard G. Burton, D.D.S., and Karl D. Kieburtz, M.D., MPH, Co-chairmen, presiding.

PRESENT:

RICHARD BURTON, D.D.S, Co-chairman

KARL D. KIEBURTZ, M.D., MPH, Co-Chairman

SALOMON AMAR, D.D.S., Ph.D., Member, DPP

THERESA A. COWLEY, Patient Representative, DPP

MASON DIAMOND, D.D.S., Industry Representative, DPP

MICHAEL FLEMING, D.D.S., PA, Consumer Representative, DPP

YIMING LI, D.D.S., Ph.D., Member, DPP

PRESENT (Continued):

MAN WAI NG, D.D.S., MPH, Member, DPP

WILLIAM J. O'BRIEN, M.S., Ph.D., Member, DPP

DOMENICK T. ZERO, D.D.S., MS, Member, DPP

JOHN R. ZUNIGA, Ph.D., DMD, Member, DPP

MICHAEL E. ADJODHA, MCHE, Executive Secretary, DPP

LARRY B. GOLDSTEIN, M.D., Member, PCNSDAC

MICHAEL D. HUGHES, Ph.D., MSC, Member, PCNSDAC

SANDRA F. OLSON, M.D., Member, PCNSDAC

ROGER J. PORTER, M.D., Industry Representative,
PCNSDAC

MATTHEW RIZZO, M.D., Member, PCNSDAC

RALPH L. SACCO, M.D., MS, Member, PCNSDAC

LT. DARRELL LYONS, BSN, R.N., Executive Secretary,
PCNSDAC

MICHAEL ASCHNER, Ph.D., Consultant

MICHAEL DOURSON, Ph.D., Consultant

LYNN R. GOLDMAN, M.D., MS, MPS, Consultant

MARGARET HONEIN, Ph.D., MPH, Consultant

CURTIS D. KLASSEN, Ph.D., Consultant

MICHAEL I. LUSTER, Ph.D., Consultant

GEORGE WESLEY TAYLOR, III, DMD, DPH, Consultant

NORRIS E. ALDERSON, Ph.D., FDA

C O N T E N T S

C O N T E N T S (Continued)

PAGE

Open Public Comment (Continued):

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

(8:15 a.m.)

CO-CHAIRMAN BURTON: Good morning, and welcome to this joint meeting of the Dental Products Panel of the CDRH Medical Devices Advisory Committee and the Peripheral and Central Nervous System Drug Advisory Committee.

My name is Dr. Richard Burton. I am the Chairman of the Dental Products Panel and Co-chair of this joint committee.

I would like to call this meeting to order. The Executive Secretary will now make some introductory remarks.

MR. ADJODHA: Thank you, Chairman Burton.

My name is Michael Adjodha, the Executive Secretary of the Dental Products Panel and this joint committee.

As a joint committee, this committee will be chaired by both Drs. Burton and Kieburtz.

The Chairman of the Dental Products Panel and Co-Chair of this committee is Dr. Richard Burton. Dr. Burton is the Vice Chair of the Hospital Dentistry Institute at the University of Iowa, Hospitals and Clinics, Iowa City, Iowa.

The Chairman of the Peripheral and Central

Nervous System, or PCNS Committee, and Co-chair of this committee is Dr. Karl Kieburtz. Dr. Kieburtz is Professor of Neurology and Preventative Medicine at the School of Medicine and Dentistry at the University of Rochester, Rochester, New York.

Dr. Burton will chair the morning sessions, while Dr. Kieburtz will chair the afternoon sessions.

The Executive Secretary of the PCNS Committee is Lieutenant Darrell Lyons. He is seated in the audience, and before turning the meeting over to Dr. Burton, I am required to read two statements into the record, a conflict of interest statement and a deputization of temporary voting members statement.

I will now read into the record the conflict of interest statement for this meeting.

The Food and Drug Administration is convening today's meeting of the Dental Products Panel of the Medical Devices Advisory Committee at the Center for Devices and Radiological Health and the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972. This will be a joint meeting of two committees.

With the exception of industry representatives, all members and consultants of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, rules found in Title 18 of U.S. Code, Section 208, are being provided to the participants in today's meeting and to the public.

FDA has determined that the members and the consultants of these committees are in compliance with federal ethics and conflict of interest laws under 18 USC Section 208. Congress has authorized FDA to grant waivers of special government employees who have financial conflicts when it has been determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members and consultants of these committees who are special government employees at today's meeting have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their

employer, spouse, minor child, related to today's discussions.

These conflicts of interest include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

Today's agenda involves review and discussion of peer review scientific literature on dental amalgam and its potential mercury toxicity specifically as it relates to neurotoxic effects.

Based on the agenda for today's meeting and all financial interests supported by members and consultants of the committees, conflict of interest waivers have been issued in accordance with 18 USC 208 to Drs. Larry Goldstein and Sandra Olson. These waivers allow these individuals to participate fully in today's deliberations.

Copies of these waivers may be obtained by visiting FDA's Website or by submitting a written request to the agency's Freedom of Information Office, Room 630 of the Parklawn Building. A copy of this statement is available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Mason Diamond is serving as the device

industry representative, as acting on behalf of all related industry and is employed by TyRx Farmer, Incorporated.

Dr. Roger Porter is serving as a drug industry representative, acting on behalf of all related industry, and is a retired employee of Wyeth Research.

Dr. J. Rodway Mackert, who is a guest speaker for us today, has acknowledged a financial interest in and professional relationship with a firm at issue.

We would like to remind members and consultants that if discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships they may have with any firms at issue.

Next I will read a temporary voting member statement from CDRH.

Pursuant to the authority granted in the Medical Devices Committee charter, as amended, dated

April 27, 1990, as amended April 20, 1995, I appoint the following consultants as voting members of the Dental Products Panel for the joint meeting to be held on Wednesday, September 6th, and Thursday, September 7th:

Michael Dourson

Lynn Goldman

Peggy Honein

Curtis Klaassen

Michael Luster

George Wesley Taylor

For the record, these individuals are special government employees and are consultants to this panel and the Medical Devices Advisory Committee. They have undergone customary conflict of interest review, and they have reviewed the material to be considered for this meeting.

Signed, Daniel G. Schultz, M.D., Director, Center for Devices and Radiological Health, dated August 25th, 2006.

I have another memo from Center for Drug Evaluation. Michael Aschner is attending the meeting as an expert consultant in neurotoxicology, and we would like him to serve as a full voting member.

Concur, Steven Goldston, Director of

Center for Drug Evaluation and Research.

I have a note for the panel members here to use the microphone you have to actually press the button and have the light come on. Otherwise the mics do not work. And when you are completed speaking, you press the button again to turn off the light.

I would like to request everyone in attendance at this meeting to take the opportunity to sign the attendance sheet that is available at the table outside.

Also, if you are scheduled to present during the open public session, please be sure to obtain your number from Ms. Ann Marie Williams. Can you raise your hand, Ann Marie? That is Ms. Ann Marie Williams Back there.

Okay, and please also silence your cell phone ringers and refrain from taking flash photography, as this can disrupt the meeting.

Also, note not to disrupt the meeting for safety concerns, and for local codes, we are not allowing large signs in the rooms with sticks in the meeting room. The hotel has allowed a display area in the lobby.

And with that, I will turn the meeting over to Chairman Burton.

CO-CHAIRMAN BURTON: Thank you, Michael.

My name is Dr. Richard Burton. I am from the University of Iowa, and I would like to welcome all of the panel members, our consultants, the FDA staff, and the public to this meeting.

I would like to start off by having each of the members of the two committees that we have present here please just introduce yourself, stating your name, your area of expertise, position, title, the institution you're with, and again, your status on the committee, whether you're a voting member, industry consumer or patient representative or consultant.

I would start over here on the left, please.

DR. PORTER: Roger Porter, 20 years at NIH, ten years at Wyeth; currently an Adjunct Professor of Neurology at University of Pennsylvania and Adjunct Professor of Pharmacology at the Uniformed Services University; nonvoting PHRMA member

DR. DIAMOND: Dr. Mason Diamond. I am with a company called TyRex Pharma. I'm the Vice President of Clinical and Regulatory Affairs; over 20 years' experience in clinical, academic, and product development. I am the nonvoting industry

representative to the Dental Products Panel.

DR. FLEMING: Dr. Michael Fleming, a private practitioner, Durham, North Carolina, for 28 years. I'm the consumer representative under the Dental Products Panel, nonvoting member.

MS. COWLEY: Terry Cowley, co-founder and President of the TMJ Association; patient representative, nonvoting.

DR. ASCHNER: Michael Aschner. I am a Professor of Pediatrics and Pharmacology at Vanderbilt University Medical Center. My interest is in neurotoxicology. I am a consultant to this committee.

DR. KLAASSEN: Curtis Klaassen, professor at the University of Kansas Medical Center, Department of Pharmacology and Toxicology, and I'm a consultant to this committee.

DR. RIZZO: Matthew Rizzo. I'm a Professor of Neurology, Engineering, and Public Policy at the University of Iowa, and I'm a voting member of the committee.

DR. SACCO: Ralph Sacco, Professor of Neurology and Epidemiology at Columbia University where I've been for over 20 years, Director of Stroke and Critical Care, and a voting member of the PCNS Panel.

DR. TAYLOR: George Taylor, Associate Professor in epidemiology and dentistry at the University of Michigan. I'm a consultant to the panel.

DR. LI: Yiming Li, Professor of Full Restorative Dentistry at Loma Linda University School of Dentistry and a Professor of Microbiology and Molecular Genetics in the School of Medicine, Loma Linda University, and I also serve as the Director for Center for Dental Research at the university. My area of expertise is the biological property of biomaterials and dental materials. I am a member of the Dental Products Panel.

DR. OLSON: Sandy Olson. I'm a Professor of Clinical Neurology at Northwestern University Medical School, where I have been for over 35 years. I am a general neurologist, and I am a member of the Peripheral and Central Nervous System Advisory Panel for the FDA, and I am a voting member.

CO-CHAIRMAN KIEBURTZ: Karl Kieburtz. I'm a Professor of Neurology at the University of Rochester in Rochester, New York, and I'm the Chair of the PCNS Advisory Committee.

DR. HUGHES: I'm Michael Hughes. I'm Professor of Biostatistics at Harvard University. I'm

a member of the PCNS Committee.

DR. NG: Good morning. I'm Man Wai Ng. I'm a pediatric dentist, and I'm also the Chief of the Department of Dentistry at Children's Hospital, Boston. My interests are in early childhood caries and public health.

