Session V

Sterilisation processes

Moderator:
J. C. Darbord
09:00-11:30

Biological Indicators of Sterilisation

Standards and Pharmacopoeial Requirements

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Why Do We Need Bioindicators ?

Use of Bioindicators (BIs)

- Confirmation of Sterilization Efficacy (F-value)
  - > Inactivation in positions of the load most difficult to access by the sterilant
  - > Inactivation in or on the product
  - > Effectiveness of alternative cycles
- Model for Bioburden
  - > Simulation of the most resistant bioindicator organisms
- Monitoring Tool
  - > Demonstration of lethality in routine sterilization

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Position of the Authorities

BI‘s in Annex I to EU Guide to GMP

- Efficacy in achieving the desired sterilising conditions in all parts of each type of load should be demonstrated by physical measurements and by BI’s where appropriate.
- Biological Indicators are considered as an additional method for monitoring of sterilisation.
- Not mentioned in NFG on Development Pharmaceutics (!)

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Position of the Authorities

BI‘s in FDA Guidance on Sterilization Documentation

Microbiological Efficacy of the Cycle

- Identification and Characterisation of Bioburden Organisms
  - > More information needed for bioburden-based processes than for overkill processes. Type, Number, Resistance
- Specifications for Bioburden
  - > Alert and action levels required
- Identification, Resistance and Stability of Biological Indicators
  - > D, z values, stability, corroboration of manufacturer data
- Resistance of BI Relative to that of Bioburden
  - > Eventually resistance of spores on carriers relative to directly inoculated spores.
- Microbial Challenge Studies
  - > Biological indicators at master site.

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European Pharmacopoeia

Choice and Use of Bioindicator Organisms

- The resistance of the test strain to the particular sterilisation method is great compared to the resistance of all pathogenic micro-organisms and to that of micro-organisms potentially contaminating the product,
- The test strain is non-pathogenic,
- The test strain is easy to culture.

- After incubation, growth of the reference micro-organisms subjected to the sterilisation procedure demonstrates that this procedure is unsatisfactory.

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Choice of Bioidicators

Species of Sporeformers Used (USP <1035>)

- Steam Overkill Cycles
  - > Typically *G. stearothermophilus*

Steam Bioburden Cycles

- > *G. stearothermophilus* and alternatively other spores e.g.
- > *C. sporogenes, B. coagulans* and

- Dry Heat
  - > B. subtilis, or *C. sporogenes, B. coagulans*
- Gas sterilization
  - > *G. stearothermophilus* or *B. subtilis* or *C. sporogenes*

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European Pharmacopoeia
Biological Indicators for Steam Sterilisation

- Recommended for the validation of sterilisation cycles.
- Spores of *Bacillus stearothermophilus*
- More than 5 _ 10^5 viable spores per carrier.
- $D_{121\ °C}$ -value exceeds 1.5 min.
- Verification by survival kill method:
  - > Exposition at 121 ± 1 °C for 6 min leaves viable spores,
  - > No growth after exposition at 121 ± 1 °C for 15 min,
  - > Theoretical time of inactivation: for 10^6 spores 9 min.

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European Pharmacopoeia
Biological Indicators for Dry-heat Sterilisation

- Spores of *Bacillus subtilis* (e.g. var. *niger* ATCC 9372)
- More than 1 _ 10^5 viable spores per carrier.
- $D_{160\ °C}$ -value approximately 5 min to 10 min.
- For temperatures greater than 220 °C (sterilisation and depyrogenation of glassware) demonstration of a 3 log reduction in heat resistant bacterial endotoxin can be used as a replacement for biological indicators.

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European Pharmacopoeia
Biological Indicators for Radiation Sterilisation

- Biological indicators recommended as an additional possibility to monitor effectiveness of the set dose in routine operations, especially in the case of accelerated electron sterilisation.
- Spores of *Bacillus pumilus* (e.g. ATCC 27.142)
- More than 1 _ 10^7 viable spores per carrier.
- D-value exceeds 1.9 kGy.
- Verification by total kill after exposition to 25 kGy (*minimum absorbed dose*).

