Sterilization – A to z

James Agalloco

Agalloco & Associates

Sterilization – A to z

- Sterilization is a critical process in the pharmaceutical industry for the control of microbial populations.
- While most prevalent in the manufacture of sterile products it can be used in a variety of settings where microbes have potential impact on patients or products.

What's the Objective?

- Removal of objectionables / specified microorganisms
- Control of microbial population
  - Reduction in count
  - Complete elimination
- It's important to understand the real process need more completely than what this might otherwise suggest.

What's the Target to be Sterilized?

- Bacterial Spores
- Mold spores
- Vegetative cells
- Viruses / prions
- Combinations of the above

Order of Resistance

- Prions
- Bacterial spores
- Nonlipid or small viruses
- Mold spores / Fungi (*Aspergillus, Candida)*
- Vegetative bacteria (*Staphyloccus, Pseudomonas)*
- Lipid or medium-sized viruses

What Process to Choose - 1

- There's a fly in your living room, what do you use to kill it?
  - A fly swatter
  - A shotgun
  - A piece of artillery
- Obviously we would use the fly swatter and that advice is appropriate in microbial control as well.
- We should use the process that best fits the target objective.
- Unfortunately, most practitioners in microbial control take the process to extremes as a matter of routine. That's acceptable at times, but not always.

Microbial Control Processes

- Disinfection – a process that will eliminate infective organisms.
- Sanitization – a process will reduce the overall microbial population. Depending upon the agent this includes spores
- Sterilization – a process that will destroy or remove all microbial life.

What's Wrong?

- Despite the maturity of the subject, the practice of sterilization within the global healthcare industry has descended into rote repetition of wrong headed expectations.
- Regulatory obfuscation and industry apathy have caused all manner of unnecessary complications and added patient risks.
- Rather than making products safer, we may have actually increased patient risk!

Why did it go Wrong?

- We've paid only limited attention to the basic science underlying sterilization.
- We've ignored the effect the various processes have on the materials.
- We have relied on overly simplistic models and ignored the core scientific principles upon which sterilization process must be constructed.
- If we haven't made it sterilization any safer or easier, we've sure made it dumber.

What are the Problems?

- Failures to adequately sterilize.
- Aseptic processing where terminal sterilization could be used.
- Increased impurities, particles, extractables.
- Wasted energy costs and lost capacity.
- Oversimplification of key concepts.
- Confusion among disciplines.
- Excess caution built into protocols.
- Regulatory excess.
- Industry is risk averse to an extreme.
- Industry would rather switch than fight!

Where to Start

There's 2 Parts to the Puzzle

What's the item?

- Fluids
- Glass
- SS & other metals
- Elastomeric materials
- Combinations of the above

What's the target?

- Bacterial Spores
- Mold spores
- Vegetative cells
- Viruses / prions
- Mixtures of the above

The selection of an appropriate sterilization process requires consideration of both issues, however the target is often ignored.

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What's the Items to be Sterilized?

- Fluids
  - Gases, Liquids (formulated products, solutions, suspensions, media, waste streams)
- Glass
  - Containers, vessels,
- SS & other metals
  - Tanks, valves, fill parts, utensils, etc,
- Elastomeric materials
  - Containers, closures, filters, tubing, gaskets, valve components, medical devices, etc.

Whatever process is used must not impair the items essential characteristics. Unless it's glass or stainless steel there's a potential issue and even they can be affected.

What's Been Done Wrong

- We fixate on killing the most resistant microbe we can imagine. This results in over-treatment of many items especially product, media & elastomeric materials.

- This creates numerous problems including: degradation of product, loss of flexibility, loss of integrity, increased particles, change in essential properties, changes in color, increased process time, increased extractables & leachables, lost capacity, increased costs, etc.

What’s Missing?

The Forgotten Objective

- Achieving sterility (aka minimum PNSU) is only half of what must be accomplished.
- In order to use the materials after the process their essential quality attributes have to be maintained.
- We can most definitely have too much of a good thing. If in the effort to kill microorganisms, we do lasting physical or chemical damage to the items being sterilized we have accomplished nothing of value.

Keep an Eye on the Target

- Sterilization processes must be capable of eliminating undesirable microbes while maintaining the target items essential quality attributes. No more, no less.