DR. ZUNIGA: I am John Zuniga. I'm a professor and Chair of the Division of Oral and Maxiofacial Surgery in the Department of Surgery at the University of Texas, Southwestern Medical Center in Dallas. My particular interest is oral maxiofacial surgery and sensory disorders of the oral cavity. I'm a voting member of the Dental Products Panel.

DR. GOLDSTEIN: And I'm Larry Goldstein. I'm Professor of Medicine, Division of Neurology at Duke University, where I have been also for over 20 years. I'm also Director of the Duke Stroke Center, and I'm a voting member from the PSNC panel.

DR. ZERO: Domenick Zero. I'm a professor and Chair, Department of Preventive and Community Dentistry at Indiana University School of Dentistry. I also serve as the Associate Dean for Research there, and the Director of the Oral Health Research Institute. My main interest is in the prevention of dental caries, and I'm a voting member of the Dental

Products Panel.

DR. GOLDMAN: I'm Lynn Goldman. I'm a pediatrician and professor of Environmental health sciences at the Johns Hopkins Bloomburg School of Public Health, and I am a consultant to the committee.

DR. DOURSON: Mike Dourson. I'm a toxicologist with a nonprofit group, Toxicology Excellence for Risk Assessment, where I serve as its director for the last 12 years. Prior to that, 15 years with U.S. EPA. My specialty is risk assessment, specifically non-cancer.

DR. O'BRIEN: I'm Dr. William O'Brien, Professor of Biomaterials at the University of Michigan in Ann Arbor, and my interest is in the enviromaterials, and I'm a voting member of the Dental Panel.

DR. AMAR: Good morning. Salomon Amar from Boston University. I'm Professor of Periodontology and Oral Biology, and I serve also as Associate Dean of Research at Boston University; 15 years of experience in host response and inflammation, and I serve as a voting member in the Dental Product Panel.

DR. LUSTER: I'm Mike Luster. I'm Chief of the Toxicology and Molecular Biology Branch at NIOSH, which is under CDC. My expertise is in

toxicology, particularly immunotoxicology and risk assessment, and I'm a consultant.

DR. HONEIN: I'm Margaret Honein. I'm an epidemiologist with the Division of Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention.

CO-CHAIRMAN BURTON: Thank you all for taking the time and effort to be present.

I would like to note for the record that the number of members present constitute a quorum for a meeting as required by 21 CFR, Part 14.

We will now proceed with our published agenda. Dr. Alderson.

DR. ALDERSON: Thank you, Mr. Chair, and good morning, panel members. I want to thank you in advance, the two committees, for their work today and tomorrow in helping us evaluate the potential health risks from mercury in dental amalgam.

I also wish to welcome the members of the public, consumers, patients, health care providers who have joined us today. One committee chaired by Dr. Burton is the Dental Products Panel of the Metal Device Advisory Committee of the Center for Devices and Radiological Health.

The second committee, chaired by Dr.

Kieburtz, is the peripheral and Central Nervous System Drug Advisory Committee for the Center for Drugs and Research.

Together these two committees formed a joint advisory committee for this meeting. The Joint Committee will be co-chaired by the chairs of these two committees.

To aid in our considerations of some of the key science issues raised during public comment on the proposed rule on dental amalgam, we are holding this Joint Advisory Committee meeting to review the draft FDA white paper, reviewing the peer reviewed scientific literature on the safety of mercury in amounts released from dental amalgams, fillings.

The draft white paper was prepared by the FDA's National Center for Toxicological Research located at Jefferson Arkansas and is intended to cover the literature published since the last review of this subject by the U.S. Public Health Service in 1997. NCTR provides research support to FDA's product centers and has recognized expertise in risk assessment.

We have provided the draft FDA white paper to the committee members, and we have also provided them copies of the questions we want them to

deliberate.

We posted these materials on our Website last week, and copies are also available here.

As I said earlier, the primary purpose of this Joint Advisory Committee meeting is to provide a peer review of the draft FDA white paper which summarizes and interprets recent peer reviewed scientific literature about possible health effects of exposure to amalgams containing mercury and assesses whether this research merits change to the conclusions based on earlier risk assessments.

It has been nine years since we released the last update on the issue of dental amalgam. Several well conducted studies have been published since then. Therefore, it is appropriate to conduct this review to insure that we have considered all of the relevant scientific information.

In addition, this meeting gives us an additional opportunity to receive public comment on the issue of whether significant new and valid scientific information has arisen since our last review of this subject in 1997.

Public comment is important to FDA because it gives us a chance to hear directly from all affected parties about their views on the issue at

hand. Practical considerations, however, limit the time we can allocate to public comment at this meeting. We have many public speakers, registered to speak today and tomorrow, and after consulting with the Chairs, we have allocated an equal amount of time to each presenter.

If there is additional information that anyone would like to submit to us on this issue, please submit it to the public docket. We are open to accommodate any written comments.

We will review all submissions to the docket to evaluate evidence that contributes to our decision on the issues raised in the Federal Register notice. Other comments we have recently received on dental amalgam will also we placed in the public docket.

As part of the program today, Dr. Mackert will provide information on the use of dental amalgams and other restorative materials.

Following Dr. Mackert will be Ms. Rosecrans, who is the head of the FDA's Device 510(k) Program. She will provide an overview of the device classification and regulation process, which may be unfamiliar to many of our panel members and speakers.

As other countries also regulate dental

amalgam under different legal provisions, we wanted you to hear their approaches to regulation and the scientific basis for their decisions.

Dr. Conn, who is a dental advisor, Medical Devices Bureau, Health Canada, and Dr. Philipson, Director of Medical Devices, Medical Products Agency, Sweden, will address the regulation of dental amalgam in their respective countries. We appreciate their participation in this meeting.

Their presentations will be followed by Dr. Canady from the FDA's Office of Science, who will provide background information about evaluations of the risk of dental amalgam conducted by the Federal Public Health Agencies prior to 1997.

The agenda for late this morning until tomorrow morning is an open public meeting. This is the opportunity for the public to provide information to the joint committee on the objective of this meeting.

We are honored to have Congressman Diane Watson be our lead speaker for the public session immediately after lunch today.

Following the end of the time allocated for public speakers tomorrow morning Drs. Slikker and Paule will present the FDA white paper evaluating the

scientific literature on dental amalgams since 1997.

The rest of the meeting will feature a discussion by you, our distinguished panel of experts and your answers to our questions provided by FDA. We want an independent evaluation of whether we have identified and properly assessed the relevant scientific literature on the potential for health risks from dental amalgam.

After this meeting, the next steps depend on what you, the joint committee, gives us in your response to our questions. However, one thing that is certain is that we will consider any recommendations of the committee and all of the information provided here and to the docket in a determination of the need for any further action on dental amalgam.

Mr. Chairman, we look forward to your discussions and deliberations.

Thank you.

MR. BROWN: Mr. Chairman, Charles Brown, Consumers for Dental Choice.

The first --

CO-CHAIRMAN BURTON: I'm sorry. I'm sorry. There will be an open comment period later this morning.

MR. BROWN: No notice was given to comment

on the proposed FDA rule at 2002.

CO-CHAIRMAN BURTON: Well, we will deal with that when we get to the open portion of this. This is not -- this is not the public hearing session. Please take your seat.

MR. BROWN: Okay, sir, but you're in the --

CO-CHAIRMAN BURTON: Thank you.

It has been duly noted. Thank you very much.

In returning to our agenda, the next item is the presentation by Dr. J. Rodway Mackert, Professor of the Medical College of Georgia, on dental amalgam and other restorative materials.

Dr. Mackert.

DR. MACKERT: Mr. Chairman, distinguished members of the panel and guests this morning, my name is Rod Mackert, and as you can see I'm from the Medical College of Georgia in Augusta. I realize that many of the members of the panel have no dental background or have familiarity with dentistry as patients, and I just wanted to try and go over some of the aspects of dental amalgam as used by dentists.

Dental amalgam is manufactured and supplied by manufacturers in the form of capsules

usually which contain in separate compartments powdered amalgam alloy, which I'll talk about in a minute here; liquid mercury. Some are manually activated, and others are self-activated, and they usually have a pestle that aids in the mixing of these materials.

These are placed in a machine called an amalgamater or a triturator, and these have speeds which the arms of this device move back and forth as you can see right here at speeds up to about B from 3,000 rpms and higher.

The mixing times vary from five to 20 seconds, and these machines mix the powder and liquid components to achieve a pliable mass, and the reaction between the mercury and the alloy powder begins after the components are mixed.

There are several different types of dental amalgam. Copper amalgam, which was used in the last two centuries, the 1800s and 1900s, is no longer used. The so-called conventional or low copper amalgam was standardized in the 1890s, and then high copper amalgams were first developed in the 1960s and almost all amalgams used today are of this composition.

Just a couple of examples of popular

dental amalgams. There's one called Dispersalloy, and this is the composition of the metal powder that's mixed with mercury. It's about 69 percent silver, and the rest is copper, tin, and one percent zinc. And this particular alloy is mixed in proportion with mercury, 50 percent of the alloy and 50 percent mercury.

Another amalgam alloy is called Tytin, and it is about 59 percent silver and 28 percent copper and 13 percent tin.

Amalgam is, as you can see from this dictionary definition, any alloy of mercury with another metal or other metals, and this is the example given in the dictionary. Silver amalgam is used as a dental filling.

In the McGraw-Hill Dictionary of Scientific and Technical Terms, the definition is given simply as an alloy of mercury.

An alloy, this is an example of a silver-gold alloy composition. This is called a constitution diagram or a phased diagram, binary phased diagram, showing from 100 percent silver over to 100 percent gold, and this is actually a rare type of alloy called continuous solid solution. Temperature is shown on the Y axis and composition on the X axis.

This is what is called a continuous solid solution, and this is kind of a rare type of alloy, but gold and silver are completely miscible in the solid state.

More commonly we have alloys that look like this. This is a silver-tin phased diagram where we have only a limited area of solid solution of tin in silver and virtually no solid solution of silver in tin, and then we have various compounds across the composition which indicate chemical compounds call intermetallic compounds between silver and tin.

This is the diagram for silver and mercury in which we see a similar kind of arrangement where here is the liquid phase here. Here is the solution of mercury in silver, and then once we reach a certain composition, intermetallic compounds begin forming which are labeled by their Greek letters starting with alpha and going down.

The reaction for low copper alloys, we have this intermetallic compound, which is called a gamma phase, silver and tin, Ag_3Sn. I'm sorry. Okay. Silver. The gamma phase, Ag_3Sn reacts with mercury to form several intermetallic compounds which cause the amalgam to set into a hard material.