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European Pharmacopoeia

Biological Indicators for Gas Sterilisation

- Use of BIs required for cycle validation and for routine operations of all gas sterilisation procedures.
- For H_2O_2 or peracetic acid *Bacillus stearothermophilus*
  For ethylene oxide (EtO) and formaldehyde *Bacillus subtilis*
- More than 5 _ 10^5 viable spores per carrier.
- Parameters of resistance known (e.g. ethylene oxide):
  - > D-value exceeds 2.5 min for a test cycle with 600 mg/l of ethylene oxide, at 54 °C and at 60% relative humidity.
  - > Verification by survival kill: No growth after 60 min cycle, viable spores after 15 min at reduced temperature cycle (30 °C).
  - > Exposition of indicators to 600 mg/l of ethylene oxide at 54 °C for 60 min without humidification must leave viable spores.

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US Pharmacopoeia 26

BI Resistance Performance Tests <55>

- Mandatory test procedure for manufacture of BI‘s
- Total viable spore count
  - > Performed on 3 specimen: Homogenize, heat shock, plate on CSA, incubate 48 h at suitable temperature, count.
- D-value determination
  - > Use appropriate equipment BIER-vessels for gas or steam
  - > Use appropriate numbers of units and expose to a series of exposure times.
  - > Recovery not later than 4 h after exposure by immersion into CSB medium
  - > Incubation for 7 days if negative
  - > Calculation: Spearman_Karber method is described as reference, but Survival Curve or Stumbo Murphy Cochran are acknowledged.

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US Pharmacopoeia 26

BI General Information Chapter <1035>

- Non-mandatory chapter giving advice on
  - > Types of Biological indicators (Spores on carrier, spores in suspension, self contained BIs)
  - > Suitable species: Other species than the ones specified in monographs are acceptable
- Selection for specific sterilization processes
- Performance Evaluation
  - > Manufacturer‘s responsibility
  - > User‘s responsibility
  - > Spore crop preparation
  - > Instrumentation
- Use for In-Process Evaluation

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US Pharmacopoeia <1035>
Performance Evaluation Manufacturer's Responsibility

- Characterization using specialized equipment
  - > as specified in Performance Test <55>
- Certificate of analysis for each lot
  - > D-value
  - > Microbial count
  - > Shelf life
  - > Storage conditions (temp., humidity, other conditions)
  - > Reference to results of performance tests

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US Pharmacopoeia <1035>
Performance Evaluation User's Responsibility

- Establish acceptance standards for BI's
- Obtain certificates
- Audit manufacturers facilities and procedures
- Acceptance tests
  - > Verify morphology of BI-organisms
  - > Identification at least to genus is desirable
  - > Microbial count to determine mean count per BI
  - > Verification of D-value assessment according to Performance Test <55> is optional. Especially important if BI's are stored
- If BI's are prepared in house testing according to <55> is mandatory

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US Pharmacopoeia 26
Biological Indicator Monographs

BI for Steam Sterilization, Paper Carrier

- Specified strain of *Bacillus stearothermophilus*
  - > nlt. 10^4 nmt. 10^9 viable spores on suitable grade paper carrier
  - > individually packaged in steam penetrable container
- Survival time nlt. $D_{(label)} \times \log N_{0\,(label)} - 2$ [min]
- Kill time nlt. $D_{(label)} \times \log N_{0\,(label)} + 4$ [min]
- Expiration date nlt. 18 months from manufacturing date
- ID complies with *Bacillus stearothermophilus*
- Resistance performance: nmt. 20% from label claim
- Viable spores nlt. 0.3 log of labeled count, nmt. factor 4.8 higher than labeled count

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Position of the Pharmacopoeias
Comparison of European and US BI Reqirements

- USP
  - > Detailed monographs for various types of BI with requirements to verify label claims
  - > Detailed test method <55> for resistance performance with total viable spore count and D-value determination
  - > General information <1035> with guidance on use and definition of Manufacturer's and user's responsibility in performance evaluation.
- Ph.Eur
  - > One short informational chapter on BI's
  - > Requirements only D-value and number of spores
  - > Verification by survival/kill
  - > No guidance on use of BI's
  - > No detailed guidance on evaluation of BI's

