Aseptic Processing – Achieving Sterility by Design

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FDA Aseptic Perspective

“In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization.”

FDA, Aseptic Processing Guidance 2004
Aseptic Processing Definition

“Handling sterile materials in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.”

PDA, TR# 22, 2011 revision
Sterility & Sterility Assurance - 1

• Sterility is an absolute concept, and cannot be directly measured.

• Sterility assurance is easy to define, but no easier to quantify:
  • In sterilization, it is estimated using a PNSU (or SAL) for each process. Actual sterilization process performance is much better than the minimum expectation of 1x10^-6.
  • In aseptic processing, process simulation demonstrates a maximum contamination rate from a point-in-time evaluation.

• Neither sterility nor sterility assurance can be accurately quantified!
Sterility & Sterility Assurance - 2

• There are no direct means to measure sterility assurance in aseptic processing.
  • Sterility testing is severely limited by sample size and microbial recovery.
  • Environmental monitoring suffers from inadequate recovery and limited sample size. In addition it’s not looking at the production materials.
  • Process simulation demonstrates maximum contamination rates in an individual exercise.

• All are means for testing ‘sterility into the product’! They are unacceptable as ‘proof’ of anything, let alone something as important as patient safety.
Sterility Testing, Environmental Monitoring & Media Fills cannot assure Product Sterility
Sterility Testing

• Sterility testing is so severely limited statistically it could be renamed “the test for gross microbial contamination”.
• The sterility test was introduced in the 1930’s when lot sizes were smaller, processing was manual and contamination rates were likely much higher. Advances in process capability have made it more of a ceremonial regulatory exercise, than an effective means of process control.
Limitations of Sterility Testing
Environmental Monitoring

• Viable monitoring is not an ‘in-process sterility test’.
• Microbial monitoring can never recover all microorganisms present in the air or on a surface.
• The absence of microorganisms in an environmental sample is not confirmation of asepsis; nor is their presence indicative of process inadequacy.
• Aseptic processing does not require a ‘sterile’ environment, but even if it did we’d never be able to prove an environment was actually ‘sterile’ anyway.
Environmental Monitoring

• The recovery efficiency of active air samplers varies as much as 5-10 fold.
• There are no ‘standard’ methods for use in environmental monitoring.
• Environmental monitoring recovers only a small percentage of the actually microorganisms present.
• Sampling can never ‘measure’ the actual environmental conditions.
• The difference between a recovery of 1 CFU and 5 CFU is not microbiologically significant.
Monitoring Realities

• Aseptic environments (including isolators) aren’t now and never have been ‘sterile’.

• Detection of low numbers of microorganisms in manned cleanrooms should be considered a rare, but not unusual event.

• Investigations into recoveries of low numbers of human related microorganisms in manned cleanrooms is predominantly a make work exercise. There’s few sustainable corrective actions that can be taken when it does occur.

• Significant excursions (>1 log higher) from the routine microbial prolife should be investigated.
Media Fills / Process Simulations

• Media fills or process simulation are point in time assessments of aseptic process capability and even then only confirm a maximum contamination rate, not a level of sterility assurance.

• Media filling EM has the same recovery limitations as routine EM sampling.

• It’s a snapshot in time, and the media fill results are very difficult to use effectively in the assessment of prior lots or prediction of future performance.
Process Simulations

• They cannot establish the ‘sterility’ of any material.

• Process simulations in excess of 5-10,000 units are of limited value. Media fills longer than the duration of a single operator’s work session have no real value. Aseptic operations are specifically designed not to increase in microbial level over time with personnel present.

• Their best use is in the evaluation of aseptic set-up and intervention practices.
• Rapid microbiology only gives the same uncertain results somewhat sooner than before. The limitations of sample size, density/frequency and recovery efficiency are unchanged.

• Fluorescence or real-time RNA/DNA tests may confirm the presence of microorganisms we should already understand are present. That knowledge doesn’t change anything, though it might cause some anxiety.
Advanced Microbial Methods - 2

• The ‘holly grail’ for sterility testing would be a non-destructive and 100% effective method suitable for use at high speeds across the full range of products, containers and microorganisms. Nothing like that exists.

• There’s questions on how to use a test like that even if it did exist:
  • Viable, but non-culturable microorganisms
  • Population threshold to create actual infections
  • Correspondence to current controls
  • ??
Last Word on Microbial Tests

• None of the current microbial methods are capable of ‘proving’ sterility or sterility assurance!!

• The newer methods aren’t going to enable that either.
  • They share the same sampling limitations,
  • and/or
  • They tell us something we already understand.
• Given the number of influences on sterility assurance, let’s reconsider what really provides the ‘sterility’ of an aseptically produced product.

