



JUN 18 2003

The Honorable Dave Weldon
House of Representatives
Washington, D.C. 20515-3807

Dear Mr. Weldon:

Thank you for the letter of March 12, 2003, regarding thimerosal in vaccines. In your letter, you raise important questions about thimerosal use in licensed pediatric vaccines. This letter contains minor corrections in response to your questions and replaces our original response of June 17, 2003.

Background

In a recent review, the National Academy of Sciences' Institute of Medicine¹ concluded that the evidence "is inadequate to accept or reject a causal relationship between thimerosal exposures from childhood vaccines and the neurodevelopmental disorder of autism, attention deficit hyperactivity disorder, and speech or language delay." The Food and Drug Administration (FDA or the Agency) does not have evidence to support a conclusion that there is an imminent or substantial hazard to the public health from vaccines that contain thimerosal as a preservative. However, FDA, together with other Public Health Service agencies, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians, supports the goal of reducing exposure to mercury from all sources. Reducing exposure to mercury from vaccines is achievable in the United States because it is possible to replace multi-dose vials with single-dose presentations, which do not require its use as a preservative. As noted below, very substantial progress has been made toward this goal.

The routinely recommended pediatric vaccines (namely, those recommended by the Advisory Committee on Immunization Practices) that are administered during the first two years of life are: hepatitis B vaccine, inactivated polio virus vaccine (IPV), the 7-valent pneumococcal conjugate vaccine, the Haemophilus influenza type b conjugate vaccine, the diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, the mumps, measles, and rubella vaccines, and the varicella vaccine. Since 2001, all of these routinely recommended pediatric vaccines for the U.S. market have been manufactured to be either thimerosal-free or contain only trace amounts of mercury (< 1 microgram per dose) from thimerosal as a residual from the manufacturing process. The influenza virus vaccine is not, at this time, a routinely recommended pediatric vaccine.

¹ *Immunization Safety Review: Thimerosal-containing Vaccines and Neurodevelopmental Disorders*, Stratton, K., Gable, A., and McCormick, M.C., Eds., National Academy Press, Washington, D.C., 20001

Package Inserts for Vaccines

The package inserts for a number of vaccines mention both preservative-free presentations and thimerosal preservative-containing presentations, even when thimerosal preservative-containing presentations are not available. Labels are updated for a variety of reasons including changes in use or indications/contraindications for the vaccine, clarifications about the use of the vaccine and the addition of newly uncovered adverse events. There are a number of updates that need to be made to these inserts, some of which are discussed later in this letter, and these updates are in progress. However, the label affixed to the package containing the particular vaccine presentation notes whether that particular product contains a preservative and, if so, how much.

For your information, the term "labeling" (see Section 201(m) of the Federal Food, Drug, and Cosmetic Act) refers generally to written and graphic matter that is upon the immediate container (e.g., the vial containing the vaccine), that is upon the box or package in which the container is packaged, as well as any other written or graphic material that accompanies the vaccine, including the package insert. The information that must accompany the product is described in detail in the Code of Federal Regulations [21 CFR, Parts 201 and 610, Subpart G]. The "label" refers to the written or graphic matter that is placed on the immediate container (the container label) or the box in which that container is placed (the package label); the "package insert" is the written and graphic material that accompanies the vaccine and which, *inter alia*, describes the vaccine, its indications and contraindications, the clinical studies that were carried out in support of the vaccine license, instructions for use of the vaccine, and ways in which the vaccine is supplied.

Detailed information on individual vaccines is as follows:

HibTITER: The 2003 Physician's Desk Reference (PDR) reference to HibTITER (Wyeth's *Haemophilus influenzae* type b conjugate vaccine) mentions a thimerosal preservative-containing, multi-dose vial (10 dose vial). However, the only presentation of this vaccine that is now marketed in the U.S. is the single dose presentation that does not contain thimerosal. We have checked with the manufacturer of this vaccine (Wyeth) and they have stated that the last date of shipment of the 10-dose, thimerosal preservative-containing presentation for the U.S. market was August 2000 (with an expiration date of November 2001). The package insert for HibTITER notes that multi-dose vials contain thimerosal (1:10,000) as a preservative. According to Wyeth, the multi-dose presentation is no longer being marketed anywhere in the world, therefore, reference to this presentation can be changed in the package insert.

Tripedia: Similarly, for Tripedia (the Aventis Pasteur DTaP vaccine), only single dose presentations are being marketed in the U.S. The "How Supplied" section of the label notes:

1. *Vial, 1 dose (contains NO preservative) (10 per package) – Product No. 49281-298-10*
2. *Vial, 15 dose (contains preservative)(7.5 mL) – Product No. 49281-288-15*
3. *TriHIBit, Five 0.6 mL vials of Tripedia vaccine as diluent (contains NO preservative) packaged with Five 1 dose vials of lyophilized ActHIB (contains NO preservative). Administer vaccine immediately (within 30 minutes) after reconstitution – Product No. 49281-597-05*

Although the package insert does mention a thimerosal preservative-containing, multidosage presentation, Aventis Pasteur has stated that it did not distribute this presentation after FDA approved the preservative-free Tripedia formulation in March 2001. According to Aventis Pasteur, the final lots of Tripedia containing thimerosal as a preservative that were released in the U.S. market had expiration dates in 2002.