Impact of Sterilization

- A balance must be achieved between the need to maintain a safe, stable and efficacious product while providing sufficient lethality to attain a minimum level of sterility assurance.

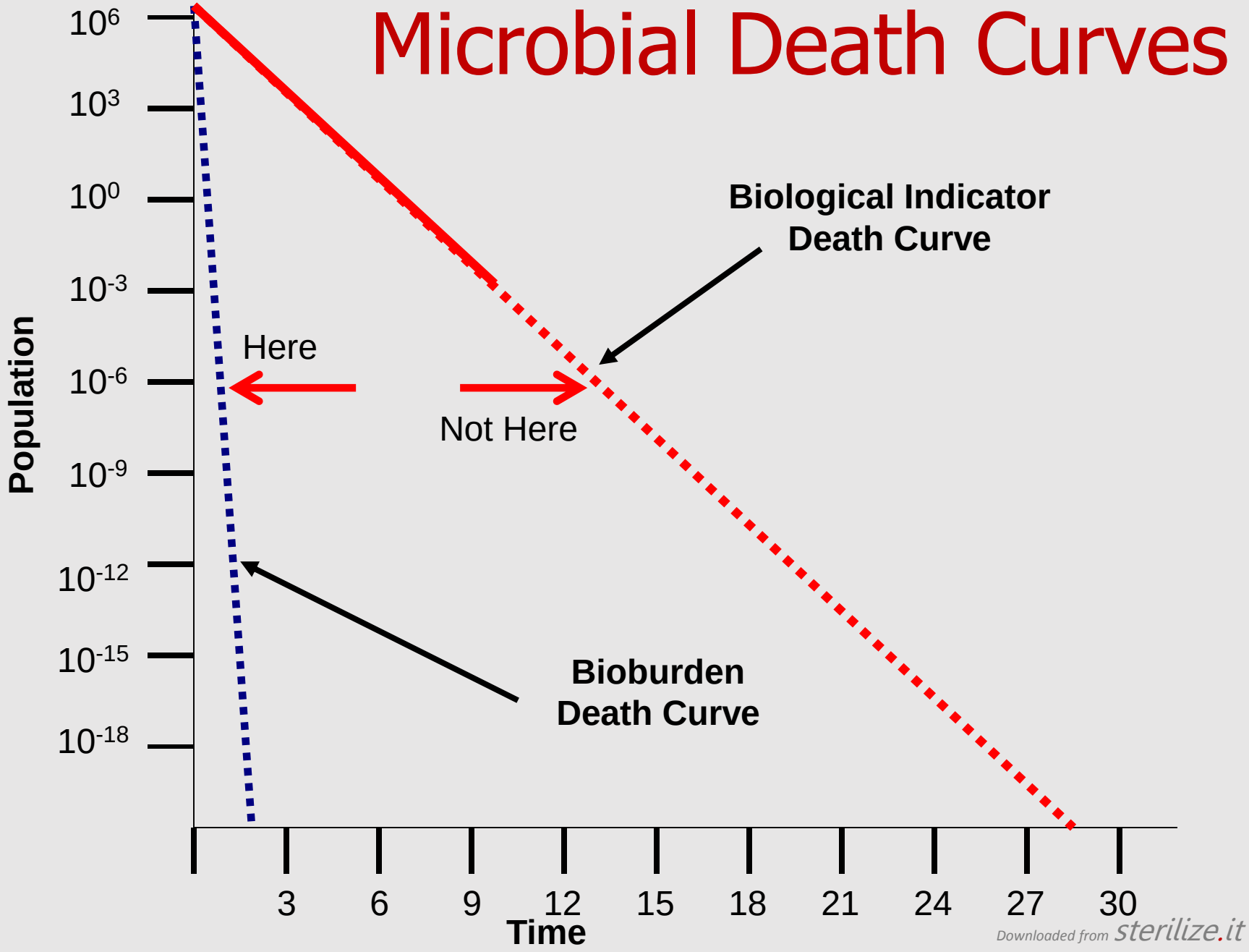
Sterilization Microbiology 101:

What you absolutely must
know in only 5 slides!

What's the Primary Objective?