The high copper reaction is similar,

except that there is an additional reaction between the tin-mercury phase, which is the corrosion prong phase called the Gamma 2 phase. That reacts with the silver-copper phase and forms some additional phases, the ADA copper-tin phase and more Gamma 1 phase, which is the main reaction product with silver and mercury.

This removes the corrosion prone phase, which is the Gamma 2 phase, and makes the high copper alloys last longer in the mouth.

So in summary, the power is the silver-tin-copper alloy with other elements depending on brand. The liquid is elemental mercury, and these react together to form intermetallic compounds, including primarily the Gamma 1 phase, which is Ag_2Hg_3, and there is no free elemental mercury remaining in set dental amalgam.

The composition of set amalgam, therefore, is a matrix of the Gamma 1 phase and the ADA copper-tin phases with imbedded particles of the unreacted gamma phase and the unreacted silver-copper phases.

It is important to note amalgam is not a solid emulsion as it has been called or a mixture. It is an aggregate of intermetallic compounds. And a belief that amalgam is a kind of mixture, a solid emulsion has led to much of the current controversy.

And I contacted Laurier Schramm, who is an expert in colloid science the author of the Dictionary of Colloid and Interphase Science. He's at the University of Calgary in Canada, and he replied and noted that it is not correct to refer to an aggregate of intermetallic compounds, all of which are solid at room temperature as a solid emulsion.

Mercury is, of course, the element of controversy here, and mercury is unique in that it is the only liquid metal at room temperature and one of only two liquid elements at room temperature. It has an evaporation rate according to Langmuir's equation at 20 degrees. The theoretical maximum is 58 micrograms per square centimeter per second. At body temperature that evaporation rate goes up to 229 micrograms per square centimeter per second, and oxidation of mercury lowers its rate by a factor of 1,000, which allows things like this to be done, which this is an azimuth staring liquid mirror telescope at the University of LaValle in Quebec, and as you might guess, the reflective surface here is liquid mercury, and the reason that these people can be standing around without respiratory gear on is that an oxide forms on the surface of this pool of liquid mercury and reduces the vaporization rate, and this is

courtesy of Eugene Borra at the university of LaValle.

Below the exposure limits, that would be dangerous for people to be standing around like that. If amalgam were a mixture instead of an aggregate of intermetallic compounds, the vapor pressure above mixtures is given by Raoll's law, which indicates that mixture components contribute according to their mole fraction, and if it were a mixture, amalgam would have a mercury vapor pressure of 0.0016 torr at 37 degrees C., which would be about one-third that of liquid mercury.

At this vapor pressure, amalgam would emit mercury at a rate of 76 micrograms per square centimeter per second, according to Langmuir's equation. In fact, however, measured as vaporization rates from amalgam are only on the order of .027 nanograms per square centimeter. That should be minus two per second, and the average vaporization rate over a 24 hour period measured in humans is .048 nanograms per square centimeter per second.

The evaporation rate of mercury from amalgam is over four million times lower than that from unoxidized liquid mercury. The evaporation rate predicted from Langmuir's equation, assuming amalgam as a mixture, would be 76 micrograms per square

centimeter per second. And the measured vaporization rate, as I've stated, is .048 nanograms per square centimeter per second, which is over 1.6 million times lower than that predicted, assuming amalgam is merely a mixture.

Because amalgam contains mercury, people have been concerned ever since the 1830s when amalgam was first used about escape of mercury from set amalgam. In 1957, Frykholm studied the release of mercury from amalgam and including in animal studies, and he found no detectable mercury in organs of animals after nine weeks after placement.

The late Carl Svare, et al., at Iowa in 1972 measured mercury vapor release during setting of amalgam, and they found after 400 minutes that there was no detectable release of mercury from amalgam. However, in 1972, that same year John McNerney, et al., developed a mercury vapor detector, which was much more sensitive than the current technology at that time, and as a result also at Iowa, Gay, Cox and Reinhardt in 1979 first demonstrated the release of mercury from set amalgam. This was published in the Lancet in 1979, and that sparked the current controversy.

Here's the paper in Science, John McNerny,

et al., with the mercury vapor detector based on gold films.

And that became the Jerome mercury vapor detector manufactured by the Arizona Instrument Corporation. This instrument is designed to measure mercury vapor where room volume is much larger than sample volume. Differences in sampling volumes and flow rates must be taken into account if it's used in a method otherwise than the way it's designed to be used or gross errors will result.

And this is just a schematic showing how the Jerome instrument is designed to be used. A 250 milliliter sample volume is collected in a room that in this example has a mercury vapor concentration of 32 micrograms per cubic meter, and as the instrument is turned on and draws in that volume over a 20 second period, then the instrument registers the same reading as what is present in the room.

Similarly, if a human being is in that room and inhales in a two and a half second period, which assuming a respiration rate of 12 breaths per minute, inhalation would be half of that five second breath cycle and so the inspiratory volume being 500 milliliters, that person would inhale the air with that same concentration of 32 micrograms per cubic

meter.

However, if the Jerome instrument is used intraorally and we compare these two things, we have the human being inhaling air in a two and a half second period, and if the amalgams in that person's mouth are giving off mercury vapor at a rate of one nanogram every two and a half seconds, then the person would inhale that 500 milliliter breath with a one nanogram amount of mercury in that breath. Whereas the Jerome instrument would be only one-eighth of the way through its cycle, drawing in that 250 milliliter volume.

And so as that continues for the 20 second period that it takes to draw that 250 milliliter volume into the instrument, mercury vapor continues to be emitted from the fillings during that period. So by the time we reach 20 seconds, there are eight nanograms of mercury in that 250 milliliter volume.

And so if we compare those two, we have a smaller volume, half as large, 250 milliliters, with eight times as much mercury in it. So we have an apparent mercury vapor concentration, and this is what the instrument would show, of 30 micrograms per cubic meter, whereas what the person would actually inhale

is only two micrograms per cubic meter.

So in summary, this instrument is designed to measure mercury vapor in a room where the volume of the air is larger compared to the sample volume, and the volume of the flow rate issues cause the Jerome instrument to overestimate the mercury concentration by at least a factor of 16 if these are not taken into account, and this is not, I would emphasize, a fault of the instrument. It is just that it is not designed to be used in this manner.

Other factors that will affect the meter reading, mercury accumulation in the oral cavity for each second of delay will cause the meter reading to be an additional five percent too high, and there are also known interferences that can be detected as mercury, particularly -- garlic was one example of different foods shown by Shelton Newman in 1987.

Okay. Alternatives to amalgam. In comparing particularly restoration longevity, it is difficult to measure because of selection bias. In all of the studies that have been done, there have been no studies prospective, randomized trials looking at the longevity of amalgam versus composite. So all of these have been retrospective.

There's a selection bias just because

people will assume that a certain type of restoration should go in a particular toothpaste on its size and other factors. So these have to be taken into account as we look at these retrospective studies.

These almost always suffer from effects of selection. Another problem with retrospective studies is that often only failed restorations are analyzed instead of restorations that are in situ.

A 2001 study, a median age of over 1800 failed amalgam restorations was nearly 12 years, but slightly less than five years for over 1,500 failed resin composite restorations.

A 2000 study of 6,761 replaced restorations. The median age of replaced amalgams was ten years, but that of composite was eight years.

A 1999 study of over 9,000 restorations showed that amalgam outlasted resin composite in Class 1, 2, and 5 restorations, which are types of restorations in different parts of the tooth.

In 1998, a study showed the median age of a replaced amalgam restoration was 15 years versus only eight years for a replaced composite restoration.

A 2002 study of insurance claims database of 207,000 replace amalgam restorations, 93,000 replaced composite restorations found that resin

composites were significantly more likely to fail than amalgams. And as I've mentioned, no prospective clinical studies comparing amalgam and composite restoration longevity per se have been performed.

However, the Casa Pia study recently published in April of this year showed that after five years the need for additional restorative treatment was approximately 50 percent higher in the composite group.

Some clinical issues regarding composites. A difficult area for composite restorations has been the proximal contacts where the teeth touch the adjacent teeth, and so manufacturers have tried to develop composites that would be easier to place and achieve better proximal contacts and the so-called packable composites were developed for this purpose, but a study in 2001 of these compared to regular composites didn't show any advantage in yielding better proximal contacts.

Even with the newest composite materials, greater wear than amalgam is apparent after two years, and this has been an ongoing problem with composites. A five-year comparative prospective study showed a higher incidence of secondary caries in Class 2 composite restorations than Class 2 amalgam

restorations by Evon Mjor, et al, in 1993.

Composite resin components may contribute to plaque formation, Kawai and Sutjiani in 2000.

The levels of cariogenic bacteria at the margins of composite restorations have been shown to be higher than those of amalgam restorations.

Glass ionomers are the other category of materials that could be alternatives to amalgam. These are made with fluoride containing glass and have been thought to inhibit formation of recurrent decay around fillings, but this has been a theoretical concept and has not really been demonstrated clinically.

And in spite of the fluoride release which occurs from glass ionomer restorations, studies have shown that the leading cause of failure of glass ionomer restorations is secondary caries.

And no preventive effect was exerted in vivo from the glass ionomer to protect the adjacent enamel wall from secondary caries attack.

There are some biological risks of composites. The estrogenicity issue has been debated for the last ten years or so, and the debate is ongoing about that because there are other components besides Bisphenol A which show estrogenicity in

composite materials.

Cytotoxicity and other effects, allergenicity is also an issue with composites. Patients are slightly more likely to be allergic to one or more resin components than to mercury.

In addition to the material itself, virtually all composites used today unless they are cements are cured by exposing them to a blue light, and John Wataha, et al., in 2004 published a study showing that dental photocuring lights pose at least some risk to oral cells.

And on a personal note, I realize as we focus on vaporization rates and intermetallic compounds it's easy to lose sight of human factors in this. I assure you that I am very aware of the human factors. I have multiple sclerosis myself, and I'm very interested in finding a cure, but if we spend time barking up the wrong tree, that's only going to delay finding the real cause for this disease and other diseases that have been attributed to dental amalgam.

Thank you very much.

CO-CHAIRMAN BURTON: Thank you very much, Dr. Mackert.

I would like to ask the committee members

if any of them have any questions for the speakers on this presentation. Yes.

DR. O'BRIEN: Yes. Dr. O'Brien, University of Michigan.

That was an excellent presentation, and I wonder if there's a copy of it in the folder that was handed out and if we could get a copy of it.

