



**FDA**

U.S. Department of Health and Human Services

**Food and Drug Administration**

**C·D·R·H** Center for Devices and  
Radiological Health

**CDER** Human Drugs

**Joint Meeting of the Dental Products Panel of the Medical  
Devices Advisory Committee of 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**

**MEETING AGENDA**

**September 6-7, 2006**

**Holiday Inn  
Ballroom  
Two Montgomery Village Avenue  
Gaithersburg, MD**



## **BACKGROUND**

Several interested parties have raised concerns about the effects of using mercury as a component of dental amalgam devices. Dental amalgam, also called “encapsulated amalgam,” consists of dental mercury and amalgam alloy. The Food and Drug Administration (FDA) has convened a meeting of the Dental Products Panel of the Medical Devices Advisory Committee of 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 (the joint committee) to review the latest science on dental amalgam.

## **COMMITTEE ACTION**

The joint committee will review and discuss peer-reviewed scientific literature on dental amalgam and mercury toxicity.



U.S. Department of Health and Human Services

**Food and Drug Administration**

**MEETING AGENDA**  
**JOINT MEETING OF DENTAL PRODUCTS PANEL AND**  
**PERIPHERAL AND CENTRAL NERVOUS SYSTEM**  
**DRUGS ADVISORY COMMITTEE**

**September 6-7, 2006**

**Holiday Inn**  
**Ballroom**  
**Two Montgomery Village Avenue**  
**Gaithersburg, MD**

**Wednesday, 6 September 2006**

**MORNING SESSION – Dr. Richard Burton, Co-Chairman**

8:00 a.m.

**CALL TO ORDER**

- Dr. Richard Burton, Co-Chairman

8:00 - 8:30 a.m.

**Introductory Remarks**

- Mr. Michael E. Adjodha, Executive Secretary
- Dr. Norris E. Alderson, Associate Commissioner for Science, FDA

## MEETING AGENDA (continued)

Wednesday, 6 September 2006

8:30 - 10:30 a.m.

### Background

- Dental amalgam and other restorative materials
  - Dr. J. Rodway Mackert, Professor, Medical College of Georgia
- Overview of Device Classification under the FFD&C Act
  - Ms. Heather Rosecrans, 510(k) Section Chief, Program Operations Staff, CDRH
- Scientific basis for the regulation of dental amalgam in Canada
  - Dr. Arthur Conn, Dental Advisor, Health Canada
- Scientific basis for the regulation of dental amalgam in Sweden
  - Dr. Lennart Philipson, Medical Devices Director, Medical Products Agency (Sweden)
- U.S. public health agencies' evaluations relevant to dental amalgam prior to 1997
  - Dr. Richard Canady, Senior Health Scientist, Office of Commissioner, FDA.

10:30 - 10:45 a.m.

### BREAK

10:45 – 12:00 p.m.

### Open Public Hearing

*Public attendees who have contacted the Executive Secretary prior to the meeting will address the Committee and present information relevant to the agenda. Speakers are asked to state whether or not they have any financial involvement with the product or competing products being discussed.*

12:00 - 1:00 p.m.

### LUNCH BREAK

## **MEETING AGENDA (continued)**

**Wednesday, 6 September 2006**

**AFTERNOON SESSION – Dr. Karl D. Kieburtz, Co-Chairman**

1:00 – 5:00 p.m.      **Open Public Hearing** (continued)

2:30 - 2:45 p.m.      **BREAK**

5:00 p.m.              **BREAK** – reconvene the next day at 8:00 a.m.

# MEETING AGENDA

**Thursday, 7 September 2006**

**MORNING SESSION** – Dr. Richard Burton, Co-Chairman

8:00 a.m.                    **MEETING RECONVENES**

8:00 - 10:00 a.m.        **Open Public Hearing**

*Public attendees who have contacted the Executive Secretary prior to the meeting will address the Committee and present information relevant to the agenda. Speakers are asked to state whether or not they have any financial involvement with the product(s) or competing products being discussed.*

