



**STATEMENT BY**

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## **INTRODUCTION**

Mr. Chairman and Members of the Subcommittee, I am Dr. William Egan, Acting Director, Office of Vaccines Research and Review (OVRR), of the Food and Drug Administration's (FDA or the Agency) Center for Biologics Evaluation and Research (CBER). CBER's OVRR is responsible for the regulation and oversight of vaccines in the United States. On behalf of FDA, I appreciate the opportunity to participate in this hearing as the Subcommittee explores the availability of influenza vaccine, including preservative-free formulations of influenza vaccine. I want to assure the Subcommittee, and the public who are here today, that FDA takes their concerns about vaccine safety and availability very seriously. I welcome this opportunity to describe FDA's ongoing efforts to ensure the safety, effectiveness, and availability of influenza and other vaccines licensed in the U.S.

## **VACCINE SAFETY**

Vaccines have contributed greatly to the health and well being of the people of our nation; however, we must nonetheless be vigilant of any potential safety concern related to vaccines. I will briefly describe some of FDA's vaccine safety activities. In the pre-licensure phase, FDA monitors the safety of investigational vaccines as they are studied in clinical trials conducted under investigational new drug applications. When a manufacturer submits a license application to FDA, we review extensive information describing the manufacture and characterization of the vaccine, the safety and efficacy data from the clinical trials, and we typically inspect the manufacturing facility where the vaccine will be made. In addition, we usually seek advice from our Vaccines and Related Biological Products Advisory Committee

on the safety and effectiveness of vaccine candidates. If we determine that a vaccine is safe, effective, and that quality and consistency of manufacture have been demonstrated, we will license the vaccine.

Post-licensure, we typically review the manufacturer's test results before the manufacturer can release new lots of vaccine to the market. We also inspect the manufacturing facilities every two years. In addition, CBER and the Centers for Disease Control and Prevention (CDC) jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program, collecting information about adverse events (side effects) that occur after the administration of U.S. licensed vaccines. Reports to the VAERS program are welcome from all concerned individuals: patients, parents, health care providers, pharmacists, and vaccine manufacturers. We review these reports on an ongoing basis and obtain additional information as needed.

### **INFLUENZA VACCINES**

In contrast to many other vaccine-preventable diseases, disease caused by the influenza virus remains common; 36,000 deaths and 200,000 hospitalizations each year are attributed to complications of influenza. To increase our control of this very important vaccine-preventable disease, efforts are ongoing to increase the availability of influenza vaccine and increase coverage, especially of those individuals at increased risk of complications from influenza.

Influenza vaccine is unique among vaccines in that its active ingredients change almost every year and thus presents new manufacturing challenges each year. Influenza viruses are continuously evolving or mutating, and the recommendations of which viruses to include in the vaccine each year are based on the surveillance data provided from laboratories worldwide. Early each year, public health experts evaluate the data to determine the strains of virus to be used in the manufacture of the Influenza Virus Vaccine that will be administered in the fall. Currently, licensed vaccines contain three virus strains representing the strains predicted to be in U.S. circulation, as recommended by the U.S. Public Health Service (PHS) [including FDA, CDC, National Institutes of Health (NIH), and National Vaccine Program] for incorporation into the vaccine for 2004-2005. Because of the necessity to have a vaccine that matches the virus strains currently in circulation, vaccines manufactured for the previous year cannot be used.

FDA works closely with manufacturers to facilitate the rapid production of influenza vaccine each year. As soon as the strains are recommended, manufacturers begin to grow the virus strains in fertile hen's eggs. These strains of vaccine, known as "seed strains," used by each manufacturer are tested by FDA's CBER to assure they are the same as the recommended strains. FDA and manufacturers conduct tests to assure the safety and efficacy of the vaccine. Manufacturers submit the results of their testing along with sample vials from each lot to CBER for our "lot release." Because of the complexity of the manufacturing process, CBER performs "lot release" on each lot of influenza vaccine manufactured prior to distribution of the product. "Lot release" consists of CBER's review of the manufacturers' test results,

including tests on the lots of monovalent virus strains and tests on the final trivalent product. Furthermore, to assure the safety and efficacy of these products, CBER performs additional testing as appropriate.

Although the manufacturing process and lot release is completed for some lots of influenza vaccine as early as July, the manufacturing of additional lots continues until September-October in order to manufacture and complete the testing on a very large number of vaccine doses. This year, approximately 100 million doses of influenza vaccine will be manufactured, the largest amount ever produced. There has been a very significant increase in production over the past decade, as compared with approximately 20 million doses per year distributed in the mid-1980s. Currently, there are three licensed manufacturers of Influenza Virus Vaccine: Chiron Corporation (Evans Vaccines Ltd.) manufactures Fluvirin, and Aventis Pasteur, Inc. (AP) manufactures Fluzone; both of these vaccines are inactivated influenza vaccines. MedImmune, Inc. manufactures FluMist, a live attenuated influenza vaccine.

