DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

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Introduction
Mr. Chairman and Members of the Committee, I am Dr. Lester Crawford, Deputy Commissioner, Food and Drug Administration (FDA or the Agency). I appreciate the Committee's interest in the current shortage of childhood vaccines and welcome the opportunity to participate in this hearing. FDA is concerned about the fragility of the Nation's vaccine supply and is committed to the availability of safe and effective vaccines to protect our children and ourselves from many serious infectious diseases.

Recently there has been an unanticipated shortage of some of the recommended vaccines in the United States. The pediatric vaccines that have been or are in short supply include Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP); Measles, Mumps and Rubella Vaccine (MMR); Varicella (chickenpox) Vaccine; and Pneumococcal-conjugate vaccine. Tetanus and Diphtheria toxoids adsorbed for adults (Td) has also been in short supply, and delays in the availability of influenza vaccine have occurred in the past.

I am happy to report that several of these shortages are easing. FDA's recent licensure of a new DTaP vaccine manufactured by Aventis Pasteur, Limited, and their recent announcement of an increased supply of Tetanus and Diphtheria Toxoids, means that relief in the shortage of these two products is in sight. The manufacturer has reported to its customers that the MMR vaccine shortage has eased and that the Varicella vaccine shortage will likely improve soon. In the case of Varicella, the supply will be sufficient to return to the recommended schedule by August or September, although additional time will be needed to build up inventory. Due to manufacturing challenges as well as an unexpected demand for Pneumococcal-conjugate vaccine, this vaccine is still in short supply for the foreseeable future. An ample supply of Influenza vaccine is expected for the 2002-2003 influenza season, and no delays are anticipated at this time.

Potential Causes of Vaccine Shortages
Vaccine shortages can stem from a number of causes and the more recent shortages are not due to any single factor. In fact, the recent shortages stem from a number of factors including: 1) the withdrawal from the market of one manufacturer, 2) difficulties in manufacturing processes, 3) temporary shutdowns of facilities for upgrades or maintenance, or to correct manufacturing deficiencies observed by the manufacturer or FDA during inspections, and 4) other factors, such as transition to thimerosal-free vaccine formulations.

Given the complexity of biological materials and manufacturing, and the need to maintain quality and consistency during production, manufacturers may experience problems achieving the desired production yields or maintaining quality of final materials. As a result, production delays or shortages often surface. Vaccine manufacturers may decide to change or improve their processes, to renovate and update their facilities or to perform regular maintenance. When this process takes longer than expected it can result in decreased vaccine production. Occasionally, manufacturers will issue voluntary recalls that have an impact on vaccine supply. Although the manufacture of biologic products is complex and demanding, and the need to update and maintain modern facilities is costly, the current prices paid for many vaccines are comparatively low compared to the prices of many other drug products. Manufacturers may choose to discontinue production of a vaccine (or of vaccines altogether) as a business decision, such as when they believe that the production and sale of a particular vaccine or needed investments in manufacturing facilities are no longer economical. When there are a limited number of manufacturers for a particular vaccine, the impact of one firm withdrawing from the market may cause a significant shortage. If other manufacturers are available and willing, considerable time may be needed to increase production to respond to a shortage. Many vaccines require a year or more of production time.

A temporary shortage may occur when the public health community alters existing vaccination recommendations. For example, the Advisory Committee on Immunization Practices recommended that influenza vaccine be administered to a wider-age range of people in 2000-2001. If implemented, this recommendation would have meant that in order to meet demand, manufacturers would have to increase production. However, production limitations prevented the implementation of the new recommendation.

