DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

July 27, 2005

Kathryn M. Williams
Co-founder and Vice-President
National Vaccine Information Center
421-E Church Street
Vienna, Virginia 22180

Re: Docket No. 2002P-0025/CP1

Dear Ms. Williams:

This letter is in response to your citizen petition dated December 18, 2001, in which you asked the Secretary of Health and Human Services and the Commissioner of the Food and Drug Administration (FDA) to order the immediate suspension and expedited revocation of all vaccines containing thimerosal for which there is a thimerosal-free replacement available. We apologize for the delay in responding to the petition. After review and consideration, we deny the petition, for the reasons stated below.

Thimerosal Content of Routinely Recommended Pediatric Vaccines

FDA recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has been working with manufacturers for several years to facilitate the development of new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines.[1]

Under the Food and Drug Administration 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.[2] However, as a precautionary measure, and 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 are challenging to eliminate, the Public Health Service

[1] Statement of Karen Midthun, M.D., Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services, before the Committee on Government Reform, United States House of Representatives, December 10, 2002.

[2] Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 2001; 1147-1154. The information you provide on pages 4 and 5 of your petition concerning FDA's advice on the use of OTC products and fish consumption is not relevant to the discussion of childhood vaccines because the mercury concentrations and amounts from these sources is much higher and the exposures are chronic. For more information, see http://www.fda.gov/cder/fdama/mercuryreport.htm and http://www.cfsan.fda.gov/~dms/admehg3.html.

(including the FDA, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA)) established the goal of removing as soon as possible thimerosal as a preservative from vaccines routinely administered to infants.

The agency's efforts have been successful. Since 2001, all vaccines routinely recommended for children 6 years of age and under (Diphtheria and Tetanus Toxoids and acellular Pertussis Vaccine (DTaP), hepatitis B, Haemophilus b conjugate (Hib), pneumococcal conjugate, Inactivated Polio Virus Vaccine (IPV), Measles, Mumps and Rubella Vaccine (MMR), and varicella)) manufactured for the U.S. market have contained no thimerosal or only trace amounts, with the exception of inactivated influenza vaccine, that was first recommended by the Advisory Committee on Immunization Practices in 2004 for routine use in children 6 to 23 months of age.

As to influenza vaccine (the only routinely-recommended pediatric vaccine that is still preserved with thimerosal), your petition states that the only vaccine licensed for influenza in the United States is made from killed influenza viruses, contains 1:10,000 thimerosal, and is licensed for children 6 months and older (Petition, p. 6). This information is no longer accurate.

FDA has approved preservative-free formulations (which contain either no or only trace amounts of thimerosal) for each of the two licensed inactivated influenza vaccines. These influenza vaccines continue to be marketed in both the preservative-free and thimerosal-preservative-containing formulations. Of the two licensed inactivated influenza vaccines, Sanofi Pasteur's Fluzone is approved for use in children down to 6 months of age. Last influenza season (2004-2005) Sanofi Pasteur had a capacity to manufacture only approximately 4 million doses of preservative-free influenza vaccine. Chiron's Fluvirin is approved for individuals 4 years of age and older; however, Chiron was not able to distribute vaccine in the United States for the 2004-2005 influenza season. The live attenuated influenza vaccine (FluMist, manufactured by MedImmune) contains no thimerosal, and is approved for individuals 5 to 49 years of age.

Based on an estimated annual birth cohort in the United States of 4 million, there are 6 million infants and children between the ages of 6 to 23 months, most of whom would need two doses each. The amount of thimerosal-preservative-free vaccine that is available based on current manufacturing capacity is well below the amount needed for this age group alone, let alone for the approximately 180 million Americans for whom the vaccine is recommended. FDA is in discussions with manufacturers of influenza vaccine regarding their capacity to increase the supply of thimerosal-preservative-free vaccine.

Prior to the initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 micrograms.[3] (Your petition notes this figure on page 4.) With the introduction of thimerosal-preservative-free formulations of DTaP, hepatitis B,

[3] Id.

and Hib, the maximum cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life. With the addition in 2004 of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age, and even in this case, the maximum exposure to mercury via routine childhood vaccinations would be 28 micrograms. This level is significantly below the Environmental Protection Agency calculated exposure guideline for methylmercury of 65 micrograms for a child in the fifth percentile body weight. (See Attachment A for an up-to-date table listing the thimerosal content of routinely recommended pediatric vaccines.)

You mention DT vaccine in your petition, a product that is generally given to a small group of children in place of DTaP in certain circumstances. However, there are no in-date thimerosal-preserved DT vaccines available in the United States at this time.

The goal of reducing mercury exposure from vaccines must be balanced against the goal of having enough vaccine available. If FDA now revoked the licenses for all thimerosal-containing vaccines as you request, many people would be in serious danger from the diseases that those vaccines prevent. That is true even where a thimerosal-free formulation of the vaccine exists because at this time manufacturers simply cannot produce enough of those formulations for all those who should be immunized. You have asked that thimerosal-containing vaccines "be delicensed and removed from the market immediately" because you believe that "[a]llowing Thimerosal-containing vaccines to remain in use, when Thimerosal-free versions are currently available, unnecessarily exposes American children to a heightened risk of serious adverse reactions." As discussed below, neither the evidence that you submitted with your petition nor the extensive evidence on the safety of thimerosal-containing vaccines that FDA has reviewed over the years supports that conclusion or contradicts FDA's determination that licensed vaccines containing thimerosal are safe.

