DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

AUG 16 2000

Ms. Lyn Redwood
Coalition for SAFE MINDS
14 Commerce Drive, 3rd Floor
Cranford, NJ 07901

Dear Ms. Redwood:

This is in response to your letter of July 31, 2000, requesting an immediate recall of vaccines containing thimerosal. I am pleased to address the issues raised in your letter.

All vaccines licensed in the United States by the Food and Drug Administration (FDA) have been demonstrated to be safe and effective. Safety and efficacy data for all products are submitted to the FDA for review prior to licensure. Human clinical studies of experimental drugs and biologicals including vaccines are subject to the provisions of 21 CFR Part 312. In these studies, the sponsor seeks licensure of the complete product, not the individual components, as it is formulated for use. Such safety data would generally indicate any acute toxicity, whether from one ingredient or a combination of ingredients. Therefore, if thimerosal caused acute toxicity, the pre-market safety data would indicate acute toxicity, even if the association could not be confirmed. To date, the pre-market data have not shown acute toxicity in vaccines containing thimerosal. Because pre-market data typically do not include long-term safety data, FDA monitors post-marketing adverse event reports and subsequent clinical studies for long-term safety problems involving the product. There are no post-marketing long-term data that provide convincing evidence of significant safety problems with the long-term use of vaccines containing thimerosal.

A mandatory recall requires that a product present "an imminent or substantial hazard to the public health," §351(d)(1) of the Public Health Service Act (PHS Act), 42 U.S.C. 262(d)(1). A voluntary recall may be requested when a marketed product is in violation of any FDA law or regulation, and presents a risk of injury. Voluntary recall is reserved for urgent situations, §7.40 and 7.45. A market withdrawal involves a voluntary removal of product by a company for reasons that are not considered violations of the regulations. Since there are insufficient scientific data and information to establish that vaccines containing thimerosal within prescribed limits as a preservative creates an imminent or substantial hazard to public health or are in violation of FDA laws or regulations, a voluntary or mandatory recall of vaccines or other drugs containing thimerosal is not warranted.

FDA shares the concern for the apparent rising incidence of autism in the United States. The primary issue outlined in your letter is whether autism is caused by the thimerosal in vaccines. FDA does not believe that the scientific data, at this time, support this hypothesis. Under the FDA Modernization Act of 1997 requiring the

study of the "adverse effects on health of children and other sensitive populations from exposure to ... mercury" FDA's Center for Biologics Evaluation and Research conducted a review of the use of thimerosal in childhood vaccines. One component of this risk assessment was an exposure assessment for the U.S. recommended childhood immunization schedule based on thimerosal content in vaccines prior to licensure of thimerosal-free hepatitis B infant vaccines. FDA compared exposure levels of infants to ethylmercury from vaccines to existing guidelines for exposure to methylmercury, as there are no existing guidelines for safe exposure to ethylmercury, the metabolite of thimerosal.

While this review found no evidence of adverse effects caused by thimerosal in vaccines, except for minor local hypersensitivity reactions, the assessment determined that the use of thimerosal as a preservative in vaccines might result in the intake of mercury during the first six months of life that exceeded recommended guidelines from the Environmental Protection Agency. However, the recommended guidelines developed for methylmercury exposure from dietary exposures set by the FDA, the Agency for Toxic Substances and Disease Registry, and the World Health Organization were not exceeded. Of note, such guidelines contain as much as a 10-fold safety factor, and are meant as starting points for the evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur. It is important to recognize that such guidelines are meant to be starting points for evaluation of mercury exposure, and should not be viewed as absolute levels above which toxicity can be expected to occur. In their Mercury Study Report to Congress of December 1997, the EPA describes their reference dose, or RfD as follows:

> The RfD is a quantitative estimate of levels expected to be without effect even if exposure persists over a lifetime. It is not intended to be compared with isolated or one time exposures. Exceedance of the RfD does not mean that risk will be present. Acceptability of uncertain risks is a risk management decision. Risk management decisions may consider the RfD but will take into account exposures, other risk factors and non-risk factors as well.

It should also be recognized that the EPA guidelines were meant to be protective of the developing fetus. It is likely that EPA guidelines provide an even greater margin of safety for infants and small children than they do for fetuses.

Under FDA's exposure assessment, the total amount of mercury by weight was calculated for each vaccine in the infant schedule. Assessment of exposure to mercury from vaccines at 6 months of age was thought to be most relevant because the toxic effects of mercury could be cumulative in infancy, and most vaccines in the infant series are completed by that time. The agency guidelines were applied to a female infant at the lowest 5th, 50th and 95th percentile of weight between birth and 26 weeks, the period during which most infant vaccines are given. Depending on the particular vaccine formulation and schedule, an infant may have received a total mercury dose from thimerosal in vaccines of approximately 187.5 μg (or mcg) during the first 6 months of life. In special high risk populations, influenza vaccine

may have been administered at 6 months of age, increasing the total dose to approximately 200 μg. It was observed that some 6-month old infants may have received doses of mercury from vaccines in excess of EPA guidelines; however, guidelines established by other agencies, e.g., FDA, ATSDR, and WHO, would not have been exceeded. Exposure at 24 months of age was also assessed to capture exposures from booster doses administered in the 2nd year of life. By 24 months of age, the cumulative dose of mercury in vaccines does not exceed any established guidelines due to growth and increased weight of the older children. Thus, the exposure to mercury from currently available infant vaccines in the U.S. may have exceeded EPA guidelines after routine vaccines are administered during the first 6 months of age; however, EPA guidelines for mercury exposure at other assessed time points are not exceeded.

