In-Process Changes to USP <1211> Sterilization & Sterility Assurance of Compendial Articles

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<1211> The Revisions

- Started Here: Sterilization at a more basic level: more instruction, less standardization
  - Individual chapters on each sterilization method: allows for easier revision.
  - Separate gas & vapor sterilization; Separate dry heat sterilization & depyrogenation; separate steam for parts and liquid filled containers; none of these are really the same process
  - New chapters on chemical sterilization: no prior information
  - Aseptic processing as a separate chapter: not strictly a sterilization subject; needs better connection to other supportive chapters
  - Update references throughout. New definitions for sterilization validation models. Clarify the role of the biological indicator. Clarify PNSU, SAL and risk to patient.
  - Integrate Endotoxin Indicator chapter as well as BI & CI content.
  - Move BI monographs out of "official chapters".
  - Allow for easier development of other needed content in future.
  - Depyrogenation treated independently of sterilization
- Finished Here: Separation of Sterilization, Depyrogenation and Sterility Assurance content.

<1229> Introductory Chapter

- Provides an overview and introduces common elements related to all sterilization methods. Includes:
  - Establishing & Justifying Sterilization Processes
  - D-value and Microbial Resistance
  - Biological & Physical Data
  - Sterilization Indicators & Integrators
  - Selection of an Appropriate Method
  - Routine Process Management

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.
- It has little to do with the biological indicator, and even less to do with the BI population.

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

Calculation of PNSU (SAL)

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

The bioindicator and physical measurements confirm this

The bioburden defines these

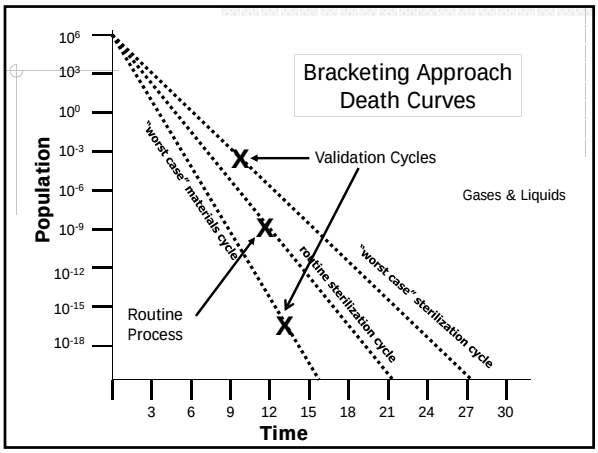
Highlights from the Content

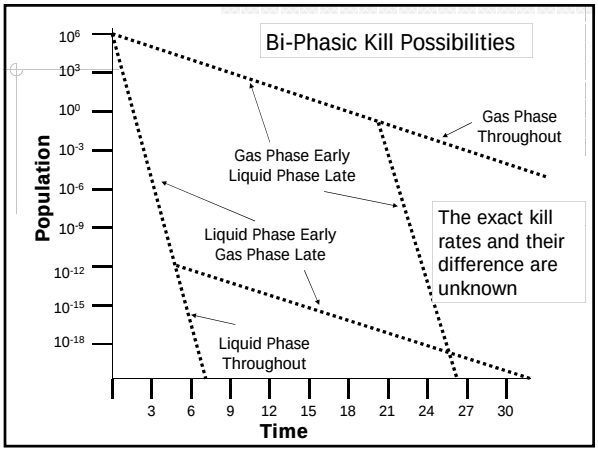
Steam Sterilization

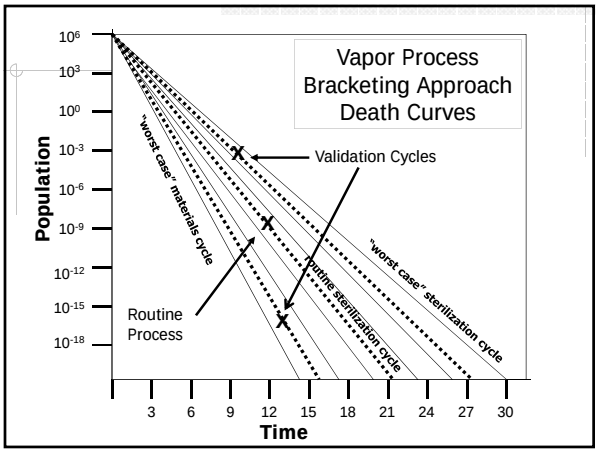
- Separated prior sub-chapter into parts <1229S> and liquids <1229A> to allow for real differences, and greater clarity.
- Separates processes where over-processing is not a concern from those where it is.
- 1229S stresses “overkill, while <1229A supports BB/BI & Bioburden approaches
- In theory parts sterilization has no upper limit, while terminal / liquid sterilization is bounded both above and below the desired process.

Gas, Liquid & Vapors - D-Values

- A D-value is only meaningful if referenced to specified lethal conditions. For example wet or dry heat D-values should always be referenced to a temperature, without that reference they have no meaning, i.e., $D_{121.1°C}$ or $D_{170°C}$.
- For D-values in gases / liquids the agent concentration, RH and temperature must be indicated, i.e., $D_{900\ PPM,\ 75\%\ RH,\ 30°C}$
- D-values cannot be accurately determined for vapors.