What it Means for FDA to Find a Vaccine Safe

Safety is relative, rather than absolute. FDA 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 Code of Federal Regulations 600.3(p)). If the benefit of the vaccine outweighs the risk of the side effects, then FDA finds the vaccine 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. In applying the regulatory standards, FDA must weigh a vaccine's risks against its benefits when determining whether the vaccine is safe.

The Risks and Benefits of Vaccines Containing 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. Nevertheless, some people have raised concerns about the use of thimerosal in vaccines, and in particular about potential adverse effects of the cumulative amount of mercury that might be administered to a child as a result of routine childhood immunization. These concerns were based on the public's increased awareness of a theoretical potential for neurotoxicity of mercury in vaccines, including new vaccines added to the infant immunization schedule in the 1990's,[4, 5] a number of which contained thimerosal as a preservative.

In 2001, the Institute of Medicine's Immunization Safety Review Committee issued a report based on a review of available data, concluding that the evidence was inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder, and speech or language delay. The Committee stated that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible."[6] The IOM issued a follow-up report on May 17, 2004, concluding that the body of epidemiological evidence favors rejection of a causal relationship between the thimerosal-containing vaccines and autism. That report was based on the IOM's extensive review of the epidemiological studies performed after it issued the 2001 report. The IOM explained its conclusions as follows:

> Epidemiological studies examining thimerosal-containing vaccines and autism, including three controlled observational studies (Hviid et al., 2003; Miller, 2004; Verstraeten et al., 2003) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003), consistently provided evidence of no association between thimerosal-containing vaccines and autism, despite the fact that these studies utilized different methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom). Other studies reported findings of an association. These include two ecological studies (Geier and Geier, 2003a; 2004a), three studies using passive reporting data (Geier and Geier, 2003a,b,d), one unpublished study using Vaccine Safety Datalink (VSD) data (Geier and Geier, 2004b,c), and one unpublished uncontrolled study (Blaxill, 2001). However, the studies by Geier and Geier cited above have serious methodological flaws and their analytic methods were nontransparent making their results uninterpretable, and therefore non-contributory with respect to causality (see text for full discussion). The study by Blaxill is uninformative with respect to causality because of its methodological limitations. Thus, based on this body of evidence, **the committee concludes that the evidence favors**

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[4] Thimerosal in Vaccines, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, http://www.fda.gov/cber/vaccine/thimerosal.htm.

[5] IOM (Institute of Medicine). Thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press; 2001.

[6] IOM (Institute of Medicine). Immunization Safety Review: Vaccines and Autism. Washington, D.C.: National Academy Press: 2004 (Executive Summary, at 4) (emphasis in original).

rejection of a causal relationship between thimerosal-containing vaccines and autism.[7]

The committee also examined research on hypothesized biological mechanisms for vaccine-induced autism. That information, however, is still at a basic research level, and consequently, the committee concluded that the hypothesized biological mechanisms that have been considered thus far are theoretical only.[8]

On the other hand, it is well established that vaccines have widespread benefits, preventing diseases that are frequently fatal. As to influenza, for example, recent analyses estimate an average of 36,000 annual deaths from influenza during the 1990s and an average number of hospitalizations between 114,000 and 200,000, with rates highest among those under 23 months of age and those over 65 years of age.[9] During the 2003-2004 influenza season, several states had reported by December 2003 severe complications and deaths related to influenza in children.[10] Because some of these deaths were in children under 23 months of age, we believe the actual benefit of preventing complications and death from infection with influenza using a thimerosal-containing vaccine outweighs its theoretical risk of causing autism.

On page 7 of your petition you stated that CDC's Advisory Committee on Immunization Practices (ACIP) would issue a recommendation in January 2002 to remove all thimerosal-containing vaccines from the shelves by March 31, 2002. In fact, the ACIP never issued such a recommendation. The ACIP's website states: "Because of the known risks of severe illness from influenza infection and the benefits of vaccination, and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the theoretical risk, if any, from thimerosal."[11] Thus, the ACIP does not express a preference that children receive thimerosal-reduced or thimerosal-free influenza vaccine rather than the standard preservative formulation, even if it is available.

Your petition extends to all vaccines, not just those used in infants and children. Generally, concern about thimerosal in vaccines has focused on infants and children because of the number of vaccines they receive, the size of their bodies, and their developmental status. Standard recommendations for adults lead to far fewer vaccinations, and correspondingly lower mercury exposure; moreover, because adult bodies are larger and no longer developing, any potential risks of thimerosal would be considerably reduced. In addition, adults are not at risk for developing autism.

