

U.S. Food and Drug Administration

**Statement of
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U.S. Department of Health and Human Services
before the
Committee on Government Reform,
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FDA's Ongoing Response to the Issue of Vaccines and Autism

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Introduction

Mr. Chairman and Members of the Committee, I am Dr. Karen Midthun, Director, Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency). CBER regulates the development and licensure of vaccines. We appreciate the opportunity to participate in this hearing on autism and to respond to the Committee's concerns regarding a potential link between vaccines and autism. It is important to note that to date, the existing data do not demonstrate or even suggest a causal relationship between vaccines and autism. Nevertheless, we want to assure this Committee, the public and, especially the parents that are here today, that FDA takes these concerns very seriously. We want to explain FDA's ongoing efforts in response to the issue of vaccines and autism.

Childhood vaccines have contributed to a significant reduction of vaccine-preventable diseases (e.g., polio, measles, and whooping cough). In fact, vaccine-preventable infectious diseases are at an all-time low and now it is rare for American children to experience the devastating effects of these illnesses. Before vaccines were routinely administered, there were over 175,000 cases of diphtheria annually (1920-22), over 147,000 cases of pertussis (1922-25), and over 503,000 cases of measles (1951-54) reported in the United States. These diseases have essentially disappeared in countries with high vaccination coverage, such as the U.S. Prior to the introduction of an infant vaccine in 1985, an estimated 20,000 cases of invasive *Haemophilus influenzae* type b (Hib) disease, primarily meningitis, occurred annually in the U.S. Now, because of vaccination, the number of cases of invasive Hib disease has decreased by more than 98 percent. All of the diseases mentioned above were associated with significant mortality and morbidity. Nevertheless, we need to follow up on any safety concerns related to vaccines.

Background

Like all products regulated by FDA, vaccines undergo a rigorous review of laboratory and clinical data by highly trained scientists and clinicians to help ensure the safety, purity, and potency of these products. From an FDA regulatory perspective, there are four stages in vaccine development: the pre-investigational new drug (IND) stage (before the product is used in people), the IND stage (where human use occurs under limited study conditions), the license application stage (where FDA reviews the results of the clinical studies and the manufacturing process), and the post-licensure stage (following approval of the product for marketing).

A sponsor seeks licensure of a complete product as it is formulated for use, not of its individual components. Human clinical studies, as required under Title 21, Code of Federal Regulations (CFR) Part 312 should provide evidence of any acute toxicity from the use of an investigational drug, including vaccines. If any ingredient or ingredients cause acute toxicity, the pre-market safety data would most likely indicate acute toxicity from use of the vaccine product. However, such data generally would not show whether any particular ingredient or combination of ingredients is the source of toxicity.

Like other approved drug and licensed biological products, vaccines licensed for marketing may also be required to undergo additional, Phase IV, studies to further evaluate the vaccine or to address specific questions about the vaccine. For example, the manufacturer of Varicella Virus Vaccine committed to perform a post-licensure study with fifteen years of safety follow-up. These studies will provide information about the effects of the vaccine in a population much larger than that exposed during clinical trials. The population will also be observed for a far longer period. If additional side effects are identified during the post-marketing phase, either pursuant to adverse event reports filed by health care providers or consumers, or pursuant to Phase IV studies, FDA would take appropriate regulatory action to protect the public health. Some of the options we would consider include changing the product's labeling information to reflect the possible side effects, or, in cases of imminent or substantial hazard to the public health, ordering a recall of the product.

Because of the complex manufacturing processes for most biological products, each product undergoes thorough laboratory testing for purity, potency, identity, and sterility. Manufacturers may release lots only after this testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review, and where appropriate, further testing by FDA. The lot release program is part of our multi-part strategy that helps ensure product safety by providing a quality control check on product specifications.

