Changing Paradigms in Aseptic Processing

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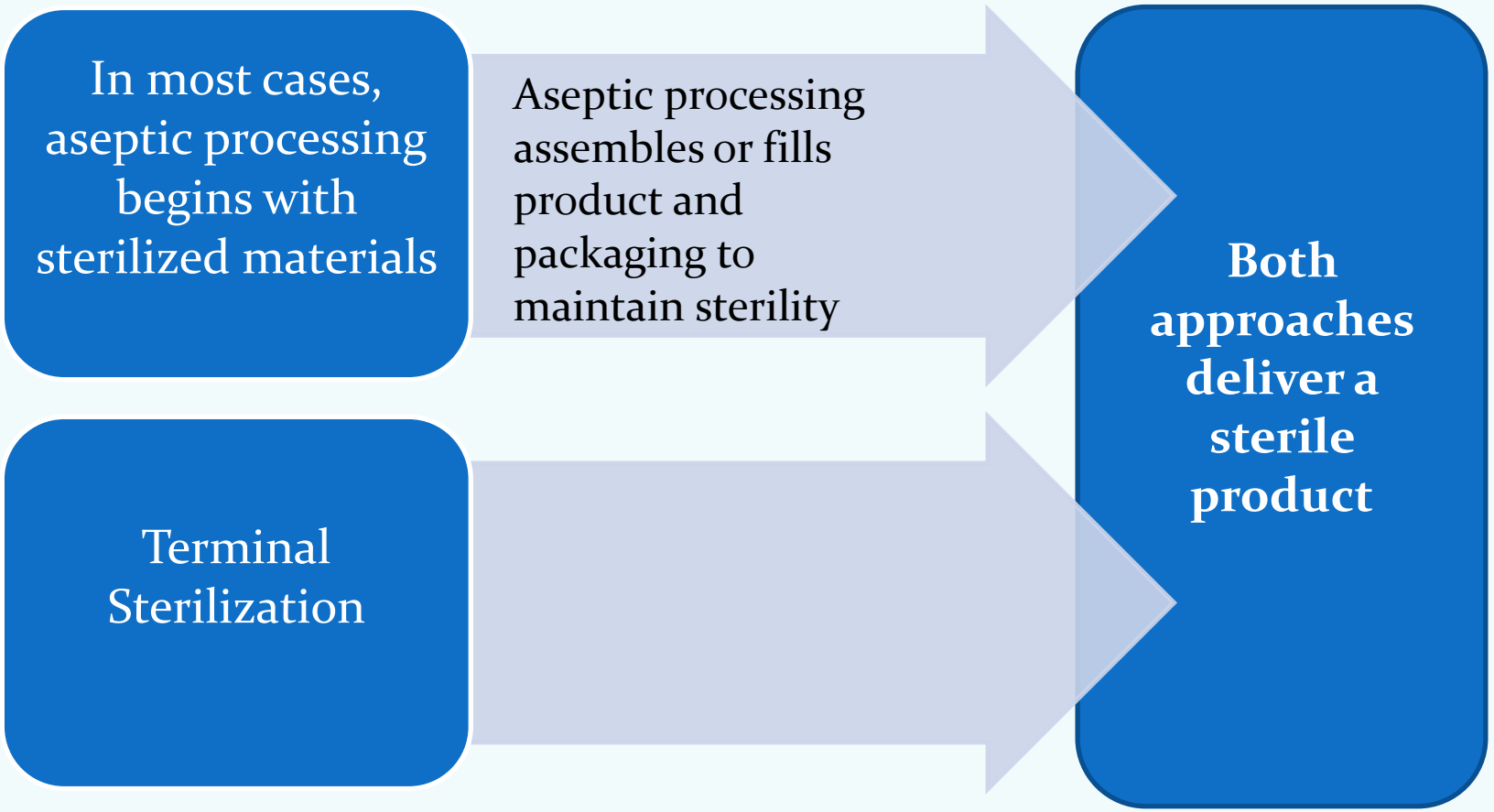