DR. MACKERT: I will give a photocopy to Mr. Adjodha, and he can make that available to you.

CO-CHAIRMAN BURTON: Thank you very much, Dr. Mackert.

DR. MACKERT: Thank you.

CO-CHAIRMAN BURTON: We will move on to our next speaker, which is Ms. Heather Rosecrans, who is the Section Chief for the 510(k) program operation staff here at CDRH, and she will be talking an overview of device classifications under the FFD&C Act.

Ms. Rosecrans.

MS. ROSECRANS: Thank you, Dr. Burton.

It is my pleasure today to address the distinguished members of the joint committee, the agency, and members of the public to discuss overview of device classification process.

The medical device amendments to the

Federal Food, Drug, and Cosmetic Act were enacted on May 28th, 1976. They defined a device, required classification of device types according to potential risk, required pre-market review of devices for the first time.

Prior to 1976, there was no pre-market review of medical devices in the United States.

The act divided the arena of medical devices into two categories, the pre-amendment devices, those that were legally marketed prior to May 28th, 1976, the date of the enactment of the Medical Device Amendments. Those devices are called grandfathered devices if they were legally marketed, and the post amendment devices, those that were to come to market after May 28th, 1976. They all required pre-market review unless they were exempt by regulation.

The pre-amendment devices, again, those devices on the market prior to May 28th, 1976, are grandfathered devices for purposes of pre-market review. They serve as predicate devices for the post amendment, those new devices, after May 28th, 1976. Pre-amendment devices can remain on the market unless legal action is taken to remove them or unless classified into Class 3 through our rulemaking

process, and FDA has issued a regulation requiring pre-market approval applications for these device types.

Pre-amendment devices include dental mercury, amalgam alloy, and encapsulated amalgam. Post amendment devices, again, are those introduced into commercial or wished to be introduced into commercial distribution after May 28th, 1976. They require pre-market review.

If a new manufacturer wishes to market the same type device as one that is grandfathered, the manufacturer must submit a pre-market notification, also known as a 510(k) submission, demonstrating substantial equivalence to the agency for review and receive a clearance prior to marketing in the United States.

So, for example, a new manufacturer of dental mercury would need a 510(k) review and clearance in order to market their dental mercury in the United States.

Device regulation is risk based. Section 513(a)(2) of the act requires FDA to determine safety and effectiveness of a device by weighing any probable benefit to the health from the use of the device against any probable risk of injury or illness from

the use.

Classification of devices is risk based under the act. There are three regulatory classes, that is, the level of control based on risk necessary to provide reasonable assurance of safety and effectiveness of a device type in the United States. These three classes are Class 1, general controls; Class 2, general controls and special controls; and Class 3, general controls along with pre-market approval.

Now, Class 1 is our lower risk category of device. In order to provide reasonable assurance for the device types, reasonable assurance of safety and effectiveness is provided, again, as we said, through general controls.

Some examples of Class 1 type devices that are exempt from 510(k) requirements would be toothbrushes and liquid bandages as a skin protectant over a stump.

On the other hand, a Class 1 type device that would require 510(k) review and clearance are liquid bandages on open burns and wounds.

Class 2 devices again are intermediate level of risk, include devices such as most anesthesia equipment, dialysis equipment, and even though these

devices are for high risk situations, the devices are well understood and reasonable assurance of safety and effectiveness can be provided at the Class 2 level with special controls.

Class 3 devices, again, are our highest risk category. Premarket approval is required and include devices such as drug eluting stents for coronary artery disease and implanted nerve stimulators for Parkinson's disease.

So let me go over the description of the classes. Again, Class 1 are devices for which general controls alone are sufficient to provide reasonable assurance of safety and effectiveness. General controls include prohibition against misbranding. An example of misbranding would be if a device were labeled for an indication for use that had not been cleared by FDA and the firm was marketing it in that manner.

For example, if a dental restorative material was advertised for preventing dental caries and FDA has not cleared such a device, that device would be misbranded.

General controls also include prohibitions against adulteration. An example of an adulterated device would be one that was cleared for marketing to

be sold sterile. There was a problem with the manufacturing process and it's manufactured in a non-sterile manner and introduced into commerce. That would be an adultered device.

Another general control are premarket notification, the 510(k) premarket review requirements are good manufacturing practices, adverse event reporting, and repair, replacement and refund.

Class 2 devices, again, are devices which cannot be classified into Class 1 because general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish performance standards or after 1990, special controls to provide such assurance.

Special controls include performance standards, national or international consensus standards recognized by rulemaking. Now, prior to 1990, we only had performance standards, mandatory performance standards for our Class 2 type devices. After the Safe Medical Devices Amendments in 1990, the act expanded to add additional special controls.

These include voluntary standards, guidance documents, post market surveillance, patient registries, and other actions the agencies decide are

necessary to provide reasonable assurance of safety and effectiveness for a device type.

Lastly, Class 3 devices are devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device type.

Such devices are life sustaining or life supporting, are of substantial importance in preventing impairment of human health, and present potential unreaonsable risk of illness or injury. Again, some examples of a Class 3 type device are the drug eluting stents for coronary artery disease or TMJ implants to reconstruct the jaw joint.

The regulatory class determines the type of premarket submission submitted to the agency. Class 1 devices are exempt from premarket review -- that's the 510(k) review process -- unless a 510(k) is required by regulation. All Class 2 type devices require a 510(k) unless they are specifically exempt from 510(k) requirements by regulation.

And Class 3 device types require a premarket approval application. The applicant must demonstrate their device is safe and effective without relying on a grandfathered predicate device. It's not

a piggyback system. Each device must stand on its own in the premarket approval area.

So what is a 510(k) premarket notification? It comes from Section 510(k), from the 1976 medical device amendments to the act. It is the most common path to market for medical devices in the United States.

It is a review to determine whether a device is substantially equivalent to a device that was legally on the market prior to May 28th, 1976. Again, those grandfathered type devices, and for which premarket approval applications have not been required and the submitter is required to show that a post amendment device, their new device, is substantially equivalent to a legally marketed device for which premarket approval is not required.

FDA's determination of substantial equivalence serves as the classification process for the individual new post amendments device.

A new device is deemed to be substantially equivalent to the predicate device if it has the same intended use, if it has the same technological characteristics or if it has different technological characteristics, but it does not raise different questions of safety and effectiveness from that

predicate.

And lastly, it is determined to be at least as safe and effective as the predicate device.

Under the 1976 law, a substantial equivalence determination is a classification. That means the new device is in the same class and will be regulated the same way as that grandfathered or predicate device type.

For example, because amalgam alloy is classified in Class 2, there was a grandfathered device on the market prior to '76. A new manufacturer's amalgam alloy that is determined to be substantially equivalent would also be classified into Class 2 through that 510(k) review process.

So how do device types first get classified? As required by the 1976 Medical Device Amendments to the act, FDA met publicly with our advisory panel to receive their recommendations on the classification into Class 1, 2, or 3 of legally marketed pre-amendment device types, those grandfathered products.

Recommendations were risk based to address safety and effectiveness of each individual device type.

FDA reviewed these recommendations. FDA

issued proposed rules classifying each device type, which included the panel's recommendation, and FDA's proposed classification for each device type.

After reviewing the comments we received publicly, FDA published the final classification regulations, including FDA's responses to every comment we received. There have been over 1,700 device types classified through this process.

So can the classification of a preamendment device type be changed? Yes, it can. Through notice and comment rulemaking and based on new information that was not presented previously to those panels.

Can a device type be banned from the market? Yes, it can. Our banning provision is found in Section 516 of the act. The legal standard for banning is that the device type presents substantial deception or an unreasonable and substantial risk of illness or injury, and labeling or a change in labeling cannot address the deception or risk.

Okay. This is a very high standard and difficult to meet. The agency has only banned one device: prosthetic hair fibers intended for implantation into the human scalp to simulate natural hair fiber or conceal baldness.

The risks included, for example, severe scarring and severe infection. The benefit of this device did not outweigh its risk. The deception and risk could not be addressed through labeling, and again, that was banned.

The Dental Classification Advisory Panel first met in 1976 through 1978 to go over classifying device types. After the public meetings and notice and comment rulemaking, FDA classified the following: dental mercury, a device composed of amalgam alloy and the restoration of a dental cavity or a broken tooth into Class 1 requiring a 510(k) submission and review.

Amalgam alloy, a device that consists of a metallic substance intended to be mixed with mercury to form filling material for treatment of dental caries into Class 2, also requiring a 510(k) submission prior to marketing.

Dental amalgam consists of dental mercury and amalgam alloy mixed together in a dentist's office to form dental amalgam. It can be sold separately or together, and when packaged together is called encapsulated amalgam.

Dental amalgam and encapsulated amalgam were not separately classified during the 1976 to '78

classification process. FDA has subsequently classified dental amalgam and encapsulated amalgam through the 510(k) process. Dental amalgam, including encapsulated amalgam, are both a combination of dental mercury, a Class 1 type device; and amalgam alloy, a Class 2 type device.

When a Class 1 and Class 2 device type are combined, the device is regulated at the higher class, in this case Class 2.

Because they are a combination of a Class 1 and Class 2 device, dental amalgam and encapsulated amalgam are regulated as Class 2 devices.

So an example for substantial equivalence review for dental amalgam, we look at in comparison to a grandfathered device. Those are amalgams on the market prior to 1976 or another dental amalgam that has gone through the 510(k) process predicate device.

So, for example, dental mercury and amalgam alloy, they have been found through the 510(k) process to have the same intended use, to have the same technological characteristics, or at times different technological characteristics, for example, a change in the alloy particle size, that do not raise different questions of safety and effectiveness in comparison to those grandfathered or predicate

devices, and the performance data or information, for example, bench testing data, show it to be at least as safety and effective as the predicates, dental mercury and amalgam alloy.

To date, FDA has cleared 75 510(k) submissions for dental amalgams as Class 2 type devices, most recently in 2005, and three 510(k) submissions for dental mercury as Class 1 devices by themselves, most recently in 1998.

FDA proposed reclassification. In 1990, the Safe Medical Devices Act gave FDA additional authorities, as I mentioned earlier, over Class 2 type devices. Instead of simply mandatory performance standards, they gave us special controls.

From 1993 to 1994, the Dental Products Advisory Panel met and recommended up classification for dental mercury from Class 1 into Class 2 in order to apply uniform special controls for dental mercury and dental amalgam products.

From 1994 through 1998, various international meetings were held and reports on the risks and benefits of dental amalgams published.

