Recent USP Updates

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Bioburden Control of Non-sterile Drug Substances and Products <1115>

- The chapter emphasizes control as a risk mitigation strategy
- The chapter recommends a risk-based approach to bioburden control in non-sterile drug products

Content of <1115>

- Introduction
- Guidance Documents
- Microbial Control Considerations in Product Development
- Microbial Control Considerations in Routine Manufacturing
- Water Systems and Usage
- Role of Active Pharmaceutical Ingredients, In-process Materials and Excipients
- Equipment Design and Use Considerations
- Personnel
- The Manufacturing Environment
- Microbial Assessment of Non-sterile Product Manufacturing Environments
- Microbial Sampling
- Microbial Control of Drug Substance Manufacturing
- Overall Management of a Microbiological Control Program

<1115> approach

- A scientific approach to the management of the microbial bioburden in non-sterile products requires consideration of patient risk and control objectives.
- A risk-based approach to control potential contamination in non sterile product manufacturing.

  It is important to understand that the manufacture and management of microbiological content of non-sterile products is distinctly different from that required for sterile products.

Microbiological Influences

What to learn from <1115>

- A microbiological contamination control program should be developed with identifying and controlling product risk based upon a formal assessment of risk modalities.
- The risk analysis activity should result in the establishment of critical control points and should facilitate proper equipment selection, process and facility design requirements.
- To be published in July –August 2013 issue of Pharmacopeial Forum.

<1116> Microbiological Control and Monitoring of Aseptic Processing

USP 35 NF 30 (2012)

- ISO-14644 standards are referenced for clean rooms
- **New paradigm for monitoring control of clean rooms based on trending contamination rates**
- Discussion about uncertainty of microbial recovery in ultra clean environments

Overview of <1116>

- Contamination rates suggested instead of alert and action levels for manned and unmanned environments.
- Suggestion for investigation in the event of a significant excursion, which is defined as >15CFU for surface, personnel, or active air sampling.
- Discussion on analytical measurement and result interpretation.
- Intended to be applied only for environments in which aseptic processing is performed / supported;
- Drops all reference to EU Grades; all clean room classification is based upon ISO 14644.

Contamination Rate Table 3

Grade	Active air sample	Settle Plate (9cm) 4hr exposure	Contact Plate or Swab	Glove or Garment
Isolator or Closed RABS (ISO 5 or better)	<0.1%	<0.1%	<0.1%	<0.1%
ISO 5	<1%	<1%	<1%	<1%
ISO 6	<3%	<3%	<3%	<3%
ISO 7	<5%	<5%	<5%	<5%
ISO 8	<10%	<10%	<10%	<10%

Classifications and Applicability in <1116>


- A comment made by several stakeholders on the final revision of <1116> was that they could not meet the incidence rate expectations for some ISO 7 and ISO 8 rooms.
- This question raises a general issue regarding attempts to apply similar or identical requirements to rooms of the same classification but differing contamination control intention.
- Not all rooms of the same ISO classification can be expected to perform at the same level of microbiological contamination control.

Aseptic Processing and <1116>


- We developed <1116> with the intention that it applied only to classified clean space in which full aseptic gowning was required.
- ISO 7 or 8 environments that do not require full aseptic gowning will in most cases not meet the contamination rates recommended in <1116>.
- <1116> will not apply to many preparation rooms, sterilizer rooms, corridors, or even changing rooms prior to the donning of the full aseptic gown.
- Users should develop their own rate criteria for their controlled and classified environments that do not require complete aseptic gowning.

Summary of <1116>

- We believe that the contamination rates in <1116> are routinely attainable in aseptic environments where typical full gowning is required.
- Microbiological classification of environments is not a value added activity.
- It is analytically wrong to treat minor differences such as 1CFU compared to 3 or 4CFU to be significant from a process control perspective.
- EM should be treated as a general hygienic survey rather than a measure of sterility assurance.

Why the designation of 15CFU as a significant excursion?

- Assessment of environmental contamination is not a precise science, it is not at all clear that a finding of 8CFU is clearly more significant that one of 2CFU or 3CFU.
- 15CFU is a result that is more likely to be the result of a significant excursion rather than the result of a sampling artifact.
- If a finding of 15CFU or more turns out to be an isolated finding and does not correlate with short term increase in contamination rate it may not warrant any corrective action.

Two General Information chapters

- Aseptic Process
- Bioburden Control of Non-sterile

A pragmatic approach to educate