Vaccine Adverse Event Reporting System

Licensure of all vaccines marketed in the U.S. is based on a benefit-to-risk analysis of the safety and efficacy data submitted by sponsors to FDA. During the pre-market review process, manufacturers and FDA focus on identifying and understanding risks before an overall risk-benefit decision can be made on the product's licensure. When using any drug or medical product, a person runs the risk of experiencing reactions. These reactions are commonly termed "side effects." They usually are identified in clinical trials conducted before licensure and are described in a product's labeling. Known side effects, discovered in the course of clinical trials, upon which a product's licensure or approval is based, comprise the majority of reported adverse events after licensure.

Like all other medical products, vaccines are not entirely risk-free. While serious complications are rare, they can occur. Vaccines are unique medical products in that they are generally

administered to a large number of healthy individuals, primarily children. Therefore, it is very important to identify even rare adverse reactions. 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 that collects information about adverse events that occur after the administration of U.S. licensed vaccines. Any event that an individual, whether a health care provider or a consumer, believes may have resulted from the administration of a vaccine may be reported to VAERS. Such reports will be included in the system, regardless of whether there appears to be a causal relation to the vaccine. Under FDA regulations, 21 CFR, Subpart D - Reporting Adverse Experiences, section 600.80, licensed vaccine manufacturers must report to FDA adverse experience information, and establish and maintain records.

It should be emphasized that adverse event reports can be made by anyone, including health care professionals, patients, and parents. If a patient's physician does not file a VAERS report, the patient can do so. FDA protects the confidentiality of patients for whom an adverse event has been reported. FDA encourages individuals to report to VAERS any clinically significant adverse event occurring after the administration of any vaccine licensed in the U.S. Individuals who want to make a report to VAERS can call VAERS at a toll-free number, 1-800-822-7967, to obtain a reporting form. Forms and reporting instructions also are available on the Internet at <http://www.fda.gov/cber/vaers/vaers.htm> and www.vaers.org. Further, VAERS reports can be made electronically at www.vaers.org.

Follow-up Study of VAERS Autism Reports

FDA has taken seriously VAERS reports of developmental delay following vaccination and wants to assure the public that the Agency is researching any possible relationship between vaccines and autism. CBER is conducting a follow-up study of VAERS reports of autism. As part of the study, CBER, in conjunction with outside autism experts, is reviewing available medical records and surveying parents and others who have reported autism after vaccinations. The goal of the interviews is to gather information about demographics, clinical features, potential risk factors, family history, vaccines administered, time interval from vaccination to autism onset, rapidity of symptom onset, and interval from diagnosis to submission of reports. Another goal is to determine how a parent makes the association between a child's autism and vaccination. Though this study will not be able to determine whether vaccines cause autism, it might suggest hypotheses that could be further evaluated in subsequent controlled, epidemiologic studies.

Autism-related Laboratory Activities

FDA is actively pursuing research involving the characterization and development of the first virus-induced animal model for autism - Borna disease virus (BDV) infection of the neonatal rat. There is no direct evidence for any relationship between BDV infection and human autism. However, BDV is used as the environmental damaging agent because it infects the brain of newborn rats. It is important to note that BDV is not a cause of autism. The damage it does and the disease syndrome it produces in rats are used only as a "model" to study general biological principles of autism. The features of this model, which FDA scientists have developed over the past ten years, have excellent correlation with what is known about human autism including neuroanatomical, behavioral, and neurochemical correlations. This model is being used in laboratories throughout the U.S. and internationally.

Thimerosal

FDA, together with other U.S. public health agencies, recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has encouraged manufacturers for several years to develop new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines. This joint effort by manufacturers and FDA is reflected by the licensure of thimerosal-free products such as Comvax [Haemophilus b Conjugate Vaccine and Hepatitis B Vaccine (Recombinant) manufactured by Merck & Company, Inc.], licensed October 2, 1996, Infanrix [Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) manufactured by GlaxoSmithKline], licensed January 29, 1997, and Prevnar (Pneumococcal 7-valent Conjugate Vaccine manufactured by Wyeth-Lederle Vaccines and Pediatrics), licensed on February 17, 2000, and the removal or reduction of thimerosal from previously licensed products. More recently, FDA has licensed two additional thimerosal-free vaccines, Twinrix, a combination hepatitis A and B vaccine for adults (May 2001) and Daptacel, a new DTaP vaccine manufactured by Aventis Pasteur Limited (May 2002).

