USP Activities Impacting Sterilization & Sterility Assurance

James Agalloco
Agalloco & Associates
Member, USP Microbiology & Sterility Assurance Expert Committee

Disclaimer

- This presentation draws on in-process drafts currently in preparation within USP's Microbiology & Sterility Assurance Expert Committee.
- The interpretations and emphasis placed on subjects within this presentation are the author's personal opinion and not official USP positions.
- The draft chapters issued by USP on these subjects (beginning in mid-2010) will likely differ somewhat from this presentation.

Who's on the MSA Committee?

- James Akers, Ph.D., AK&A, Chairman
- Scott Sutton, Ph.D., ex-Vectech, Vice-Chair
- James Agalloco, A&A
- Ivan Chin, Ph.D., ex J&J
- Anthony Cundell, Ph.D., Merck & Co.
- J. Kirby Farrington, Ph.D., Lilly (ret) Auburn University
- Dennis Guilfoyle, Ph.D., FDA ORA
- David Hussong, Ph.D., FDA CDER
- Leonard Mestrandrea, Ph.D., Pfizer (ret.)
- David Porter, Ph.D., Vectech
- Donald Singer, GSK
- Radha Tiramuli, Ph.D, USP Staff liaison

What I Will & Won't be Discussing

- Included Subjects
  - <71>Sterility Testing (very briefly)
  - <1211>Sterilization & Sterility Assurance of Compendial Articles
- Excluded Subjects
  - Just about everything else

<71> Sterility

- Continued revision process in efforts to finalize the harmonized draft.
- Eliminated any content in <1211> on sterility testing, leaving <71> as the only relevant USP content.

<1211> Completed Activities

- Step 1 in the revision process was completed in 2008.
- Eliminated the entire discussion of sterility testing at the conclusion of the chapter. The only content in USP relative to sterility tests will be the harmonized <71>.
- Eliminated the older radiation sterilization guidance & directed reader to ISO standards.
- Comments recently received; course of action undecided.
- Sets the stage for future changes.

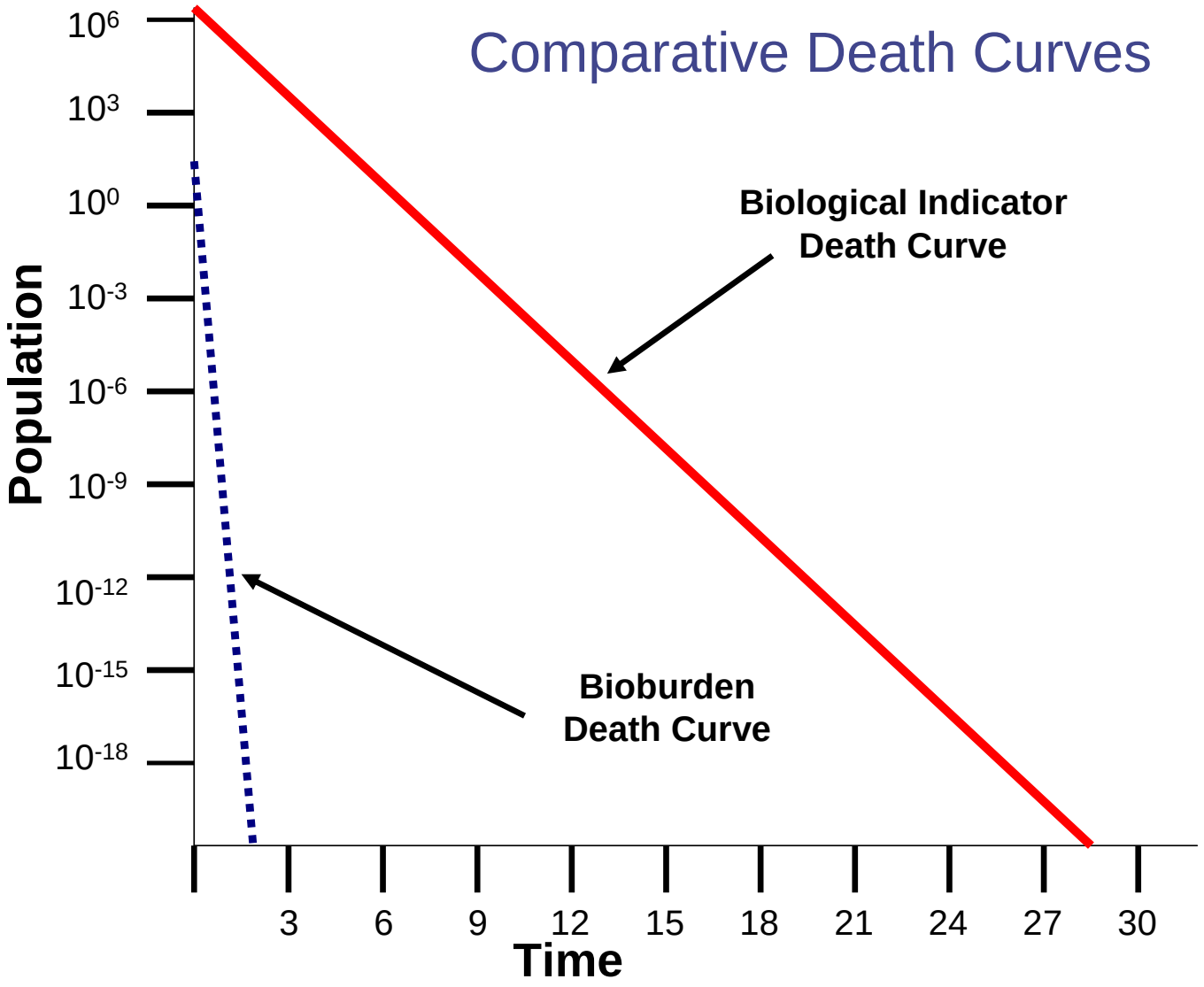
<1211> Goals of the Revision

- 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: not the same process.
  - Separate dry heat sterilization & depyrogenation: not 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 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
  - Move BI monographs out of "official chapters".
  - Allow for development of other needed content
- Finished Here: Separation of Sterilization content from Sterility Assurance content.

<1229> Main Points

- "It is generally accepted that sterilized articles or devices purporting to be sterile attain a 10^{-6} microbial survivor probability, i.e., assurance of less than 1 chance in 1 million that viable ***bioburden*** microorganisms are present in the sterilized article or dosage form. With process stable articles, the approach often is to exceed the critical process parameters necessary to achieve the 10^{-6} microbial survivor probability (overkill) of any pre-sterilization bioburden. The sterility assurance of a sterilization process is attained through the use of a biological indicator; however its efficacy for any application is associated with the bioburden present during routine operation."