- A minimum PNSU of 10-6 is required.
- That means that in routine operation of the sterilizer, the possibility for a surviving bioburden microorganism must be less than 1 in 1,000,000.
  - 1 non-sterile unit in 1,000,000 units or
  - 1 chance in a 1,000,000 that a single unit is non-sterile
- It has little to do with the biological indicator, and even less to do with the BI population.

Microbial Death Curves



Calculation of PNSU (SAL)

$$\log N_u = \frac{-F}{D} + \log N_0$$

where:

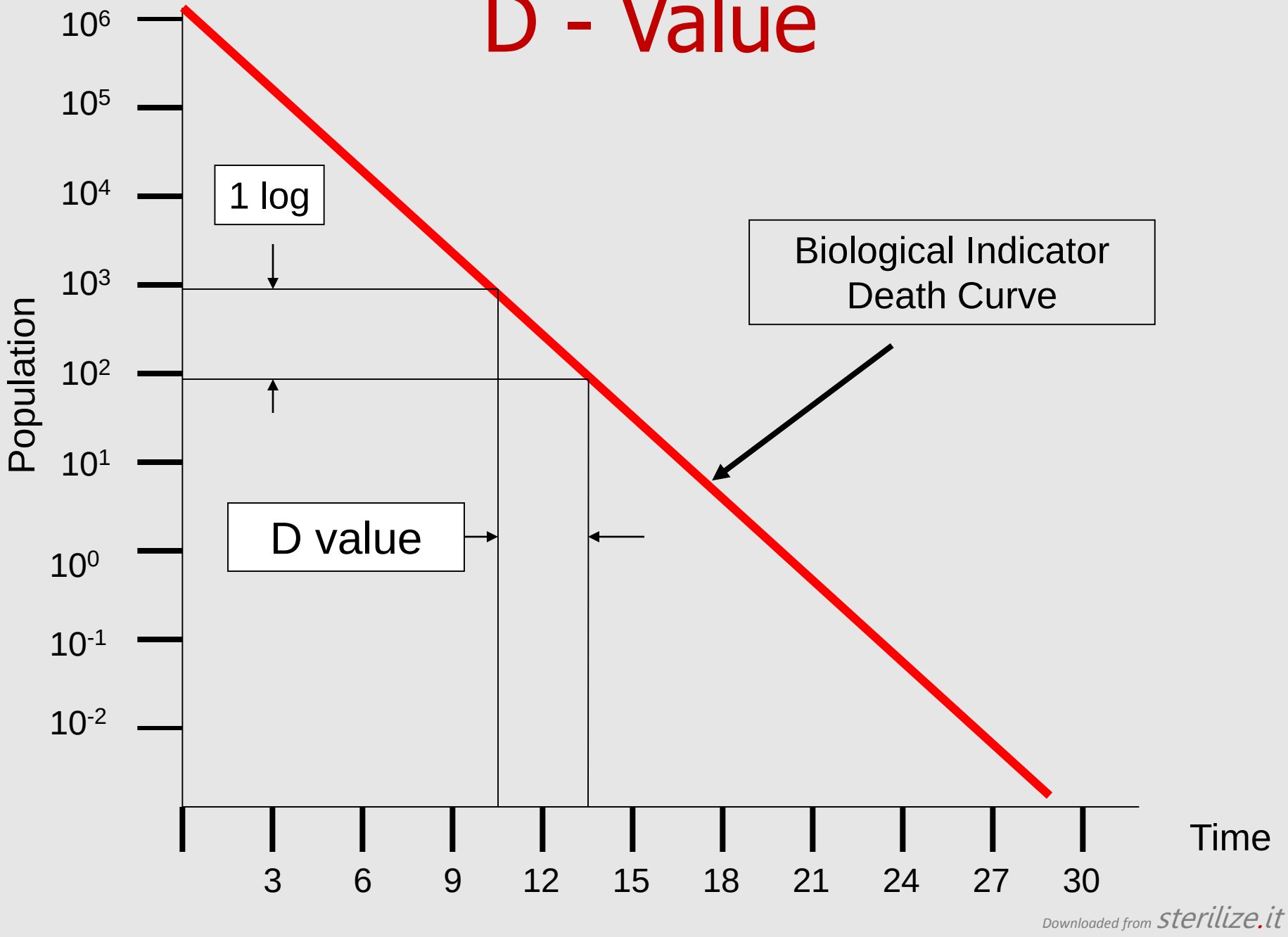
N_u = SAL / PNSU

D = D-value of the natural bioburden

F = F-value (lethality) of the process

N_0 = bioburden population

D - Value



The D-Value

- The D-value is the time required to reduce a population of microorganisms by one log or a 90% reduction in count.
- A D-value is only meaningful if referenced to specified lethal conditions.
- For example D-values should always be referenced to a temperature, without that reference they have no meaning, i.e., moist heat D121.1°C or dry heat D170°C.
- For D-values in gases / liquids the agent concentration, RH and temperature must be indicated, i.e., D900 PPM, 75% RH,30°C