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Sterilization of Health Care Products
ISO 11138 Biological Indicators

- Part 1: General requirements
- Part 2: Biological indicators for ethylene oxide sterilization processes
- Part 3: Biological indicators for moist heat sterilization processes
- Part 4 : Biological indicators for radiation sterilization (deleted from series)
- Part 5: Biological indicators for low-temperature-steam-formaldehyde sterilization processes
- Part 6: Biological indicators for dry heat sterilization processes

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ISO 11138 Biological Indicators
Purpose and Content of the Standards

- Addressed to manufacturers of bioindicators
  - > Give general requirements for quality systems
  - > Define BIs as test systems
  - > Define basic quality standards
  - > Give standardized methods for testing (see USP <55>)
- Standards for specific applications
  - > Define the specific requirements for Bis
  - > Similar to USP monographs
  - > No equivalent in Ph. Eur.

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ISO 11138 Biological Indicators

CD Part 1: General Test Conditions

ISO 11138-1	Min. No of test samples	Min. No of Exposure Conditions	Min. total No of Bioindicators
Initial count	4	-	4
Survivor curve	4	5	20
Fraction negative	20	7	140
Survival-kill	50	2	100
Total No of BI's needed for evaluation with 2 methods			124 to 244

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CEN/ISO Bioindicators

Specific Approach to Medical Devices

- BI is defined as indicator organisms on a carrier in a protecting envelope
- Medical devices standards describe an interrelated system:
  - > the product
  - > the sterilizer
  - > the bioindicator

  are all medical devices each defined by standards.

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Sterilization of Health Care Products

ISO 14161 Biological Indicators

Guidance to the selection, use and interpretation of results

- Very detailed guideline. Main Chapters:
  - > General Requirements
  - > Properties of BIs
  - > Selection of the Supplier
  - > Use of BIs for process development
  - > Use of BIs for sterilization process validation
  - > Use of BI's for routine monitoring of sterilization processes
  - > Results; Application of BI standards
  - > Culture conditions
  - > Training; Storage and Use, Safe Disposal of BIs

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Steam Sterilization
Different Approaches

Hospital Approach	Canning Approach
◆ First Priority: kill infectious agent	◆ First Priority: preserve texture/taste
◆ Second Priority: preserve material	◆ Second Priority: kill spoiling microorganisms
◆ Sterilized Good: heat resistant open, porous material, bedding, instruments	◆ Sterilized Good: heat sensitive closed containers
◆ Load: complex/heterogeneous	◆ Load: homogeneous batches

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Steam Sterilization
Standard and Overkill Cycles

- Conditions inactivate microorganisms with a wide margin of safety.
- Effectiveness of the cycle is accepted as given
  - > Standard conditions must be maintained in all parts of the load
  - > BIs are used during cycle validation to demonstrate effectiveness as theoretically expected
- Priority in physical cycle monitoring
  - > BIs only for additional verification

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Sterilisation Processes
Definition of Overkill Cycles

- Cycles with and F_o of 12 minutes
  - > (Parenteral Drug Association, 1978. Technical Monograph Nr 1: Validation of Steam Sterilisation Cycles)
- Cycles which provide more than a 12 log reduction of a resistant BI with a known D-value of not less than 1 minute
  - > (Parenteral Drug Association, 1999. Technical Monograph No. 30: Parametric Release of Sterile Pharmaceuticals)
- Cycles with and F_o of 8 minutes
  - > (FDA, 1978. Preliminary GMP`s for Large Volume Parenterals. withdrawn 1990.)
- Cycles with and F_o of 15 minutes
  - > Äquivalent Procedures to pH. Eur. Standard-Procedure, Ph. Eur. 1997. Methods of Sterilisation.

