DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003D–0380]

Guidance for Industry: Process Analytical Technology—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance entitled ''Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.'' The guidance explains a science-based, risk-based framework, ''Process Analytical Technology, or PAT,'' to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. This framework is founded on process understanding, with the goal of facilitating innovation and risk-based regulatory decisions by industry and the agency. Working with existing regulations, this guidance describes a regulatory approach that will enable the agency and the pharmaceutical industry to address technical and regulatory issues and questions anticipated during the implementation of PAT.

DATES: General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT:

Chris Watts, Center For Drug Evaluation and Research (HFD–003), 5600 Fishers Lane, Rockville, MD 20857, 301–443–5197; or

Dennis Bensley, Center for Veterinary Medicine (HFV–143), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6956; or

Robert Coleman, Office of Regulatory Affairs (HFR–SE150), Food and Drug Administration, 60 8th St. North East Atlanta, GA 30309, 404–253–1200, ext. 1295.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance entitled ''Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.'' The guidance explains a science-based, risk-based framework, ''Process Analytical Technology, or PAT,'' that supports innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The framework is founded on process understanding, which can be used to facilitate innovation and risk based regulatory decisions by industry and the agency.

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control. Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that the existing regulatory system is rigid and unfavorable to the introduction of innovative systems. In August 2002, recognizing the need to eliminate the hesitancy to innovate, FDA launched a new initiative entitled ''Pharmaceutical Current Good Manufacturing Practices for the 21st Century: A Risk-Based Approach.'' Development of this guidance was part of that initiative.

Pharmaceutical development and manufacturing is evolving with increased emphasis on science and engineering principles. Effective use of pharmaceutical science and engineering principles and knowledge, throughout the life cycle of a product, can improve the efficiencies of both manufacturing and regulatory processes. FDA's initiative is designed to do just that using an integrated systems approach to regulating pharmaceutical product quality. This approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality. The desired future state of pharmaceutical manufacturing may be characterized as the following: (1) Product quality and performance achieved and ensured through the design of effective and efficient manufacturing processes, (2) product and process specifications based on a mechanistic understanding of how formulation and process factors affect product performance, (3) continuous real time quality assurance, (4) regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting products and processes, (5) risk-based regulatory approaches that recognize the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, as well as, the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product. This guidance is intended to facilitate progress to this desired state.

II. Comments Received on the Draft Guidance

In the **Federal Register** of September 5, 2003 (68 FR 52781), FDA published a document announcing the availability of a draft version of this guidance. The draft guidance was issued with the goal of soliciting comments from the public on related issues. The agency received a number of comments on the draft guidance, and those comments were considered carefully as the guidance was finalized. A number of changes were made to the guidance. Most of them were of an editorial nature. The following three substantive changes were made to the guidance as a result of the comments: (1) The scope of the guidance was expanded to include the Center for Drug Evaluation and Research's Office of Biotechnology Products, (2) links were established to ASTM Technical Committee E55 entitled ''Pharmaceutical Application of Process Analytical Technology,'' and (3) the section on process understanding was moved forward to emphasize the guidance's focus.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative

approach may be used if the approach satisfies the requirements of the applicable statutes and regulations.

III. Electronic Access

Persons with access to the Internet may obtain the guidance at either *http://www.fda.gov/cder/guidance/index.htm* or *http://www.fda.gov/ohrms/dockets/default.htm*.

Dated: September 28, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Docket No. 2003D–0382]

Food and Drug Administration

Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled ''Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice.'' This guidance explains FDA's current thinking on manufacturing of sterile drug products produced by aseptic processing in the context of complying with certain sections of the current good manufacturing practice (CGMP) regulations for drug and biological products. This guidance is issued with the goal of providing clear and consistent communication of regulatory expectations to promote voluntary compliance with current FDA requirements.

DATES: General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT:

Richard Friedman, Center for Drug Evaluation and Research (HFD–320), Food and Drug Administration, 11919 Rockville Pike, Rockville, MD 20852, 301–827–9031; or

Robert Sausville, Center for Biologics Evaluations and Research (HFM–624), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6201; or

Robert Coleman, Office of Regulatory Affairs (HFC–240), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 404–253–1295.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''Sterile Drug Products Produced by Aseptic Processing— Current Good Manufacturing Practice.'' This guidance explains FDA's current thinking on manufacturing of sterile drug products produced by aseptic processing in the context of complying with certain sections of the CGMP regulations for drug and biological products (21 CFR parts 210, 211, and 600 through 680, respectively).

In the **Federal Register** of September 5, 2003 (68 FR 52782), FDA announced the availability of a draft guidance entitled ''Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice.'' The draft guidance was finalized after consideration of received public comments. Consistent with the objectives of FDA's CGMPs for the 21st Century initiative, this guidance provides updated information regarding CGMP expectations for aseptic processing facilities, reflects the latest science in the area of sterile drug quality, and promotes innovations in manufacturing that achieve increased sterility assurance. Through this guidance, FDA hopes to facilitate a higher assurance of process consistency and promote better contamination prevention practices.

Sterile drug products are a high priority in FDA's risk-based inspectional program. These drug products are generally of high therapeutic significance. Clarifying relevant regulatory standards for sterile drug products will help reduce the incidence of manufacturing problems with this class of pharmaceuticals, thus facilitating the ready availability of these therapeutically significant pharmaceuticals and avoiding drug shortages.

This guidance document is the product of extensive public input. FDA first published a preview of its current thinking in the form of a concept paper on September 23, 2003. We presented our CGMP approach for aseptic processing at the Advisory Committee for Pharmaceutical Science on October 22, 2002. At this meeting, the concept paper was discussed in a public forum and critiqued by the advisory committee's members as well as a panel of invited aseptic processing experts. The advisory committee meeting yielded a number of issues that provided impetus for further discussion. In December 2002, an aseptic processing working group was formed under Product Quality Research Institute (PQRI) to address these issues. The working group, composed of 41 prominent aseptic processing experts from industry, academia, and FDA, prepared technical recommendations on the guidance document. The PQRI Steering Committee forwarded the working group's final report to FDA on March 19, 2003, and it was subsequently posted on PQRI's Web site (*www.pqri.org*).[1] The draft guidance was published on September 3, 2003.

The advisory committee and PQRI Working Group recommendations provided valuable contributions and many of these recommendations have been adopted in the guidance.

II. Comments Received on the Draft Guidance

A number of comments were received on the draft guidance, most of which concerned the need to further enhance the precision of guidance provided on certain topics. As a result, many clarifying changes were made. Major changes include the revision of the Sterility Testing section of the guidance to clearly emphasize and reference the United States Pharmacopeial Sterility Test <71>. In the guidance, table 1 entitled ''Air Classifications,'' which

[1] FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.