10:00 - 10:15 a.m.        **BREAK**

10:15 - 11:15 a.m        **Literature Review**

- FDA White Paper review of recent scientific studies
  - Dr. William Slikker, Acting Center Director, NCTR
  - Dr. Merle Paule, Director, Division of Neurotoxicity, NCTR

11:15 - 12:00 pm        **Committee Discussion**

- Questions for Committee Consideration
  - Dr. Norris E. Alderson, Associate Commissioner for Science, FDA

12:00 - 1:00 p.m.        **LUNCH BREAK**

## **MEETING AGENDA (continued)**

**Thursday, 7 September 2006**

**AFTERNOON SESSION** – Dr. Karl D. Kieburz, Co-Chairman

1:00 – 4:15 p.m.      **Committee Discussion** (continued)

2:30 – 2:45 p.m.      **BREAK**

4:15 – 4:30 p.m.      **Committee Summation**

4:30 p.m.              **MEETING ADJOURNED**

## Questions for Committee Consideration

- 1) Based on the peer-reviewed scientific literature, the draft FDA White Paper, and any other information, including the information you heard in the public session, please discuss the following topics, including any issues of quality, experimental design, or other attributes of specific studies that may affect the weight that should be given to conclusions drawn from them:
  - a) Please discuss the direct evidence, if any exists, supporting or refuting the occurrence of adverse health effects from mercury vapor released from dental amalgam devices.
  - b) Please discuss the indirect evidence (e.g., extrapolation from higher dose studies, animal studies), if any exists, supporting or refuting a link between dental amalgam devices and adverse neurological effects at the absorbed doses received from these devices.
  - c) Please discuss the indirect evidence (e.g., extrapolation from higher dose studies, animal studies), if any exists, supporting or refuting a link between dental amalgam devices and adverse non-neurological effects at the absorbed doses received from these devices
  - d) Please discuss the indirect evidence (e.g., extrapolation from higher dose studies, animal studies) , if any exists, supporting or refuting a link between dental amalgam devices and adverse effects specific to vulnerable populations such as children and pregnant women at the absorbed doses received from these devices.
- 2) Does the draft FDA White Paper objectively and clearly present the current state of knowledge about the exposure and health effects related to dental amalgam?
- 3) Given the amount and quality of the information available for the draft FDA White Paper, are the conclusions reasonable?

# DENTAL PRODUCTS PANEL

September 2006

CHAIRMAN	EXECUTIVE SECRETARY
Richard Burton, DDS Professor, Oral and Maxillofacial Surgery University of Iowa College of Dentistry Iowa City, Iowa	Michael E. Adjodha, MChE Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGID) Center for Devices and Radiological Health Food and Drug Administration Department of Health and Human Services

## PANEL MEMBERS

Name	Affiliation	Role
Salomon Amar, DDS, PhD	Professor and Associate Dean, Periodontology Boston University, School of Dental Medicine Boston, Massachusetts	Member
Theresa A. Cowley	President The TMJ Association Milwaukee, Wisconsin	Member Patient Representative
Mason Diamond, DDS	Vice President, Clinical and Regulatory Affairs TyRx Pharma, Inc. Monmouth Junction, New Jersey	Member Industry Representative
Michael Fleming, DDS, PA	Dentist, Private Practice Durham, North Carolina	Member Consumer Representative
Yiming Li, DDS, PhD	Professor, Restorative Dentistry Loma Linda University, School of Dentistry Loma Linda, California	Member
Man Wai Ng, DDS MPH	Dentist-in-Chief Children's Hospital Boston, Massachusetts	Member
William J. O'Brien, MS, PhD	Professor, Materials Science University of Michigan, School of Dentistry Ann Arbor, Michigan	Member
Domenick T. Zero, DDS, MS	Professor and Chairman, Preventative Dentistry Indiana University, School of Dentistry Indianapolis, Indiana	Member
John R. Zuniga, PhD, DMD	Professor and Chair, Oral and Maxillofacial Surgery University of Texas, Southwestern Medical Center Dallas, Texas	Member

# PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

September 2006

CHAIRMAN	EXECUTIVE SECRETARY
Karl D. Kieburtz, MD, MPH Professor, Neurology and Preventative Medicine University of Rochester, School of Medicine and Dentistry Rochester, New York	LT Darrell Lyons, BSN, RN Advisors and Consultants Staff Center for Drug Evaluation and Research Food and Drug Administration Department of Health and Human Services

