

Aseptic Processing Working Group Work Plan

Overview:

The PQRI Aseptic Processing working group will cover a defined list of points. The composition of the group will be made up of experts from the FDA, industry, and academia. The points to be covered have been divided into two categories: points for which recommendations will be made and points for which clarification comments will be made.

Working Group Members:

James P. Agalloco Agalloco & Associates	Carol M. Lampe Baxter Healthcare Corporation
James E. Akers, Ph.D. Akers Kennedy & Associates	John Lindsay Aseptic Solutions Inc.
Barbara Bassler Bridge Associates International	Russell E. Madsen PDA
Martyn Becker Merck & Co.	Andy Minor Eli Lilly & Co.
Susan Bruederle FDA	Leonard Mestrandrea Pfizer Inc.
Don Burstyn Alkermes	Kenneth Muhvich, Ph.D. Micro-Reliance.
Roger Dabbah USP	Terry Munson KMI/PAREXEL, Inc.
Roger Deschenes Astra Zeneca	Rainer F. Newman Johnson & Johnson
Joseph Famulare FDA	Jean I. Olsen GlaxoSmithKline
William R. Frieben, Ph.D. Pharmacia Corporation	Robert Sausville FDA
Rick Friedman FDA	Neal Sweeney FDA
John G. Grazal AstraZeneca Pharmaceuticals	Ian D. Symonds GlaxoSmithKline
Klaus Haberer Compliance Advice & Services	✓ Laura Thoma, Ph.D University of Tennessee
Nigel Halls, Ph.D. GlaxoSmith Kline (ret.)	Debbie Trout FDA
Karl L. Hofmann Bristol-Myers Squibb Co.	Martin Van Trieste Abbott Laboratories
David Hussong FDA	Brenda Uratani FDA
Richard M. Johnson Abbott Laboratories	Richard T. Wood, Ph.D. Pfizer, Inc.
Kunio Kawamura Otsuka Pharma. Co., Ltd.	Glenn E. Wright Eli Lilly & Co.
Lee Kirsch, Ph.D. University of Iowa	Jeff Yuen Jeff Yuen and Associates

✓ Indicates Not Confirmed

Process:

The working group will work on the 10 recommendations and 8 clarifications as a single group. A project kickoff meeting will be held the first week in January. Members will be required to attend one 90-minute conference call each week.

Listed below are the working groups deliverables and the processes to be used. Included in the deliverables is the industry survey.

- Clarifications
 - Clarifications on 8 specific topics are to be worked on by the working group.
 - Topic leaders will be chosen from the PQRI working group for each point.
 - Suggested redline clarifications are to be made by the working group and sent to the topic leader. This activity is to begin in early January.
 - The topic leader will collect and collate the suggested clarifications and develop a redline strikeout version of the text that incorporates the various suggestions.
 - The topic leader will lead discussions on the clarifications and make the modifications needed.
 - A final clarification will be developed and approved by the working group.
 - The redline clarifications are to be completed by January 31st and sent to the PQRI steering committee for approval.
- Survey
 - An industry survey will be performed to collect current industry information.
 - The survey will be a data collection type of survey designed to provide information on the industries current practices.
 - The target date to receive completed surveys will be January 20th.
 - The surveys will be blinded by PQRI and data tabulated.
 - The tabulated data will be provided to the work group on February 4th.
- Recommendations
 - Recommendations on 10 specific topics are to be worked on by the working group.
 - Discussions relating to environmental monitoring and sterilization options will be lead by Carol Lampe while the discussion on process simulation and aseptic processing isolators will be led by Richard Johnson. Discussions are targeted to begin the first week in February.
 - The recommendations are to include the question being asked, the recommendation being provided and a brief rational section that provides information on how the recommendation was reached.
 - A final recommendation will be approved by the working group.
 - The recommendations must be completed by February 28th and sent to the PQRI steering committee for approval.

Timeline:

- Week of December 16th - Work Plan and Survey sent to Steering Committee for approval.
- Week of December 23rd - Survey sent to companies.
- First week in January - Work group begins work on clarifications.
- January 20th - Surveys due to PQRI.

- January 31st - Clarification work completed and sent to Steering Committee for Approval.
- February 4th - Survey results compiled and provided to work group.
- First week in February - Work Group begins work on recommendations.
- February 28th - Work group completes recommendations and sends the recommendations to PQRI Steering Committee for approval.

Clarifications:

The PQRI working group will develop suggested clarifications for the following 8 points. The clarifications will be presented in the form of redlined revisions to the current text.

1.) *Concept Paper Line Number Reference: 637*

Subsequently, routine semi-annual revalidation runs should be conducted for each shift and processing line to evaluate the state of control of the aseptic process.

Clarification: What clarification should be provided in regards to each shift to help the reader understand that the process simulation needs to represent the various shifts but that a separate media fills for each shift may not be required.

