



July 7, 2017

Lyn Redwood, R.N., M.S.M.
Executive Director
World Mercury Project
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Dear Ms. Redwood,

We are writing in follow-up to the meeting between the Food and Drug Administration (FDA) and representatives from the World Mercury Project regarding the use of thimerosal in vaccines and other prescription medications. Ensuring the safety and effectiveness of vaccines for the United States is one of FDA's top priorities.

Vaccines have contributed to a significant reduction of disease in the United States and globally. Some vaccine-preventable infectious diseases are no longer common, while thanks to a vigorous vaccine program, others such as smallpox and polio have been eradicated entirely from the United States. Most viruses and bacteria that cause vaccine-preventable diseases and death still exist, however, and can cause disease in people who are not protected by vaccines.

The Public Health Service Act (PHSA), 42 U.S.C. §§ 201, *et seq.*, authorizes FDA to license vaccines and other biological products if they have been demonstrated to be "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). In order to receive a license, an applicant must submit, among other things, data derived from clinical and laboratory studies showing the product's safety, purity, and potency; a full description of manufacturing methods; data establishing the product's stability through the dating period; and a representative sample of the product (21 CFR 601.2(a)). Similarly, before approving a non-biologic drug, FDA must determine, based on its review of clinical trial and other data submitted by the product's sponsor, that the drug is safe and effective for its intended uses. 21 U.S.C. § 355(b); 21 CFR Part 314.

FDA biologics regulations define safety as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." 21 CFR 600.3(p). In applying this regulatory standard, FDA must weigh the risk of a vaccine - indeed, the risk of any drug - against its benefits when determining whether the product is safe. If the benefits of the vaccine or other pharmaceutical product outweigh the risk of its side effects, then FDA finds the product to be safe. Applying that relative standard for safety is critical to the public health because virtually every vaccine - and every drug, for that matter - carries the risk of some side effects. Thus, the determination of a product's safety is a relative rather than an absolute measurement, and FDA's judgment as to what is required to ascertain the safety of a product is within the agency's discretion and expertise.

In making a determination about the safety of preservatives, the agency evaluates whether a preservative contained in a biological product is at such levels that the finished product itself, when used at the recommended dose, is not toxic to the recipient. FDA has applied sound scientific judgment in evaluating the products at issue and has repeatedly found that the vaccines currently being marketed that contain thimerosal as a preservative are safe within the meaning of the PHSA, the Federal Food, Drug and Cosmetic Act (FDCA), and their implementing regulations.

All vaccines licensed by FDA for use in the United States have been demonstrated to be safe and effective; including those that contain thimerosal, a mercury-containing preservative.

Thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines, with no ill effects other than occasional hypersensitivity and minor local reactions at the site of injection.

FDA has actively addressed the issue of thimerosal as a preservative in vaccines. The use of thimerosal as a preservative in U.S. FDA-licensed vaccines has significantly declined due to reformulation and development of new vaccines presented in single-dose containers. Under the FDA Modernization Act (FDAMA) of 1997, the FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines. Conducted in 1999, this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions (Ball et al. 2001).

As part of the FDAMA review, FDA evaluated the amount of mercury an infant might receive in the form of ethylmercury from vaccines under the U.S. recommended childhood immunization schedule and compared these levels with existing guidelines for exposure to methylmercury, as there are no existing guidelines for ethylmercury, the metabolite of thimerosal. At the time of this review in 1999, the maximum cumulative exposure to mercury from vaccines in the recommended childhood immunization schedule was within acceptable limits for the methylmercury exposure guidelines set by FDA, the Agency for Toxic Substances and Disease Registry, and the World Health Organization. However, depending on the vaccine formulations used and the weight of the infant, some infants could have been exposed to cumulative levels of mercury during the first six months of life that exceeded Environmental Protection Agency (EPA) recommended guidelines for safe intake of methylmercury.