In most cases, aseptic processing begins with sterilized materials
Terminal Sterilization
Aseptic processing assembles or fills product and packaging to maintain sterility
Both approaches deliver a sterile product

Sterility, Sterilization and Sterility Assurance - Definitions

Sterile/Sterility

- **Sterile/Sterility** is a simple concept. Most dictionary definitions say, “free from living microorganisms”
  - Generally the microorganisms of interests are bacteria, yeasts and molds
  - Definition of sterile is straight forward, determining and proving sterility is not
  - Current methods are destructive and therefore limited
  - No one method reliably detects the entire range of microorganisms

Sterilization

- **Sterilization** is any process intended to kill or remove microorganisms
  - Processes lethal to microorganisms include heat, radiation, and chemical exposure
  - Sterilization processes have defined parameters, developed and confirmed by their lethality effects on standardized microorganism of a relatively high resistance, e.g. spores of *Geobacillus stearothermophilus,* a BI to confirm steam sterilization efficacy
  - Sterile filtration retains, or precludes microorganisms from the process, but is not lethal to microorganisms.

Sterility assurance

- **Sterility assurance** is the degree of confidence we have that each unit is sterile.
  - For terminal sterilization the ability of the process to kill the appropriate BI can be equally as a Sterility Assurance Level (SAL), which is essentially the log of the number of BIs killed by the process.
  - The commonly used SAL of 10^{-6} means that the process resulted in less than one survivor in a population of one million BI organisms.

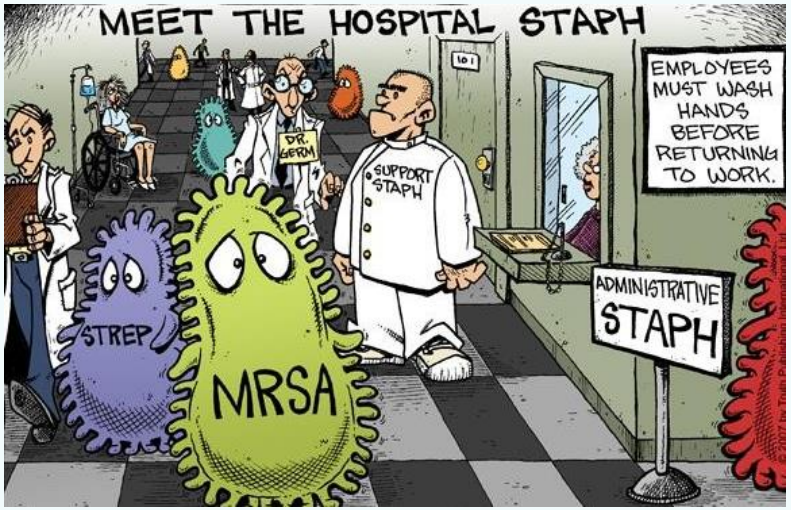
Sterility assurance

- In terminal sterilization, achieving the appropriate SAL or an equivalent surrogate measure is the basis for claiming sterility
- In aseptic processing, we have a problem, SAL does not apply
- Although references persist claiming Aseptic Processing has an SAL of 10^{-3}
- Moreover, in AP no single test or battery of tests, calculations or assessments yields a numerical result relative to sterility
- AP becomes a continuing exercise of trying to prove a negative, i.e., no microorganisms.