• We must view the goal of avoiding microbial contamination holistically and address each of the supportive elements to optimize them individually and collectively to provide the highest confidence in the overall aseptic process.
Influences on Sterile Products

Adapted from Leonard Mestrandrea
Risk In Aseptic Processing

• Globally, there’s a great deal of interest in risk assessment in the pharmaceutical industry.
• It’s been greatest with respect to aseptic processing.
• Dr. William Whyte led the way to more rigorous methods, but until recently most aseptic risk evaluation has been informally done.
• The following images show how risk was reduced over time.
The Aseptic Evolution - 1

~1915 Hand Fill
The Aseptic Evolution - 2

~1935 Semi-automatic Hand Fill
The Aseptic Evolution - 3

~1950 Glovebox Filling
The Aseptic Evolution - 4

~1965 Manned Cleanrooms
The Aseptic Evolution - 5

~2000 RABS
The Aseptic Evolution - 6

~1995 Isolators
The Aseptic Evolution - 7
The objective never changed

• Throughout the evolution of aseptic technology there’s a single theme - Move the operator farther and farther away from sterile materials
  • Initially, just with barriers between operator and sterile items.
  • Next, using automation of filling and sealing.
  • Then, with more complete separation.
  • Lastly, with extensive automation and advanced technology.

• All with the same goal - avoidance of contamination risk from the operator.
Success in Aseptic Processing

• For the present, we need to make the operator’s role less invasive and more remote.

• The most capable aseptic processing systems are those that operate without direct human intervention.

• For all others the goal should be to enable the operator to successfully execute the aseptic processing activities on their ‘worst’ day. Only than can we be even somewhat confident in the outcome.
Risk in Aseptic Processing

• There are 2 distinctly different elements of risk management with aseptic processing
  • Risk Assessment / Analysis – efforts to quantify the risks resulting from the prior decisions.
  • Risk Mitigation – consideration of contamination potential during the design of facilities, selection of equipment, definition of procedures and operation of the process itself.

• Risk assessment is a hot topic in the industry; far more important is the risk mitigation exercise that should be used to reduce level of identified risks.
Risk Mitigation->Sterility by Design

• Risk mitigation is more important, because it should result in actual improvements to the aseptic process.
• Risk mitigation entails application of the elements of “Sterility by Design” described in this presentation that are intended to provide meaningful reduction in contamination rates and thus reduction in risk to the patient.
Influences on Aseptic Processing

- Raw Materials
- Equipment Utensils
- Containers / Closures
- Procedures
- People
- Environmental Air Supply
Contributors to Sterility Assurance

- Facilities
- Environmental Air Systems
- Equipment / Utensils
- Containers / Closures
- Product / Product Delivery
- Procedures
- Personnel
Facilities
Facilities

• Facilities should be designed for easy sanitization / decontamination through proper use of construction materials, ease of access and design details that facilitate cleaning.
Facilities

- Facility layouts should minimize the potential for mix-ups, contamination and cross-contamination.
Facilities

• Advanced aseptic processing designs such as closed RABS and isolators should be given preference in selection of processing environments.
Facilities

• All facility / environmental surfaces should be resistant to the potential corrosive action of sanitizing and decontamination agents.

• The aseptic portion of the facility should be maintained in ‘clean’ state at all times and periodically sanitized or decontaminated. Isolators and closed RABS should be treated with sporicidal agents on a periodic basis.
Facilities

• Only a minimum of materials should be retained in the aseptic portion of the facility.
Environmental Air Systems
Environmental Air Systems

- Air flow patterns should facilitate the removal and/or exclusion of contamination from critical environments.
Environmental Air Systems

• Air systems should provide adequate air pressurization to preclude the ingress of contamination from surrounding less clean environments.

• Air systems should be supplied with HEPA filters that are periodically integrity tested.
Environmental Air Systems

• Differential pressure should be monitored and alarmed to demonstrate continuous integrity of the core aseptic area.
• Interlocks should be utilized to prevent inadvertent pressure reversal.
Environmental Air Systems

- Temperature and humidity should be controlled to maximize personnel comfort during operations consistent with product stability/safety requirements.
Environmental Air Systems

• Progressively cleaner environments should be utilized as products, components, and equipment are cleaned, prepared for sterilization, and eventually assembled into the finished product.

• The environments should be decontaminated on a periodic basis to minimize microorganisms present during operations.
Equipment / Utensils
Equipment / Utensils

• Product contact surfaces of equipment must be sterilized by a validated method.
Equipment / Utensils

• Equipment should be assembled to the fullest extent possible prior to sterilization.

• Sterilization-in-place and clean-in-place should be utilized wherever possible.
Equipment / Utensils

• Equipment and utensils should be sterilized in sealed containers. The use of paper and tape is not recommended.
Equipment / Utensils

• Equipment and utensils should be sterilized / depyrogenated using a just-in-time approach. Inventories of materials in the aseptic environment should be minimized.
• Equipment should be selected for high reliability, ease of change over and adjustment.
• Remote adjustment of equipment parameters should be utilized where possible.
Equipment / Utensils

• Tool free change over from one format to another should be possible.
• Equipment should be tolerant of container / closure miss-feeds, jams and other problems to minimize the need for interventions.
• Equipment (and to some extent the facility itself ) should use PAT and other feedback systems for ease of control, operation, and documentation.
Containers / Closures
Containers / Closures