Bioburden & Biological Indicators



Overkill Method

- "Overkill sterilization is a process where the destruction of a high concentration of a resistant microorganism supports the elimination of bioburden that might be present in routine processing. That objective can be demonstrated by attaining any of the following: a defined minimum lethality; a defined set of process conditions or confirmation of minimum log reduction of a biological indicator."
- Used wherever possible, consistent with impact on the materials.

Bioburden / Biological Indicator Method

- "Bioburden/biological indicator sterilization is a method in which the incomplete destruction (or destruction of a modest population) of a resistant biological indicator can be used to demonstrate the capability of the process to reliably destroy any bioburden. This is accomplished using detailed knowledge of the bioburden/biological indicator populations and their relative resistance."
- Use where product quality attributes may be adversely impacted by severe processing conditions.

Bioburden Method

- "Bioburden sterilization is a method in which multiple bioburden isolates from the material are evaluated for resistance to the sterilization method and to demonstrate the lethality of the process. Frequent monitoring of the bioburden population and resistance is mandatory for success."
- Used primarily for radiation sterilization, because of the inadequacy of biological indicators as "worst case" challenges.

Material Impact Consideration

- "The choice of the appropriate process for a given item requires knowledge of sterilization techniques and information concerning effects of the process on the material being sterilized. Recognition that the selection of a particular sterilizing treatment (and the details of its execution) often represents a compromise between those conditions required to destroy the bioburden to the desired level and the impact of the sterilization process on the materials being processed. Sterilization processes should be no more robust than required for certainty of microbial control to avoid adverse consequences to material quality attributes."

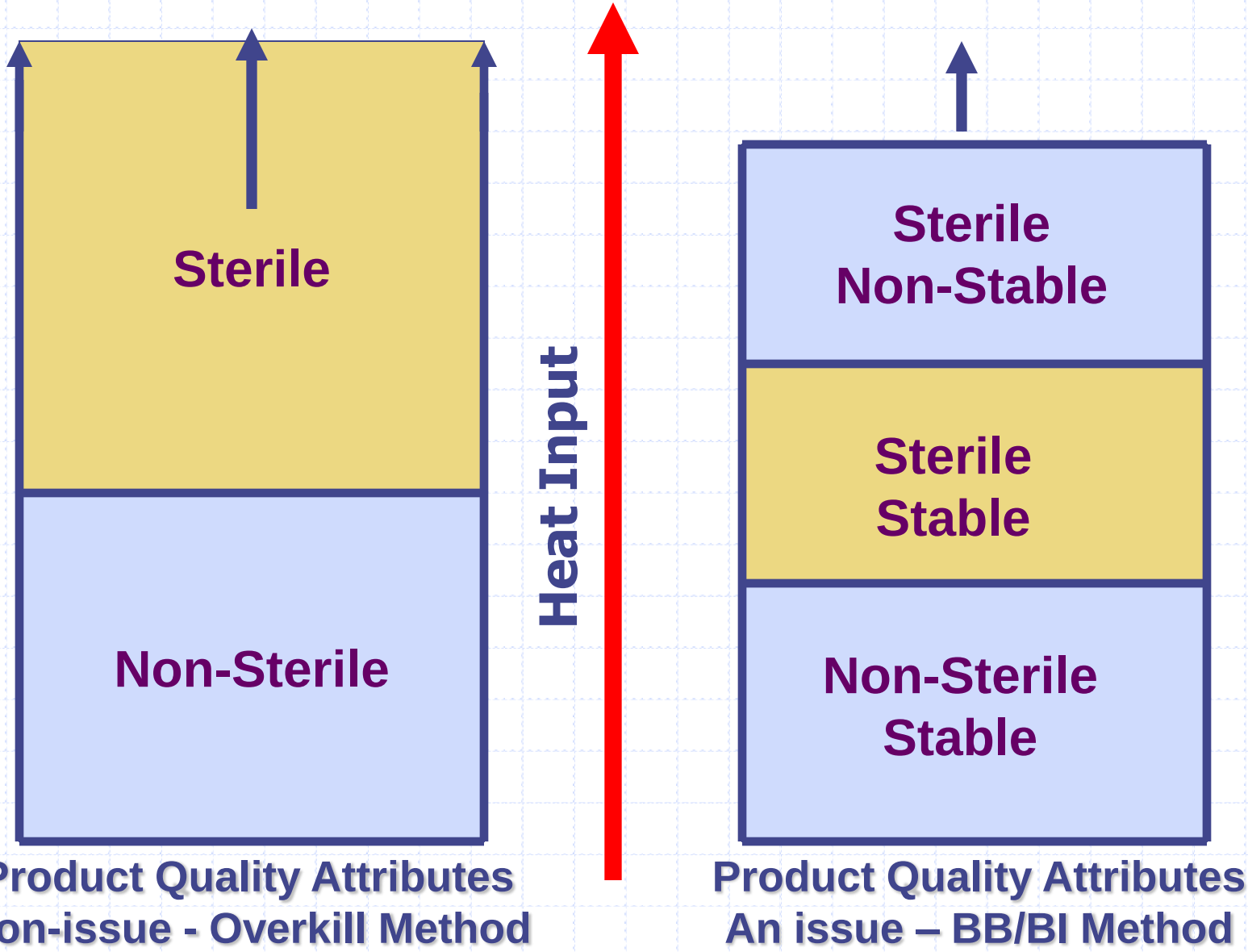
<1229> Sterilization Methods

- <1229C> – Chemical Sterilization – new
  - Includes aldehydes, oxidizers, halides, acids, bases
- <1229D> – Dry Heat Depyrogenation
- <1229F> – Sterilization by Filtration – heavily revised
- <1229G> – Gas Sterilization
  - Includes ETO, Chlorine Dioxide, Ozone
- <1229H> – Dry Heat Sterilization
- <1229L> – Steam Sterilization of Liquids
- <1229R> – Radiation Sterilization
- <1229S> – Steam Sterilization of Parts
- <1229V> – Vapor Sterilization – new
  - Includes H_2O_2, and Peracetic acid

<1229S> Steam Sterilization

- Separated prior sub-chapter into parts <1229S> and liquids <1229L> to allow for differences, and greater clarity.
- The "overkill approach" is the method of choice.
- Separates processes where over-processing is not a concern from those where it is.
- In theory parts sterilization has no upper limit, while terminal sterilization is bounded both above and below the desired process.