Step 1:

Choosing a Sterilization Process

What Process to Choose - 2

The methods aren't interchangeable. The choice is dictated by what impacts the materials least. In order of increasing use:

- Vapors & Liquids – heat sensitive items
- Dry heat – items with very high heat resistance
- Gases – plastics & medical devices, heat sensitive items
- Radiation – some plastics & medical devices
- Filtration – solutions & gases
- Steam – stainless steel, glass and whatever can handle it.

Vapors & Liquids

- The least used methods, used only where nothing else is compatible.
- Both are difficult to use, but for different reasons.
- Vapors are problematic because there are two phases present.
- Liquids are troublesome because they have to be aseptically removed or neutralized in order for the item to be used safely.

Dry Heat Sterilization

- Primarily for glass, stainless steel and very few other materials.
- Items must be able to withstand temperatures in the 160-180°C range.
- Typically a lengthy batch process because air has very low heat capacity.
- Items are wrapped or covered in aluminum foil

Gas Sterilization

- Primarily ETO, with ClO2, O3 and NO trying to gain traction.
- ETO is largely at contractors because it is explosive, carcinogenic and requires extensive safety precautions. Post-cycle aeration times can exceed 14 days. It penetrates best and dominates the market.
- The other gases are all seeking to replace ETO, but have a long way to go despite their effectiveness and absence of extreme safety concerns.

Radiation

- Gamma sterilization is predominantly a contract service. Best suited for high volumes.
- X-ray provides gamma like penetration without the Co60. An emerging method.
- E-beam is also available as a contract service, though smaller units are being used in conjunction with isolators for material entry. Doesn’t have the penetrating power of Gamma or X-rays.

Filtration

- The only methods for many heat sensitive products especially biologics, antibiotics, oncology products and others.
- Requires a subsequent aseptic process
- Removes but does not destroy microorganisms so it must be considered separately from the other methods.

Steam Sterilization

- Really 2 different processes.
  - Steam in direct contact for filling parts, hoses, tools, stoppers and sterilization-in-place.
  - Steam as a heating medium for sealed containers of product, media, or other liquids.
- These processes work differently and have such different operating constraints that it might be best to consider them as completely separate processes.

Step 2:

Determining Process Duration

How Long Should a Process Be?

- No longer than absolutely necessary to confidently destroy the expected bioburden population, plus a modest safety factor.
- There absolutely can be too much of a ‘good thing’.
- The same thinking holds true for filtration. Using smaller filters to retain ‘everything’ increase filtration costs, process times and leachables/extractables.

Step 3:

Controlling the Bioburden

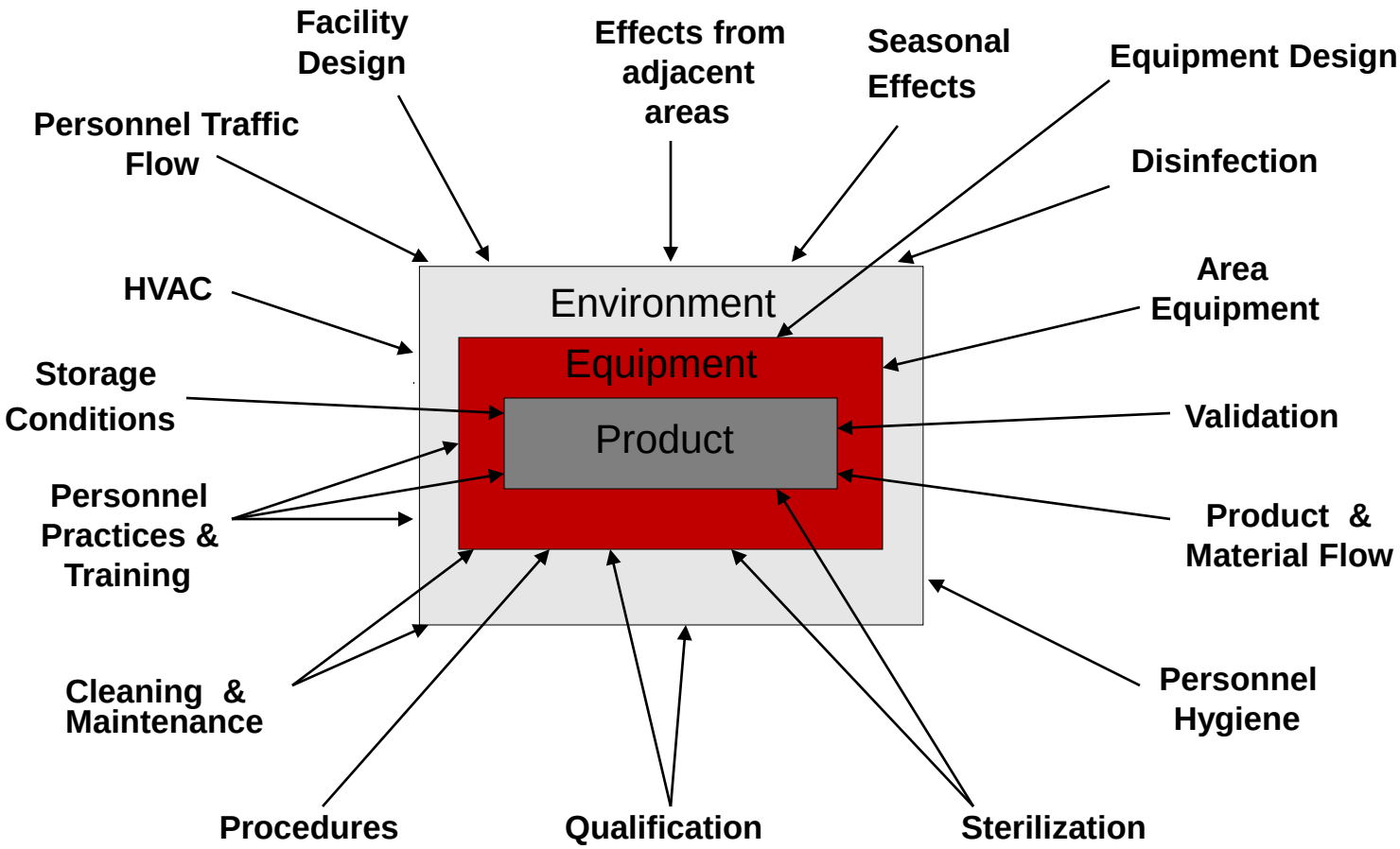
Microbial Control

- Except for spores, most microorganisms require water, air and carbon to maintain their viability.
- We can’t eliminate air from our facilities, but proper operation of operating facilities & cleanrooms can keep water and carbon presence to a minimum.
- Time limits on aqueous process are essential to keep microbial proliferation in products to a minimum.