Other than allergic responses in some individuals, there was no known health risk from thimerosal-preservative at the concentration used in vaccines, but in 1999, the Public Health Service (including FDA, National Institutes of Health (NIH), CDC, and Health Resources and Services Administration (HRSA)), along with the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) concluded that because of scientific uncertainty at the time, as a precautionary measure, that it was prudent to reduce childhood exposure to mercury from all sources, including vaccines, as feasible. On July 1, 1999, FDA sent a letter to all licensed manufacturers of vaccines requesting their plans to remove thimerosal from U.S. licensed vaccines. This step was taken because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of mercury are challenging to eliminate.

In 2014, Mitkus et al, because of continued concerns by some that exposure to thimerosal preservative in vaccines may pose a risk to infants, estimated the body burden of mercury

following exposures to ethylmercury (EtHg), from inactivated influenza vaccines and compared those levels to the body burden of mercury following daily exposure to dietary levels of methylmercury (MeHg) that are considered to be safe by the United States Environmental Protection Agency (USEPA). Body burdens were estimated using kinetic parameters derived from experiments conducted in infant monkeys that were exposed to either EtHg or MeHg at equivalent doses. It was found that the time-integrated body burden of mercury over the first 4.5 years of life following daily ingestion of safe levels of MeHg was approximately two orders of magnitude higher than that estimated for yearly exposures of infants to thimerosal (EtHg) from inactivated influenza vaccines supplied in multi-dose vials. In addition, peak body burdens of mercury following episodic exposures to thimerosal in this worst-case did not exceed the corresponding safe body burden of mercury from MeHg at any time.

Although all vaccines routinely recommended for children 6 years of age and younger in the U.S. are available in formulations that do not contain thimerosal, thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines, with no ill effects established other than hypersensitivity and minor local reactions at the site of injection (Ball et al, 2001).

There is a robust body of peer-reviewed, scientific studies conducted in the United States and countries around the world that support the safety of thimerosal-containing vaccines. The scientific evidence collected over the past 15 years does not show any evidence of harm, including serious neurodevelopmental disorders, from use of thimerosal in vaccines. Specifically, the Institute of Medicine (now known as the National Academy of Medicine), and others have concluded that the evidence favors rejection of a link between thimerosal and autism. Scientific studies of the risk of other serious neurodevelopmental disorders have failed to support a causal link with thimerosal summarized as follows:

A number of epidemiological studies independently conducted by different investigators using various designs in different samples and countries, (e.g., Sweden, Denmark, United States, United Kingdom and Canada), all have consistently provided evidence of no association between thimerosal-containing vaccines and autism, despite the fact that different methods were used and different populations were examined.¹ With the exception of the study performed by Fombonne, et al., and reported in 2006, these studies were reviewed in 2004 by the IOM, which concluded that they consistently provided evidence of no association between thimerosal-containing vaccines and autism.² Fombonne and colleagues estimated the prevalence of pervasive developmental disorder in Montreal, Canada in cohorts born from 1987 to 1998 and evaluated the relationship of trends in prevalence rates with changes in cumulative exposure to

¹ Andrews, N., et al., Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association. *Pediatrics* 2004;114:584-591; Stehr-Green, P., et al., Autism and Thimerosal-Containing Vaccines Lack of Consistent Evidence for an Association. *Am. J. Prev. Med.* 2003;25(2), 101-106; Madsen, et al., Thimerosal and the Occurrence of Autism: Negative ecological evidence from Danish population based data. *Pediatrics* 2003; 112; 604-606; Hviid, A., et al., Association Between Thimerosal-Containing Vaccine and Autism. *JAMA* 2003;290;13 1763-6; Fombonne, E., et al., Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations. *Pediatrics* 2006;118:e139-e150.