In 1997, the Public Health Service updated their peer reviewed literature on dental amalgams.

In 2002, FDA proposed regulations that

would up classify dental mercury from Class 1 to Class 2 and place all of these device types into Class 2. FDA also proposed a special controls guidance document, consensus standards, labeling requirements, and labeling recommendations. This final rule has not issued and is, therefore, not in effect at this time.

To give you a status update, FDA received more than 700 comments on this proposed reclassification. The public comments raised potential safety concerns that the agency wanted to evaluate. FDA performed a new literature review. It had been nine years since the last Public Health Service review.

A draft of this white paper on the literature review will be presented to the panel at this meeting.

I thank you for your time.

CO-CHAIRMAN BURTON: Thank you very much for your presentation.

Again, I would like to ask the committee members if they have any questions for the speaker on this presentation. Yes.

DR. ASCHNER: Michael Aschner of Vanderbilt.

Can you give us please the definition of

medical device?

MS. ROSECRANS: The definition of medical device. I did not bring that with me. Sorry, but it's an article, component for a condition or disease that does not achieve its primary action through chemical means, through a mechanical means. let's see.

Does that more or less cover it? I'm sorry. I can go get it and read it into the record.

DR. ASCHNER: Would it be possible to get the definition later on?

MS. ROSECRANS: Yes, it would.

DR. ASCHNER: Thank you.

MS. ROSECRANS: Actually I have it right here. Would you like me to get it?

CO-CHAIRMAN BURTON: Does any other member have any other questions? Yes.

DR. GOLDMAN: Yes, Lynn Goldman.

I'm just wondering. It may just be a shading of difference, but if you could explain a little bit more. If you've got dental mercury in Class 1, but a 510(k) is required, and an amalgam alloy in Class 2, but a 510(k) is required, then what is the actual difference in how these are managed by FDA when they both require a 510(k)?

That's what I'm trying to understand.

MS. ROSECRANS: Most Class 1 devices are exempt, but we have reserved some Class 1 devices are requiring 510(k), and dental mercury is a type of Class 1 device that 510(k) has been reserved. Class 1 devices have general controls. Class 2 devices, we have the ability through rule-making to identify special controls, such as voluntary standards, mandatory standards, guidance documents, et cetera, and when we move something from Class 1 to Class 2, we can make those devices require those special controls in order to make our equivalence determination basically.

Okay. I do have the definition of a device now. It will be much better than my quick summation.

The term device, except when used in Paragraph N of this section and in Section 301(i), blah, blah, blah, means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including any component, part or accessory which is, number one, recognized in the official national formulary or the United States pharmacopeia or any supplement to them;

Two, intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment or prevention of disease in man or other animals; or

Three, intended to affect the structure or any function of the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

And we can get copies for everyone if that would help. Okay?

CO-CHAIRMAN BURTON: Thank you very much.

Do we have any other questions? Yes.

DR. LUSTER: Mike Luster.

This might be a difficult question to ask, but maybe you can give me an example of what would constitute a significant change in formulations for, say, an amalgam to constitute re-evaluation. Would a ten percent, 20 percent change in mercury content, for example, would that be a flag that re-evaluation would be necessary?

MS. ROSECRANS: Yes. We have regulations on modifying the device, and if they modified the

device in that way, as you've described, that would require a new 510(k) submission, and in that 510(k) submission it sounds to me that what you are saying is that would have that exact intended use.

It would have a different technology from those that were legally marketed. We would look at that technology to determine whether or not it raised new type questions that we didn't ask of other devices that were legally marketed in that area, that device type.

If it raised new type questions, that would fall out of the review process there. If not, then they have the same type questions. Then we would evaluate the device's safety and effectiveness in comparison to the other legally marketed devices in order to make a determination if it was, indeed, at least as safe and effective as the other devices.

That's how we would do it.

CO-CHAIRMAN BURTON: Yes.

DR. AMAR: Salomon Amar from Boston University.

Thank you very much.

In the Class 2 devices there's an item on special control that calls for post market surveillance.

MS. ROSECRANS: Yes.

DR. AMAR: Was there any post market surveillance done by the FDA in regard to dental amalgam?

MS. ROSECRANS: Post market surveillance is a section of the act that would require for that specific type product post market surveillance. So dental amalgams at this time do not have a required post market surveillance.

However, we do have the medical device reporting process and all sorts of adverse event reporting processes that are subject to all devices. That's a general control, but there's not a specific post market surveillance required for mercury amalgams or mercury or dental amalgams.

DR. AMAR: Even after the upgrade from Class 1 to Class 2?

MS. ROSECRANS: We propose going from Class 1 to Class 2, but it has not been finalized, and that's one reason we're having the meeting here today, to listen to the science. So we did propose that up classification, but until it would come through rulemaking and be a final rule, it's not in effect at this time.

DR. AMAR: Thank you.

CO-CHAIRMAN BURTON: Yes, sir.

DR. FLEMING: Dr. Mike Fleming.

I wanted to ask you what would be the effect of amalgam being classified as Class 3? In other words, what would that mean in terms of controls?

MS. ROSECRANS: Okay.

DR. FLEMING: Communications to patients, doctors, and so forth, things like that.

MS. ROSECRANS: Okay. Class 3, again, is general controls along with premarket approval because the special controls, the guidance documents and whatnot are for the Class 2 type devices. So if we were to place the device type into Class 3, we would have to issue a proposed rule moving it to Class 3, receive public comments, and then publish a final rule determining whether it should be moved to 3 or not. There would be a final rule and every comment would be addressed through that rulemaking process.

If the device type is put into Class 3 the way the law works to kind of get to the point, it has to be in Class 3 for at least 30 months and require 510(k) review. It doesn't just go Class 3 premarket approval. There's a 30 month period. It stays in Class 3 requiring 510(k). Then the agency goes out

with another rulemaking calling for PMAs on that type device.

Because in 1976 when we put devices that were legally on the market into Class 3, they couldn't have a PMA the next day. So there had to be this time frame. So the law says 30 months.

So after being in Class 3 for 30 months, then we could call for premarket approval applications on those device types. If that happened, every firm who marketed the device type would have to come in with a fillable PMA application, premarket approval application, and if not, they would have to come off the market. They would be removed from the market if they could not have a fillable premarket approvable application.

When the PMA came in, it would individually be evaluated for safety and effectiveness, each individual device type on its own.

DR. FLEMING: So they could continue using the material until such a determination was made or what would be the effect at the practical clinical level for a dentist, do you think?

MS. ROSECRANS: What would be the practical --

DR. FLEMING: Meaning if it went to Class

3. Would he or she be --

MS. ROSECRANS: As long as we have premarket approval applications under review that are administratively complete and under review, the firm can stay on the market. And you know, if no one had a premarket approval application that was fillable, they would all have to come off the market theoretically speaking. But as long as they're under review, they would continue on the market and each one would -- if they were denied, they would have to come off the market. During the premarket approval application, if it were denied, then that firm would have to discontinue marketing if that were ever to happen.

DR. FLEMING: Thank you.

CO-CHAIRMAN BURTON: yes.

DR. HONEIN: Margaret Honein.

Can you just clarify what the obstacles are to moving dental mercury from Class 1 to Class 2, the time period that has elapsed sine it was a proposed rule?

MS. ROSECRANS: I don't know if I would categorize this an obstacle, but again, we met with the panel. We received a recommendation to move it to Class 2. I can maybe go back to the slide and maybe that would help.

Again, the dental mercury was placed into Class 1 going way back to the recommendations from the mid-1970s. In 1990 we had additional authorities given to us under the new law. Besides mandatory performance standards, we have these various other controls we could use for Class 2 type device.

The panel met and recommended they would like to use these controls and they recommended to FDA that dental mercury move to Class 2. FDA concurred with this recommendation from the panel. We proposed that in the Federal Register, and you can see the various other mediums.

In 2002, we proposed that in the Federal Register, and we identified the controls as a guidance document, consensus standards, labeling requirements, and labeling recommendations, and as you saw, we have received over 700 comments, and this public meeting is one way to hear more about the science.

The public comments raise potential safety concerns that we wanted to evaluate, and that's one reason we're here today. So right now that regulation is not in effect. It's just a proposal that we had issued at that time.

CO-CHAIRMAN BURTON: Any other questions?

(No response.)

CO-CHAIRMAN BURTON: Thank you again very much for your presentation.

MS. ROSECRANS: Thank you.

CO-CHAIRMAN BURTON: We will be moving to our next presenter, which is Dr. Arthur Conn from the Dental Advisor from Health Canada, who will be speaking on the scientific basis for the regulation of dental amalgam in Canada.

Dr. Conn.

DR. CONN: Thank you very much, Mr. Chairman, and let me say it's a pleasure to be here, to be invited to make a presentation to the FDA and also to participate. I expect this will be a very informative two days, and Health Canada appreciates the opportunity to be here.

The subject this morning is the scientific basis for Canada's regulation of dental amalgam, and I thought before specifically referring to dental amalgam I'd set a scene for the regulatory framework, where dental amalgam fits in Canada's regulatory framework, and then we can apply some of that information directly to -- (pause in proceedings.)

Before joining the Canadian Public Service, I was a general dentist in downtown Ottawa. I have just recently become a dental regulator ore

regulator of medical devices, but I spent the bulk of my career primarily in restorative dentistry.

The authority to regulate medical devices and dental materials in Canada comes to us through the medical devices regulations, and while I work in the Medical Devices Bureau, the scientific basis for our regulation is a department-wide, is a Health Canada-wide initiative. Well, the Medical Devices Bureau is responsible for administering the regulations. The overall approach is a department-wide initiative.

Most of the scientific review work on this file was done in the early to mid-1990s. I have seen references in literature recently that referred to published materials from that time, and I can say that since the mid-1990s, the activity on this file in Canada has been relatively quiet. The regulatory activity on this file has been primarily one of monitoring the current literature and monitoring the safety of dental amalgam.

Since I joined the Public Service in 2000, Health Canada has received two applications for dental amalgam. One was refused for a complete lack of evidence of safety and effectiveness. The other was approved after a number of requests for additional information.

The second one was approved and authorization to sell the material in Canada was provided.

I have listed here a number of the key features of our regulatory system. I won't go into too much detail here because it parallels in many respects the presentation from the FDA.

We regulate the sale and manufacture of medical devices. We do not regulate the use of medical devices.

