



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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STATEMENT OF
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BEFORE THE
SUBCOMMITTEE ON WELLNESS AND HUMAN RIGHTS
COMMITTEE ON GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES
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INTRODUCTION

Mr. Chairman and Members of the Committee, I am William Egan, Acting Director, Office of Vaccine Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration (FDA or the Agency). OVRR regulates the development and licensing of vaccines. We appreciate the opportunity to participate in this hearing regarding Simian Virus 40 (SV40) and polio vaccine.

One of the most significant public health achievements of the 20th century has been the availability of vaccines to immunize the American public against a variety of diseases. It is important to remember how far we have come and how many vaccine-preventable diseases have been significantly reduced or eradicated in the United States. Many of us can recall the devastation caused by diseases such as polio; a time when children survived in iron lungs or walked only with the help of leg braces and crutches. The polio vaccine and other childhood vaccines can be credited with saving more lives and preventing more illnesses than any other medical intervention. While vaccines are generally very safe and effective, FDA is committed to continuing to monitor and, wherever possible, improve their safety. Therefore, we share your committee's concerns about assuring vaccine safety and appreciate the opportunity to comment on the potential risk from SV40, a risk that has been eliminated from U. S.-licensed vaccines.

BACKGROUND

In the early 1900s, Americans were frightened of polio and with good reason. Polio is a highly contagious disease that paralyzes or kills its victims and children are especially vulnerable. During the early 1950s, Dr. Jonas Salk developed a killed-virus polio vaccine. After large scale testing in 1955, the Salk polio vaccine became an important immunization tool when four million doses of the vaccine were manufactured and distributed.

In the late 1950s, Albert Sabin theorized that a weakened, live-virus polio vaccine would provide longer-lasting immunity. By the end of the 1960s, the vaccine developed by Sabin, which was administered orally, became the primary weapon for polio prevention in the U.S. The widespread use of polio vaccines throughout the world – primarily oral poliovirus vaccine (OPV) – has led to the eradication of wild-type polio in the Americas and the near eradication of polio worldwide. Although highly effective, the Sabin vaccine is an attenuated form of the poliovirus that can mutate. Vaccine recipients can, in rare cases, develop polio after taking this vaccine. In the U.S., there were approximately 6-8 cases per year of vaccine-associated paralytic polio (VAPP). Because the risk of VAPP exceeded the risk of disease from wild-type polio, the Salk inactivated vaccine became the only product recommended and used for routine childhood vaccination in the U.S. in 2000.

SIMIAN VIRUS 40

The inactivated Salk vaccine was not without problems. Where problems were identified, however, the science community quickly responded to improve the safety of the vaccine.

A significant number of early vaccine lots were contaminated with the previously unknown viral agent, SV40. In 1960, Drs. Sweet and Hilleman identified SV40 in monkey kidney cells and seed stocks used to produce the poliovirus. In 1961, Drs. Gerber, Hottle, and Grubbs discovered that the treatment used to inactivate SV40 was not completely effective.

In response to these problems, scientists, including those at the Public Health Service's (PHS) Division of Biological Standards (DBS), developed a tissue culture procedure to detect SV40. Once this procedure was developed, DBS notified manufacturers that “. . . no lots of poliomyelitis vaccine will be released in the absence of negative results of a valid tissue culture test for SV40.” This requirement was later codified in regulations. Nevertheless, before SV40 was recognized as a problem and appropriate tests were developed, millions of people were vaccinated with poliovirus vaccines that contained SV40. Since this unfortunate event four decades ago, FDA has required that manufactures perform routine testing for oral poliovirus vaccines to demonstrate the absence of SV40.

Studies in the 1960s showed that SV40 could produce certain cancers in newborn hamsters. More recent studies reported finding SV40 genes in several types of human tumors. These findings have raised the question of whether SV40 may cause, or

contribute to causing, some types of cancer in humans. Several epidemiological studies found no link between exposure to SV40 contaminated vaccines and development of cancer. However, a study of immunization of pregnant women showed an increase in certain cancers in the offspring of women immunized with IPV compared to women immunized with either OPV or influenza vaccine. However, a recent report by the Institute of Medicine of the National Academy of Sciences concluded that “the evidence is inadequate to accept or reject a causal relationship between SV40 containing polio vaccines and cancer.”

Recent studies have reported finding SV40 genes in several types of human cancers. This has raised questions about the potential for various modes of SV40 transmission in the human population and the question of whether SV40 was circulating in the human population before the advent of the polio vaccines. However, other research suggests that the tissue culture tests may not be sufficiently sensitive to detect low levels of SV40 that might potentially be present in current polio vaccines. In response to this concern, FDA researchers developed a highly sensitive test based on the polymerase chain reaction technology to probe for the presence of SV40 DNA in vaccines. Random samples of live oral polio vaccines manufactured in the U.S. between 1972 and 1996 were tested using this technology. No SV40 DNA was found in any of the 30 vaccine monopools we tested. The results of this testing were published in 2000 in the peer reviewed journal, Biologicals.

