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 06-07, 2006

Holiday Inn
Walker/Whetstone Room
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 alloys. 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 devices.

COMMITTEE ACTION

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

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

September 06-07, 2006

Holiday Inn
Walker/Whetstone Room
Two Montgomery Village Avenue
Gaithersburg, MD

Wednesday, 06 September 2006

8:00 a.m. CALL TO ORDER

- Dr. Richard Burton, Chairman

8:00 - 8:15 a.m. Introductory Remarks

- Mr. Michael E. Adjodha, Executive Secretary
- Dr. Norris E. Alderson, Office of the Commissioner

8:15 - 10:15 a.m. Background

- Dental amalgam and other restorative materials
  - Dr. J. Rodway Mackert

- FDA regulation of dental amalgam
  - Ms. Heather Rosecrans
MEETING AGENDA

Wednesday, 06 September 2006

- Scientific basis for the regulation of dental amalgam in Canada – Dr. Arthur Conn
- Scientific basis for the regulation of dental amalgam in Sweden – Dr. Lennart Philipson

10:15 - 10:30 a.m. BREAK

10:30 - 12:30 p.m.

12:30 - 1:30 p.m. LUNCH BREAK

1:30 – 2:15 p.m.
- FDA white paper review of recent scientific studies – Drs. W. Slikker and Merle Paule
MEETING AGENDA

Wednesday, 06 September 2006

2:15 – 4:15 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.

3:00 - 3:15 p.m. BREAK

4:15 – 5:00 p.m. Committee Discussion

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

Thursday, 07 September 2006

8:00 a.m.   MEETING RECONVENES
8:00 - 11:30 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

11:30 -12:00 pm  Committee Discussion

•   Questions for Committee Consideration
    – Dr. Norris E. Alderson

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

1:00 – 4:00 p.m.  Committee Discussion

Thursday, 07 September 2006

4:00 – 4:30 p.m.  Committee Summation

4:30 p.m.  MEETING ADJOURNED
Draft Questions for Committee Consideration

1) Based on the peer-reviewed scientific literature, the draft FDA White Paper, and any other information, 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

<table>
<thead>
<tr>
<th><strong>CHAIRMAN</strong></th>
<th><strong>EXECUTIVE SECRETARY</strong></th>
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</table>
| 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  
Department of Health and Human Services |

## PANEL MEMBERS

<table>
<thead>
<tr>
<th><strong>Name</strong></th>
<th><strong>Affiliation</strong></th>
<th><strong>Role</strong></th>
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| 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*

<table>
<thead>
<tr>
<th>CHAIRMAN</th>
<th>EXECUTIVE SECRETARY</th>
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</table>
| 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**

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role</th>
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</table>
| 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

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

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<tr>
<th>FDA</th>
<th>Guest Speakers</th>
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| Norris E. Alderson, PhD  
Associate Commissioner  
Office of Science and Health Coordination  
Office of Commissioner | J. Rodway Mackert, DMD, PhD  
Professor, Oral Rehabilitation  
Medical College of Georgia, School of Dentistry |
| 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  
NCTR | Lennart Philipson, PhD  
Director, Medical Devices  
Medical Products Agency  
Kingdom of Sweden |
| 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:

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.
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 form 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 Millsaps 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 TIs. 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, 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. Parents and has co-edited 6 books in the area of immunotoxicology and is considered one of the founders in this area.

**Guest Speakers:**

**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.

**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.