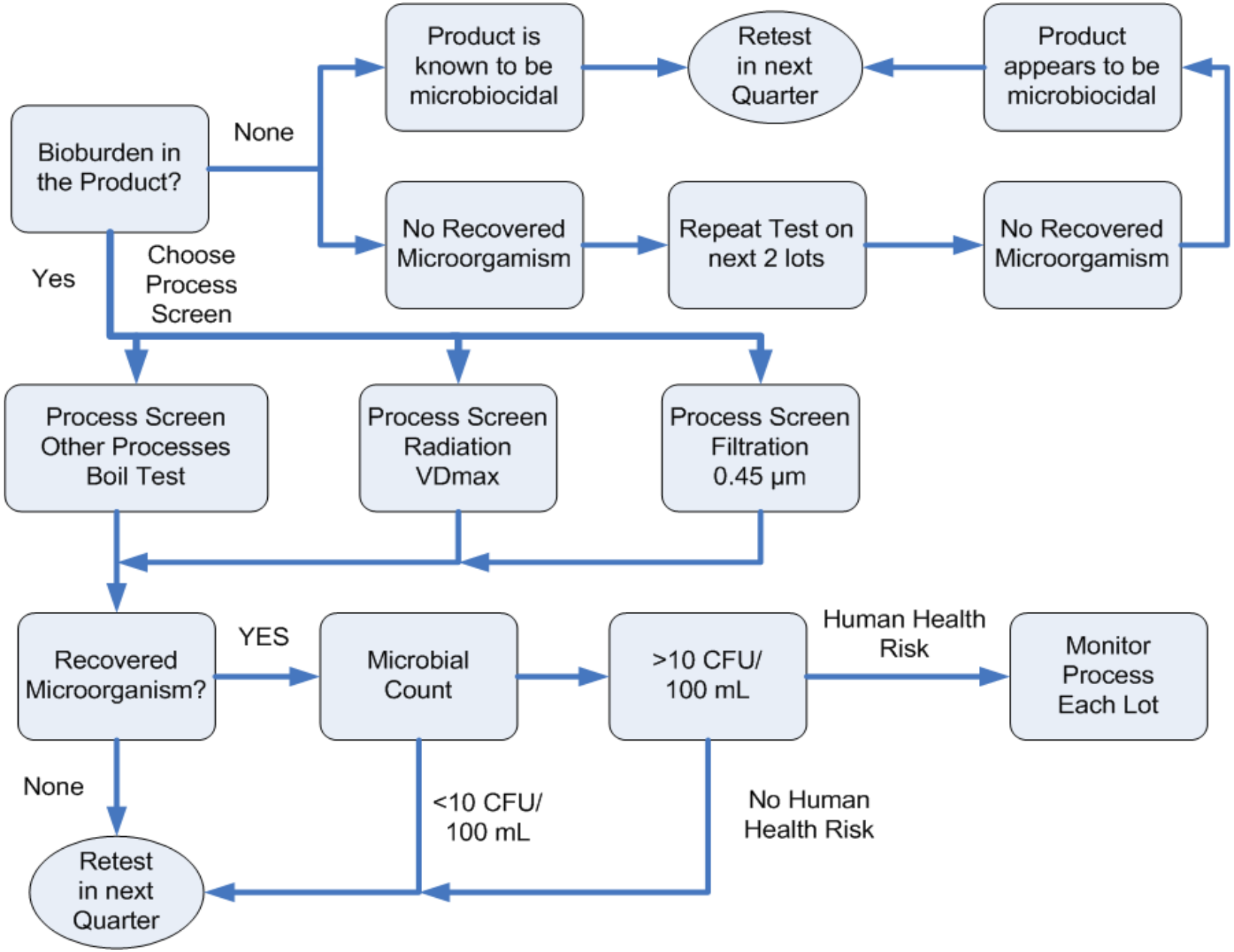
Bioburden Monitoring

- Every sterilization process (including those using overkill) should be supported by a bioburden monitoring program. If it's not an overkill process, this is a must have!!
- That's because routine process safety is assured by knowledge of its initial population prior to the process.
- Ignoring this is not a good idea.

Factors Influencing Bioburden



Adapted from Leonard Mestrandrea



Step 4:

Cycle Development

Cycle Development Activities

- Confirm that the chosen process doesn't adversely affect the materials to be sterilized.
- Evaluate chemical, and physical properties for changes. Stability required for radiation sterilization & product sterilization processes.
- Change materials if necessary to use more standard processes(EMA expectation).
- Determine process lethality internally at difficult to penetrate locations.
- Consider alternate methods and/or aseptic processing in the event of failure.
- If everything seems acceptable move forward to scale-up.

Step 5:

Equipment Qualification

Sterilizer Validation Elements

- Process Development
- Validation Master Planning
- (Purchase)
  - User Requirements Specifications
  - Commercial Proposals
  - Factory Acceptance Testing
  - Installation at Site / Shakedown/ (Commissioning in NA)
  - Site Acceptance Testing
  - Equipment Qualification (Commissioning in the UK)
- Process / Performance / Product Qualification
- Maintenance of Validation
  - Change Control
  - Process Monitoring / Bioburden Sampling
  - Preventive Maintenance / Calibration

Sterilizer Qualification – 1

- Critical items are verified to be installed and fully functional.
- Performed according to a pre-approved protocol.
- Forms the basis for change control.
- May be design / installation specific, but that is not required nor always valuable.
- Qualification tests usually don’t require repetition.
- Can include results from FAT & SAT without repetition.