Parts vs. Liquid Sterilization



<1229L> Liquid Sterilization

- The method of choice for liquid parenteral products, and similar processes are utilized for laboratory media and process intermediates.
- "A balance must be maintained between the need to assure sterility of the items and the preservation of its important characteristics as a finished sterile product, process intermediate or laboratory aid. In order to assure this balance, the process definition and validation approach utilized must incorporate both lower and upper limits on the process conditions in order to assure sterility without adverse impact on material quality."

<1229L> Liquid Sterilization

- "Where the overkill approach can be utilized for terminal sterilization of sealed liquid containers, it is the preferred approach."
- "a dual set of requirements is established for nearly every important processing parameter. Sterilization time-temperature or F_0 conditions will include both lower (sterility related) and upper (stability related) limits to simultaneously assure safety and efficacy of the processed materials."

<1229L> Liquid Sterilization

Probability of a Non-Sterile Unit (PNSU)

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

Where

N_u	=	Probability of a Non-Sterile Unit
D	=	D-value of the natural bioburden
F	=	F-value of the process
N_0	=	bioburden population per container

Validation	Routine Usage
F_0 = 8.0 minutes	F_0 = 8.0 minutes
D_{121} of BI = 0.5 minutes	D_{121} of bioburden = 0.005 minutes
N_0 of BI = 10^6	N_0 of bioburden = 100 (or 10^2)
PNSU for BI = 10^{-10}	PNSU for Bioburden = $10^{-1,598}$

<1229H> Dry Heat Sterilization

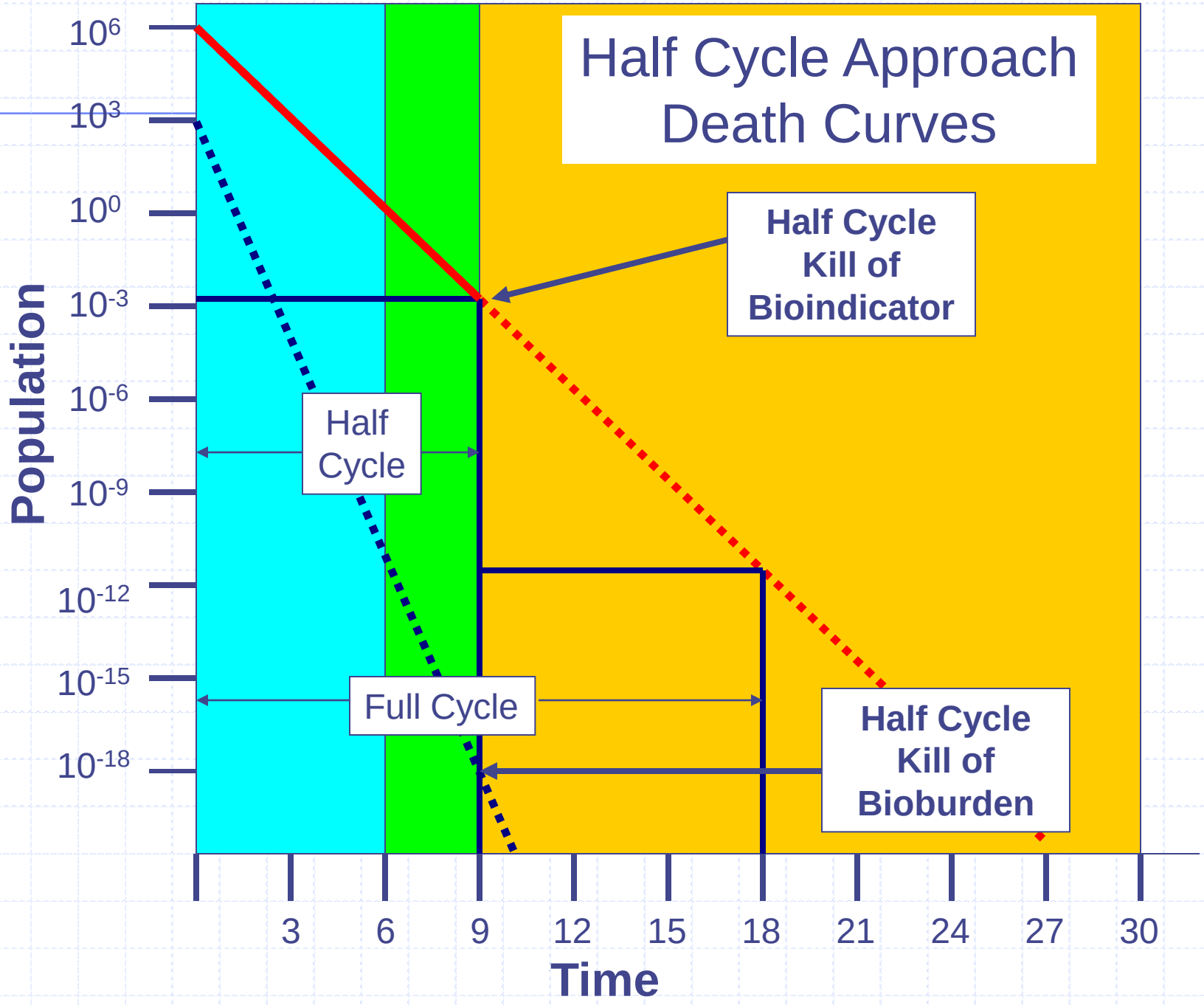
- Distinction made between dry heat sterilization and depyrogenation because of major process differences.
- Dry heat sterilization:
  - Is almost always performed in ovens in a batch process.
  - Uses a biological indicator *B. atrophaeus.*
  - Usually in the 160-180°C temperature range.
  - A reasonable mathematical correlation between physical data and microbial effect exists.
- Physical requirements are less definitive than for steam processes.