Similarly, the response by manufacturers to the recommendation by public health officials that the mercury-containing preservative (thimerosal) be removed from routinely recommended pediatric vaccines in an effort to reduce mercury exposure in children exacerbated the shortage of DTaP vaccines that arose when one of the three major manufacturers of DTaP decided to withdraw from the market in 2001. One approach to eliminate the need for a vaccine preservative is to change from a multi-dose to a single-dose presentation. However, manufacturing for a single-dose presentation means that the filling-line capacity must be increased. According to one

manufacturer, more vaccine is lost through overfilling of single-dose vials than multi-dose vials. This significantly reduces the number of doses of vaccine available from each production lot or batch.
A shortage may also stem from a firm deciding to temporarily suspend operations to improve manufacturing practices, or to correct deficiencies identified during an internal review of its operations or by an FDA inspection. Firms often initiate corrective action independent of FDA regulatory action, in order to ensure production quality. When FDA inspects a vaccine manufacturer and finds deficiencies, the Agency carefully considers the impact on product availability before taking action. In some situations, the Agency may determine, after balancing all factors, that a decrease in the availability of a "medically necessary product" could pose a substantial risk to patients. In such cases, FDA regulatory action may allow manufacturing of the critical product to continue, provided that certain conditions are established to ensure product safety. The Agency evaluates each circumstance on its own facts, balancing the medical need for the product against the safety assurances in place before product is released for use.

While FDA works proactively and interactively with manufacturers to address shortage issues, it is important to note that FDA does not have the authority to require manufacturers to stay in the market and produce a given vaccine, nor does FDA have the authority to direct manufacturers to increase production when a shortage occurs.

FDA's Response to Vaccine Shortages
FDA is constantly working with National of Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and with industry to take whatever steps possible to prevent and alleviate vaccine shortages. We work to maintain open and continued dialogue with vaccine manufacturers, and assist firms who may seek licensure and to enter the vaccine manufacturing market. FDA routinely meets with manufacturers prior to submission of a licensing application to facilitate the regulatory process and provide guidance on requirements for new vaccines. The Agency also encourages and works with manufacturers to enhance their production capabilities and capacities through meetings, teleconferences, review of submissions and related regulatory activities.

Whenever possible, FDA informs manufacturers of potential shortages to allow them to reallocate product to those who need it most and to take action to increase product inventory. In addition, FDA works with manufacturers that want to correct manufacturing deficiencies in order to avoid shortages of critical products. In October 2000, for example, one of the manufacturers of influenza vaccine entered into a judicially approved consent decree of injunction. Under the decree, the manufacturer was able to continue distributing influenza vaccine, and FDA worked with the manufacturer to develop a satisfactory compliance plan to help ensure the safety and availability of this medically important product. As a result, this company, a major supplier of influenza vaccine in the United States, was able to supply vaccine for use during the 2000-2001 flu season. In contract, another manufacturer of influenza vaccine decided not to take action to correct manufacturing problems. Instead, it elected to withdraw from the market in 2000.

Several other manufacturers of influenza vaccine experienced decreased production yields due to the slow growth of one of the influenza strains used in the vaccines. This development led to a temporary delay in vaccine availability, which created temporary spot shortages. To address this situation, in early 2001, FDA contacted each of the three remaining influenza vaccine manufacturers to discuss their projections for influenza vaccine production and facilitate any possible expansion of manufacturing capacity. Two manufacturers submitted supplements to their licenses for changes in their manufacturing process that allowed for increased capacity or production. These manufacturing changes led to an increase in the production of influenza vaccine for the 2001-2002 season, with a shorter delay. As a result, the greatest number of doses ever produced in a given year was released for the 2001-2002 season (approximately 87 million doses).

Licensing Process and Assuring Vaccine Safety
Vaccines are different from most drugs in several respects and achieving the highest quality in manufacturing is especially challenging and critical. First, they are most often produced from or use living cells and organisms, as well as complex growth materials derived from living sources. Thus, the potential for contamination is higher than for most drugs, so the quality and purity of all source materials must be carefully monitored. In fact, a separate Federal entity for regulating biological products was first established, well before the FDA itself, under the Biologics Control Act of 1902. Congress took this step following an incident in which horse serum intended for the treatment of diphtheria actually transmitted tetanus, killing 13 children. Second, the production of most

preventative vaccines requires growing the immunizing agent, i.e., bacteria, viruses, etc. in the production facility, and the subsequent purification of complex molecules from these organisms. Growth conditions are complex, and subtle changes in materials, in the process itself, or in conditions such as temperature can result in changes in the final vaccine that can affect its safety, its effectiveness or both. Third, the final vaccine itself is usually not, like most drugs, a simple molecule that can be tested for its purity and potency using simple chemical and physical methods. Instead, each lot of vaccines must be carefully tested for its composition and potency, through the lot release process. Finally, unlike most drugs, which are given to people to treat an illness, vaccines are administered to large numbers of healthy people to prevent infectious diseases. For this reason, even very rare adverse effects are generally not viewed as acceptable to healthy children and adults. For all of these reasons, the entire process of vaccine manufacturing is highly demanding and complex, and both the licensing of vaccines and the regulation of vaccine production is subject to the highest expectations and standards.