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[7] Id., at 6-7 (footnote omitted).
[8] Id., at 1-20.
[9] Plotkin, Stanley A. et al., Vaccines, 4th Edition (2004).
[10] MMWR, Centers for Disease Control and Prevention, December 12, 2003, Vol.52, No. 49, 1197-1202.
[11] Prevention and Control of Influenza: Recommendations and Reports, CDC's Advisory Committee on Immunization Practices (ACIP), April 25, 2003. Available: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5208a1.htm (emphasis added).

However, FDA supports the development of adult vaccines in thimerosal-preservative-free formulations and has been encouraging the reduction or removal of thimerosal from all existing vaccines. As with pediatric vaccines, these efforts have succeeded in reducing mercury exposure from thimerosal in these vaccines. For example, the adult vaccines Hepatitis B and Td (tetanus diphtheria) are now also available in thimerosal-free versions. A complete list of thimerosal-preservative-free or thimerosal reduced adult vaccines is posted at http://www.fda.gov/cber/vaccine/thimerosal.htm#t1.

Actions Requested and Agency Conclusion

Petitioners request the suspension and expedited revocation of all vaccines containing thimerosal for which there is an existing thimerosal-free formulation. Such action would require FDA to suspend or revoke existing biologics licenses.

All routinely recommended vaccines for children 6 years of age or less, except for the influenza vaccine, currently do not contain thimerosal or contain only trace amounts of thimerosal. Moreover, prior formulations of those vaccines that were preserved with thimerosal are no longer available because their expiration dates have passed and those formulations are no longer manufactured. Therefore, none of the routinely recommended vaccines for children 6 years of age or less, except for the influenza vaccine, is within the scope of your revocation and suspension request.

As to influenza vaccines, even though thimerosal-preservative-free formulations exist, manufacturers cannot currently manufacture enough doses of thimerosal-preservative-free vaccine for all those who need it. FDA is in discussions with manufacturers of influenza vaccine regarding their capacity to increase the supply of thimerosal-preservative-free vaccine. As discussed above, influenza carries known, life-threatening risks, while the existing evidence does not support the conclusion that licensed influenza vaccines cause any serious adverse reactions related to their thimerosal content. Similarly, the available evidence supports the conclusion that all other currently licensed vaccines containing thimerosal are safe.

For these reasons, we deny the petition.

Sincerely,

Jeffrey Shuren, M.D., J.D.
Assistant Commissioner for Policy

cc: Division of Dockets Management (HFA-305)

Attachment A. From Thimerosal in Vaccines:

Table 1. Thimerosal Content of Vaccines Routinely Recommended for Children 6 Years of Age and Younger

Vaccine	**Tradename (Manufacturer)***	**Thimerosal Status Concentration**(Mercury)**	**Approval Date for Thimerosal Free or Thimerosal/Preservative Free (Trace Thimerosal)***Formulation**
DTaP	Infanrix (GSK	Free	Never contained Thimerosal
	Daptacel (AP)	Free	Never contained Thimerosal
	Tripedia (AP)	Trace (≤0.3 μg Hg/0.5mL dose)	03/07/01
DTaP-HepB-IPV	Pediarix (GSK)	Trace (<0.0125 μg Hg/0.5mL dose)	Never contained more than a Trace of Thimerosal
Pneumococcal Conjugate	Prevnar (WL)	Free	Never contained Thimerosal
Inactivated Poliovirus	IPOL (AP)	Free	Never contained Thimerosal
Varicella (chicken pox)	Varivax (M)	Free	Never contained Thimerosal
Mumps, measles, and rubella	M-M-R-II (M)	Free	Never contained Thimerosal
Hepatitis B	Recombivax HB (M)	Free	08/27/99
	Energix B (GSK)	Trace (<0.5 μg Hg/0.5mL dose)	03/28/00

Haemophilus influenzae type b conjugate (Hib)	ActHIB (AP)/OmniHIB (GSK)	Free	Never contained Thimerosal
	PedvaxHIB (M)	Free	08/99
	HibTITER, single dose (WL)[1]	Free	Never contained Thimerosal
Hib/Hepatitis B combination	Comvax (M)	Free	Never contained Thimerosal
Influenza	Fluzone (AP)	0.01% (12.5 µg Hg/0.25 mL dose, 25 µg Hg/0.5 mL dose)[2]	
	Fluzone (AP)[3] (no thimerosal)	Free	12/23/2004
	Fluvirin (Chiron/Evans)	0.1% (25 µg Hg/0.5 mL dose)	
	Fluvirin (Chiron/Evans) (Preservative Free)	Trace (<1 µg Hg/0.5mL dose)	09/28/01
Influenze, live	FluMist[4] (MedImmune)	Free	Never contained Thimerosal

* Manufacturer abbreviations:
GSK = GlaxoSmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck.
** Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50 µg of Hg per 1 mL dose or 25 µg of Hg per 0.5 mL dose.
*** The term "trace" has been taken in this context to mean 1 microgram of mercury per dose or less.
1 HibTITER was also manufactured in thimerosal-preservative containing multidose vials but these were no longer available after 2002.
2 Children 6 months old to less than 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL; children 3 years of age and older receive 0.5 mL.
3 A trace thimerosal containing formulation of Fluzone was approved on 9/14/02 and has been replaced with the formulation without thimerosal.
4 FluMist is not indicated for children less than 5 years of age.