- Containers / closures must be prepared and sterilized / depyrogenated using a validated process.
Containers / Closures

- Containers / closures should be introduced in a manner that retains at least one layer of sterilized protective covering or wrap until entry into the critical zone.
Containers / Closures

- Containers / closures should be selected for reliability of handling in the processing equipment.
- Containers / closures should be sterilized / depyrogenated using a just-in-time approach. Inventories of materials in the aseptic environment should be minimized.
Containers / Closures

• Containers / closures should of suitable quality for their intended use. Higher AQL’s for defects can result in a reduction in the need for interventions.

\[ C_{pk} = \frac{\min(\bar{X} - SL)}{3\sigma} \]

| \( C_{pk} \) | \( |X - SL| \) | Expected Avg. OOS%* |
|-------------|----------------|---------------------|
| 2           | 6\( \sigma \)  | -0                  |
| 1.7         | 5\( \sigma \)  | -0                  |
| 1.33        | 4\( \sigma \)  | 0.003%              |
| 1           | 3\( \sigma \)  | 0.135%              |
| 0.7         | 2\( \sigma \)  | 2.28%               |
| 0.33        | 1\( \sigma \)  | 15.9%               |

Industry Practice is to consider processes with \( C_{pk} \) below 1.33 as “not capable” of meeting specifications.

*Percent out of specification beyond the high risk specification limit.
Product / Product Delivery
Product / Product Delivery

• The product should be sterilized using a validated process, and delivered to the aseptic processing environment in a manner that protects its sterility.

• Any connections necessary to deliver sterilized product should be made in the critical zone of the aseptic processing area.

• Complex / difficult products. i.e., sterile powders, suspensions, etc. further complicate delivery.
Procedures
Procedures – Sanitization

• The environments should be decontaminated on a periodic basis to minimize microorganisms present during operations.
• These should be performed by specifically trained and extremely diligent personnel.
Procedures - Monitoring

• Monitoring must not subject the product to increased risk of contamination. No monitoring is preferable to monitoring that risks contamination.

• Environmental monitoring that relies on interventions should be subject to same constraints and expectations.

• Monitoring must be recognized as subject to adventitious contamination unrelated to the environment, material or surface being sampled.
Procedures – Monitoring

• The environments should be periodically monitored to establish their suitability.
Procedures - Operating

• Processes should be defined to eliminate / minimize interventions throughout the process.
Procedures

• All interventional activities should be carefully defined, practiced and executed using proper aseptic technique

• Particular consideration should be given to corrective interventions with the goal of reducing their impact and frequency.

• Intervention procedures should be established in detail for all inherent interventions, and more broadly for corrective interventions (where some flexibility is necessary due to their greater diversity).

The Truth about Interventions In Aseptic Processing

James Agalloco and James Akers

Pharmaceutical Technology Aseptic Processing 2007
Interventions Types

• **Inherent interventions** are required parts of the aseptic process and necessary in every batch.

• **Corrective interventions** are activities that address failures of the equipment, or components to perform as expected and may not be a part of every batch.

• **Critical interventions (a repeat of a portion of the set-up)** require direct contact with sterile product contact surfaces, e.g., replace fill pump, stopper track, stopper bowl, in-line filter, etc.

• **Heroic interventions** *activities that really should not be permitted because of excessive contamination risk.*

• **New Interventions** are corrective or critical interventions not previously considered.
Interventions & Risk

• Inherent interventions - *Least risk*
• Corrective interventions - *Greater risk*
• Critical interventions - *Greatest risk*
• Heroic interventions - *Excessive risk*
• New Interventions - *Unknown risk*
The Proper View of Interventions

• Interventions always mean increased risk to the patient.
• There is no truly safe intervention.
• Interventions are to be
  • Eliminated if possible,
  • Have their frequency reduced,
  • Simplified with respect to their execution.

• The ‘perfect’ intervention is the one that is eliminated from the process!
Personnel
Personnel

• The aseptic operator is the primary source of contamination in aseptic processing. The design concerns for the other contributing factors in aseptic processing are intended to reduce the impact of the operator on the materials.

• “It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identified.” - Hank Avallone – circa 1988
The 90 Kg gorilla in the room
Conclusion
“Many of the things you can count, don't count, and many of the things you can't count really count.”

Sign in Albert Einstein’s office
Sterility by Design

• As aseptic technology has changed, the importance of design has increased while that of microbial testing has decreased.
• Reliance on microbial testing as a means for establishing the ‘sterility’ of materials must continue to be reduced as process capability improves even further.
• Increasingly ‘sterility’ has been attained through adherence to “Sterility by Design” concepts, though it was never called that.
Sterility by Design

• The phrase may be new; the thinking isn’t.
• Informal risk mitigation brought about the technology advances seen in aseptic processing.
• Confidence in aseptic processing is not derived from monitoring or testing; it is the result of attention to detail in aseptic processing design.
• With newer technologies the emphasis must shift even farther from monitoring & testing.
Reference