FDA's regulatory responsibilities with regard to vaccines can be divided into pre-approval and post-approval activities. Prior to licensure of a vaccine, sponsors (most often manufacturers) conduct clinical trials to generate safety and efficacy data that can be used as a basis for approving a marketing application. For studies conducted under an Investigational New Drug Application (IND), FDA provides guidance on clinical trial conduct and design. Foreign clinical studies not conducted under an IND also can be used in support of a marketing application if they were well designed, well conducted, performed by qualified investigators, and properly conducted to protect the rights and safety of the study participants.

Under the regulations, vaccines not licensed for use in the U.S. may be used in the U.S. only as an investigational product under an IND application. The development of product under IND is usually sequential, beginning with safety testing in a small number of subjects (Phase I), following by dose-ranging and safety studies (Phase II), and a large trial for efficacy and safety (Phase III). Volunteers receiving an investigational vaccine must be fully informed that the product is experimental and must give signed informed consent before they may receive the product. In order to obtain a license, a manufacturer has to submit a biologics license application. In many instances, trials are performed in foreign countries because the disease that the vaccine is intended to prevent has a higher incidence than in the U.S. and because the use of vaccines is increasingly global. For example, vaccines to prevention typhoid fever, Japanese encephalitis, pertussis, and hepatitis A have been licensed using efficacy data from clinical trials conducted in a foreign country. FDA applies the same standards to vaccine studies and manufacturing, wherever they are performed.

To obtain a license for a biological product, section 351(a) of the Public Health Service (PHS) Act requires a manufacturer to demonstrate that the biological product is "safe, pure, and potent," and that the "facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent." As part of these requirements, manufacturers must meet the standards established in FDA regulations applicable to biologics, including current good manufacturing practices (CGMP). CGMPs are established by the current industry practices and in FDA regulations (Title 21, Code of Federal Regulations (CFR) Parts 210 and 211). The term CGMP has its origin in the Federal Food, Drug, and Cosmetic (FDC) Act, section 501(a)(2)(B), which states that a drug is adulterated if "a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

FDA determines conformity with CGMP and the standards set forth in the manufacturer's license primarily through inspection and surveillance, both before and after licensure. The goal is to ensure that consumers receive vaccines and other FDA-regulated products that meet the statutory requirements for safety and effectiveness. It is essential to recognize that CGMP non-compliance may affect the safety and effectiveness of a vaccine product, and therefore may place the public health at risk. Even seemingly minor CGMP violations, especially when they occur in multiples and are considered in aggregate, may indicate a systemic problem affecting product quality. The Agency strives for consistency in its inspections, paying particular attention to violations, such as contamination in the production facilities and processes, and looking for underlying systemic problems, such as lack of a documented and validated process, inadequate quality control, and repeated record-keeping omissions or errors.

Once FDA licenses a vaccine, we continue to monitor the product to help ensure continued safety and effectiveness. For vaccines, this is accomplished through ongoing review of adverse events reported through the Vaccine Adverse Event Reporting System (VAERS), post-licensure inspections, and other post-marketing activities. FDA performs inspections to determine whether manufacturers are following current good manufacturing practice and the standards set forth in their biologics license application. FDA may also perform targeted inspections when, for example, there are changes to the manufacturing processes, facility, or equipment, or other significant events.