## ADVISORY COMMITTEE MEMBERS

Name	Affiliation	Role
Larry B. Goldstein, MD	Professor, Medicine Duke University, Medical Center Durham, North Carolina	Member
Michael D. Hughes, PhD, MSc	Professor, Biostatistics Harvard University, School of Public Health Boston, Massachusetts	Member
Lilly K. F. Jung, MD, MMM	Medical Director, Neurology Clinic Swedish Neuroscience Institute Seattle, Washington	Member Consumer Representative
Sandra F. Olson, MD	Professor, Clinical Neurology Northwestern University, Medical School Chicago, Illinois	Member
Roger J. Porter, MD	Consultant, Anti-epileptic drugs Devon, Pennsylvania	Member Industry Representative
Matthew Rizzo, MD	Professor, Neurology, Engineering, and Public Policy University of Iowa Iowa City, Iowa	Member
Ralph L. Sacco, MD, MS	Professor, Neurology and Epidemiology Columbia University, Neurological Institute New York, New York	Member

## COMMITTEE CONSULTANTS

September 2006

Name	Affiliation	Role
Michael Aschner, PhD	Professor, Pediatrics and Pharmacology Vanderbilt University, Department of Pediatrics Nashville, Tennessee	Consultant
Michael Dourson, PhD	Director Toxicology Excellence for Risk Assessment Cincinnati, Ohio	Consultant
Lynn R. Goldman, MD, MS, MPH	Professor, Environmental Health Sciences Johns Hopkins University Baltimore, Maryland	Consultant
Margaret (Peggy) Honein, PhD, MPH	Epidemiologist Centers for Disease Control and Prevention Atlanta, Georgia	Consultant
Curtis D. Klaassen, PhD	Professor and Chairman, Pharmacology and Toxicology Kansas University Medical Center Kansas City, Kansas	Consultant
Michael I. Luster, PhD	Branch Chief, Toxicology and Molecular Biology National Institute for Occupational Safety and Health Morgantown, West Virginia	Consultant
George Wesley Taylor, III, DMD, DPH	Associate Professor, Cariology University of Michigan, School of Public Health Ann Arbor, Michigan	Consultant

## Other Meeting Participants

FDA	Guest Speakers
Norris E. Alderson, PhD Associate Commissioner for Science Director, Office of Science and Health Coordination Office of Commissioner	J. Rodway Mackert, DMD, PhD Professor, Oral Rehabilitation Medical College of Georgia, School of Dentistry, University of Georgia
William Slikker, PhD Acting Center Director, National Center for Toxicological Research	Arthur Conn, DDS, Dental Advisor, Medical Devices Bureau Health Canada Canada
Merle Paule, PhD Division Director, Division of Neurotoxicology National Center for Toxicological Research	Lennart Philipson, PhD Director, Medical Devices Medical Products Agency Kingdom of Sweden
Richard Canady, PhD DABT Senior Health Scientist Office of Science and Health Coordination	
Heather S. Rosecrans Chief, 510(k) Section Program Operations Staff Center for Devices and Radiological Health	

## **Biographical Sketch of Advisory Committee Members and Consultants**

### CDRH Members<sup>1</sup>:

#### **Richard Burton, DDS (C)**

Dr. Richard G. Burton is Vice-Chair of the Hospital Dentistry Institute, University of Iowa Hospitals and Clinics. He is also a Professor of Oral and Maxillofacial Surgery at the University of Iowa College of Dentistry. Dr. Burton received a DDS degree from Ohio State University in 1977. His areas of expertise include TMJ reconstruction, reconstructive pediatric surgery, cleft and craniofacial surgery, skeletal orthodontic anchorage, esthetic orthognathic surgery, and implant restoration in atrophic bone and special needs populations.

#### **Salomon Amar, DDS, PhD (V)**

Dr. Amar is Professor and Associate Dean of Research at the Boston University School of Dental Medicine. Dr. Amar received a DDS degree and MS and PhD degrees from the University Louis Pasteur, France. His areas of expertise include inflammation and inflammatory pathways, periodontal diseases and periodontal systemic connections, wound healing and tissue regeneration, transcriptional regulation, and cytokine regulation.