Recombivax HB: Although the package insert for Recombivax HB (Merck's hepatitis B vaccine) does refer to several thimerosal preservative-containing presentations (in this case both multi-dose and single-dose presentations), the pediatric/adolescent formulation is currently marketed in the U.S. only in the single-dose, thimerosal-free presentation. According to the manufacturer, the last date of shipment of thimerosal-containing pediatric/adolescent formulation of hepatitis B vaccines from Merck was October 1, 2001, for the pre-filled syringe lots (March 2002 and November 2002 expiration dates) and June 26, 2000, for the single-dose vial lots (with May 2002, August 2002, and September 2002 expiration dates). Merck has noted that the pre-filled syringe presentation that was distributed on October 1, 2001, was intended for school-based clinics (not infant use). Merck's hepatitis B adult vaccine formulation continues to be marketed both with and without thimerosal as a preservative.

Diphtheria and Tetanus Toxoids: The pediatric formulation of Diphtheria and Tetanus Toxoids (the DT vaccine), which is not one of the routinely recommended pediatric vaccines, is available from Aventis Pasteur. It is available as a preservative-free presentation, containing only trace levels of thimerosal (< 1 microgram of mercury from thimerosal per dose), but a thimerosal preservative-containing presentation is also available. Aventis Pasteur is now the only supplier of this vaccine to the U.S. We do not know why Aventis Pasteur has chosen not to publish the package insert for this vaccine in the PDR. Please note that not all manufacturers publish all their products in the PDR.

Tetanus and Diphtheria: The adult formulation of Tetanus and Diphtheria (Td) vaccine, which is indicated for individuals 7 years of age and older, as reflected in the PDR, is correct. At this time, only the thimerosal preservative-containing formulation of this vaccine is available.

Influenza Vaccines (FluShield, Fluvirin and Fluzone): The influenza virus vaccine is not a routinely recommended pediatric vaccine (it is recommended annually for select populations), although the Advisory Committee on Immunization Practices encourages its use for all infants 6 months of age or greater. With the departure of Parkedale and, more recently, the announced departure of Wyeth (the manufacturer of FluShield) as manufacturers of influenza virus vaccines, there will be two U.S.-licensed manufacturers of influenza virus vaccine, namely, Evans and Aventis Pasteur. Of these, only the vaccine from Aventis Pasteur (Fluzone) is licensed for use in children 6 months to 3 years of age. The vaccine from Evans (Fluvirin) is not licensed for infants and children younger than 4 years of age. Fluvirin is available in preservative-free (containing less than 1 microgram of mercury per dose) and preservative-containing formulations. The pediatric (6 months to 35 months of age) dose of Fluzone is 0.25 mL; the 0.25 mL pre-filled syringe is only available preservative-free (containing only trace amounts of residual thimerosal, resulting in less than 1 microgram of

mercury per dose in the vaccine). For persons 3 or more years of age, the dose is 0.5 mL, which is available either as a preservative free (0.5 mL pre-filled syringe) or a preservative containing (0.5 mL pre-filled syringe and multi-dose vial) presentation.

FDA approved the license supplement for the preservative-free presentation of Fluzone in September 2002. The preservative-free presentations are not noted in the package insert that is published in the 2003 PDR. We do not know why Aventis Pasteur did not publish the most current version of the package insert, which reflects the preservative-free presentations. The most current package insert, under the "How Supplied" section states:

1. *Syringe with 1" needle, 0.25 mL (10 per package)(contains NO preservative) Shake syringe well before administering. -- Product No. 49281-369-25*
2. *Syringe with 1" needle, 0.5 mL (10 per package)(contains NO preservative) Shake syringe well before administering. -- Product No. 49281-369-50*
3. *Syringe with 1" needle, 0.5 mL (10 per package)(contains preservative) Shake syringe well before administering. -- Product No. 49281-370-11*
4. *Vial, 5 mL, for administration with needle and syringe (contains preservative) Shake vial well before withdrawing each dose. -- Product No. 49281-370-15*

Some single-dose presentations of Fluzone contain thimerosal as a preservative. Thimerosal is added to the influenza vaccine during the manufacturing process. It is subsequently removed for some of the single-dose presentations. This manufacturing step results in a loss of vaccine and consequently lowers the number of available doses of vaccine. It remains in other, single-dose presentations, where those presentations are marketed for convenience of administration, rather than specifically for reduction of thimerosal.

Other Issues

In your letter, you asked if mercury-containing presentations of each of six vaccines (Tripedia, Recombivax HB, HibTITER, FluShield, Fluzone, and Td) were still being produced, distributed, or sold for use in the adult population. In addition to the above response for Recombivax HB, FluShield, Fluzone, and Td, we note that Tripedia and HibTITER are pediatric vaccines; they are not indicated for use in adults.