2.) *Concept Paper Line Number Reference: 984*

Written procedures should include a list of locations to be sampled. Sample timing, frequency, and location should be carefully selected based upon its relationship to the operation performed. Samples should be taken throughout the aseptic processing facility (e.g., aseptic corridors; gowning rooms) using appropriate, scientifically sound sampling procedures, standards, and test limits.

Clarification: What clarification should be provided for the term “test limit” so that it is not confused with a specification?

3.) *Concept Paper Line Number Reference: 1047*

Upon preparation, disinfectants should be rendered sterile, and used for a limited time, as specified by written procedures. Disinfectants should retain efficacy against the normal microbial flora and be effective against spore-forming microorganisms. Many common sanitizers are ineffective against spores, for example, 70% isopropyl alcohol is not effective against *Bacillus*, spp. spores. A sporicidal agent should be used regularly to prevent contamination of the manufacturing environment with otherwise difficult to eradicate spore forming bacteria or fungi.

Clarification: What clarification should be suggested regarding a disinfectants efficacy against spore forming microorganisms?

4.) *Concept Paper Line Number Reference: 1055*

After the initial assessment of sanitization procedures, ongoing sanitization efficacy should be frequently monitored through specific provisions in the environmental monitoring program, with a defined course of action in the event samples are found to exceed limits.

Clarification: What type of clarification should be made in regards to expectations surrounding sanitization efficacy being monitored by the environmental program?

5.) *Concept Paper Line Number Reference: 1070*

b. Active Air Monitoring-

Manufacturers should be aware of a device's air monitoring capabilities, and should determine suitability of any new or current devices with respect to sensitivity and limit of quantification.

Clarification: What type of clarification should be made in regards to determining the suitability of new or current devices and the comment around sensitivity and limit of quantification?

6.) *Concept Paper Line Number Reference: 1419*

Properly operated RTPs (rapid transfer ports) are also generally considered to be an effective transfer mechanism. The number of transfers should be kept to a minimum because the risk of ingress of contaminants increases with each successive material transfer.

Clarification: What clarification should be suggested regarding the number of RTP transfers and the risk of contamination?

7.) *Concept Paper Line Number Reference: 1033*

In addition to microbial counts beyond alert and action limits, the presence of any atypical microorganisms in the cleanroom environment should be investigated, with any appropriate corrective action promptly investigated.

Clarification: What clarification should be suggested regarding the expectation concerning the “typical microflora”, and the definition for an atypical microorganism?

8.) *Concept Paper Line Number Reference: 981*

Evaluating the quality of air and surfaces in the cleanroom environment should start with a well-defined written program and validated methods. The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces in contact with product and container/closures.

Clarification: What clarification should be made regarding the validation of the environmental monitoring methods?

Recommendations:

The PQRI working group will develop recommendations using data from the industry survey as well as good scientific principals for the following 10 points (questions). The recommendation format will follow the example given in the Attachment.

Process Simulations

1.) *Concept Paper Line Number Reference: 661*

Questions: What is an appropriate number of units to be filled during a process simulation (media fill)?

2.) *Concept Paper Line Number Reference: 730*

Question: What is an acceptable temperature range for the incubation of media fill units using TSB and FTM? If alternative practices are used what type of justification is required?

3.) *Concept Paper Line Number Reference: 787*

Question: What is an appropriate limit for the contamination rate in a process simulation (media fill)?
 What is an appropriate target for contaminated units in a process simulation (media fill)?

Environmental Monitoring

4.) *Concept Paper Line Number Reference: 981*

Question: When should critical surfaces be monitored? What are appropriate expectations in regards to results obtained?

5.) *Concept Paper Reference Line Number Reference: 1014:*

Question: What data should be considered when establishing monitoring limits? What is an appropriate frequency for re-evaluating monitoring limits?

6.) *Concept Paper Line Number Reference: 82*

TABLE 1- Air Classification^a

Clean Area Classification	≥0.5 um particles/ft ³	≥0.5 um particles/m ³	Microbial Limit ^b	
			cfu/10 ft ³	cfu/m ³
100	100	3,500	<1 ^c	<3 ^c
1000	1000	35,000	≤2	≤7
10,000	10,000	350,000	≤5	≤18
100,000	100,000	3,500,000	≤25	≤88

a - All classifications based on data measured in the vicinity of exposed articles during periods of activity.

b- Alternate microbiological standards may be established where justified by the nature of the operation.

c- Samples from class 100 environments should normally yield no microbiological contaminants.

Question: What is the maximum number of viable organisms allowed in air samples for the various classifications?

Aseptic Processing Isolators

7.) *Concept Paper Line Number Reference: 1369*

Question: What type of airflow is required in closed isolators?

8.) *Concept Paper Line Number Reference:1372*

Question: What is the appropriate requirement for air handling systems in isolators?

9.) *Concept Paper Line Number Reference: 1448*

Question: What are appropriate methods for use in the development of decontamination cycles?

Sterilization Options

10) *Concept Paper Line Number Reference: 57*

Question: With respect to terminal sterilization and adjunct processing what flowcharts represent the most risk-based and scientifically developed approach?