FDA also utilizes the mechanism of lot release review to help ensure quality and potency in the final vaccine that is distributed to consumers. Lot release plays an important role in FDA's vaccine regulations, by helping to assure the public that biological products are safe, pure, and potent. Because of the complex manufacturing process for most biological products, each lot of product undergoes thorough testing by the manufacturer prior to release for distribution. The manufacturer performs specific tests as set forth in its license application, such as those for sterility and potency. The manufacturer submits the results of its tests for potency, safety, and sterility to the Agency. The manufacturer also submits lot release protocols, and if applicable, product samples, before the product may be distributed in interstate commerce. The lot release program provides a quality control check on product specifications and is part of FDA's multi-part strategy designed to help assure biological product safety.

FDA's regulation of vaccine manufacturing is critical to maintaining public confidence in U.S. licensed vaccines. The importance of public confidence must be stressed. No other single health intervention has had the impact on disease prevention and our nation's health as immunization with U.S. licensed vaccines. For this reason, FDA carefully evaluates each licensing and regulatory action it takes, balancing the importance of product availability while working with manufacturers to help assure that products are as safe as current technologies allow will be distributed to consumers.

The Role of FDA Research in Promoting Vaccine Development and Availability

The complex and changing field of vaccinology presents both scientific challenges and opportunities for FDA. Maintaining FDA's core scientific expertise is critical to help assure quality review and quality products. First, FDA reviewers must maintain expertise to deal with changing basic, clinical and manufacturing sciences. Fostering an environment where such knowledge is current and valued helps to ensure that scientific reviewers, wherever possible, foresee or promptly identify important product issues with the potential to affect safety or effectiveness of a new or existing vaccine, perform a balanced assessment, and respond appropriately. Second, FDA research plays a unique and important role in improving the quality and availability of biologics, particularly in areas that affect multiple products and manufacturers. Every year FDA scientists help to provide to manufacturers new strains for the yearly influenza vaccine as well as biological standards for assessing the vaccine's potency. Ongoing FDA research on influenza is also designed to prepare for the possibility of another global influenza pandemic. These efforts by FDA reduce the need for duplicative efforts by manufacturers and shorten the time frames required for vaccine production every year. FDA scientists have also standardized assays for the potency of other vaccines, including those for acellular pertussis and polysaccharide-protein conjugate vaccines (e.g., Haemophilus type b conjugate and pneumococcal conjugate vaccines). FDA is conducting research to improve neurovirulence tests we hope may further enhance the safety of viral vaccines such as polio and mumps. FDA has also applied modern and novel technologies to the detection of potentially harmful contaminating agents in vaccines and the cell lines used to produce them, and these technologies are also applicable to new vaccines, such as for smallpox, urgently needed to help protect against the threat of bioterrorism.

A Collaborative Approach to Vaccines and Vaccine Policy Issues

FDA works proactively in collaboration with established interagency working groups and vaccine committees. Vaccine issues are a priority for the Agency and the Department of Health and Human Services (HHS or the Department). The Department has shown its commitment to vaccine issues through coordinating interagency groups to focus on vaccine safety and supply, among other issues. FDA participates as an ex officio member of the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the National Vaccine Program Office's (NVPO) National Vaccine Advisory Committee, and the Health Resources and Services Administration's (HRSA) Advisory Commission on Childhood Vaccines (ACCV). In turn, the CDC, NVPO, and NIH participate in FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). These advisory committees have specific and unique responsibilities, and provide

important opportunities for input from the public, including consumers, industry, and academia. FDA also participates in the Interagency Vaccine Group (IAVG) and its executive committee. The IAVG includes various HHS agencies and representatives from the U.S. Agency for International Development and the Department of Defense. FDA is also a member of an IAVG Working Group that is developing options to present to the Department to address the vaccine supply issues, and participated in a recently held vaccines shortage workshop held in February 2002.

Conclusion

Vaccines, licensed for use in the United States by FDA, have been protecting our nation's children from deadly infectious diseases for almost 100 years. In fact, immunizations represent one of the most significant public health achievements of the 20th Century. Vaccines can be credited with saving more lives and preventing more illnesses than any medical treatment. Without question, continuing to ensure the availability of safe and effective vaccines is critical to protect the public health and to prevent disease outbreaks.

Mr. Chairman, I look forward to the recommendations of the ongoing study requested by the Congress concerning vaccine shortages and assure you that FDA will continue to be vigilant in searching out opportunities to enhance the supply of safe and effective vaccines.