In your letter, you ask what steps FDA, the Centers for Disease Control and Prevention (CDC), AAP, and the Environmental Protection Agency (EPA) have taken to ensure that no child or adult receives more than the EPA maximum permissible dose for the oral ingestion of methylmercury (0.1 µg/Kg/day) from ethylmercury that is present in thimerosal preservative-containing vaccines. First, it is essential to note that the EPA's reference dose (RfD) of 0.1 µg/Kg/day is not the maximum permissible dose but rather "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."²

² EPA Mercury Study Report to Congress Vol. 5: Health Effects of Mercury and Mercury Compounds: page D-1 (December 1997)

Secondly, FDA has taken many steps in this area, including working with manufacturers to remove or reduce thimerosal from pediatric and other vaccines. As a result of these actions, all of the routinely recommended pediatric vaccines are now manufactured as thimerosal-free or thimerosal-reduced (containing less than 1 µg of mercury per dose) presentations. Moreover, both of the influenza vaccine manufacturers now offer thimerosal-reduced presentations (containing less than 1 µg of mercury per dose), although thimerosal preservative-containing presentations are also available. The Agency has licensed Aventis Pasteur for a thimerosal-reduced (containing less than 1 µg of mercury per dose) presentation of their DT vaccine. FDA continues to work with the vaccine manufacturers to make additional thimerosal-free or thimerosal-reduced vaccine presentations available to the public. Additionally, FDA continues to act in accord with the Public Health Service goal of "...reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate." CDC, AAP, and EPA are in the best position to describe their efforts.

You have asked if it is possible for a child in the U.S. today to get an exposure to 75 µg, 100 µg, or more of mercury in routine 2, 4, and 6 month well-baby visits. We believe that this is very unlikely. As we mentioned, Wyeth has told us that thimerosal preservative-containing HibTITER was last released in August 2000 and had an expiration date of November 2001. Thus, thimerosal preservative-containing HibTITER should no longer be available. According to the manufacturers, the final lots of thimerosal preservative-containing pediatric formulations of hepatitis B vaccine (both Recombivax HB and Engerix B) that were released to the U.S. market had expiration dates in 2002. Thus, thimerosal preservative-containing pediatric formulations of hepatitis B vaccine should no longer be available. Aventis Pasteur has indicated that it did not distribute any Tripedia containing thimerosal as a preservative after its preservative-free formulation was approved in March 2001. The final lots of Aventis Pasteur's Tripedia containing thimerosal as a preservative that were released in the U.S. market had expiration dates in 2002. Thus Tripedia containing preservative is no longer available. Based on the information available to us at this time, we do not believe a child born today could receive 300 µg of mercury during the first six years of life from the childhood vaccines, including possible influenza vaccines each year.

You ask whether the thimerosal preservative-containing presentations are still licensed in the U.S., and if so, when FDA plans to remove these licenses. The thimerosal-preservative containing presentations are all still licensed in the U.S. FDA does not believe that there is a basis for revoking these licenses at this time. There is insufficient scientific data to justify a voluntary or mandatory recall of vaccines containing thimerosal within prescribed limits. A mandatory recall requires that the product present "an imminent or substantial hazard to the public health" (§351(d)(1) of the Public Health Service Act, 42 U.S.C. 262(d)(1)). FDA may request a voluntary recall when a marketed product is in violation of any FDA law or regulation and presents a risk of injury; voluntary recall requests are reserved for urgent situations (21 CFR § 7.40(b)). Current scientific data and information do not establish that products containing thimerosal within prescribed limits as a preservative create an imminent or substantial hazard to public health or are in violation of FDA laws or regulations.

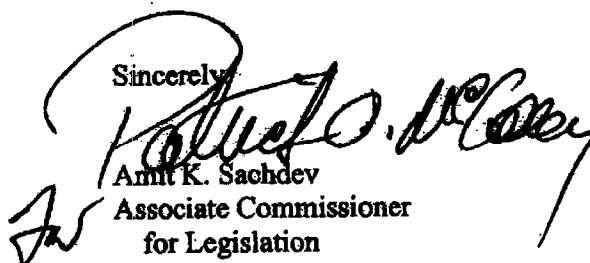
Additional Comments

You indicate that physicians have informed you that "thimerosal is still a component in its full concentration" for certain vaccines. If physicians are currently able to purchase the routinely recommended pediatric vaccines in thimerosal containing presentations (as a preservative), we would appreciate hearing from them. FDA is unaware of a manufacturer supplying such a product.

With regard to your question about the oral uptake of mercury, various studies have indicated that the systemic uptake of ingested organomercurials, such as methyl-mercury, is very high. There is little, if any difference between the systemic levels whether the organomercurial is ingested orally or administered parenterally.

Thank you for contacting us concerning this matter. Please let us know if you have further questions.

Sincerely,


Amit K. Sachdev
Associate Commissioner
for Legislation