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Steam Sterilization
Bioburden Based Cycles

- BI simulation of most resistant bioburden
  - > Approach used mainly in the US
- BI population and resistance related to worst case bioburden
  - > Higher challenge than worst case bioburden isolated in the product (safety factor) or
  - > Close simulation of routine bioburden
- Inactivation of challenge is used to demonstrate SAL

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Alternative Cycles in Europe

- Alternative cycles are still understood to be minimum overkill cycles
  - > Non standard cycles are not well recognized in Europe
  - > F_0 of 8 minutes is minimum alternative cycle in Europe
- Other Cycles may be used in aseptic processing
  - > "Additional heat treatment" is recommended in Europe
  - > Conditions of such heat treatment are not defined
- Bioburden based sterilization cycles are not commonly used in Europe

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Validation of Steam Sterilis(z)ation
Approach in Europe and in the USA

Europe
- Priority for standard cycle.
- Emphasis on sterilizer qualification.
- Bioindicator inactivation as additional verification.
- Development of alternative cycles is the exception, little experience in companies and authorities.
- Tendency to undervalidate standard procedures.
- Product should be developed to be sterilizable

USA
- Priority for SAL.
- Emphasis on cycle development.
- Bioindicator inactivation as key process development study.
- Not much reliance on standard cycles, demonstration of cycle effectivity is expected.
- Tendency to validate even basic facts of microbiology.
- Cycle developed to fit product

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Possible Future Development

Sterilisation Procedures

- Sterilisation approach selected according to type of load.
- Overkill cycles where possible.
- Alternative cycles where needed.
- Load specific approach for terminal sterilisation of different products as well as for sterilisation of parts, hollow bodies, or textiles.
- Emphasis on sterilisation cycle development and validation in combination with product development.
- More flexibility by using the European or US approach wherever appropriate.

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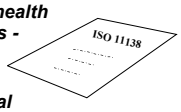
Microbiological Control Methods in the European Pharmacopoeia: Present and Future

Update on Harmonized Revision of ISO and CEN Biological Indicator Standards

Copenhagen, Denmark
6 May 2003

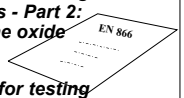
Current ISO B.I. Standards

- **ISO 11138-1, (1994)** ***Sterilization of health care products - Biological Indicators - Part 1: General***
- **ISO 11138-2, (1994)** ***Part 2: Biological indicators for ethylene oxide sterilization***
- **ISO 11138-3, (1995)** ***Part 3: Biological indicators for moist heat sterilization***



Current CEN B.I. Standards

- **EN 866-1, (1996)** ***Biological systems for testing sterilizers and sterilization processes - Part 1: General requirements***
- **EN 866-2, (1996)** ***Biological systems for testing sterilizers and sterilization processes - Part 2: Particular systems for use in ethylene oxide sterilizers***
- **EN 866-3, (1996)** ***Biological systems for testing sterilizers and sterilization processes - Part 3: Particular systems for use in moist heat sterilizers***



Current CEN B.I. Standards

- **EN 866-4, (1999)** ***Biological systems for testing sterilizers and sterilization processes - Part 4: Particular systems for use in irradiation sterilizers***
- **EN 866-5, (1999)** ***Biological systems for testing sterilizers and sterilization processes - Part 5: Particular systems for use in low temperature steam and formaldehyde sterilizers***
- **EN 866-6, (1999)** ***Biological systems for testing sterilizers and sterilization processes - Part 6: Particular systems for use in dry heat sterilizers***

Current CEN B.I. Standards

- **prEN 866-7, (1999)** ***Biological systems for testing sterilizers and sterilization processes - Part 7: Particular requirements for self-contained biological indicator systems for use in moist heat sterilizers***
- **prEN 866-8, (1999)** ***Biological systems for testing sterilizers and sterilization processes - Part 8: Particular requirements for self-contained biological indicator systems for use in ethylene oxide sterilizers***

ISO 11138 and EN 866 B.I. Series Standards

Specify general production, labeling and *performance requirements* for the *manufacture* of biological indicators and spore suspensions for use in sterilization processes

ISO 11138 and EN 866 Differences

Two standards series similar but some differences:

- **Resistance testing:**
  - **direct enumeration and MPN methods (EN)**
  - **direct enumeration, fraction negative (MPN) methods *or* verification of calculated survival/kill - any 2 (ISO)**
- **D value tolerance ± 0.5 minutes for steam (ISO), ± 0.2 minutes for steam (EN)**
- **Self-contained biological indicators addressed in ISO 11138-1**
- **No radiation, dry heat or LTSF in ISO 11138**
- **Method for viable count (ISO)**

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ISO 11138, 1 & 2, EN 866, 1 & 2, Performance Requirements

Performance Criteria Ethylene Oxide B.I.