Aseptic Processing Risks – Getting it Close to Right

- US hospital annual admission rate ~12% (35MM).
- About 5% (1.75MM) of US admissions result in at least one HAI.
- About 25,000 – 35,000 (2% of infected) die due to HAI

  the odds of dying from an infection you didn't have before the hospital admission 1:1250:
  - Bicycle
  - HAI
  - Motorcycle
  - …
  - Plane crash



More on HAI

- In a UK survey an HAI rate of 7.8% was identified.
- Infected patients, on average, incurred hospital costs 3 times higher than uninfected patients
- The most frequently identified cause of HAI reported by CDC in 2011 include
  - ventilator associated pneumonia
  - surgical site infection
  - urinary tract catheters
  - central line blood infections
  - Gastrointestinal infections
- Absent are reports of infections determined to be from Tier 1 sterile drugs
- Between 500MM and 1BN doses of sterile drugs are produced world-wide each year. The majority is aseptically produced and most from Tier 1

HAI

- Re-usable vs. single use surgical tools and devices.
- In order of highest to lowest risk, how would you rate these if you were admitted to a hospital?

- IV lines
- Catheters
- OR contamination
- Tier 1 produced drugs
- Pharmacy compounded drugs
- Single use surgical materials
- Multiple use surgical materials

Consider

What might it mean if sterile drugs were involved in 30,000 deaths annually?

Defining Tier 1 Operations

- Aseptic processing organizations that embrace and follow GMPs
- Sterile drugs produced by Tier 1 organizations have an exemplary record of patient safety… with regard to sterility
- What kinds of organization would not qualify?
  - HEADLINE Oct 9, 2012: *13,000 People Exposed to Big Pharma Shots Contaminated with Rare Fungal Meningitis. 8 Deaths reported*

Tier 1 Operations

Conclusion:
Tier 1 drug based infections occur at a statistical rate approaching 0%

Are we that good, that lucky, or both?

- We are pretty good, but we get some help from mother nature
- A properly designed and functioning Grade A/B space maintains an extremely low bioburden environment - But then we send in people and materials
- It is difficult to introduce airborne bioburden to a typical drug vial.
  - Sterile vials, stoppers and TSB – 0, 1hr, 2hr, 4 hrs, 8 hrs, 16 hrs, 48 and 72 hours. 2 vials at each point. No growth except a 72 hour vial with mold.
- Why? Stokes Law, inertia, etc.
- Our products frequently are not suited for microbial survival or proliferation. Biostatic, biocidal.

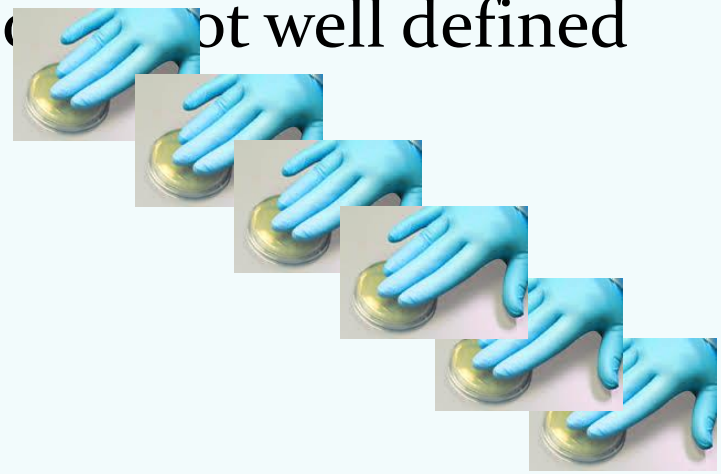
Changing Paradigms in Aseptic Processing

What am I trying to say?

- Am I advocating for less rigor? Lowered expectations of sterility? Not at all
- I am proposing better, more logical applications of science and technology by manufacturers and regulators in assessing risks

Surrogates for SAL in AP

- Assurance of sterility in AP is based on many parameters some are subjective, so[illegible]ot well defined
  - Facility design
  - Media fills
  - EM programs
  - Sterility Tests
  - Validation adherence
  - etc.
- Since there is always something more that can be done
- Since none of these are entirely satisfactory surrogates
- We typically do more… more media fills, more EM, more smoke studies, etc.