Sterilizer Qualification – 2

- Description of equipment physical characteristics and function.
- P&ID drawing of the system “as built.”
- A list of other pertinent drawings. These may include structural, layout, detail drawings, and electrical schematics.
- Detailed specifications for the sterilizer and all of its components.
- Confirmation of proper installation according to the P&ID.
- List of system instrumentation.

Sterilizer Qualification – 3

- References to the calibration of all instrumentation. Calibration records must be maintained and available for review.
- Listing of vendor supplied documentation, including operation and maintenance manuals, parts list, and computer software documentation.
- “Cut sheets” for all vendor purchased items, i.e., valves, gauges, transmitters, etc.
- Listing of all utility connections. Utilities are usually qualified individually.

Sterilizer Qualification - 4

- Qualification / validation of the sterilizer control system as performed by the vendor.
- Owner should audit the control system qualification / validation. Summaries of this effort should be available to the owner.
- Custom designs require system specific confirmation of control system acceptability.
- Details of software are generally not provided nor required for standard control system designs.

Step 6:

Initial Performance Qualification

Performance Qualification

- Empty chamber studies to establish baseline
- Triplicate studies with loads to support initial use of the system. Maximums (and minimums for some) required.
- Can use equivalence, bracketing & matrixing to reduce the initial workload.
- Studies with independent physical/chemical monitoring and biological indicators.

Step 7:

Everyday Process Control

Maintenance of Validation - 1

- Change Control
  - Process change control
    - Procedures, set-points, load patterns, etc.
  - Equipment change control
    - Valves, filters, utility connections, etc.
  - Material change control
    - Containers, wraps, etc.
- Training
  - Professional staff, especially those responsible for sterilization cycle development / validation
  - Sterilization equipment operators, filtration technicians, and maintenance mechanics.

Maintenance of Validation - 2

- Process Monitoring
  - Confirmation that the sterilizer operates as validated every cycle of every day.
  - Review of sterilizer records by operating (real-time with process completion) & quality personnel (before release)
    - Operational records
    - Calibration records
  - Performance trending, etc.
- Bioburden Monitoring
  - Periodic sampling for most processes
    - Daily, weekly, EM like
  - Every lot for radiation sterilization
  - Every sterilizer load for terminal sterilization
  - Cooling water

Maintenance of Validation - 3

- Preventive Maintenance
  - Intended to ensure continued reliable operation of the sterilizer over time.
  - Begins with fabricators recommendations as adapted through owners experience.
  - Scheduled replacement of components, i.e., gaskets, filters, seals, bearings, etc.
  - Scheduled adjustments, lubrication, cleaning, i.e., door positioning, hinges, strainers, motors, etc.
  - Periodic filter integrity testing (in-situ)
  - Periodic filter replacement

Step 8:

Periodic Process Re-Qualification

Performance Re-Qualification

- Empty chamber studies are supplemental (never primary evidence).
- Single studies with ‘worst case’ loads compared to initial qualification results. Minimum lethal load is selected where known.
- Studies with independent physical/chemical monitoring and biological indicators.

Sterilization Tips & Cautions

Biological Indicators

- They are process measurement tools, much like the thermocouple.
- **Their destruction in the PQ need NOT be mandatory.**
- They should be placed in the load in difficult to penetrate locations.
- They come in many formats: strips, coupons, threads, wire, & suspension.
- Their resistance to the process must be known.

Physical Measurements

- The US mantra is – ”The bugs don’t lie”.
- If the physical data doesn’t agree with the biological results, investigation and resolution is in order.
- Physical estimates of lethality are all based on assumptions of microbial resistance, and are thus always secondary.
- The EMA has this backwards, and refuses to understand that reality.

Load Items

- The use of sealed bags, and containers is preferred to maximize post-sterilization hold times.
- When placing BI's and other monitors in load items it is essential that the item be sealed as it would ordinarily.
- Autoclave tape is inadequate for re-sealing most packages.

Conclusion

- Sterilization really isn't that difficult, but inattention to science through excess criteria and constraints can make it an onerous task.

"If a thousand people do a foolish thing, it is still a foolish thing!!"