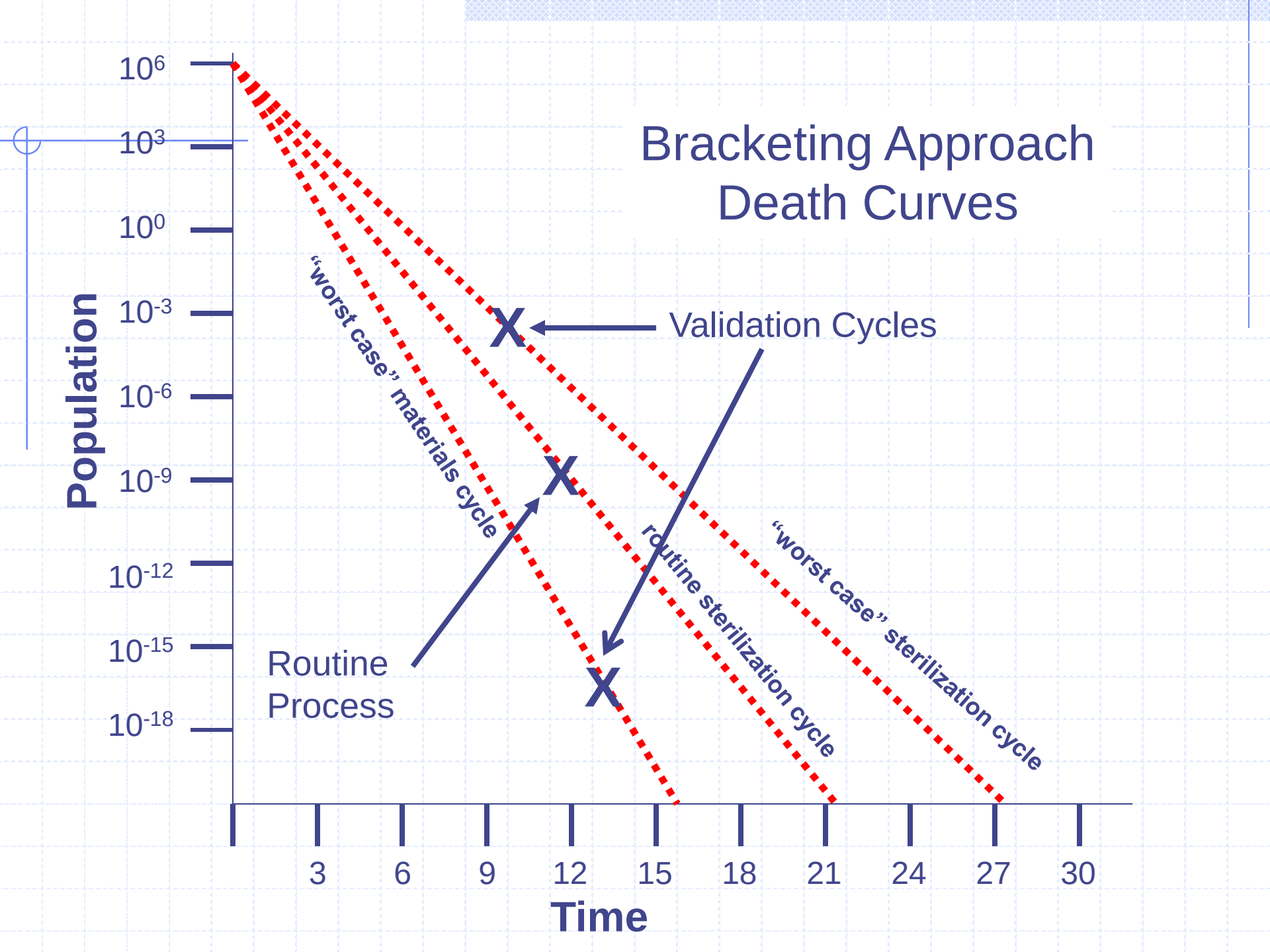
<1229D> Dry Heat Depyrogenation

- Differs from dry heat sterilization in several ways:
- Dry heat depyrogenation:
  - Predominantly utilized for glass and stainless steel items.
  - Batch and continuous processes are in use.
  - An endotoxin monograph has been drafted, but insertion into USP is awaiting the overall 1211 revision.
  - Usually in the >200-300°C temperature range.
  - Mathematical correlation between physical data and microbial effect is extremely poor. Defined physical parameters have proven problematic.
- Endotoxin destruction is the primary goal.

<1229G> Gas Sterilization

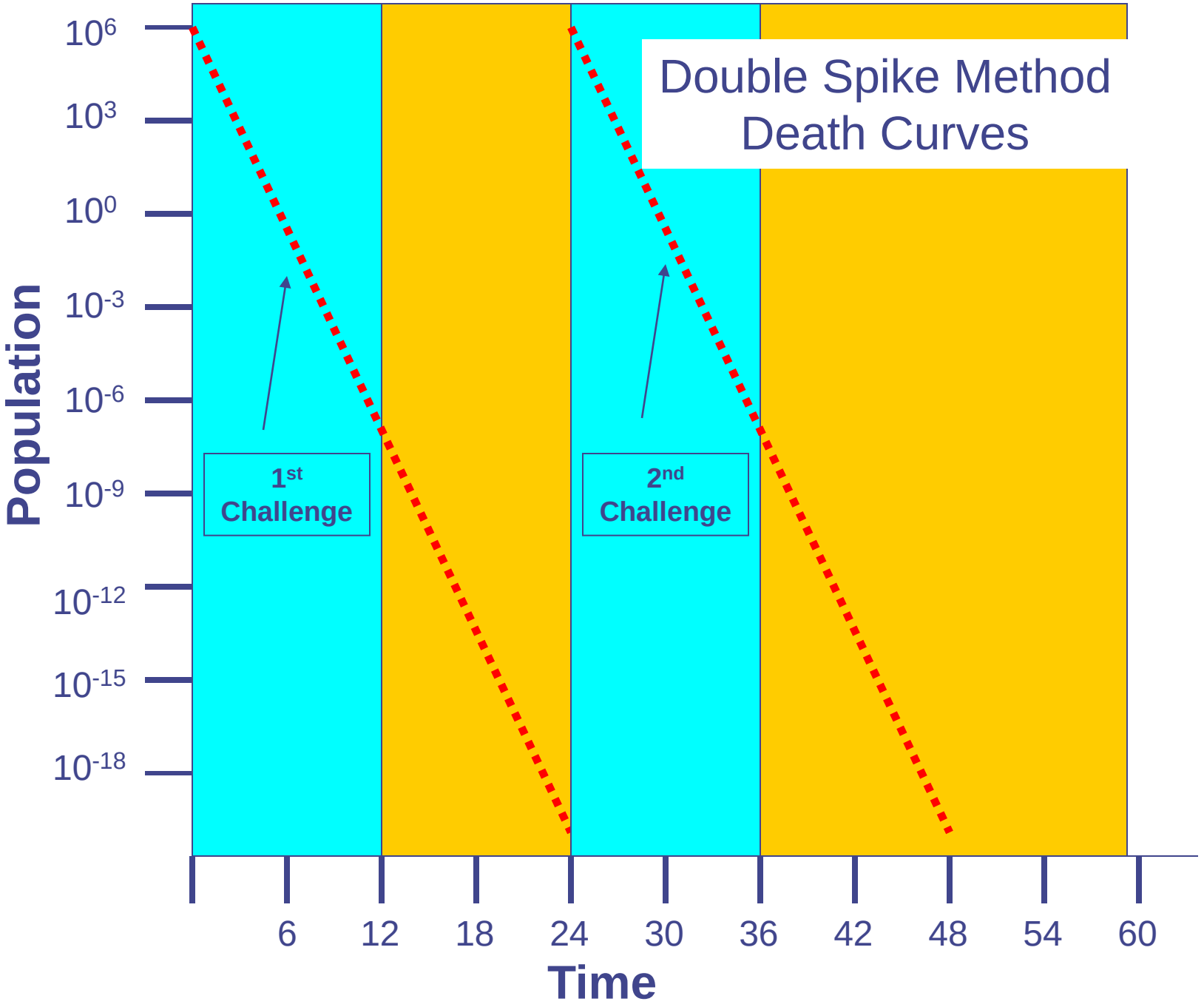
- Applicable to single phase gaseous processes only.
  - Condensation of the agent is not a consideration in the execution of these processes.
  - Ethylene oxide – model for all systems
  - Chlorine dioxide
  - Ozone
- Two validation approaches defined
  - Traditional half-cycle method
  - Bracketing method