Population	**Not less than 1.0 X 10^6**
D value	**Not less than 2.5 min. at 54°C, 60% RH, 600 mg/L**
Survival Time	**Not less than D_{value} x (Log_{10} Pop. - 2)**
Kill Time	**Not more than D_{value} x (Log_{10} Pop. + 4)**

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ISO 11138, 1 & 2, EN 866, 1 & 2, Performance Requirements

Performance Criteria Steam B.I.

Population	**Not less than 1.0 X 10^5**
D value	**Not less than 1.5 min. @ 121°C**
Survival Time	**Not less than D_{value} x (Log_{10} Pop. - 2)**
Kill Time	**Not more than D_{value} x (Log_{10} Pop. + 4)**
Z value	**Not less than 6°C**
"10"- Rule	**Not less than 10 min.; Log_{10} Pop. x D_{value}**

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European Pharmacopoeia (EP)

(1997) 5.1.2 Biological Indicators of Sterilization

- **B. I. for EO Sterilization**
  - **Population exceeds 5.0 x 10^5 per carrier**
  - **D_{value} exceeds 2.5 minutes**
  - **Survival @ 15 minutes; kill @ 60 minutes**
  - **Survival @ 60 minutes without humidification**

- **B. I. for Steam Sterilization**
  - **Population exceeds 5.0 x 10^5 per carrier**
  - **D_{121} exceeds 1.5 minutes**
  - **Survival @ 6 minutes; kill @ 15 minutes**

- **B.I. for Dry Heat & Ionizing Radiation Sterilization**

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EO B.I. Resistance Calculation

Required minimums:

D_{value} = 2.5 minutes

Population = 1.0 x 10^6 CFU/unit

***Survival time* = 10 minutes minimum**

***Kill time* = not more than 25 minutes**

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Steam B.I. Resistance Calculation

Required minimums:

D_{value} = 1.5 minutes

Population = 1.0 x 10^5 CFU/unit

***Survival time* = 4.5 minutes minimum**

***Kill time* = not more than 13.5 minutes**

12

ISO/CEN B.I. Standards Harmonization

- **5 year revision of ISO 11138 and EN 866 standards series**
- **ISO/TC 198 and CEN/TC 102 , 15-16 Sept. 1999, London, England**
- ***Joint revision* under the Vienna Agreement with:**
  - **ISO lead**
  - **CEN format & structure**
  - **2004 target for final versions**

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ISO/CEN B.I. Standards Revision Meetings

- **ISO/TC 198 and CEN/TC 102 , 15-16 Sept. 1999, London, England**
- **ISO/TC 198/WG 4, Biological Indicators 4-6 April, 2000, Frankfurt, Germany (interim meeting)**
- **ISO/TC 198, 20-21 Sept. 2000, Berlin, Germany**
- **ISO/TC 198/WG 4, Biological Indicators 4-6 February, 2001, Copenhagen, Denmark (interim meeting)**
- **ISO/TC 198, 11-15 May, 2002, Kyoto, Japan**
- **ISO/TC 198/WG 4, Biological Indicators 21-22 January, 2003, Washington, DC (interim meeting)**

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ISO 11138 Series Standards Current Drafts

Combined Biological Indicator Standards:

- **ISO 11138 – Part 1, General Requirements**
- **ISO 11138 – Part 2, B.I.'s for Ethylene Oxide process**
- **ISO 11138 – Part 3, B.I.'s for Steam process**
- **ISO 11138 – Part 4, B.I.'s for Dry Heat process**
- **ISO 11138 – Part 5, B.I.'s for Low Temperature Steam Formaldehyde process**

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ISO 11138 Series Standards Changes

- Elimination of EN 866, Parts 7 & 8 (self-contained B.I.'s); incorporated into Parts 1, 2 & 3
- Elimination of EN 866 - 4 (radiation sterilization)
- Elimination of "10 rule" (Part 3)
- Allow use of "dual species" B.I.'s
- Allow D value calculation by either survivor curve or MPN method
- Allow D value calculation by either SMC or LSK
- Contain resistometer test methodology only; equipment specifications in separate document

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ISO 11138 Series Standards Status

- The current drafts are in the Committee Draft (CD) stage
- A second ballot will be conducted prior to the 2003 annual ISO/TC 198 meeting in December (New Orleans, USA)
- The documents will move forward to the Draft International Standard (DIS) stage at the December, 2003 ISO/TC 198 meeting
- Best estimate for publication: early 2005

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Mange tak for deres opmærksomhed!