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, vaccines 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 and, hence, the quality and purity of all source materials are carefully monitored. In fact, a separate Federal entity for regulating biological products was first established, well before FDA itself, under the Biologics Control Act of 1902 to address these concerns.

Second, the production of most preventative vaccines requires growing the immunizing agent (i.e., bacteria, viruses, etc.) in the production facility and the purification of complex molecules from these organisms. Growth conditions are complex, and subtle changes in materials, 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 is usually not, like most drugs, a simple molecule that can be tested for purity and potency using simple chemical and physical methods. Instead, each lot of vaccine must be carefully tested for composition and potency. They are also tested to ensure that they are free from contamination through the manufacturing and, where necessary, lot release process.

Finally, unlike most drugs, which are provided to people to treat an existing illness, most vaccines are administered to large numbers of healthy people to prevent infectious diseases

prospectively. For this reason, even very rare adverse effects are of concern and generally not viewed as acceptable to healthy children and adults if they can be prevented. For all of these reasons, the entire process of vaccine manufacturing is highly demanding and complex; both the licensing of vaccines and the regulation of vaccine production is subject to rigorous expectations and standards. In addition, FDA works with multiple partners to help encourage development and implementation of new and improved methods of vaccine production and improved testing that may further enhance vaccine safety.

VACCINE APPROVAL PROCESS

FDA's vaccine approval process can be divided into pre-approval and post-approval activities.

Pre-approval Activities

Early in the pre-approval process, sponsors test candidate vaccines in animals, where appropriate, to be sure they are safe and confirm that they induce appropriate protective responses against the infectious disease. They then conduct clinical trials in humans to determine appropriate dosing and 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 often provides guidance on both animal studies and on clinical trial conduct and design. This guidance is intended both to protect human subjects and to assure that the studies performed are likely to help determine whether the product is safe and effective.

Current Good Manufacturing Practices

Section 351(a) of the PHS Act requires that a vaccine manufacturer demonstrate that the biological product is “safe, pure, and potent.” It further requires 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 consist of the current industry practices and FDA regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). The term CGMP has its origin in the Federal Food, Drug, and Cosmetic (FD&C) Act, section 501(a)(2)(B), which states that a product 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 CGMPs 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 uses inspection and surveillance, both before and after licensure, to help assure conformity with CGMP and the standards set forth in the manufacturer’s license. The goal is to ensure that consumers receive vaccines and other FDA-regulated products that meet requirements for safety and effectiveness. The Agency strives for consistency in its inspections, paying particular attention to serious 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.

POST APPROVAL ACTIVITIES

Once FDA licenses a vaccine, the Agency continues to monitor product safety and effectiveness. For vaccines, FDA accomplishes this through ongoing review of adverse events reported under the Vaccine Adverse Event Reporting System, through post-licensure inspections, and through other post-marketing activities. FDA performs inspections to determine whether manufacturers are applying CGMP 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.

Lot Release

FDA also utilizes the mechanism of lot release review to monitor the quality and potency of the final vaccine before manufacturers distribute their product. Because of the complex manufacturing process for most biological products, each lot of product undergoes appropriate 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, and then submits the results to the Agency. The manufacturer also submits lot release protocols, and if applicable, product samples, before the product may be distributed. The lot release program is an essential quality check on product specifications and is part of FDA's multi-pronged strategy designed to help assure biological product quality.

CONCLUSION

Prior to 1962, poliovirus vaccines produced in rhesus monkey kidney cells were contaminated with SV40, a virus that can cause tumors in some rodents. Recent studies reporting that SV40 was detected in some human tumors raised concerns that SV40 may be pose a risk in humans. Following the recognition that SV40 could contaminate cell cultures used to produce polio vaccine and the availability of testing for SV40, FDA required specific tests to assure that poliovirus vaccines are not contaminated with SV40 virus. FDA retested samples of live oral polio vaccines manufactured in the U.S. between 1972 and 1996, and no SV40 DNA was found in any of the lots tested.

FDA's regulation of vaccine manufacturing, including its continuing activities to assure and enhance vaccine safety, 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 distributed to consumers are as safe as current technologies allow will.

Although scientists have not reached consensus on the potential risks posed by SV40 and whether it may contribute to causing some types of tumors in humans, the one thing we all agree on is that poliovirus vaccine has provided an enormous public health benefit and has practically eradicated this horrible disease. As with all medical products, there are potential

known and unknown risks with any vaccine. FDA will continue its efforts to help ensure the safety of all vaccines and protect the public health.

Thank you again for this opportunity to appear before you today. I am happy to answer your questions.