#### **William J. O'Brien, PhD, MS (V)**

Dr. O'Brien is Professor in the Department of Biologic and Materials Sciences at the School of Dentistry, University of Michigan. Dr. O'Brien received an MS degree in metallurgy from New York University and a PhD degree in metallurgical engineering & dental materials from the University of Michigan. His areas of expertise include dental materials, metallurgy, surface science, and color science.

#### **Man Wai Ng, DDS, MPH (V)**

Dr. Man Wai Ng is Dentist-in-Chief at the Children's Hospital Boston. Dr. Ng received a DDS degree from the State University of New York at Stony Brook and a MPH degree from the Harvard School of Public Health. She completed residency training in Pediatric Dentistry at Children's Hospital Boston. Her areas of expertise include public health, preventing and managing early childhood caries, and public policy and advocacy to improve the oral health of children, especially on behalf of underserved children.

#### **Domenick Zero, DDS, MS (V)**

Dr. Zero is Associate Dean for Research, Director of the Oral Health Research Institute, and Professor and Chair of the Department of Preventive and Community Dentistry at Indiana University School of Dentistry. Dr. Zero received his DDS degree

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<sup>1</sup> C = Chair

V = Member

IR = Industry Representative

CR = Consumer Representative

PR = Patient Representative

from Georgetown University, Washington, D.C., in 1975. Dr. Zero completed a general dentistry residency at the Eastman Dental Center and then a three-year research fellowship leading to a master's degree from the University of Rochester in 1979. His areas of expertise include the role of bacterial virulence factors in dental caries, clinical efficacy of topical fluorides, the use of remineralizing agents, new early caries diagnostic systems, and erosive potential of foods and beverages.

**John Zuniga, DMD, PhD (V)**

Dr. Zuniga is Professor and Chair of the Department of Oral and Maxillofacial Surgery at the University of Texas Southwestern Medical Center. Dr. Zuniga received a DMD degree at Tufts University and MS and PhD degrees in neuroscience at the University of Rochester. His areas of expertise include oral and maxillofacial surgery, chronic and acute facial pain, and neurosensory disorders.

**Yiming Li, DDS, PhD (V)**

Dr. Li is Professor of Restorative Dentistry, Director of Center for Dental Research, Director of Biocompatibility and Toxicology Research Laboratory, Loma Linda University School of Dentistry. He is also a Professor in the Department of Microbiology and Molecular Genetics, Loma Linda University School of Medicine. Dr. Li received his dental education from Shanghai Second Medical University, MS in Dentistry in Dental Materials with a minor in Operative Dentistry from Indiana University School of Dentistry, and PhD in Dental Sciences from Indiana University Graduate School. His areas of expertise include biological properties of dental materials, toxicology with emphasis in genetic toxicology, biological and pharmacological properties of fluoride, and biological properties and clinical effects of peroxide-based tooth whiteners.

**Mason Diamond, DDS (IR)**

Dr. Diamond is the Vice President of Clinical and Regulatory Affairs at TyRx, Pharma, Inc. Dr. Diamond received a BA from Columbia University, a DDS degree from NYU, and graduate training in pharmacology from St. John's University. His specific areas of expertise include clinical dentistry, combination product development, clinical and preclinical study design, adverse experience evaluation and reporting, and regulatory affairs regarding drug, device, and biologic products.

**Michael Fleming, DDS, PA (CR)**

Dr. Fleming has maintained a private practice of general dentistry in Durham, North Carolina for over twenty-five years. He received a DDS degree from the University of the North Carolina School of Dentistry in Chapel Hill, North Carolina. Dr. Fleming's area of expertise includes consumer advocacy and providing dental treatment for patients who are medically compromised as well as those with multiple chemical or environmental sensitivities.

**Theresa A. Cowley (PR)**

Terrie Cowley is the President and co-founder of The TMJ Association. Ms. Cowley received a B.A. from Millsap College, Jackson, MS in the field political science. She also attended Harvard University in which she studied government affairs. Ms. Cowley works to increase awareness of the needs of TMJ patients among key groups, including the public, patients, healthcare providers, policy-makers, Congress, the National Institutes of Health (NIH) and the media.