Back in the 1990s, Health Canada or the Canadian government, rather, decided to take some initiatives around budgetary deficits and at the same time an advisory committee to Health Canada recommended that in situations where resources may not be as abundant as might be desired, it was recommended that Health Canada devote its primary attention to the devices that are of highest risk, and so that gave rise in 1998 to the amendment of the medical devices regulations which resulted in four classes of risk, and the degree of premarket scrutiny for the device depends on the risk class, with Class 4 devices being the highest risk and receiving the highest degree of scrutiny.

Dental amalgam, encapsulated amalgam and

dental mercury are Class 3 medical devices. Examples of some Class 4 devices, cardiovascular and central nervous system devices, and Class 3 devices, dental amalgam, as I said, endosseous dental implants and ceramic bone void fillers.

I won't spend too much time on these particular issues.

Medical device license application, the process involves the submission by a manufacturer of a premarket review document, and this document contains all of the objective information supporting the manufacturer's contention of safety and effectiveness.

The information provided in the premarket review document needs to demonstrate how the device meets all of the requirements of the medical devices regulations. The document itself has four basic components. I won't spend too much time on this either, but basically background information and summary of safety and effectiveness labeling and quality systems requirements.

Interest in the background information section is the chemical composition and the physical mechanical properties of the device, and this particularly applies to dental restorative materials.

Marketing history can be of some

persuasion if the device has enjoyed a long marketing history in another jurisdiction with a relatively low or a low rate of incidents reports, and that would be taken into account as well.

Each device license application with its premarket review document is reviewed on its own merits, and from what I understand of the 510 review process down here in the United States, this may be where we slightly differ. We do not place quite as much emphasis on a direct comparison to currently licensed products.

Under safety and effectiveness for a Class 3 medical device, such as a dental restorative material, we're looking for a summary of all the preclinical and clinical testing. We're not looking for the detailed testing reports. We're looking for a summary of the clinical and preclinical testing.

We're also looking for the conclusions that the manufacturer has drawn from that testing, and then the question is asked: are these conclusions are they reasonable given the objective evidence?

When we're looking at preclinical studies, we request the manufacturer provide us with a list of the standards that have been utilized in the design and the manufacture of the device, if applicable a

declaration of conformity to international standards, international consensus standards, bi-compatibility, sterilization validation.

And I put this picture of these individuals doing a bit of a balancing act here because I would say that in our regulatory approach when it comes to striking a balance between risk and benefit, when it comes to dealing with a new technology, when it comes to dealing with conflicting evidence in the submission, conflicting evidence relative to the literature, health care has always tended to come down on the side of caution.

These are some of the things that we look for by way of clinical evidence of effectiveness, and again, we ask ourselves: are the manufacturers' conclusions from the testing that has been conducted, are they reasonable? Are they consistent with the evidence? Are there internal discrepancies? Do they B Are they in compliance with Health Canada's understanding of the literature at the present time?

I recall a submission in the recent past when the manufacturer provided information in the bibliography that contained a report that was actually negative with respect to the device. In that situation the manufacturer was asked to explain the

contradiction and to offer up evidence as to why that contradiction did not impact negatively on the safety and effectiveness.

In labeling, we're looking for the administrative details with respect to the product, and one thing I might note is that in Canada we do not require a complete description of the chemical composition of the material to be placed in the labeling.

Our quality systems process is a little bit different from the process down here in the United States. We have a series of auditors that have been accredited by the Standards Council of Canada, and these auditors assure that manufacturers' quality management systems were in compliance with ISO 13485.

So just to summarize safety and effectiveness in Health Canada, I would say it really is a blend between the premarket review of objective evidence, post market surveillance, adverse reactions, problems, problem reports, recall reports, and the third element being management of quality systems as audited by independent auditors.

So now I'll just shift for a moment specifically to dental amalgam, and as I said at the outset, most of the work on this file was done about

ten years ago and to date there really has been very little regulatory activity, and we are not currently initiating any action similar to what the FDA has put in place two or three years ago.

The monitoring of the safety and effectiveness of dental amalgam takes place in the Medical Devices Bureau, of course, but it also takes place with a department-wide task force that's comprised of experts with a wide variety of expertise.

Health Canada does not at the moment have a guidance document or policy on dental restorative materials. This means that the manufacturers are required to provide evidence themselves as to the safety and effectiveness of the device. We do not have a guidance document at this moment. We rely instead on conformity with international consensus standards. We want to know exactly what the chemical composition of the material is.

We rely on the physical mechanical properties to insure that they are adequate for the intended use. We look for evidence by way of conformity to standards, to the validation of mercury vapor escaped during amalgamation, evidence of biocompatibility.

Historically, there are a number of

events, if you like, that I would just like to draw to your attention that might be considered to be Health Canada's position on the regulation of dental amalgam. In 1996, late 1995 and 1996, a stakeholder committee was convened to advise Health Canada. That resulted in the publishing in 1996 of a position paper on the safety of dental amalgam.

In 1998, amalgam, along with all other dental restorative materials, again became subject to premarket review as a Class 3 medical device, and just recently the mercury issues task group at Health Canada has published this document, "Mercury: Your Health in the Environment, a Resource Tool."

The Stakeholder Review Committee had wide representation. It had representation from the dental industry, from consumer health advocates, dentists favoring amalgam-free practice, environmental advocates.

Consensus on this committee was something of a challenge for the chairperson to come to consensus on this. There were, in the executive summary of this report they talk about there being really two extremes of views between those that felt that amalgam was a material that simply should be banned outright right now.

On the other end of the pole was group that felt that there is absolutely no problem with this material. It has been available for 150 years. We need to stop wasting time. Why are you studying this? Let's adjourn right now.

And of course, the majority of the members of the committee fell somewhere in between. I would say though that if you're looking at that wide spectrum between those two extreme views, that the committee tended to come down more on the cautious side of the middle as opposed to the less cautious side. That's just a general observation.

That committee made eight recommendations to Health Canada, and those recommendations were later reviewed and resulted in the publication of the 1996 position paper.

I think what I might do at this point is read one of the recommendations from that Stakeholder Review Committee, Recommendation No. 4. It states, "Although there is no evidence that dental amalgam contributes to immunological, neurological or kidney disease in human populations, there is some evidence that mercury exposure from all sources is of more significance to individuals with those problems than to the general population.

Dentists and physicians should be aware of these concerns in their choice of dental materials for these patients.

The position paper that was published in 1996 came to six conclusions, and this was a department-wide; it wasn't just the Medical Devices Bureau Publishing this document. It was a department-wide initiative, and I've listed here a number of elements that I think contributed to the conclusions that were drawn.

One would be the government's overall strategy towards the reduction of human exposure to mercury; Canadian overall environmental policies; of course, the stakeholder committee report; and as I alluded a moment ago, the precautionary principle where Health Canada tends to have come down on the cautious side of the center as opposed to -- just on the cautious side of the line.

The first two conclusions are written here. It was recognized that dental amalgam does contribute detectable amounts of mercury to the body, but there was not at that time -- again, we're going back to 1996 -- there was no evidence that the exposure was causing illness in the general population or causing Alzheimer's, Lou Gehrig's disease, MS, or

Parkinson's.

It was recognized that mercury crosses the placental barrier, and it was, again, I think, based on the precautionary principle. It was deemed advisable to avoid procedures involving amalgam in pregnant women or individuals with renal impairment and acknowledgment, again, of the environmental practices that favor an overall reduction in the use of mercury in all products.

There was an internal report provided to Health Canada that made an attempt to recommend a tolerable daily intake for mercury from dental amalgam. That report was considered and the overall data at that time was not considered adequate or reliable to permit an estimate of a tolerable daily intake, and again, the committee concluded that there was no evidence that the wholesale removal of existing amalgams was justified.

So that was the position in 1996, and I've stated here that the Health Canada has more or less retained that recommendation from 1996. It has retained the recommendations, and it has also modified them to some extent by the efforts of the Mercury Issues Task Group, which is a department-wide organization or group in Health Canada, and that

committee has membership from a wide variety of disciplines, biology, toxicology, epidemiology, and dentistry and medical devices.

I think I'd like to read, if I may, from two documents that get a sense of what Health Canada's current position is with respect to the safety and effectiveness of dental amalgam. The first is from the resource guide published by the Mercury Task Force.

The question is presented in a question and answer format, and the question is should I avoid mercury amalgam fillings, and again, I think this would be considered to be Health Canada's position on safety and dental amalgam.

Current evidence does not indicate that dental amalgam is causing illness in the general population. However, it is generally a good idea to reduce mercury if this can be achieved at a reasonable cost and with other adverse effects. Health Canada recommends non-mercury filling materials be considered for restoring the primary teeth in children where the mechanical properties of the material are suitable. Pregnant women and people have allergic hypersensitivity to mercury or who have impaired kidney function should avoid the use of dental amalgam

fillings.

And the second question, should I have my existing mercury amalgam fillings replaced, Health Canada's response is Health Canada does not support removal of sound amalgam fillings in patients who have no indication of adverse health effects. Patients who have developed hypersensitivity to amalgam should replace existing mercury amalgam fillings with another material if their physician recommends this.

In another document that is publicly available in the Health Canada Website, the document is called "It's your Health." It's a Health Canada initiative that deals with a number of health issues, and that document states that pregnant women -- excuse me. Let me begin again.

It states that elemental mercury from dental fillings doesn't generally pose a health risk. There is, however, a fairly small number of people who are hypersensitive to mercury. While Health Canada does not recommend that you replace existing mercury fillings, it does suggest that when the fillings need to be repaired, you may want to consider using a product that does not contain mercury.

Pregnant women, people allergic to mercury and those with impaired kidney function should avoid

mercury fillings.

So that I think might represent the current status of the regulation of dental amalgam in Canada, and I hope gives you a bit of a sense of how our system works, and I thank the FDA for the opportunity to present this morning. It looks like it will be a very interesting two days, and we're glad to be able to participate.

Thank you.

CO-CHAIRMAN BURTON: Thank you very much, Dr. Conn.

Do any of the committee members have any questions for Dr. Conn? Yes, on the left.

DR. PORTER: Roger Porter.

Just a quick question. Do you have any idea what percent of the fillings in Canada are, in fact, mercury amalgams, even a rough guess?

DR. CONN: It would be a very rough guess, and it would be based on clinical experience, not on hard data. I would say at this time probably more than half are mercury amalgam fillings.

The regulatory activity, as I mentioned, has been very, very limited. We are experiencing the same decrease in dental amalgam usage in Canada as is happening in the United States. The usage of dental

amalgam seems to be reducing. I don't have the market statistics, but I do know that the activity is reducing.

DR. PORTER: Thank you.