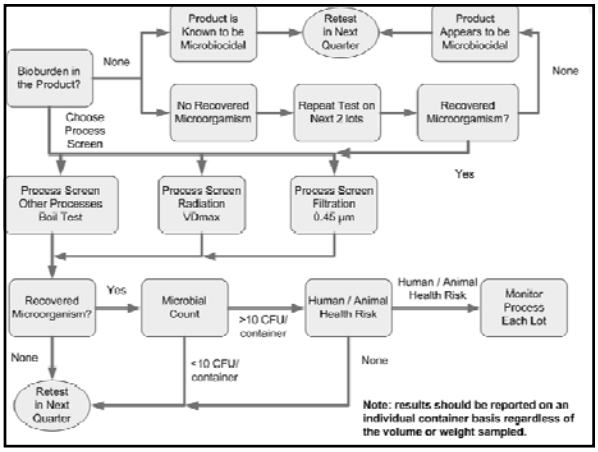

Bracketing Approach
Death Curves
Validation Cycles
Gases & Liquids
"worst case" materials cycle
routine sterilization cycle
"worst case" sterilization cycle
Routine
Process
Population
Time
10^6
10^3
10^0
10^-3
10^-6
10^-9
10^-12
10^-15
10^-18
3 6 9 12 15 18 21 24 27 30


Bi-Phasic Kill Possibilities
Gas Phase
Throughout
Gas Phase Early
Liquid Phase Late
Liquid Phase Early
Gas Phase Late
Liquid Phase
Throughout
The exact kill rates and their difference are unknown
Population
Time
10^6
10^3
10^0
10^-3
10^-6
10^-9
10^-12
10^-15
10^-18
3 6 9 12 15 18 21 24 27 30


Vapor Process
Bracketing Approach
Death Curves
Validation Cycles
"worst case" materials cycle
routine sterilization cycle
"worst case" sterilization cycle
Routine
Process
Population
Time
10^6
10^3
10^0
10^-3
10^-6
10^-9
10^-12
10^-15
10^-18
3 6 9 12 15 18 21 24 27 30

<1229> Bioburden Monitoring

- Reviews the relevant concerns for bioburden content
  - Ability to survive the process
  - Population
  - Risk to Public Health
- Considers patient & product impact
- Provides a decision tree for use in establishment of a monitoring program.



Where is the USP's BI Content?

Monographs 6 Individual Monographs	<55> Biological Indicators—Resistance Performance Tests	< 1035> Biological Indicators For Sterilization	<1211> Sterilization & Sterility Assurance Of Compendial Items
General Description	Total Viable Spore Count	Types of Bioindicators	Linkage to individual sterilization processes
Packaging & Storage	D-value Determination Methods	Performance Evaluation	
Expiration Date		Use for In-process Validation	
Labeling			
Identification			
D-value			
Survival & Kill Window			
Total Viable Spore Count			
Purity			
Shipment			
Disposal			

Where will USP's BI content be?

Monographs & Individual Monographs	<55> Biological Indicators—Resistance Performance Tests	< 1035> Biological Indicators For Sterilization	<1229> Sterilization Of Compendial Items
General Description	Total Viable Spore Count	Types of Bioindicators	
Packaging & Storage	D-value Determination Methods	Performance Evaluation	
Expiration Date	?	Use for In-process Validation	
Labeling			
Identification			
D-value			
Survival & Kill Window			
Total Viable Spore Count			
Purity			
Shipment			
Disposal			

Hidden Impacts

- The use of BI's with 10^6 spores is not (and never should have been) required. Lower populations have always been acceptable.
- Fitting the BI to the process, not the other way around. It should never have been about killing the most difficult microorganism possible.
- Greater consideration of the impact of the process on the materials, once the artificial constraints of BI kill are removed.

Where is USP Now - 1

- Official in *First Supplement to USP 36–NF 31*
  - <1229> *Sterilization of Compendial Articles*
  - <1229.1> *Steam Sterilization by Direct Contact*
  - <1229.2> *Steam Sterilization of Aqueous Liquids*
- Official in *Second Supplement to USP 36–NF 31*
  - <1229.3> *Monitoring of Bioburden*
- Published in *PF 39(2) [Mar.-Apr. 2013]*
  - <1229.4> *Sterilizing Filtration of Liquids*
  - <1229.10> *Radiation Sterilization*

Where is USP Now - 2

- To be published in *PF 39(3) [May-Jun. 2013]*
  - <1229.7> *Gaseous Sterilization*
  - <1229.8> *Dry Heat Sterilization*
- To be published in *PF 39(4) [Jul.-Aug. 2013]*
  - <1229.6> *Liquid Phase Sterilization*
- The following General Chapters are in development:
  - <1229.11> *Vapor Sterilization*
  - <1229.5> *Biological Indicators for Sterilization*
  - <1229.9> *Physicochemical Integrators and Indicators for Sterilization*
  - <1229.12> *New Methods of Sterilization*

What's Still on the Horizon

- Comparable revisions to <1211> Sterility Assurance of Compendial Articles providing similar cohesion for aseptic processing operations and sterility assurance in general. Possible new / revised content on:
  - Isolator / RABS aseptic processing
  - Parametric Release (linked to <1229>)
  - Post-Aseptic Fill Treatments
  - …