CDER Members:

**Karl D. Kieburtz, MD, MPH (C)**

Dr. Kieburtz is Professor of Neurology and Community and Preventive Medicine at the University of Rochester School of Medicine and Dentistry in Rochester, New York. He completed his MD and MPH degrees at the University of Rochester. His areas of expertise include neurology and clinical research.

**Larry B. Goldstein, MD (V)**

Dr. Goldstein is Professor of Neurology and Director of the Center for Cerebrovascular Disease at the Duke University Stroke Center. Dr. Goldstein received his MD from Mt. Sinai School of Medicine. His areas of expertise include general neurology; stroke; cerebrovascular disease; and TIAs. His special expertise includes effects of drugs on recovery after stroke and brain injury; stroke trial design and outcomes measures; carotid endarterectomy; stroke prevention and neuroplasticity and behavioral recovery after brain injury.

**Michael D. Hughes, PhD, MSc (V)**

Dr. Hughes is Professor of Biostatistics at the Harvard School of Public Health. Dr. Hughes received MSc and PhD degrees in medical statistics at the University of London, England. His area of expertise is biostatistics with a particular emphasis on the design and analysis of clinical trials and epidemiological studies.

**Ralph L. Sacco, MD, MS (V)**

Dr. Ralph L. Sacco is Professor of Neurology and Epidemiology at the Neurological Institute of Columbia University College of Physicians and Surgeons, the Mailman School of Public Health, and the Sergievsky Center. He is Associate Chair of Neurology for Clinical Research and Training and Director of the Stroke and Critical Care Division, and an Attending Neurologist at the New York Presbyterian Hospital in New York City. Dr. Sacco graduated from Cornell University with distinction, received his medical degree cum laude from Boston University School of Medicine in Massachusetts, and a master's degree in epidemiology from Columbia University, School of Public Health. Dr. Sacco completed a residency in neurology at Presbyterian Hospital of the City of New York. He completed his postdoctoral training in stroke and Epidemiology at Columbia under a NINDS-funded neuroepidemiology training grant.

**Matthew Rizzo, MD (V)**

Dr. Rizzo is a Professor of Neurology, Engineering, and Public Policy at the University of Iowa, where he directs the Division of Neuroergonomics and is a senior member of the Division of Behavioral Neurology and Cognitive Neuroscience. Dr. Rizzo received his bachelor's degree from Columbia University and his MD from the Johns Hopkins University School of Medicine.

**Sandra F. Olson, MD (V)**

Dr. Olson is Professor of Clinical Neurology at Northwestern Medical School, Chicago, IL. She received an MD from Northwestern University. Her areas of expertise include clinical neurology and health care education.

**Roger J. Porter, MD (IR)**

Dr. Porter is a consultant to the pharmaceutical industry, primarily in the development of antiepileptic drugs. Dr. Porter received an MD from Duke University in 1968 and

completed a residency in neurology at UC San Francisco in 1974. His areas of expertise include epilepsy, neurology, and clinical pharmacology.

**Lily Kam Fong Jung, MD, MMM (CR)**

Dr. Jung is the Medical Director of the Neurology Clinic and Interim Medical Director of the MS Program at Seattle Neuroscience Institute at Swedish Medical Center. Dr. Jung received an MD degree from Northwestern University and a Masters in Medical Management degree from Tulane University. Her areas of expertise include neurology and multiple sclerosis.

Consultants:

**Michael Aschner, PhD**

Dr. Aschner is Professor of Pediatrics and Pharmacology at Vanderbilt University Medical Center's Department of Pediatrics. Dr. Aschner received a PhD in neurobiology and anatomy in 1985 from the University of Rochester. His areas of expertise include mercury neurotoxicity, manganese neurotoxicity, heavy metals, and astrocyte-neuron cross talk.