Skallingen

The F_0-concept, its application and limitations

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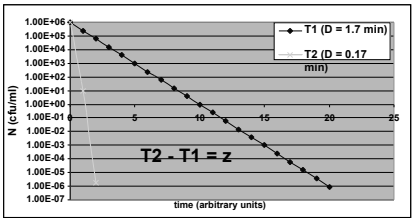
Steam sterilization
definition of D-value

Decimal reduction time (D-value):
Time to decrease the number of viable cells to one tenth of its initial value

$$\log \frac{N}{N_0} = \square \frac{t}{D}$$

Steam sterilization
Definition of z-value

Z- value is the rise in temperature necessary to decrease the D-value to one-tenth of the initial value



Steam sterilization

Definition of z-value

Z- value is the rise in temperature necessary to decrease the D-value to one-tenth of the initial value

$$Log(D_1/D_2) = (T_2 - T_1)/z$$

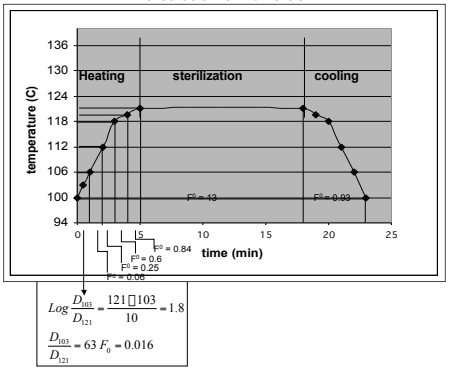
Steam sterilization

Definition of F_0-value (Ph. Eur 4.5 2003)

The F_0 value of a saturated steam sterilisation process is :

- **the lethality expressed in terms of the equivalent time in minutes**
- **at a temperature of 121 °C**
- **delivered by the process to the product in its final container**
- **with reference to micro-organisms possessing a Z-value of 10.**

Calculation of F0-value



$$Log\frac{D_{103}}{D_{121}} = \frac{121 - 103}{10} = 1.8$$

$$\frac{D_{103}}{D_{121}} = 63 \quad F_0 = 0.016$$

Steam sterilization

z- values for moist heat sterilization

organismz-valuetemperaturerangeB cereus 19.9104 -121E

Data from Russell, Hugo and Ayliff, Disinfection and sterilization

Steam sterilization

z- values for dry heat sterilization

organismz-valuetemperaturerangeB cereus 122140 - 160

Data from Russell, Hugo and Ayliff, Disinfection and sterilization

Steam sterilization

Effect of z-value on estimated D-value

z-valuetemperature6101410910015.87.21151042.7121111

Data from Russell, Hugo and Ayliff, Disinfection and sterilization

FAQ

- Can the z-value be used to design a sterisation process?

From literature (1)

- The F_0-concept of the Ph. Eur is based on the assumption of a germ specific z-value of 10°C....
  - Pfeiffer, M. Pharmaz. Ind. 63 (2001) 291-296

Factors affecting z-value

- Type of micro-organism
- Heating medium
- Temperature (?)