DR. CONN: I don't have anything further to add. Dr. Mackert made an excellent presentation on the risk-benefit of dental amalgam versus composite resin, and I would say that fits exactly with how Health Canada views that situation.

CO-CHAIRMAN BURTON: Yes, over here. Dr. Goldman.

DR. GOLDMAN: Yes, a question about -- hi -- a question about your recommendation on pregnant women. Does that encompass also women of child-bearing age who might become pregnant or is it really for women who are pregnant?

DR. CONN: My understanding is that it is related to women who are pregnant, and I think the purpose of it comes back again to the precautionary principle, that the idea was to make a recommendation of minimizing the burden on the fetus or on the case of kidney impairment on the kidney.

CO-CHAIRMAN BURTON: Dr. Amar.

DR. AMAR: Salomon Amar.

I'd like just to come back to the 1996

position paper, and you read, if I recall properly, conclusion number four where the committee identified although there was no immunological and neurological impairment or evidence for mercury, they identified, they alerted the community as to potential risk or risk of patient at risk of developing diseases.

Was the committee comfortable providing a list of illnesses of patients at risk of developing diseases with mercury or was this just empirical?

DR. CONN: I would say there would appear to be some conflict in that position paper, and I would say that it was based on the precautionary principle, that as a general approach it is wise and prudent to reduce overall exposure to mercury.

I'm not sure I'm getting the exact question.

DR. AMAR: What I'm trying to see is if we can come up with -- that's interesting to identify patients at risk and alert the community, but I wanted to be able to identify this patient at risk population so that we could be more preemptive towards that, although the evidence in my opinion doesn't exist. But at least if we can come down and filter through this population and say this population or the population at risk, including these illnesses, should

avoid amalgams.

DR. CONN: I don't think the stakeholder committee or Health Canada in its further deliberations went to that extent of identifying classes of patients at risk. I think when you look at the regulation of dental amalgam in Canada, the scientific basis of the regulation of dental amalgam does not contain any contraindications, for example. There are no requirements in our labeling that any specific patient group be contraindicated.

I come back again to, again, this is historical information I have very recently on this file, and my understanding of that information, it was based primarily on the precautionary principle as opposed to we know that there is a specific risk associated with a specific group of patients.

I'm not sure that that evidence was actually put together in that way. Does that answer your question?

DR. AMAR: Thank you.

DR. CONN: You're welcome.

CO-CHAIRMAN BURTON: Yes, Ms. Cowley.

MS. COWLEY: In following up on Dr. Amar's concern, I, too, felt that there were statements saying that there are certain people who should not

have amalgams.

Also, you alluded to an allergy to mercury, and how do we know we're allergic to mercury? Are there certain tests that are done in advance of getting an amalgam filling?

And also, would you tell me what the indications of hypersensitivity to amalgam are and how do they manifest?

DR. CONN: I have no clinical experience with hypersensitivity or allergy to amalgam whatsoever. My understanding of that phenomenon is that it results in a local rather than a systemic reaction; that there would be a local gingival reaction to adjacent amalgam.

To be perfectly honest, I cannot provide you with information on the sensitivity, hypersensitivity to dental amalgam. Clinically I have no experience with it at all. I can follow that up with you if you like later.

CO-CHAIRMAN BURTON: Thank you.

Again, on the left.

DR. DIAMOND: Mason Diamond.

Are you aware of other initiatives that are currently ongoing in Canada to reduce environmental exposure to mercury, in general?

DR. CONN: The Ministers of Health in the provinces have a Canada-wide standard on managing amalgam waste from the dental offices, and there has been some progress. The majority of dental offices in Canada now are equipped with amalgam separators that conform to international standards and that are required by regulation in the provinces.

And so that is an initiative in terms of amalgam waste that Health Canada has been very active in.

DR. DIAMOND: What about other exposures like fluorescent bulbs or industrial mercury?

DR. CONN: I'm in the Medical Devices Bureau, and I would like to be able to respond, but I can't.

CO-CHAIRMAN BURTON: Yes, Dr. Rizzo.

DR. RIZZO: Matt Rizzo.

You mentioned for the purposes of devices that you hadn't established a tolerable level for mercury exposure. Were you able to define an intolerable level?

DR. CONN: No.

DR. RIZZO: So any level, it doesn't matter? They're all the same?

DR. CONN: No.

(Laughter.)

DR. RIZZO: Thank you.

CO-CHAIRMAN BURTON: Again on the left.

DR. TAYLOR: George Taylor.

Thank you, Dr. Conn.

Did you mention any post-market surveillance that you were now doing with dental amalgams in Canada?

DR. CONN: I'm sorry. What's the question?

DR. TAYLOR: Did you mention any post-market surveillance with mercury exposure related to dental amalgam or with dental amalgams?

DR. CONN: Our regulatory system requires mandatory problem reporting, and that constitutes post-market surveillance. As I mentioned, the materials that are available for sale in Canada right now have been for sale for a long time. There are no new products with the exception of the one that I mentioned.

And so there are no requirements that manufacturers conduct post market surveillance of a Class 3 medical device. There are no requirements. The requirements are mandatory problem reporting, but in terms of formal post market study, there are no

requirements to do that.

CO-CHAIRMAN BURTON: Thank you very much for your presentation, Dr. Conn.

Yes, I'm sorry. Dr. Zuniga.

DR. ZUNIGA: John Zuniga.

How does the Health Canada administer the regulation that you stipulated that the information for specific risk populations gets that information? Is that regulated at the federal level? Is it regulated in the office? How is that transferred to that risk factor group?

DR. CONN: Regulation of dental practice in Canada is a provincial matter. There are Colleges of Dentistry in each of the provinces and territories, and they would regulate the practice of dentistry.

CO-CHAIRMAN BURTON: Thank you.

We have been running a little behind schedule. Thank you for your presentation and for those questions from all of the panel members.

Our next presentation will be on the scientific basis of regulation of amalgam in Sweden by Dr. Lennart Philipson, Medical Devices Director, Medical Products Agency, Sweden.

Dr. Philipson.

DR. PHILIPSON: Switching computers all

the time here.

I thank the Chairman, and I would like to extend my thanks to the FDA that invited me to come and present the Swedish view of dental amalgams.

Good morning to all of you.

PARTICIPANTS: Good morning.

DR. PHILIPSON: You have to watch my back. I'm sorry for that, but that's the way it's arranged.

(Laughter.)

DR. PHILIPSON: I am going to speak on the use of dental amalgams in Sweden specifically, and I'm working as the Director for Medical Devices at the Medical Products Agency in Sweden, and I am also an Associate Professor in biomedical engineering at the Linkoping University in Sweden.

For this I would like to say I am not a dentist. I am an intraneural physiologist from the beginning, but now I'm here as a regulator.

So what I would like to present to you is the short regulatory background because the regulatory system in Europe -- Sweden is part of Europe as we might know -- is different to regulatory system --

(Laughter.)

DR. PHILIPSON: -- in the States.

And then I am going to present some

figures, presenting the current use of amalgams in my country, which is not necessarily the same as the figures for the rest of Europe.

And I try to give you a look into the future, what we are planning to do with amalgams specifically.

So the regulatory framework that we sort under is the European framework, first of all, and the medical devices are regulated under what we call the Anew approach directive.@ The new approach is an umbrella directive regulating many different area, including medical devices.

So Europe has a post-market surveillance system for medical devices, and we do not have a premarket approval system at all for medical devices, but we do have premarket approval as the States have, for example for pharmaceuticals.

So in Europe the manufacturer has the full responsibility for the function and the safety of the product. It's not a federal agency that is responsible for the function of safety. It's the manufacturer.

We also have different classes for medical devices, and we seem to have a similar system to the Canadian system. We have four risk classes, but we

call them 1, 2(a), 2(b) and Class 3, but it's four different classes.

And dental amalgams belong to the Class 2(b), which would be comparable to the Canadian Class 3.

For higher risk classes of medical devices, we have the involvement of a third party. It's not the manufacturer himself. They also have to engage the third party, and they are called the notifier body.

There are several notifier bodies in Europe competent in different areas, and there are plenty of notifying bodies competent in implants. That includes amalgams, of course.

So a device that is put on the market in one member state in Europe automatically has access to all other member states' markets. So if it gets put on the market, for example, in Italy, we would also have the device in Sweden.

A device put on the European market should carry the CE mark. It's mandatory on all new medical devices within the European Union, and you shall find the mark on the product itself, on the packaging and also on the instructions for use.

And you should remember that the Z mark

is put on the device by the manufacturer. It's not the design of a governmental or agency approval, and if you find a number after the Z mark, it's the number of the notified body that helps the manufacturer with the Z marking process.

So what does the Z mark indicate? By putting the Z mark on the device the manufacturer says that the device is suitable and safe for its intended use, and it also signifies what we call the essential requirements in particular directives are met.

And part of this fulfillment of the essential requirements is that you fulfill all of the requirements of the applicable harmonized European standards.

And the manufacturer has used one of several specified methods to show that the essential requirements actually are met. So that is what the Z mark indicates.

There are three European directives regulating medical devices, and the oldest one regulates accident plans of the medical devices, and the one in '93 regulates the general devices. In part of the general devices you will find dental materials, and then the set that are active for what we call in vitro diagnostic products, and all of these three

directives are new approach directives.

So that was the end of the short regulatory background, and I will present the current situation of the use of amalgams in Sweden is, and the sources I have used for the information I'm going to present is the Swedish Ministry of Health and Social Affairs, the Swedish Ministry of Sustainable Development, the Swedish Chemicals Inspectorate, and the Swedish National Board on Health and Welfare.

So what is the quality of the data that I will present to you? We have since 2001 no central register for the use of different dental filling materials. Until then we had a national register. But data presented in December 2005, we had a recent study by the Swedish Chemicals Inspectorate that's based on information from the major companies distributing dental filling materials in Sweden, and the authors of the study, they say that they cover at least 80 percent of all dental filling materials used in Sweden.

So in Sweden, dental amalgams have been replaced almost totally by other materials over the past seven years. 980 kilograms, that is about the doubling in pounds of mercury was sold for use in amalgams in 1997, and this figure was reduced to

approximately 100 kilograms in 2003. And after that we have no actual measurements made, but there is no indication that this figure has increased. We believe it is still decreasing.

So what are the shares of dental filling materials in Sweden in the year 2005? I'm talking about direct techniques. The shares listed are by weight, and if you note that composites are lighter than amalgams, one kilogram of composite will fix many more teeth than one kilogram of amalgams. So you see it's only six percent amalgams used today, and the composites are seven to eight percent. It's a major component used, and then you see the data for yourself for the other types of materials.