Half Cycle Approach Death Curves
Half Cycle Kill of Bioindicator
Half Cycle
Full Cycle
Half Cycle Kill of Bioburden
Population
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
Time


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

<1229C> Chemical Sterilization

- Chemical Sterilants
  - Aldehydes – glutaraldehyde, formaldehyde, etc.
  - Acids – Peracetic, nitric, sulfuric, etc,
  - Bases – Sodium hydroxide, Potassium hydroxide
  - Oxygenating compounds – hydrogen peroxide, ozone, chlorine dioxide
  - Halides – Sodium hypochlorite, chlorine
- Must include an aseptic post-cycle quench step to stop process prior to adverse material impact.
- Two validation methods
  - Half cycle method with & without a second spike
  - Bracketing method – vary concentration of agent, temperature.


Double Spike Method
Death Curves
Population
10^{6}
10^{3}
10^{0}
10^{-3}
10^{-6}
10^{-9}
10^{-12}
10^{-15}
10^{-18}
1st Challenge
2nd Challenge
6
12
18
24
30
36
42
48
54
60
Time

Gas vs. Vapor Sterilization

- Gases are more penetrating, more uniform in concentration, and less subject to variations in temperature and relative humidity.
- Vapors have different concentrations in each phase. When a vapor has 2 possible condensable components it is even more difficult to predict conditions anywhere.

<1229V> Vapor Sterilization

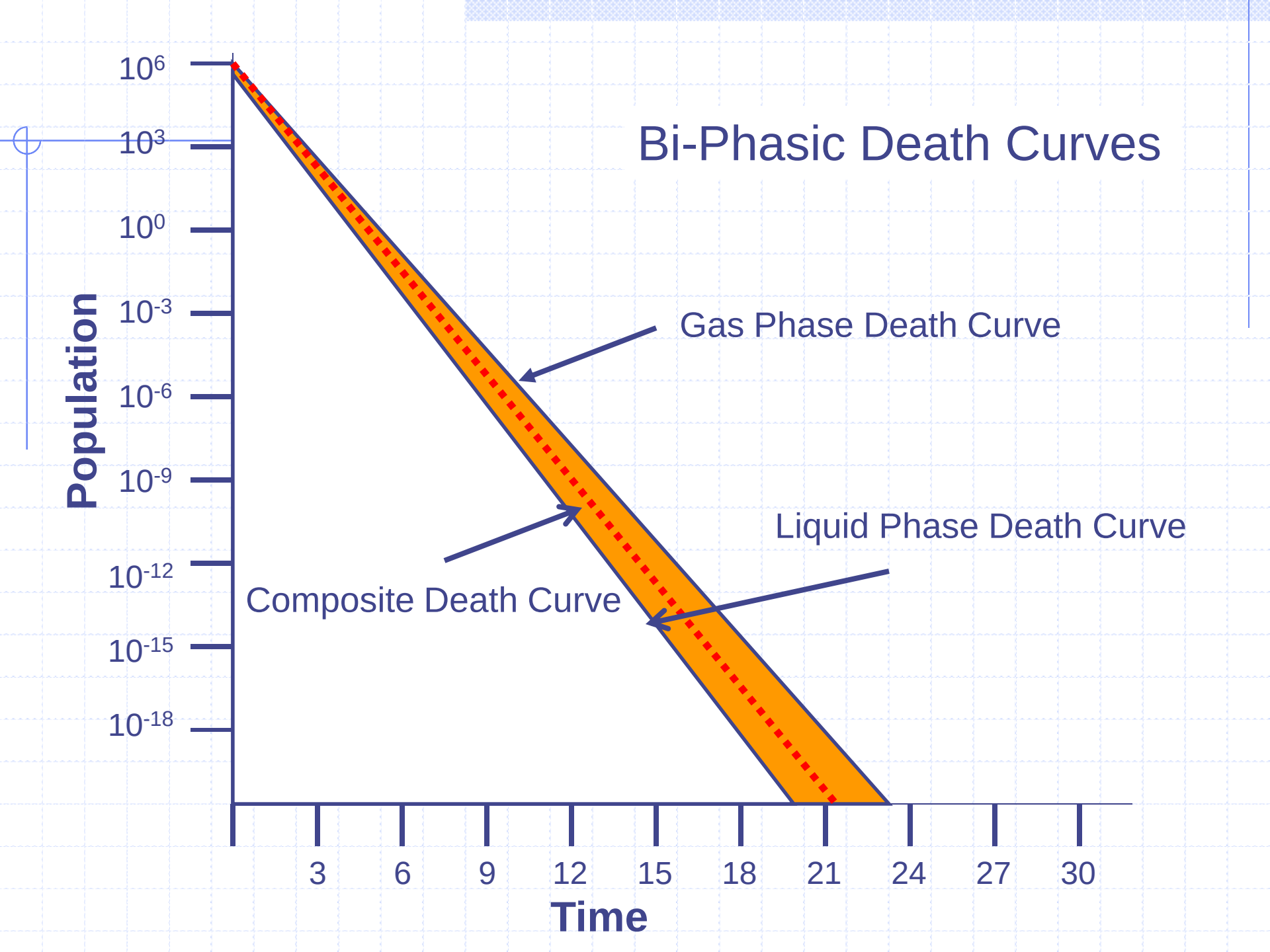
- Intended for condensing vapor systems (gas and liquid phases present simultaneously)
  - Hydrogen Peroxide
  - Peracetic Acid
- The presence of multiple phases simultaneously complicates concentration determination at the point of sterilization.
- D-value determination is problematic because of difficulties with parameter measurement in a multi-component 2 phase system.
- Approaches for validation are a hybrid of the liquid and gas sterilization methods.