**Mike Dourson, PhD**

Dr. Dourson is Director of Toxicology Excellence for Risk Assessment, a nonprofit corporation with a mission to protect public health. Dr. Dourson received a PhD in toxicology from the University of Cincinnati in 1980. An employee of EPA for 15 years, he has specific expertise on risk assessment methods, the use of animal and human data in the assessment of risk, and the risk assessments for specific chemical entities.

**Curtis D. Klaassen, PhD**

Dr. Klaassen is University Distinguished Professor and Chairman of the Department of Pharmacology, Toxicology and Therapeutics at the University of Kansas Medical Center in Kansas City, Kansas. Dr. Klaassen received a PhD in Pharmacology from the University of Iowa. He has published over 400 peer-reviewed articles and more than 75 review articles and chapters for books. His areas of expertise include toxicology, including toxicology of metals, pharmacology, and environmental health.

**Margaret (Peggy) Honein, PhD, MPH**

Dr. Honein is an epidemiologist for the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Dr. Honein received her MPH from the University of California, Los Angeles (UCLA) in 1992, and her PhD in Epidemiology from UCLA in 1995. Her areas of expertise include the role of smoking in birth defects, the impact of folic acid fortification on neural tube defects, and the use of medication use during pregnancy.

**Lynn R. Goldman, MD, MS, MPH**

Dr. Goldman is Professor of Environmental Health Sciences at Johns Hopkins University's School of Public Health. Dr. Goldman received an MS degree at UC Berkeley in 1979, an MD degree at UC San Francisco in 1981, and an MPH degree at Johns Hopkins University in 1981. Her areas of expertise include pesticides and toxic substances environmental health risks and risk management, pediatric environmental health, environmental health policy, disaster preparedness and response, public health practice, and international chemical and biotechnology safety

**George Wesley Taylor, III, DMD, DPH**

Dr. Taylor is an associate professor at the University of Michigan with joint appointments in the Department of Cariology, Restorative Sciences and Endodontics in the School of Dentistry and in the Department of Epidemiology in the School of Public Health. He received a DMD degree from Harvard University School of Dental Medicine and MPH and DrPH degrees from the University of Michigan School of Public Health. His areas of expertise include observational and intervention studies of relationships between oral diseases and other systemic diseases, particularly the role of oral infections in diabetes mellitus, oral health and pneumonia in older adults and other adverse medical outcomes;

and observational studies of factors affecting oral health status and dental care utilization of underrepresented minority populations.

**Michael Ivor Luster, PhD**

Dr. Michael I. Luster is Chief of the Toxicology and Molecular Biology Branch at the National Institute for Occupational Safety and Health in Morgantown, West Virginia. He also directs a laboratory research group studying the relationships between immune regulation and chronic workplace diseases such as asthma. Prior to joining the NIOSH in 1996, he served as Head of the Environmental Immunology and Neurobiology Section at the National Institute of Environmental Health Sciences, NIH in Research Triangle Park, North Carolina. Dr. Luster received a PhD degree in microbiology from Loyola University of Chicago. He has co-authored over 300 publications, holds several U.S. Patents and has co-edited 6 books in the area of immunotoxicology and is considered one of the founders in this area.

Guest Speakers:

**J. Rodway Mackert, Jr., DMD, PhD**

Dr. Mackert is Professor in the Department of Oral Rehabilitation at the Medical College of Georgia School of Dentistry. Dr. Mackert received his dental degree at the Medical College of Georgia and his PhD in materials science at the University of Virginia School of Engineering and Applied Science. His areas of expertise include oxidation of metals, X-ray diffraction, thermal properties of ceramics, and dental amalgam biocompatibility.

**Arthur Conn, DDS**

Dr. Conn is Dental Advisor to the Medical Devices Bureau in Health Canada, the department of health of the government of Canada. He graduated in 1970 from the University of Toronto with a DDS degree. Dr. Conn's area of expertise is in the regulation of dental and orthopedic devices.

**Lennart Philipson, PhD**

Dr. Philipson is Director of the Medical Products Agency in the Kingdom of Sweden. He received an MS degree in electrical engineering from Chalmers University of Technology in Göteborg, Sweden, in 1975 and a PhD degree in biomedical engineering from Linköping University, Sweden, in 1987. His expertise is in the area of neurophysiology.