A Little History

- Compared to the 1980's, today we:
  - Lowered sterility test failure rates from a few percent to below 0.1% in many cases.
  - Increased the typical media fill from 3,000 units to about 10,000
  - Reduced the acceptable number of media fill positive units from about 0.1% to about 0.01%
  - Curtained A/B separation has largely given way to RABS and in some cases isolators.
  - Environmental sampling has spiked
  - Smoke studies once rare are now "required"
  - *Has the sterility risk improved as a result?*

A Note on Plate Counts

- Plate counting methods have been around for 100 years
- Colony counting gives is in CFUs… not number of organisms
- Keep in mind that the CFU count is at best an approximation and is always with a low bias
- Bacteria reproduce and die at logarithmic rates
- These factors suggest that it's illogical to declare 1 CFU acceptable and 2 CFU a failure
- And…. Every microbiological sample comes with an inherent additional risk….
  - Erroneous Count
  - Lack of statistical significance
  - Erroneous ID
  - And each is in effect an intervention.

Plate Counting vs. Rapid Methods (RMM)

- RMM has been available for some time
- Many organizations have investigated RMM
- Few use RMM in production or release settings, why?
- Plate count has been used everywhere for a century
- Not only is just about everyone using the plate method, most limits, guidelines and standards, are based on this technology.
- Different RMM technologies available, which is the right choice
- RMM typically yields numerical results higher than CFU

  Are you willing to apply RMM that results in higher counts than previously achieved?

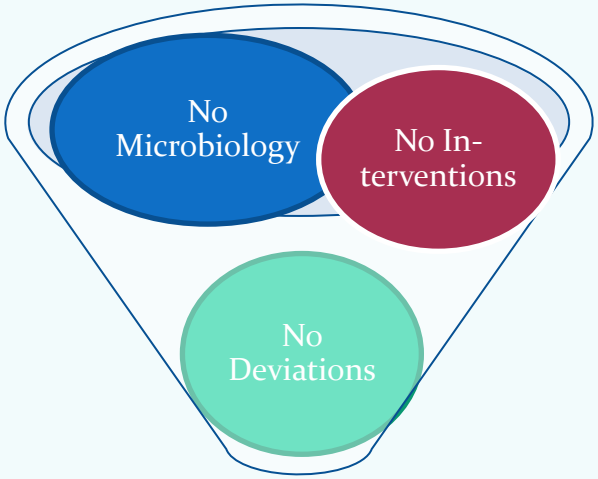
  Are you willing to bet that your RMM technology will be the preferred method a year from now?

More samples result in more deviations

- It would not be uncommon to find a large manufacturer with several sterile product lines and locations to be engaged in thousands even tens of thousands of hours conducting investigations
- Frequent outcome… a root cause finding often little more than the best guess
- CAPA… #1. Retrain the operatorsw, #2 Take more samples
- Net result, increased costs, reduced efficiencies, but has sterility improved?
- Even small aseptic facilities can approach or exceed $200MM in capital and run at an overhead rate approaching $50MM annually and rising

On Going Forward.

- I repeat… I do not advocate less vigilance, just better application of logic and science in assessing risks
- So – how might we go forward? How do we become more successful and competitive as AP organizations in the future?



New Paradigm

On Going Forward.

- **Deviations**
  - Deviations are at their root mostly human errors or faulty equipment function/design
- **Interventions**
  - Fallen vials
  - Stopper additions
  - Weight checking
  - Manual and paper record management
- We agree that people provide the highest risk of contamination in our aseptic operations.
- Sterile area gowning kits are limited in their ability to contain human contaminants.
- So, why are people still in the clean room?

Potential Solutions

- Terminal Sterilization
- Engineering out interventions
  - Minimize exposure footprint
  - Improved glass and stopper handling, etc.
- Automation of engineered solutions
  - Automate to preclude human interventions
- With well designed and engineered facilities and appropriate automation we could…
  - Remove human factors… truly reduce contamination risk
  - Eliminate microbiology… risk exceeds value

Thank You for Listening

Questions? / Comments?