The D-Value

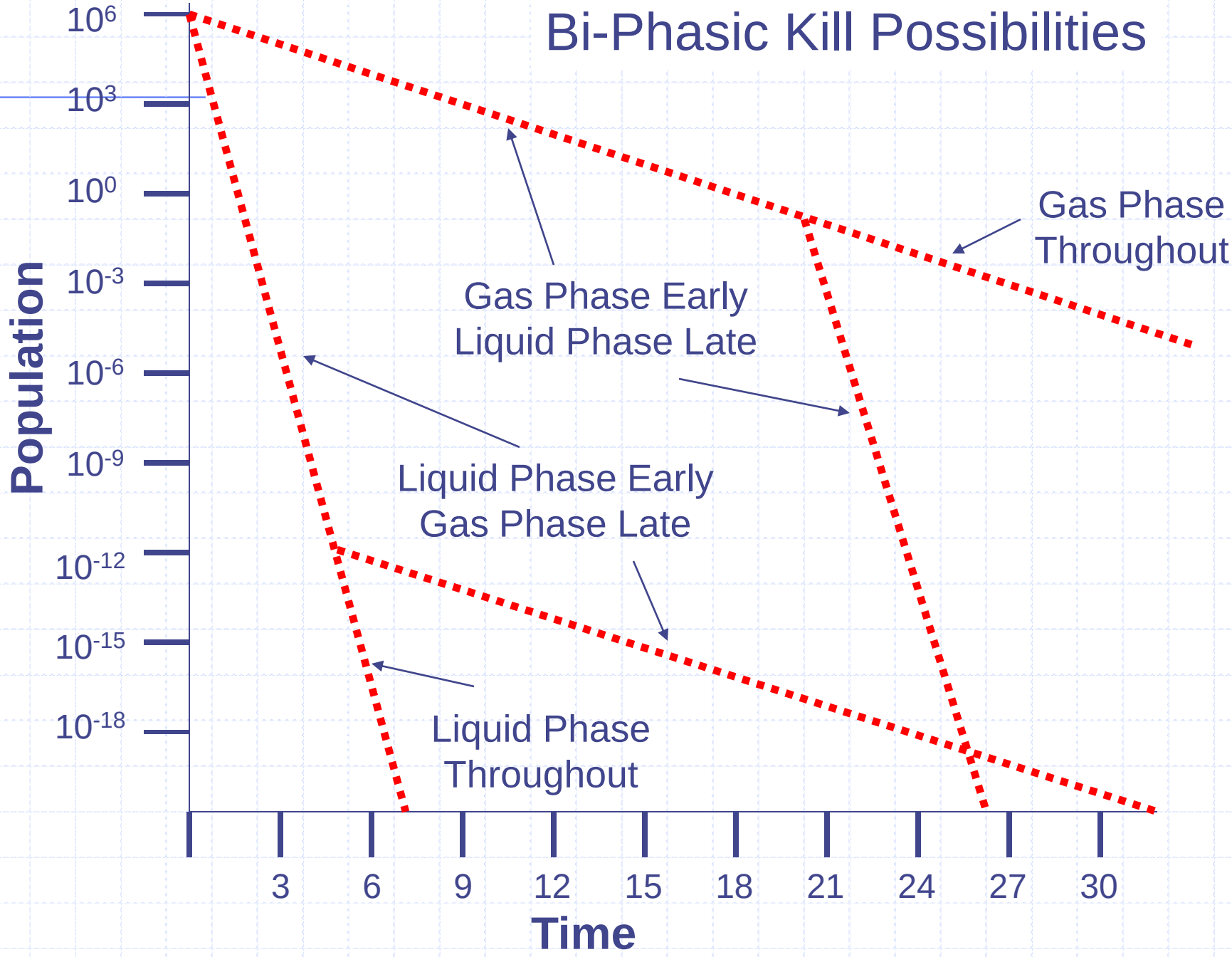
- The D-value is the time required to reduce a population of microorganisms by one log or a 90% reduction in count.
- A D-value is only meaningful if referenced to specified lethal conditions.
- For example wet or dry heat D-values should always be referenced to a temperature, without that reference 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., $D_{900\ PPM,\ 75\%\ RH,\ 30°C}$

<1229V> Vapor Sterilization

- Two validation approaches can be utilized, with the only supportive evidence from microbial destruction.
  - Traditional half-cycle method
  - Bracketing method
- The linearity of microbial destruction cannot be assured as the process may not be completely homogeneous.
- The efficacy of the agents used assures sterilization, however we do not have the ability to predict the outcome because the process parameters may vary substantially across the chamber.