### **THIMEROSAL REDUCTION IN VACCINES**

Any discussion of the use of thimerosal in vaccines should involve at least the following two questions: First, what are preservatives, and second, why are they used in vaccines? For our purposes today, preservatives may be defined as compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi. They are used in vaccines to prevent microbial growth in the event that the vaccine is accidentally contaminated, as might occur

with repeated puncture of multi-dose vials. In some cases, preservatives are added during manufacture to prevent microbial growth.

The U.S. *Code of Federal Regulations* (Title 21 *CFR* 610.15(a)) requires, in general, the addition of a preservative to multi-dose vials of vaccines. Worldwide, preservatives are routinely added to multi-dose vials of vaccine, because tragic consequences have followed the use of multi-dose vials that did not contain a preservative and have served as the impetus for this requirement. Cases of bacterial sepsis and death have been reported in the literature. Thimerosal, which contains ethylmercury and is approximately 50 percent mercury by weight, has been one of the most widely used preservatives in vaccines. FDA has been actively addressing the issue of thimerosal as a preservative in vaccines. In 1999, FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines, and found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions. However, FDA found that some children, during their first 6 months of life, might receive amounts of ethylmercury, from the preservative, thimerosal, in excess of the Environmental Protection Agency's guidelines for methylmercury, although not the Agency for Toxic Substances and Disease Registry or FDA guidelines. There are differences in how the body handles ethylmercury and methylmercury; of note, it appears that ethylmercury is eliminated from the body more rapidly than methylmercury. Because it was feasible to eliminate or reduce exposure to this source of mercury, i.e., from vaccines, as a precautionary measure, the PHS (including FDA, NIH, CDC, and Health Resources and Services Administration) and the American Academy of Pediatrics issued two Joint Statements, urging

vaccine manufacturers to reduce or eliminate thimerosal in childhood vaccines as soon as possible.

Consistent with this goal, FDA has encouraged and worked with manufacturers to develop new vaccines and new vaccine formulations that are either thimerosal-free or contain only trace amounts of thimerosal. The substantial elimination of thimerosal from pediatric as well as other vaccines has been achieved because over time, it has been possible to replace multi-dose vials with single-dose presentations (vials or syringes), which do not require a preservative.

We are pleased to report that FDA actions have resulted in a marked reduction in mercury exposure from thimerosal in vaccines. Since 2001, all vaccines routinely recommended for children 6 years and under (DTaP, hepatitis B, Haemophilus b conjugate (Hib), pneumococcal conjugate, IPV, MMR, and varicella) manufactured for the U.S. market have contained no thimerosal or only trace amounts, with the exception of inactivated influenza vaccine.

Prior to this initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury as ethylmercury via routine childhood vaccinations during the first 6 months of life could have been up to approximately 187.5 micrograms. The vaccines with trace amount of thimerosal licensed to date contain 1 microgram or less of mercury per dose. With the newly formulated vaccines, the maximum cumulative exposure during the first 6 months of life is less than three micrograms of

mercury, which represents a greater than 98 percent reduction from previous maximum exposure. Although not administered to children below the age of 6 months, the influenza vaccine could add an additional 25 micrograms of mercury during the first year of life, if each of the two doses contains thimerosal as a preservative. The influenza virus vaccine was just recommended for routine use in children 6 months through 23 months of age earlier this year, and I will address this further below.

In addition to encouraging the removal or reduction of thimerosal in vaccines, the PHS agencies have collaborated with various investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal in vaccines.

In 2001, the Institute of Medicine (IOM), at the request of CDC and NIH, convened the Immunization Safety Review Committee (the Committee) to review selected issues related to immunization safety. This Committee has completed two reviews of studies addressing a potential link between thimerosal-containing vaccines and autism. In its first review, conducted in 2001, the Committee concluded that the evidence is 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 believed 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.”