You state that there is an association between the increased incidence of autism over the past 70 years and the increase in the utilization of thimerosal-containing vaccines. This type of comparison is known as an ecological association. Ecological associations are generally not accepted as strong evidence of causality, because they do not link individual exposure to individual outcome, and can be subject to confounding by unknown or uncontrollable factors. There are many possible explanations for the apparent increase in the number of cases of autism over the past two decades. For example, numerous other influences that have changed over time may be linked to the increase in reported autism cases such as dietary and environmental factors. There has also been a broadening of the case definition to include less severe and more atypical presentations of autism, as well as an improved awareness of this disorder resulting in a greater number of cases being diagnosed. Further, it has been noted that some children with autism have high levels of mercury in hair, urine and blood. This observation cannot be interpreted without information on the levels of mercury in individuals without autism (i.e., case-control study). It also should be noted that thimerosal had been in use as a preservative in vaccines for at least 30 years prior to the apparent increase in rates of autism.

There have been no controlled studies of the relationship between thimerosal and autism, and those controlled trials that have been completed using thimerosal containing vaccines have not been conducted in a way that would allow an evaluation of the relationship between thimerosal and autism. There have been two retrospective cohort studies conducted recently by the CDC using data from two different health maintenance organization (HMO) databases. Results from these studies were presented at the CDC's Advisory Committee on Immunization Practices (ACIP) meeting on June 21, 2000. The first study did not show a statistically significant association between thimerosal exposure and autism. There were not enough cases of autism in the second database to study. There have been no case control studies of autism and thimerosal. Notwithstanding, FDA supports the continued efforts of the Department of Health and Human Services to fund studies to determine the causes and genesis of autism.

The Public Health Service, along with the American Academy of Pediatrics and the American Academy of Family Physicians, recently issued a joint statement on thimerosal and vaccines. The current joint statement reaffirmed the goal set last July to remove or greatly reduce thimerosal from vaccines as soon as possible. It also noted that "the risk of not vaccinating children on time with DTaP and Hib vaccine is believed to far outweigh the risk, if any, of exposure to thimerosal containing DTaP and Hib vaccines which are still available or still being produced."

The FDA's Office of Vaccines Research and Review (OVRR) has been encouraging manufacturers to develop new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines for several years. For example, the newly licensed pediatric vaccine against pneumococcal disease, Prevnar, does not contain thimerosal. With regard to the licensed vaccines, letters were sent by OVRR to manufacturers on July 1, 1999 and, more recently, on May 31, 2000, requesting their plans and time frames for thimerosal removal or reduction.

Substantial progress has been made in the removal of thimerosal from vaccines. In August, 1999, the FDA approved a license supplement from Merck for a thimerosal-free hepatitis B vaccine. In March of this year, FDA approved a license supplement from SmithKline Beecham Biologicals for a thimerosal reduced hepatitis B vaccine (with more than 96% of the thimerosal removed from the vaccine, from a level of 25 micrograms of thimerosal per dose to less than 1 microgram per dose). Additionally, Wyeth-Lederle Vaccines and Pediatrics is now manufacturing only a single-dose, thimerosal free formulation of their Haemophilus influenzae type b (Hib) vaccine (they intend to no longer market the thimerosal containing multi-dose formulation). The other U.S.-licensed Hib vaccines are thimerosal free. Thus, all pediatric hepatitis B and Hib vaccines currently being manufactured are thimerosal free or greatly reduced. Vaccines for polio, chicken pox, and mumps-measles-rubella have always been thimerosal free.

At present, the only routine childhood vaccine containing thimerosal as a preservative is DTaP. There are four U.S.-licensed DTaP vaccines. The DTaP manufactured by SmithKline Beecham Biologicals (SBB) does not contain thimerosal as a preservative, while the DTaP vaccines from Wyeth-Lederle Vaccines and Pediatrics, Aventis Pasteur, and North American Vaccine do contain thimerosal. However, at the June 21-22, 2000, Advisory Committee on Immunization Practices meeting in Atlanta, both Wyeth-Lederle Vaccines and Aventis Pasteur announced plans to submit supplements to their respective DTaP licenses in either July or August of this year for thimerosal-reduced DTaP vaccine formulations. The FDA is committed to the expedited review of these supplements.

In conclusion the FDA recognizes and supports the goal of reducing the exposure to mercury from all sources. However, the available scientific evidence does not support a causal link between autism or other neurological disorders and exposure to thimerosal in vaccines. Therefore, a recall of these products is not warranted.

The benefits of childhood immunization far outweigh the risk, if any, of thimerosal in vaccines.

I appreciate your letter, and hope that the information provided here has been responsive to your concerns. You can be assured that the FDA is continuing to work on the issue of thimerosal in vaccines, as well as vaccine safety in general.

Sincerely yours,

for **Kathryn C. Zoon, Ph.D.**
Director
Center for Biologics
Evaluation and Research
Food and Drug Administration