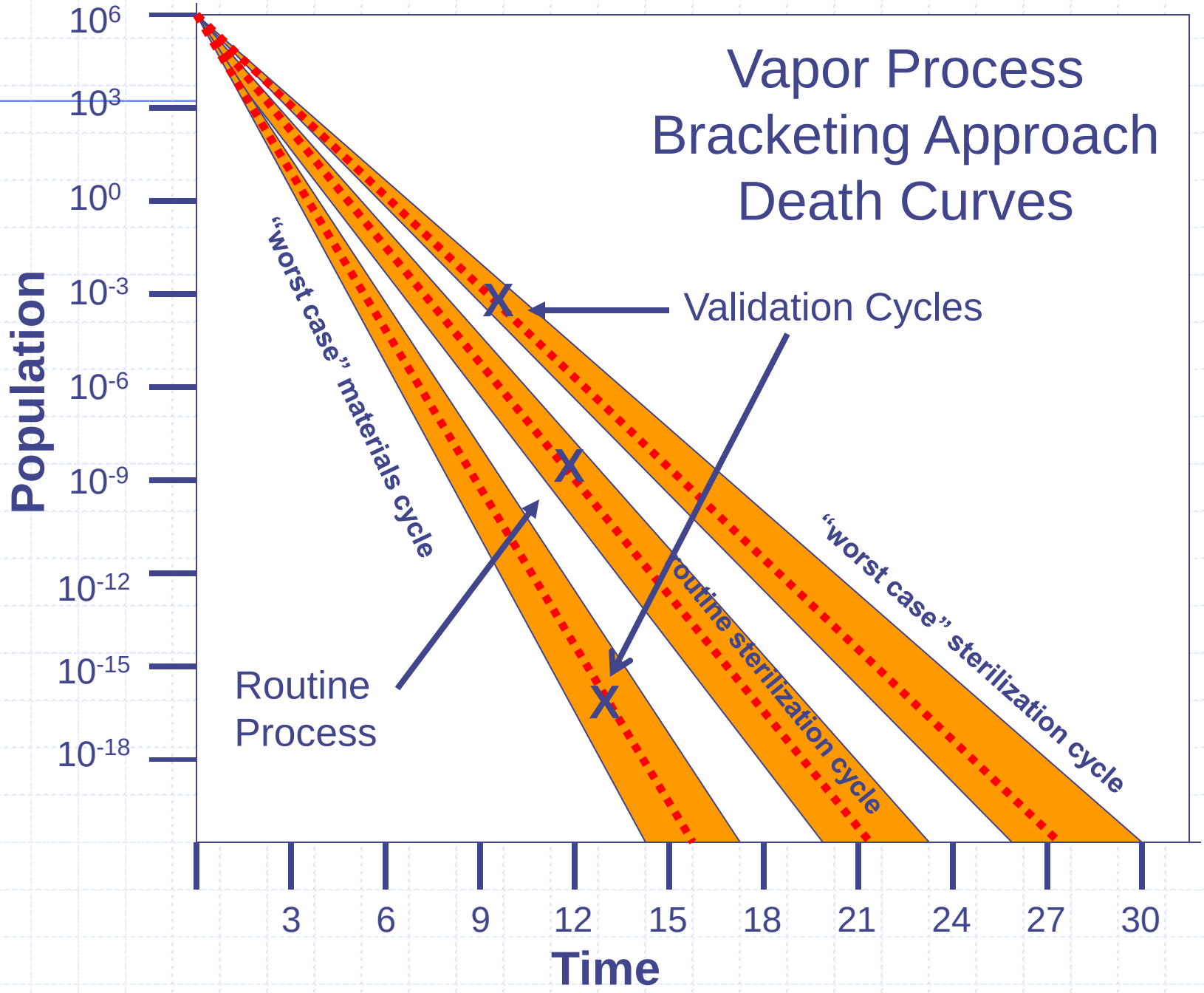

Bi-Phasic Death Curves
Population
10^{6}
10^{3}
10^{0}
10^{-3}
10^{-6}
10^{-9}
10^{-12}
10^{-15}
10^{-18}
Gas Phase Death Curve
Liquid Phase Death Curve
Composite Death Curve
3
6
9
12
15
18
21
24
27
30
Time

Bi-Phasic Kill Possibilities



<1229V> Vapor Sterilization

- The kill rates in the gas and liquid phase appear to be substantially different reflecting the different concentrations and available water in each phase.
- The conditions within an vapor system are unlikely to be uniform at all locations because the agent supply is a higher temperature than the chamber.
- The conditions at any location may change during the course of the process.
- Reproducible kill is possible despite all of the complication because the agent is lethal in both phases, it's just a far more complex a process than we generally understand.


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

Decontamination

- This is out of scope with respect to <1211> and the <1229> series. These sterilization processes can be proven to deliver a 10^{-6} microbial survivor probability.
- Decontamination treatments for environments (clean rooms, RABS and isolators) need not sterilize. Chapter <1072> Disinfectants & Antiseptics provides some current guidance.
- Decontamination treatments are planned for future chapters on aseptic processing in RABS and isolators.

<1229R> Radiation Sterilization

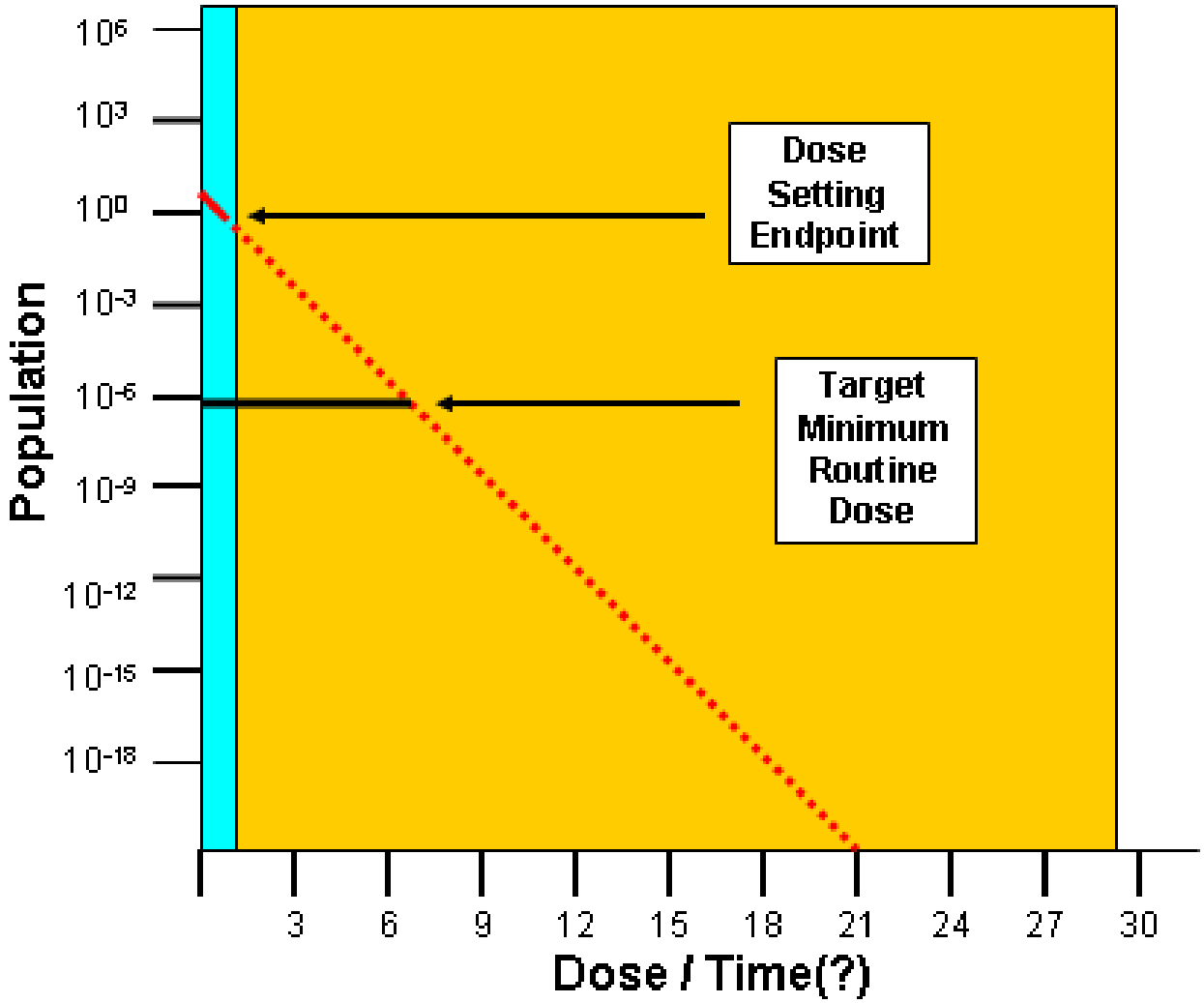
- "The prevalent radiation usage is either gamma rays or electron beams. Other methods utilize x-rays, microwaves and visible light. The impact of radiation on materials can be substantial and is a major consideration in the selection of radiation as a processing method."
- "Radiation sterilization is unique in that the basis of control … is the absorbed radiation dose, which can be precisely measured. Dose setting and dose substantiation procedures are used to validate the radiation dose required to achieve sterility assurance level."