In response to section 413 of the Food and Drug Administration Modernization Act (FDAMA) of 1997, FDA conducted a review of the use of thimerosal in childhood vaccines. Only a relatively small number of reports mentioned thimerosal as the suspected cause of the adverse event, and our review revealed no evidence of harm caused by thimerosal used as a preservative in vaccines, except for local hypersensitivity reactions. Under the U.S. recommended childhood immunization schedule, the maximum cumulative exposure to mercury from thimerosal, at the time of this review in 1999, was within acceptable limits for the methyl mercury exposure set by FDA, the Agency for Toxic Substances and Disease Registry, and the World Health Organization. Of note, such guidelines contain safety margins and are meant as starting points for evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur. However, the maximum cumulative exposure level exceeded the more conservative limits of the Environmental Protection Agency (EPA), set to protect the developing fetus, which is believed to be more sensitive to mercury exposure. The clinical significance of exceeding EPA's limits in infants is not currently known.

Nevertheless, reducing exposure to mercury from vaccines is prudent. This is achievable, in principle, because it is possible in the U.S. to replace multi-dose vials with single dose vials, which do not require a preservative. However, there are practical and temporal issues of implementation that must be addressed.

We are pleased to be able to report substantial progress in the effort to reduce thimerosal exposure from vaccines. At this time, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market contain no thimerosal or contain only trace amounts of thimerosal. The vaccines with trace amount of thimerosal licensed to date contain less than 1 microgram of mercury per dose, that is, a given dose of vaccine contains less than 1 part per million. The use of vaccines with trace amounts of thimerosal represents a greater than 98 percent reduction from previous maximum exposure in young infants.

Our efforts over approximately the past three years to accomplish this goal include the licensure of a thimerosal-free Hepatitis B Vaccine (Recombinant) manufactured by Merck and Company in August 1999, and another hepatitis B vaccine with only a trace amount of thimerosal, manufactured by GlaxoSmithKline, in March 2000. A supplement for a new formulation of Tripedia, a DTaP vaccine manufactured by Aventis Pasteur Inc., containing only

a trace amount of thimerosal was approved in March 2001. Additionally, Wyeth-Lederle Vaccines and Pediatrics now only markets a single-dose, thimerosal-free formulation of its Haemophilus b Conjugate Vaccine in the U.S.

Therefore, all routinely recommended U.S. licensed pediatric vaccines are now available in either thimerosal-free formulations or in formulations that contain only trace amounts of thimerosal. The routinely recommended vaccines include Hepatitis B Vaccine, Haemophilus b Conjugate Vaccine, Measles Mumps and Rubella Vaccine, Pneumococcal Conjugate Vaccine, DTaP Vaccine, Inactivated Polio Vaccine, and Varicella Vaccine. Prior to the recent initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the newly formulated vaccines, the maximum cumulative exposure during the first six months of life will now be less than three micrograms of mercury. This represents a greater than 98 percent reduction in the maximum amount of mercury a child would receive from vaccines in the first six months of life.

The Immunization Safety Review Committee of the Institute of Medicine (IOM) has completed reviews in two areas relevant to today's hearing. The first review by this committee focused on a potential link between autism and the combined mumps, measles, and rubella vaccine. The IOM report provides no basis for implicating the Measles, Mumps and Rubella (MMR) vaccine as a potential cause of autism spectrum disorders (ASD). Recognizing that scientific studies can never be absolute in their conclusions, the IOM recommended further research to explore the possibility that exposure to MMR vaccine is a risk factor for ASD in a small number of children. The committee concluded that there is no need to review the existing recommendations for routine use of MMR vaccine at 12-15 months of age and 4-6 years of age. The Committee's conclusion supports the current policy of giving the MMR vaccine as a combination vaccine instead of administering each of the components (measles, mumps and rubella) separately. The second review focused on a potential relationship between thimerosal use in vaccines and neurodevelopmental disorders (IOM 2001). In its report of October 1, 2001, the IOM's Immunization Safety Review 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 (ADHD), and speech or language delay. Thus, while the available scientific data do not establish that these neurodevelopmental disorders are caused by thimerosal, at the same time, they do not establish that these neurodevelopmental disorders are not caused by thimerosal. Additional studies are needed to establish or reject a causal relationship. The Committee did conclude that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was biologically plausible.