Ceramics is still under one percent.

So why have we reduced the use of amalgams in Sweden? I think there are at least four mechanisms that can explain the reduced use. I think the major reason is the increased awareness of the negative environmental impact of mercury, and maybe that's not the main reason. Maybe the second point is the main reason, and that is that the Swedish national health insurance program since '99 is not covering direct procedures, including amalgams. That means it's more expensive for patients to have an amalgam filling than

a composite filling.

And the possible impact on health has not been ruled out. So with reference to the precautionary principle, the country is trying to reduce the use of amalgams.

And there are also health concerns regarding dentists that are exposed to this material all day in an open forum.

Then the question is, is this based on science or is it based on anything else? And very, very similar to what we just heard from Canada, according to our view today, I would say there is no scientific clinical data demonstrating a connection between the use of dental amalgams and medical problems.

Then I exclude, of course, contact additives. If you're allergic to mercury, you should have not have a mercury-based implant.

But there is a possibility that reported medical problems for some patients or we have not excluded the possibility that the medical problems for some patients are related to dental amalgams because we see that some patients seem to react to dental amalgams, but we cannot explain why.

So what is happening next here? Sweden is

actually introducing a complete prohibition for the use of mercury by January 1st, next year, and with this prohibition of mercury, the use of amalgams is included and will be stopped.

And the decision to stop the use of mercury is based entirely on environmental concerns. But you should know that dental amalgams will still be allowed after this date for some procedures performed in hospital-based dental clinics for very exceptional cases.

There is still some research or we have initiated some new research in the area, and this is where the government has commissioned the National Board of Health and Welfare to allocate one million Euros until 2009. That's a bit more if you count in dollars, for research and development of methods to handle the health problems that are associated with dental materials. So we are still curious why some patients seem to react to dental amalgams.

The Swedish government has also commissioned the National Board of Health and Welfare to establish a national register for health and side effects related to dental materials, and for this purpose they allocated one million Euros until 2010. So we see the need to follow the function of this type

of devices.

That's the end of my presentation. Thank you.

CO-CHAIRMAN BURTON: Thank you.

(Applause.)

CO-CHAIRMAN BURTON: Thank you very much, Dr. Philipson.

And again, any of the committee members have any questions? Yes, over here on the left, Dr. Fleming.

DR. FLEMING: There we go. I'm on. Dr. Mike Fleming.

Sir, I wanted to ask you about a neighboring country, Norway, which I don't believe is part of the same community that you are in Europe, or are they?

DR. PHILIPSON: More or less. They're not members of the Union, but they have the same regulatory system.

DR. FLEMING: The Norwegians have done something very interesting. They have a dental biomaterials adverse reaction unit which does nothing but study adverse reactions to dental materials, and in the report that I have in front of me, they examine patients who were hypersensitive to the material, and

it seems to be, according to their statistics, about nine percent of the patients studied were hypersensitive to an amalgam component, as well as other dental materials.

Now, this seems like a wonderful model for other nations to follow. Now, does Sweden have any such unit as this that you know of?

DR. PHILIPSON: Not today, but I think the reason for this reestablishment of this register that has been -- that the National Board of Health and Welfare should start, maybe they are looking at the Norwegian model. I don't know how they are thinking, but I know they do cooperate and they talk. So maybe they will get some ideas from Norway for this new register.

CO-CHAIRMAN BURTON: Yes. I'm sorry. Right here, first. Dr. Olson.

DR. OLSON: Thank you.

Sandy Olson from Northwestern in Chicago.

I assume that dental amalgams in Sweden are similar to the ones used in the United States. I'll make that as an assumption, and as I understand it, and I believe it's prior to 2001, you had post-marketing surveillance of these products. Do you have any data on what the adverse effects were, other than

hypersensitivity to people who had them before then?

DR. PHILIPSON: I agree that they are probably constituted about the same way in Europe as they are in the States, but this register belongs to the National Board of Health and Welfare, and I am not sure about the quality of that register, and I do not know enough about that register to answer what they actually found.

What I have heard is it was very, very difficult to pin down what kind of dental fillings patients were having that were reported to this register because if you get an amalgam filling 20 years ago and you develop problems later on, it's very hard to remember and to find what you actually have in your mouth, and that was one of the main problems with the register, to actually track down the manufacturer of the specific filling.

I am not sure how they want to address this with this new register, but that is a problem to actually know what each and every patient has received.

CO-CHAIRMAN BURTON: Yes, on the left. Yes, thank you, yes.

DR. TAYLOR: George Taylor, University of Michigan.

Thank you, Dr. Philipson.

You mentioned using weight of restorations as a measure for the distribution of restorations in Sweden. Could you speak at all to how you validated weight with numbers of restorations?

DR. PHILIPSON: This report was done by the Chemical Inspectorate, and they had only measured -- the only figure they could find was the weight. So I don't know, but maybe you could calculate that yourself, you know, the specific weight of mercury compared to other materials. It would be at least a figure ten, wouldn't it, I would assume?

DR. TAYLOR: Yes, I was actually wondering about waste that might be associated with the use of the materials.

DR. PHILIPSON: You mean waste how much you actually --

DR. TAYLOR: The data would come from --

DR. PHILIPSON: -- during the procedures?

DR. TAYLOR: Yes, I was wondering if the data came from manufacturers in terms of amount of material sold or was this from the providers of the amount of material used?

DR. PHILIPSON: What I understand, it was from the distributors of dental amalgams.

CO-CHAIRMAN BURTON: Yes, I'm sorry. Over on the left, Dr. Rizzo.

DR. RIZZO: Matt Rizzo.

In the absence of any clear evidence, what's the threshold, or what are the principles for you to invoke your precautionary principle of not using mercury? Why did you decide not to use mercury?

DR. PHILIPSON: You say what is the threshold for?

DR. RIZZO: Invoking the precautionary principle, which I guess motivated the government perhaps not to pay for mercury fillings.

DR. PHILIPSON: I don't know if there is a threshold for a precautionary principle. I mean, if you suspect that there might be a problem, which I think was the case at the time, they invoked the precautionary principle.

DR. RIZZO: And so what were the suspicions? What was the evidence that you used to motivate that decision?

DR. PHILIPSON: As I hope I said in the presentation, there was not any evidence that problems were based on the mercury fillings or amalgam fillings, but they seem to have found that there are some patients that seem to react to this type of

filling materials, but they do not know why.

DR. RIZZO: If post market surveillance fails to reveal anything new over a period of time, will you change your precautions?

DR. PHILIPSON: I think it's too soon to say, but if this register, whatever comes out of this register, it will, of course, be a foundation for future decisions, this coming register.

DR. RIZZO: And over what period of time?

DR. PHILIPSON: I have no idea. The register is being built now and is going to be in function in 2010, and then you have to gather information. So it will not be tomorrow.

DR. RIZZO: Thank you.

CO-CHAIRMAN BURTON: Dr. Diamond.

DR. DIAMOND: Yes, Mason Diamond.

I find this a very interesting initiative in terms of the reduction in amalgam use. Given the complex etiology of many of the conditions that people are associating with dental fillings and given the various multiple sources of mercury exposure, it seems to me the nature of the public health system in Sweden where you have access to enormous amounts of medical data, it seems to me that there would be an opportunity to do an interesting secular trend type of

analysis where most similar analyses, you look at the overall effect on public health by the introduction of some of a new product or a new drug into the health system.

Here there's an opportunity to sort of look at what happens as a result of the removal or the reduction of amalgam use. Is that an initiative that the Swedish government is looking into?

DR. PHILIPSON: The Swedish government has asked the National Board of Health and Welfare to start this register and to gather statistics, and I think I'm sure there are lots of clever people at the National Board of Health and Welfare, and they might have thought of this, but I'm not sure. I will try to convey your idea when I meet them.

Thanks.

CO-CHAIRMAN BURTON: Ms. Cowley.

MS. COWLEY: I'm really interested in this registry and the, I presume, prospective study on amalgams, and I'm a little confused. Apparently in Sweden a lot of the evidence is to come from manufacturers. Are the dentists going to provide the information on the patients? Are the patients going to be the ones who will be followed in a post market surveillance type of method? Just how is this going

to work?

Because if we rely on patients to perhaps report that there is a problem, a lot of times they can't connect the dots that what they're going through is the result of this. And most of the time when they do go to a physician, they're told there is no relationship. So how is this going to work?

DR. PHILIPSON: I'm not sure. I think that's a very good question. I am not sure that that has been decided yet. They have just received money to start building this register or registry, I should say, and exactly how they plan to get data into the register, I'm not sure that that has been set as yet, but it's important to find ways, as you say, to not rely only on incident reports from patients and dentists because we receive too few of those.

CO-CHAIRMAN BURTON: Any other questions? Dr. Amar.

DR. AMAR: Thank you very much for this presentation.

I notice that in January 2007 your country is going to ban the use of mercury based on environmental concerns. My first question is could you elaborate on the concerns and particularly the environmental concerns that drove this legislation.

And second, in light of that, was there any concern voices in your country as to the potential of using alternative materials for amalgam given the life or the potential of having like accumulations with other materials that is well documented today in this era where we're trying to reduce plaque accumulation in the mouth and recurrent carious lesions?

DR. PHILIPSON: To your first question, I am not the person to elaborate on why, on what components on the environmental concerns are involved in this decision, but I would rather refer the question back to the Chemicals Inspectorate because they have investigated this in detail.

To me it's enough to realize and understand that mercury is going to be stopped for environmental reasons, and I think there=s many components to that.

Your question about the alternative filling materials and the quality and function of those, yes, there is a concern, especially among dentists, I think because we know that some of the other alternative materials are not well tested either and some of them are not stable over time, and some of them might cause other types of allergic reactions.

So there is a concern, but the decision is still the same that we would like to get rid of the dental amalgams and try to rely on only the other ones, and as you saw from the figures, we almost knew that already, and I think time will show if that was a good decision or not. We might see other problems around the corner with the other alternative materials.

I think the best method is not to develop any problems with your teeth.

(Laughter.)

CO-CHAIRMAN BURTON: Thank you.

Dr. Li.

DR. LI: Yes. Thank you.

Thank you very much for your presentation. I have two questions.

The first one is a follow-up on mercury use, which will no longer be permitted after January 1st, year 2007, because of environmental concerns, but it will be permitted to use it in hospital settings and dental clinics in exceptional cases.

Can you comment on whether you have any special measures for that specially permitted use in these exceptional cases?

And the second question I have is during