<1229R> Radiation Sterilization

- The use of BI's in radiation sterilization is no longer necessary:
  - Non-spore-formers have been identified as more resistant than *B. pumilus.*
  - Dose measurement is accurate and has been closely correlated to microbial destruction.
- The dose setting methods of AAMI/ISO are well established and easily adapted to pharmaceutical applications. VD_{max} has been utilized for terminal sterilization of several pharmaceutical preparations.

<1229R> Radiation Sterilization

Typical Dose Setting Death Curve



<1229F> Sterilization by Filtration

- We've departed from the narrow perspectives of the prior chapter.
- Responsibilities for control are shared between filter user and filter manufacturer.
- Filter users should control their processes influencing filtration and monitor the pre-filtration bioburden.
- Filter manufacturers must provide a filter product with performance and characteristics consistent with that initially evaluated with the fluid.

<1229F> Sterilization by Filtration

- Microbial retention is a function of fluid, filter and process elements.
- "A rigorous evaluation of all of the relevant parameters within the context of an individual filtration process is extremely cumbersome, impractical and largely valueless in a real world situation."
- "Success with sterilizing filtration has been predominantly accomplished over the last 30 years using 0.2µm filters. When coupled with appropriate process controls and integrity test methods there have been comparatively few incidents of contamination associated solely with the filtration process. In specialized settings, larger or smaller pore size filters may be appropriate."

<1222> Parametric Release of TS

- Aligns the guidance with global regulatory expectations.
- Must be aligned with <1229>,<1229L>, <1211H> and <1229R> as these chapters evolve because all of these sterilization chapters are relevant for parametric release.

Old & New Structure Overview

- <1211>Sterilization & Sterility Assurance of Compendial Articles will be divided into two major areas:
  - <1211> General Concepts for Sterility Assurance
    - Choosing a Process (AP or TS) Aseptic Processing, Environmental Monitoring, Sterility Testing, Parametric Release, Adjunct Processing & other general sterility assurance related content
  - <1229> General Concepts for Sterilization
    - Sterilization Processes, BI, CI's, Endotoxin indicators, other sterilization related content

Future of Chapter <1211>

1211

General Concepts for Sterility Assurance

1211A
Aseptic Processing
Cleanrooms / RABS/
BFS / Isolators

71
Sterility Testing

1116
EM for Aseptic

1208
Sterility Test in Isolators

1222
Parametric Release

1229T??
Terminal Sterilization

1211P???
Post-Aseptic Lethal Processes

1207
Sterile Product Packaging
Integrity Evaluation

1211BM
Bioburden
Monitoring

1211EM
Endotoxin
Monitoring

1229 General Concepts for Sterilization	1229 BI-P Biological Indicator Performance	1229BI-G Biological Indicator General	1229I Physical / Chemical Indicators
1229C Chemical Sterilization	**Possible**	**Easy**	
1229D Dry Heat Depyrogenation	**Possible**	**X**	
1229F Sterilization by Filtration			
1229G Gas Sterilization	**X**	**X**	**X**
1229H Dry Heat Sterilization	**X**	**X**	
1229R Radiation Sterilization	**N/A**	**N/A**	**X**
1229S Steam Sterilization Parts	**X**	**X**	**X**
1229L Steam Sterilization Liquids	**X**	**X**	**X**
1229V Vapor Sterilization	**???**	**Easy**	**X**
1229N Non-Heat Depyrogentation	**???**	**???**	

New Chapters in 1211 for USP?

- 1211T – Terminal sterilization perspectives covering all process types (combination with 1222 is possible).
- 1211P – Post Aseptic Fill adjunct treatment using either radiation or moist heat.
- 1211BM – definition of Bioburden Monitoring practices: sample frequency, size, limits, etc.
- 1211EM – definition of Endotoxin Monitoring practices: sample frequency, size, limits, etc.

New Chapters in 1229 for USP?

- In addition to those described previously:
- 1229N – Non-heat depyrogenation processes – primarily washing & chemical
- 1229BIG – Biological Indicators - common practices for all strains
- 1229BIP – Biological / Endotoxin Indicators – process specific performance expectations (more likely these will be rolled into individual sterilization chapters)
- 1229I – Chemical / Physical indicators & integrators (could be handled in same manner as BI's splitting general guidance & performance)

Chapters changing within USP?

- <55> relocate contents into individual sterilization chapters of 1229.
- <1035> relocate contents into a general chapter within 1229 linked closely to other content.
- <???>Endotoxin Indicator – to be located within the 1229 area.
- <1207> Container integrity for sterile products

Many **THANKS** for **YOUR** Attention

Dziękuję Ďakujem dhanya-waad Дякую
bedankt תודה go raibh maith agat
tesekkürle Спасибо شكرًا Thank yu
Merci köszi díky tack så mycket
Thank you faleminderit
Shukriyâ Danke hvala kiitos
takk Obrigada Mulţumesc nandri
Grazie anugurihiitosumi
Ευχαριστώ dhanya-waad köszönöm
tack
Muchas gracias ačiû Terima Kasih
aitäh děkuji vam mange tak salamat