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." Furthermore, the Committee urged that "full consideration be given to removing thimerosal from any biological product to which infants, children, and pregnant women are exposed."

The FDA is continuing its efforts to reduce the exposure of infants, children, and pregnant women to mercury from all sources. Discussions with the manufacturers of influenza virus vaccines (which are routinely recommended for pregnant women) regarding thimerosal-reduced and thimerosal-free presentations are ongoing. Two of the three influenza virus

vaccines, Fluvirin from Evans Vaccines and Fluzone from Aventis Pasteur, Inc., are now available in a formulation that contains only trace thimerosal. The third manufacturer of influenza virus vaccine, Wyeth Laboratories, has announced that starting next year it will no longer manufacture flu vaccine. Discussions are also underway with regard to other vaccines, in particular, the diphtheria and tetanus vaccines and one manufacturer's adolescent/adult formulation of the hepatitis B vaccine (a second manufacturer's hepatitis B vaccine contains only trace thimerosal for both the pediatric and adult formulations.) In addition, all immune globulin preparations including hepatitis B immune globulin and Rho(D) immune globulin preparations are now manufactured without thimerosal.

Thimerosal and the National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services (DHHS or the Department) to coordinate toxicology research and testing activities within the Department, to provide information about potentially toxic chemicals to regulatory and research agencies and the public, and to strengthen the science base in toxicology. The NTP has become a world leader in designing, conducting, and interpreting animal assays for toxicity and/or carcinogenicity.

NTP uses a chemical nomination and selection process as a means to best use its resources with respect to the testing of chemicals of greatest health concern. Member agencies of the NTP, including FDA, are the primary sources of nominations to the NTP. Because of the continued interest on the part of the public, as well as public health agencies, to better characterize the potential toxicity that could have accompanied an exposure to thimerosal from vaccines, FDA has nominated thimerosal to the NTP for further study to adequately assess gaps in knowledge regarding, among other things, neurodevelopmental toxicity. The nomination was accepted by the review committee earlier this year.

Vaccine Recall

Federal law is specific about the criteria that must be met before FDA can order a mandatory recall of a regulated product. Under section 351(d) of the Public Health Service Act, a licensed vaccine (or other biological product) shall be recalled if FDA determines that it "... presents an imminent or substantial hazard to the public health..." The available scientific data do not provide conclusive evidence that exposure to thimerosal in vaccines can cause neurodevelopmental disorders. Therefore, FDA does not have the scientific basis to conclude that thimerosal-containing vaccines "present an imminent or substantial hazard to the public health" for a recall order.

FDA regulations also provide for a voluntary recall of products regulated by the FDA (21 CFR, Part 7). A firm may withdraw a product from the market, of its own volition, at any time. In addition, FDA may request a firm to recall a product that is in violation of FDA laws and regulations and that presents a risk of injury or gross deception, or is otherwise defective. An agency request for recall is reserved for urgent situations such as those that are necessary to protect the public health. FDA has concluded that the scientific data and other information do not support an FDA request for a voluntary recall. Vaccines are not violative per se because they contain thimerosal as a preservative and there is no conclusive data that they present a risk of injury. Additional studies on the potential for adverse effects of mercury in vaccines are continuing. Results of these studies will be closely monitored by FDA.

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That concludes my testimony. I would be happy to respond to any questions.

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