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May 7, 2010: Vaccines and Related Biological Products Advisory Committee Meeting Briefing Document

Vaccines and Related Biological Products Advisory Committee – May 7, 2010

Background information regarding the discovery of porcine circovirus 1 (PCV1) DNA sequences in GlaxoSmithKline's (GSK) rotavirus vaccine (Rotarix®) and the development and use of advanced analytical methods in the characterization of cell substrates

Finding of PCV1 DNA Sequences in Rotarix

GSK Biologicals was informed by Dr. Eric Delwart, Department of Laboratory Medicine at the University of California in San Francisco, that DNA sequences originating from PCV1 had been detected in two batches of Rotarix®, an orally administered live, attenuated rotavirus vaccine indicated for the prevention of rotavirus gastroenteritis in infants. GSK notified FDA of the issue on 3/15/2010. The study, entitled "Metagenomic analysis of live attenuated human viral vaccines for adventitious viruses", Victoria et al., is now available on-line at <http://jvi.asm.org/cgi/reprint/JVI.02690-09v1>¹ for reference. The study described the use of a powerful new method consisting of viral particle purification, massively parallel pyrosequencing, and viral sequence similarity searches, for detecting adventitious viruses in vaccines. The researchers focused their work on eight live attenuated viruses: oral polio virus vaccine, rubella virus vaccine, measles virus vaccine, yellow fever virus vaccine, varicella virus vaccine, 2 rotavirus vaccines, and Measles/Mumps/Rubella vaccine. Rotarix® was found to contain PCV1 DNA. These sequences were not identified in the RotaTeq® rotavirus vaccine manufactured by Merck, which is also licensed by FDA for the prevention of rotavirus gastroenteritis in infants.

Upon notification of the findings by Dr. Delwart, GSK initiated studies and confirmed that DNA from PCV1 is present in the Rotarix® vaccine, as well as in the cell bank and seed from which the vaccine is derived. Once notified by GSK, FDA began its own laboratory studies and also confirmed the presence of DNA from PCV1 in Rotarix® vaccine. These findings indicated that the DNA from PCV1 has likely been present since the early stages of the vaccine's development, including during clinical studies.

PCV1 is a small, circular virus composed of a single strand of DNA. PCV1 is found commonly among pigs, but is not known to cause disease in pigs nor other animals, including humans. There is no evidence at this time that DNA from PCV1 in Rotarix® poses a safety risk. Pre- and post-market studies have shown that Rotarix® is highly effective at preventing serious gastrointestinal disease caused by rotavirus. In addition, no serious or unexpected safety concerns have been identified in postmarket surveillance of Rotarix®. Nevertheless, GSK and FDA continue to investigate the findings of PCV1 in Rotarix®, by reviewing all available data, expanding testing to determine the source of the PCV1 DNA and developing additional tests to determine whether the PCV1 DNA signal represents the presence of infectious virus. While additional information is being gathered, as a precautionary measure, the agency recommended on March 22, 2010, that clinicians and public health professionals in the United States temporarily suspend the use of Rotarix®.

A special meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will be convened on May 7, 2010. GSK and FDA researchers will update the committee on their most recent findings and the status of current investigations. These ongoing investigations at both GSK and FDA include studies designed to determine whether the PCV1 DNA is particle associated, whether infectious PCV1 virus is present in the vaccine, and whether PCV1 is capable of replication in Vero cells or other mammalian cells, including human cell lines. In addition, the committee will be informed of follow-up studies by GSK that are underway to assess the possibility of PCV1 replication in vaccine recipients by testing of stool and sera samples pre- and post-vaccination. Finally, an update on postmarketing safety data of Rotarix® since licensure will be provided. The VRBPAC will be asked to discuss the significance of the most recent findings of PCV1 in Rotarix® vaccine, the implications of the data for continued use of Rotarix®, and the need for any additional experiments or data.

Advanced Analytical Methods for the Characterization of Cell Substrates

The detection of PCV1 sequences in Rotarix® vaccine raises complex questions with potential regulatory implications, not only in regard to PCV1 specific testing of vaccines, but in regard to the general use of advanced analytical methods for characterizing vaccine cell substrates. The power of the new methodology that was used to detect the PCV1 sequences suggests that such technologies may uncover the presence of adventitious agents that might not be detected with current methods. Implementing routine use of such methods has benefits as well as challenges and risks.

Vaccine manufacturers are required to have controls in place to ensure the identity, potency, quality, and purity of vaccines (21 CFR 610). In addition, current FDA recommendations for the detection and evaluation of cell substrates used to produce viral vaccines are described in the FDA Final Guidance for Industry entitled "Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications" (March 2, 2010). This document describes a series of tests that are designed to detect general unknown adventitious agents as well as tests for specific adventitious agents and tests for novel cell substrates. Nevertheless, even though this guidance is recent, technologies for detection and discovery of new adventitious agents continue to evolve at a very rapid pace. Examples of such new technologies include:

- Representational difference analysis
- Degenerate PCR: free or particle-associated nucleic acid
- Microarray screening of nucleic acids
- PCR combined with mass spectrometry
- Digital transcriptome subtraction
- Massively parallel/Deep sequencing analysis

At the May 7, 2010 special meeting of the VRBPAC we will review current recommended tests as outlined in the FDA guidance for Industry document, as well as emerging technologies, the advantages/disadvantages associated with each (e.g., sensitivity, robustness) and how they are already being used to detect new viruses. In addition, the potential applications of such novel technologies will be discussed and the implications of using such techniques to test vaccines currently licensed and vaccines still in development.

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