² IOM. Immunization Safety Review: Vaccines and Autism. Washington, D.C.: National Academy Press: 2004 (Executive Summary, at 4).

ethylmercury resulting from changes in the childhood immunization schedule. Exposure to ethylmercury in some birth cohorts studied reached levels as high as those attained in the US immunization schedule in the 1990s. The prevalence of pervasive developmental disorder in thimerosal-free birth cohorts was significantly higher than that in thimerosal-exposed cohorts. Using logistic regression models of the prevalence data, the authors found no significant effect of thimerosal exposure. The authors concluded that thimerosal exposure was unrelated to the increasing trend in pervasive developmental disorder prevalence.

In addition, a study by Schechter, et al., (2008), evaluated whether reduced exposure to thimerosal has been associated with a decrease in reported autism.³ The researchers analyzed the California Department of Developmental Services (DDS) data to estimate time trends in the prevalence of autism in children reported in California. The authors “found that the prevalence of autism for children reported to the DDS has continued to increase consistently for children born from 1989 through 2003, inclusive of the period when exposure to thimerosal containing vaccines declined. Moreover, since 2004, the absolute increase and the rate of increase in DDS clients aged 3-5 years with autism were higher than those in DDS clients of the same ages with any eligible condition, including autism.” (Schechter, et al. 2008). In addition, the authors state that “[t]hese time trends are inconsistent with the hypothesis that thimerosal exposure is a primary cause of autism in California.” *Id.* These findings are consistent with other recent findings, e.g., Fombonne, et al. (2006).

Not only is there increasing and consistent compelling clinical evidence for a lack of association between thimerosal-containing vaccines and autism (Parker, et al. 2004; IOM Report 2004), in addition, a study published by Thompson, et al. (2007), does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and neuropsychological functioning in children aged 7 to 10 years old.⁴ The study evaluated a total of 42 neuropsychological outcomes, including speech and language skills, executive functioning/attention, fine motor coordination, perceptual organization, motor tics, academic functioning, intellectual functioning, and ADHD (attention deficit hyperactivity disorder) symptomatology. The study was designed and interpreted with extensive input from independent outside consultants and the data set is publicly available. The study enrolled 1047 children between the age of 7 and 10 years (born 1993-1997) who had received thimerosal preservative-containing vaccines and evaluated a possible association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period, and the first 7 months of life. The investigators concluded that their “study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the ages of 7 to 10 years.” (Thompson, et al., 2007). The few statistically significant associations that were detected were equally divided among better and poorer outcomes and may have been by chance findings due to the large number of statistical tests performed. According to the authors, one finding related to motor and phonic tics in boys may suggest that further study assessment is warranted.

³ Schechter, R., et al., Continuing Increases in Autism Reported to California’s Developmental Services System. *Arch Gen Psychiatry*. 2008; 65(1):19-24.

⁴ Thompson, WW., et al., Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years. *N. Engl. J. Med* 2007;357;1281-92.

In summary, the studies by Fombonne, et al. (2006), Thompson, et al. (2007), and Schechter, et al. (2008), all provide further support that thimerosal exposure of children from vaccines is not associated with neurodevelopmental disorders, including autism.

Of note these findings were discounted by some because, in their view, the studies “appear to have been designed not to find evidence of an association between the amount of thimerosal injected and the adverse outcomes observed.” However, the epidemiological studies cited above are accepted as valid by recognized scientific bodies and scientists and, despite some limitations, were generally well-designed and appropriately analyzed. In addition, the investigators of these studies have addressed methodological limitations in the discussion of their findings and considered any limitations in their overall interpretation of data. Thus, despite the fact that different methods were used and different populations were examined, the consistency of the findings observed from the epidemiological studies cited provide compelling evidence that there is no association between the administration of thimerosal-containing vaccines and the development of autism.

Thank you for contacting us. If we may be of further assistance, please let us know.

Sincerely,

A handwritten signature in black ink that reads "Peter Marks". The signature is fluid and cursive, with the first and last names being clearly legible.

Peter Marks, M.D., Ph.D.

Director

Center for Biologics Evaluation and Research

cc Mr. Robert Kennedy

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