In 2004, the IOM's Committee reviewed this topic again, including new data that had accumulated since its review in 2001. These data included several epidemiological studies conducted in the U.S., Denmark, Sweden, and the United Kingdom, and studies of biologic mechanisms related to vaccines and autism. The Committee concluded that this body of evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism, and that hypotheses generated to date concerning a biological mechanism for such causality are theoretical only. Further, the Committee stated that the benefits of vaccination are proven and the hypothesis of susceptible populations is presently speculative, and that widespread rejection of vaccines would lead to increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

#### **MANUFACTURING CHANGES TO REMOVE THIMEROSAL FROM VACCINES**

There are two options available to manufacturers seeking to remove thimerosal as a vaccine preservative: 1) Replace multi-dose presentations with single-dose containers that do not contain a preservative, or 2) Replace thimerosal with an alternative preservative. In either case, the manufacturer must submit relevant information to FDA to demonstrate that the safety and effectiveness of this product have not been adversely affected by the change in formulation. Manufacturers have, in general, opted for the first of these approaches. Reformulating vaccines in single-dose containers without a preservative requires the manufacturer to have the ability to manufacture, at least at some stages, under aseptic conditions. There are additional considerations that must be taken into account in manufacturing preservative-free vaccines, e.g., having the capacity to fill and package

adequate numbers of single-dose presentations as well as having enough storage capacity. Presently, manufacturers' single-dose filling capacity is limited, and changing to single-dose vials for all vaccines would require the construction of additional facilities.

### **CURRENT STATUS OF INFLUENZA VACCINE**

As noted above, earlier this year the Advisory Committee on Immunization Practices recommended routine use of influenza virus vaccine in children 6 to 23 months of age. FDA has approved preservative-free formulations (which contain 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. Only one of these inactivated vaccines (AP's Fluzone) is approved for use in children less than 4 years of age. The live attenuated influenza vaccine (FluMist, manufactured by MedImmune) has never contained thimerosal, but it is not indicated for children less than 5 years of age or for pregnant women.

Chiron's preservative-free formulation of its influenza vaccine, Fluvirin, contains trace amounts of thimerosal (<1 microgram mercury per 0.5 ml dose). Fluvirin is approved for individuals 4 years of age and older. The company is producing approximately 5 million doses of preservative-free vaccine for the current flu season, and it has indicated that it plans to produce approximately the same amount for the next flu season; although these projections are subject to change. At this time, Chiron projects that it could somewhat increase its production of preservative-free vaccine in response to market demand while reducing its

production in multi-dose vials. This is based on the company's assessment of its current single-dose filling capacity, but the company notes that additional analysis would be required to confirm this estimate.

AP's preservative-free formulation of Fluzone contains trace amounts of thimerosal ( $\leq 1$  microgram mercury per 0.5 ml dose;  $\leq 0.5$  micrograms mercury per 0.25 ml dose). Fluzone is approved for individuals 6 months of age and older. For the current flu season, AP is producing about 4.6 million doses of the preservative-free pediatric presentation. Next year, AP plans to produce about 8 million doses of the preservative-free formulation. Currently, the amount of preservative-free vaccine that can be produced is limited by single-dose filling capacity. AP is developing a new filling suite and, although well underway, it will likely not be operational for several years. It should be noted that approximately 12 million doses of influenza vaccine would be needed to immunize all children 6-23 months of age, assuming that two doses would be needed in most cases.

## **CONCLUSION**

Influenza is a vaccine-preventable disease that leads to many deaths and hospitalizations every year. Significant gains have been made in increasing the supply of influenza vaccine, with manufacturers producing the most influenza vaccine ever this year, roughly 100 million doses, and efforts are ongoing by the Department of Health and Human Services, CDC, professional societies, and others to increase vaccine coverage, especially of those individuals at increased risk of complications from influenza. Another important accomplishment is that

thimerosal has been removed from or reduced to trace amounts in all vaccines routinely recommended for children 6 years of age and younger, with the exception of inactivated influenza vaccine. A preservative-free version of each of the two licensed inactivated influenza vaccines (containing trace amounts of thimerosal) is available in limited supply at this time for use in infants and young children and pregnant women. Although the overall supply has more than doubled relative to last year, and may be able to increase somewhat further next year, it will likely require the construction of new filling facilities for single-dose presentations to increase to a level where all infants, children, and pregnant women could receive exclusively preservative-free vaccine. As noted earlier, AP's Fluzone is the only influenza vaccine indicated for children 6-23 months of age, and the manufacturer estimates that their filling capacity for single-dose presentations will limit production to approximately 8 million doses of preservative-free or unpreserved vaccine. To vaccinate all 6-23 month old children would require approximately 12 million doses of influenza vaccine. The known benefits of vaccinations need to be weighed against the theoretical risk of exposure to small amounts of mercury contained in the thimerosal-preservative-containing vaccines. FDA is continuing its efforts to reduce the exposure of infants, children, and pregnant women to mercury from all sources. We will continue our discussions with the manufacturers of influenza virus vaccines (which are now routinely recommended for pregnant women and children 6-23 months of age) to enhance their capacity to increase the supply of thimerosal-reduced and thimerosal-free presentations.

I would be happy to respond to any questions.