Questions and Answers

Sanofi Pasteur Warning Letter

When did FDA learn of the current situation from Sanofi Pasteur?

FDA was first contacted by Sanofi Pasteur on March 31, 2006, regarding the sterility failures of monovalent concentrates.

What steps did the agency take?

FDA immediately initiated ongoing regular discussions with Sanofi Pasteur to review the firm's investigation strategy and to provide guidance. After several discussions with the firm, FDA inspected the Swiftwater facility from April 18 – 28, 2006. At the conclusion of the inspection, FDA issued a list of inspectional observations (FDA Form 483) to the firm, identifying concerns related to its investigation into the sterility failures of the monovalent concentrates and those related to good manufacturing practice for the firm's finished products. After determining that the firm's response to the FDA Form 483 was inadequate to address the serious deviations noted, FDA issued the Warning Letter.

FDA is continuing its discussions with the firm on an ongoing basis.

Why did FDA issue this warning letter?

FDA's practice, depending upon the nature of a violation of regulations, is to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law.

Warning Letters are issued only for violations of regulatory significance. Significant violations may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the agency's principal means of achieving voluntary compliance with applicable laws and regulations.

The Warning Letter identifies several issues noted during a March 2005 inspection that were not corrected prior to the 2006 inspection. Why didn't FDA issue a Warning Letter for these issues in 2005?

Following the compliance issues surrounding Chiron's production of influenza vaccine in 2004, FDA instituted annual inspections of influenza vaccine manufacturers. The March 2005 inspection of Sanofi Pasteur was one of the first of these yearly inspections.

The FDA Form 483, such as the one issued at the conclusion of the March 2005 inspection, is a list of observations that is issued by FDA investigators at the conclusion of an FDA inspection of a firm. These observations do not represent a final agency determination of compliance. At the completion of an inspection, a firm has the opportunity to respond to the citations and correct deficiencies. Therefore, while there were issues raised in the FD-483 for the March 2005 inspection, further agency review concluded that the inspection be classified as "voluntary action indicated," meaning the firm had the opportunity to correct problems as outlined in its response.

During the April 2006 inspection of the firm, FDA determined that some of Sanofi Pasteur's corrective actions were not adequate and that additional problems existed such that a Warning Letter is appropriate at this time.

Does this mean Sanofi Pasteur's influenza vaccine, Fluzone, will not be available for the 2006 – 2007 flu season?

At this time, the deficiencies noted in the inspection of Sanofi Pasteur's Swiftwater, PA, manufacturing facility are not expected to significantly affect the availability of Fluzone for the 2006 – 2007 flu season, but we continue to review the progress made by the company.

The violations noted in the Warning Letter regarding Fluzone relate to manufacture of the monovalent concentrates. Monovalent concentrates are "intermediates" derived from one of the three influenza strains used to produce final vaccine each year. Though there will be some impact due to the loss of these monovalent concentrates, it is not expected to be significant.

What does "monovalent" mean?

Each monovalent concentrate is made from a specific virus strain. These monovalent concentrates are subsequently mixed together to make the trivalent vaccine, which protects against the three strains of influenza virus.

What does "trivalent" mean?

A trivalent influenza vaccine protects against three different types of influenza virus (H3N2, H1N1 and B). The trivalent influenza vaccine is a combination of three monovalent components that are combined to make the final vaccine product.

Does this mean that Sanofi Pasteur's flu vaccine is contaminated?

No. The sterility problems occurred in monovalent concentrates, not in the final vaccine product. The failed monovalents represented a small number of the total number of monovalents produced and were rejected by the firm and not used for further processing. Each year, influenza virus vaccine represents a "new" product, with at least one of the strains from the previous year

changed based on global epidemiological information. Three strains are used in each year's vaccine. Monovalent concentrates are intermediates that are used to formulate the trivalent vaccine. Generally, influenza vaccine manufacturers produce monovalents of each strain throughout the winter and spring months, then begin trivalent formulation and filling of final vaccine product in the early summer.

Are other Sanofi Pasteur manufacturing facilities included in this warning letter?

No, only Sanofi Pasteur's Swiftwater, PA, manufacturing facility is subject to this Warning Letter.

Are any other manufacturers affected?

No, this Warning Letter applies only to Sanofi Pasteur's Swiftwater, PA, manufacturing facility.

What is the expected availability of influenza vaccines for the 2006-2007 flu season?

Currently, an estimated 100 million doses of influenza vaccine from all of the licensed manufacturers is expected to be available for the 2006-2007 flu season.

Will this issue affect Sanofi Pasteur's efforts to develop an avian (H5N1) influenza vaccine?

FDA has no reason to believe it will affect the firm's H5N1 vaccine development efforts.

What are Current Good Manufacturing Practice (CGMP) regulations?

The CGMP regulations provide the methods to be used in and the facilities or controls to be used for the manufacturing, processing, packing or holding a drug to assure the drug meets the safety, requirements of the Federal Food Drug and Cosmetic Act and that the drug has the identity, strength, and quality and purity characteristics it is represented to possess.

The agency's risk and science based approaches under the CGMP initiative are aimed at ensuring that regulatory review, compliance and inspection policies are based on state-of-the-art pharmaceutical science, and do not impede rapid adoption of new technological advances by the pharmaceutical industry.

What is sterility testing?

Sterility testing is conducted to detect the presence of microorganisms in materials that are intended to be free of these microorganisms.