From literature (2)

- **The real z-values of the biological indicator organism....spores of *Bacillus stearothermophilus* lies in the range of 6 - 8°C rather than 10°C**
- Pfeiffer, M. Pharmaz. Ind. 63 (2001) 291-296

Heat resistance of spore forming organisms

(in aqueous solutions or pharmacuetical preparations)

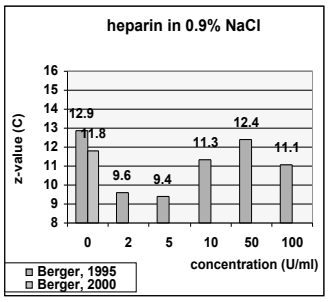
Organism	D^{121}-values(min)	z-values(°C)	temp range(°C)

1 Russel, 1999
2 Caputo 1979
3 Berger 1995, 2000

Factors affecting z-value

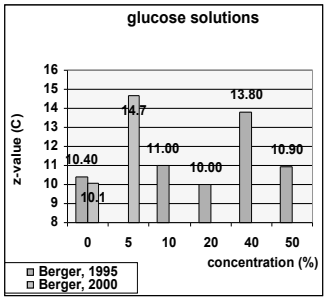
- **Type of micro-organism**
- **Heating medium**
- **Temperature (?)**

Effect of heating medium on z-value



Organism: Clostridium perfringens ATCC 7955
Temp. range: 112 - 121 °C

Effect of heating medium on z-value



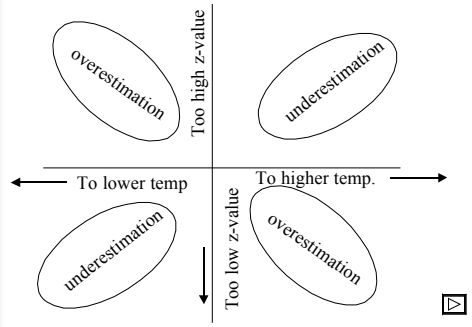
Organism: Clostridium perfringens ATCC 7955
Temp. range: 112 - 121 °C

From literature (3)

- **It lies in the mathematical nature of the F_0-concept that with z-values below 10°C and sterilization temperatures < 121°C lethal effects below those of equivalent times and sterilization temperatures but with z-values of 10°C occur.**

- Pfeiffer, M. Pharmaz. Ind. 63 (2001) 291-296

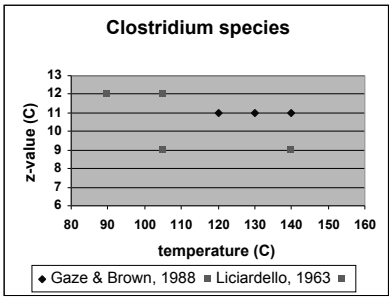
Designing of sterilization processes by extrapolation



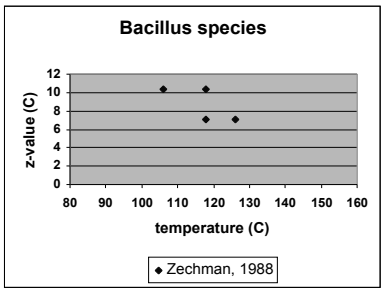
Factors affecting z-value

- Type of micro-organism
- Heating medium
- Temperature (?)

Effect of temperature on z-value



Effect of temperature on z-value



Conclusions

- The F_0-concept alone cannot be used for the design of a sterilisation process, because available data suggest that z-values are dependent on temperature, type of organism and environment.
- The F_0-concept is a suitable tool to demonstrate the reproducibility and repeatibility of sterilisation processes.

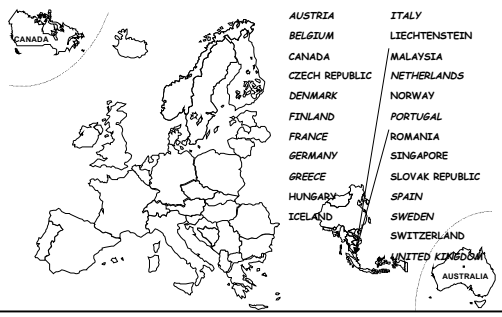
The PIC/S position on parametric release

Lilian Hamilton
Principal Pharmaceutical Inspector
Medical Products Agency
SWEDEN

Content

- PIC/S - membership and role
- Parametric release
  - Guidelines
  - Requirements
  - Implementation

PIC/S Members January 2003



AUSTRALIA
AUSTRIA
BELGIUM
CANADA
CZECH REPUBLIC
DENMARK
FINLAND
FRANCE
GERMANY
GREECE
HUNGARY
ICELAND
IRELAND
ITALY
LIECHTENSTEIN
MALAYSIA
NETHERLANDS
NORWAY
PORTUGAL
ROMANIA
SINGAPORE
SLOVAK REPUBLIC
SPAIN
SWEDEN
SWITZERLAND
UNITED KINGDOM

