- 24 hours summary December 14-15, 2010 Dental Products Panel Meeting –

The Dental Products Panel met on December 14 and 15, 2010, to discuss and make recommendations on scientific issues raised in petitions received by FDA concerning the final rule on the classification of dental amalgam, which published in the **Federal Register** on August 4, 2009 (74 FR 38686). The Panel deliberated on the exposure to mercury from dental amalgam, reference exposure levels, human clinical studies and the strength and weaknesses of the available evidence.

The meeting began with Mr. Michael Adjodha, M. ChE**.** of the Dental Devices, who gave the Panel an overview of Dental Amalgams, the Regulatory History, the Concerns Regarding Safety, the Safety Assessments, past Advisory Committee Discussions, the Proposed Rule (2002), the Final Rule (2009), the Petitions for Reconsideration and the Food and Drug Administration (FDA) Reconsideration Efforts. The Panel had questions on the Rule's definition of mild, medium or severe risk. They also had questions on the frequency of allergic reactions and hypersensitivity reactions.

The petitioners' presentations focused on their petitions concerning FDA's 2009 Final Rule. Key points for consideration were that dental amalgam should be reclassified into class III to require an affirmative demonstration of safety, that studies of mild and severely autistic children correlated the severity of autism with dental amalgam, that animal data had demonstrated that mercury from dental amalgam migrates and most is excreted in feces, and that informed consent should be required before placing amalgam. Two petitions appealed to the Panel and FDA to ban amalgams.

Dr. Mark Richardson of SNC-Lavalin Environment made a presentation focused on his latest risk assessment "Risk Assessment Mercury Exposure and Risks from Dental Amalgams (2010)". The Panel addressed questions to Dr. Richardson on whether he considered mercury exposures from other sources.

There were two hours of open public hearing on the first day, where the Panel listened to personal stories from individuals stating they had been harmed by exposure to mercury from dental amalgam and professional opinions in favor of and against the safety and effectiveness of dental amalgams.

The Expert "Homework Assignment" Consultations were presented by Dr. Gary Ginsberg, Dr. William Farland and Robert Yokel. The consultations focused on the adequacy of risk assessments that had been used to characterize the risk from dental amalgam and what considerations should be taken when calculating reference levels. Dr. Gary Ginsberg encouraged the FDA to reassess the Environmental Protection Agency (EPA) Reference Concentraion (RfC), and questioned the assumption of a threshold dose. Questions were directed towards the assumptions that should be used and the possible bioaccumulation from different sources. The Panel was interested in the suggestion of non threshold response and his thoughts on urinary mercury as a biomarker for maternal mercury levels. Dr. Yokel presented his consultation and

was questioned on the immunotoxicology data, the possible biomarkers, and studies of mercury toxicity in the brain. Dr. Farland presented his consultation and his professional experience in calculating the EPA RfC. Dr. Farland stated that the RfC will always be a subject of debate due to the uncertainty factors. He was questioned on the data concerning the population 0 to 6 years of age. He was asked if it would be appropriate to use a benchmark dose. He responded that it would be helpful for the FDA to consider other risk assessment tools like bench mark dose.

The guest speaker, Dr. Michael Martin presented his work on the Casa Pia clinical studies and responded to the critique of the Casa Pia Study of the Health Effects of Dental Amalgam in Children as presented in Mercury Exposure and Risks from Dental Amalgam of Dr. Richardson and other open public presenters. Finally, Dr. G. Jean Harry of NIH/NIEHS summarized the presentations of the first day for the Panel members, highlighted key issues they might consider in deliberations and focused the Panel towards the questions that will be asked to the Panel.

The second day opened with a two hour open public hearing, which included personal stories, professional opinions and professional associations' positions towards dental amalgams. A brief recap from the FDA was also given to focus the panel on FDA's questions to the Panel members. Drs. Susan Griffin and Mike Dourson on the panel provided background for other panel members on the key concepts and terminology in risk assessment.

The Panel deliberated on the FDA questions to close the meeting. They commented on the exposure to mercury from dental amalgam according to body type, gender, age, inhalation parameters and subsets of the population. The Panel discussed the long term effects of pregnancy and fetal exposure, genetics and tried to develop a method of assessing risk through a simple scientific model rather than a pharmacokinetic model. Panel members believed any such model should use inhalation parameters, body mass, and number of fillings and surface area. Some members cautioned on the complexity of developing such a model.

The Panel suggested that the methods and data from the newer studies should be reviewed to dictate appropriate Uncertainty Factors (UFs) and Reference Exposure Levels (RELs) as well as genomic information. A risk assessment should be drawn up for patients to read and understand in lay language. The Panel agreed that urinary biomarkers have limitations, but are the best biomarkers to measure exposure to mercury from dental amalgam currently available.

The Panel deliberated on the human clinical studies and whether those studies suggest a relationship between dental amalgam and adverse health effects including young children (less than 6) and pregnant woman. Panel members noted the importance of considering not only the risks, but also the benefits of amalgam, including that that it is better for multiple surface restorations and appears to have a longer life than current composite fillings. The panel acknowledged the limitations of the clinical trials and stated that, in some cases, the study designs were biased to the null hypothesis. The Panel suggested that the FDA should do a meta analysis of all relevant amalgam studies, including the most recent, to allow assessment of the RfC. Panel members noted such a meta analysis should rely on the raw data from previous studies. The Panel also suggested that FDA review the literature and develop its own reference exposure level (REL) for elemental mercury vapor, acknowledging that the EPA RfC needs to be updated with the latest studies.

The Panel noted a likely susceptible subpopulation that is prone to adverse health effects after receiving amalgams, but noted also that this population could not be easily pre-identified at this time. Panel members discussed the need to consider socio-economic factors in clinical studies. Several members referred to a recent study showing a correlation between number of amalgams and hearing loss in adult women, Panelists recommended an evaluation of the immunological response to mercury by measuring lymphocytes. Panelists agreed that gaps exist in the current clinical data and the data may not have addressed the most appropriate endpoints, which would relate to neurotoxicity. Several panelists offered suggestions for enhancing sources, including registries and partnering with other Federal agencies, to analyze available data.

Panelists suggested several changes to the discussion of the clinical evidence in the current instructions for use for dental amalgam. Suggested labeling changes include the addition of warnings for young children, pregnant women and metal allergies, and clearer reference to limitations in the current data. Some Panel members discussed the importance and necessity of providing informed consent and the presentation of alternatives as part of the dentist-patient relationship.

The Panel concurred that it is hard to separate the risk assessment from the clinical studies. Most members believed current studies and reanalysis of earlier studies should inform FDA's risk assessment. Further, the Panel discussed alternative composite options to use in patients, but pointed out that these alternative options may carry their own risks and data on such alternatives is limited.

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