

# The PQRI Aseptic Processing Working Group

## What Was It? What Did It Cover? What Conclusions Did It Reach? Why Was It Important?

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Members of FDA, industry, and academia formed a working group within PQRI to openly discuss topics from a scientific perspective and provide formalized clarifications and recommendations to FDA to be considered and incorporated into FDA's draft guidance on aseptic processing.

### What was it?

The Aseptic Processing Working Group was formed in December 2002 within the Product Quality Research Institute (PQRI) to provide input on specific topics presented in FDA's concept paper "Sterile Drug Products Produced by Aseptic Processing." PQRI is a nonprofit organization designed to provide a neutral environment in which FDA, academia, and industry can collaborate on pharmaceutical product quality-related topics. For this reason PQRI was an appropriate choice in which to form such a group. As designed, it allowed members from FDA, industry, and academia to openly discuss the topics on the basis of science and then provide formalized clarifications and recommendations to FDA for their consideration and incorporation into FDA's draft guidance on aseptic processing. The working group, totaling 41 members, began its work on 23 December 2002 and issued its final report on 10 March 2003.

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### What did it cover?

Not all areas of FDA's concept paper were covered in the PQRI activity. Instead, several specific areas were identified as needing additional scientific input. Some examples of the topics covered were as follows:

- What is an appropriate number of units to be filled during process simulation (media fill)?
- What is an acceptable temperature range for the incubation of media fill units using trypticase soy broth and fluid thioglycollate medium?
- What is an appropriate limit for the contamination rate in a process simulation (media fill)?
- When should critical surfaces be monitored? What are appropriate expectations with regard to the results obtained?
- What is the maximum number of viable organisms allowed in air samples for the various classifications?

In total, the working group was asked to provide eight clarifications to existing text and make recommendations on 10 specific areas. As part of the working group's activities, an industry survey also was conducted to gather specific information regarding aseptic filling practices. The responses from more than 45 aseptic filling sites were received and collated for use by the team. Since that date several additional surveys have been received. The complete survey results, including the additional surveys received, will be published in the near future.

### What conclusions did it reach?

The working group's final clarifications and recommendations were developed on the basis of the expert knowledge of the working group members, survey results,

and publications where applicable. As examples, the working group reached the following recommendations on the topics of critical surface viable environmental monitoring and terminal sterilization—adjunct processing:

#### **Critical surface viable environmental monitoring**

- The selection of sample sites should be strategic in an environmental monitoring program. This should include consideration as to when, or if, a critical site should be monitored.
- Each manufacturer should review each type of process and the points of risk for product contamination. Consideration should be given to the level of contamination risk on the basis of factors such as difficulty of set-up, length or processing time, and effect of interventions.
- It is well understood that the sampling and incubation methods used in surface monitoring are manual operations that, because of personnel involvement, result in a low rate of false positives. For this reason, the detection of microorganisms on a critical site should not necessarily result in batch rejection but should be investigated. The other environmental monitoring data and procedures that support the operation should be reviewed to determine if the positive result is supported. If this review does not support the positive result and no negative trend exists for the critical surface site, there is a strong case for not rejecting the lot because of the positive result.
- PQRI strongly supports the concept discussed on line 993 of the concept paper that, when performed, “critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing.”

This recommendation is an example in which science led the expert working group to a recommendation that clearly identifies the limitations of the sampling methods used, the associated expected low false positives rate, and that a positive result, on its own, should not result in batch rejection unless other supporting information exists.

#### **Terminal sterilization—adjunct processing**

- No detail should be added to the current text present in the concept paper.
- The comment beginning on line 56 re-

garding adjunct processing should be reworded to clearly indicate that adjunct processing is not an expectation at this point.

- The group strongly recommends to PQRI that a group be formed within PQRI or another organization to further discuss and develop this topic.

For this recommendation the working group concluded that the concept of adjunct processing to increase sterility assurance was a sound scientific principal but should be further developed before it could be included, on a scientific basis, in a guidance document. In discussing the science and goal behind adjunct processing (which is not sterilization), the working group concluded that many of the current methods (e.g., use of standard biological indicators) and processes used to qualify a process would not be appropriate. For this reason the working group commented that added scientific discussion, research, and the establishment of new standard methods would be necessary to understand how adjunct processing might be used and what the expectations from a regulatory perspective should be.

This science-based approach can be seen in all the recommendations and clarifications. As a result of this effort, it is anticipated that all the working group’s recommendations and clarifications will be incorporated into the FDA’s draft guidance, which is expected to be published in the very near future. The final report containing all the recommendations and clarifications can be accessed at the PQRI Web site at [www.PQRI.org](http://www.PQRI.org).

#### **Why was it important?**

The PQRI Aseptic Processing Working Group completed a task that many felt might not be achievable. The concept of bringing together members from FDA, industry, and academia to develop science-based recommendations and clarifications on the topic of aseptic processing guidance was new, novel, and to say the least, a bit intimidating for all parties involved. The PQRI process proved that when we bring together true experts from industry, FDA, and academia and base our discussions on science, we can together develop good guidance that is rooted in science, which is good for regulators, industry, and consumers. **PT**