PIC/S Observers

- Estonia
- Latvia
- WHO
- EMEA

Main Features of PIC/S (1)

- Commenced operating on 2 Nov. 1995
- An informal arrangement between Agencies
- Strict criteria for membership (assessment & reassessment procedure)
- Facilitates Networking and confidence building
- Exchange of information and experience on GMP

Main Features of PIC/S (2)

- Emphasis on Quality Systems for Inspectorates
- Training of inspectors (Seminars & Joint inspections)
- Meetings of GMP Experts (Expert Circles)
- International harmonisation of GMP
- No obligation of mutual recognition of inspections

Parametric release

... gives assurance

... based on the information collected

... and on the compliance with specific GMP requirements

Background to Guidelines

- PIC/S prepared Guidance on Parametric Release (PI 005-1)
- EU prepared Notes for Guidance on Parametric Release (CPMP/QWP/3015/99)
- The procedure for parallel industry consultation was used (PIC/S and EU)

Lack of

- Clear policy
  - some authorities said YES, others NO
- Guidance
  - quality of documentation may differ
  - assessors and inspectors tasks unclear

Results - Guidelines

- Annex 17 to the PIC/S GMP and EU GMP (sept. 2001 and jan. 2002)
- PIC/S Guidance on Parametric Release (PI005-1, sept. 2001)
- Note for guidance on parametric release (CPMP/QWP/3015/99, sept. 2001)

Status of PIC/S Documents

- Each participating authority should
  - apply the PIC/S GMP or an equivalent GMP
- A guidance document is for
  - training of inspectors and
  - preparation of inspections
  - not mandatory for industry

However

- Parametric release is an option

Ph Eur 4th Ed

- Methods for preparation of sterile products 5.1.1.
  Parametric release if
  - process is fully validated
  - terminal sterilisation by
    - steam
    - dry heat
    - ionising radiation
  - competent authority approves
- General Notices 1.2 (IV.2)

Annex 17

2.1

' It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finish product testing.'

Sterility Assurance System

- product design
- bioburden control
- mix up prevention
- product integrity
- sterilisation process
- quality system

Sterile products

- sterilised in final container if possible
- validated sterilisation process
- record of sterility testing scrutinized during inspections
- qualified personnel at the site
- no possibility for mix ups

Parametric release (1)

- sterilised in final container by steam, dry heat or ionising radiation
- validated sterilisation process
- established product with record of satisfactory sterility testing
- risk analysis performed
- history of good compliance with GMP

Parametric release (2)

- qualified personnel at the site
- no possibility for mix ups (physical barriers)
- additional controls before release

Annex 17

3.17

' Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specification. Non-compliance with the specification for parametric release cannot be overruled by a pass of sterility tests.'

PI005-1

- general part and appendix
- co-operation and role of assessors and inspectors
- gives detailed recommendations on control of bioburden etc.

Parametric release in PIC/S (1)

- Annex 17 is implemented (or in progress of being so) in most countries
  - Canada only for sterile products
  - Not in Island, Latvia, Slovak Republic
- PI005-1 is used as an additional guideline for inspectors in most countries and industry has been informed

Parametric release in PIC/S (2)

- Parametric release is approved in
  - Australia, Belgium, Czech Republic, Denmark, France, Hungary, Netherlands, Norway, Singapore, Sweden, Switzerland, UK
  - Some countries have not received applications
  - Applications have also been rejected

Parametric release in PIC/S (3)

- Parametric release is approved for
  - Steam sterilisation overkill cycles (all above)
  - Dry heat (DK)
  - Ionising radiation (FR, SE)
- Parametric release is approved
  - at national sites and/or
  - at foreign sites (based on inspection reports)
  - preauthorisation inspections are required

Parametric release in PIC/S (4)

- Other information
  - TGA (Australia) has issued a guideline for assessing applications
  - TGA always brings a microbiologist on inspections for parametric release
  - DK, NO, SE approved parametic release before annex 17

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