Understanding Sterilization

- Sterilization basics
- Radiation Technology & Ethylene Oxide

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PDA Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®


Sterile
Ionization
Aseptic Assembly
Clean
SAL
Radioactive
HELP!

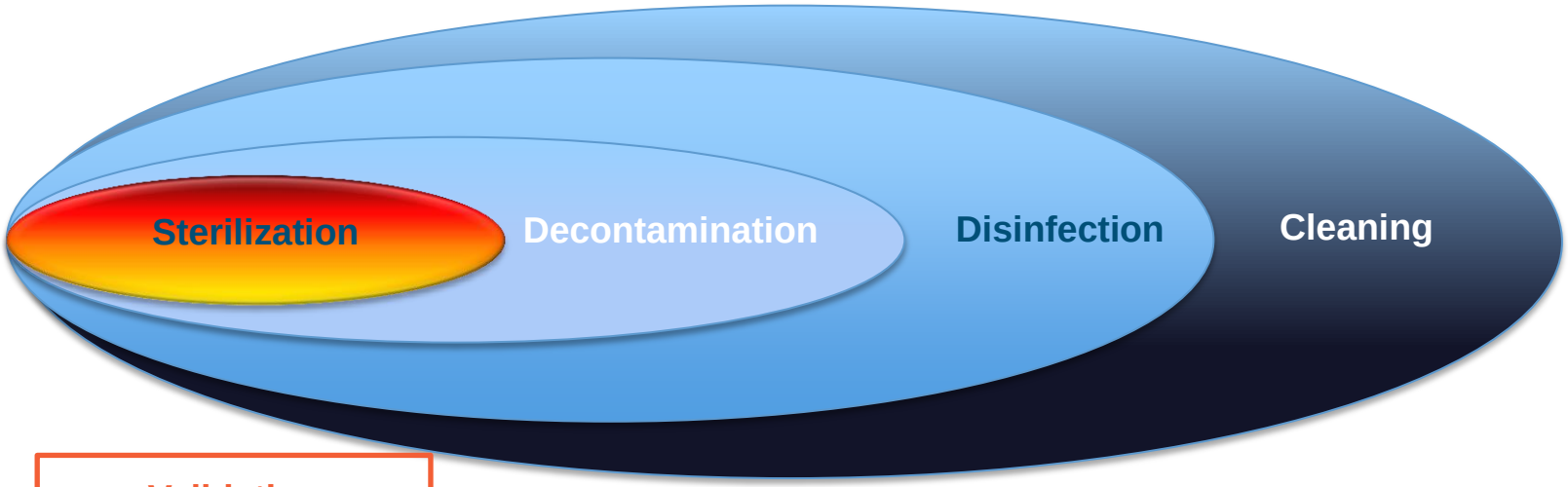
Content

- Basics of sterilization
  - Distinguish disinfection, sterilization and decontamination
  - Definition
  - Selection of sterilization method
  - Difference between Aseptic Assembly and Terminal Sterilization
- Sterilization using Irradiation
  - Gamma
  - E-Beam
- Sterilization by Ethylene Oxide
- Comparison between technologies

Sterilization Basics

- Decontamination Vs Sterilization
- Terminal Sterilization Vs Aseptic Assembly
- Method selection

Decontamination Vs Sterilization



Validation

Sterilization	Decontamination	Disinfection	Cleaning
The application of a lethal sterilizing agent to finished product within a sealed container to achieve a predetermined **sterility assurance level** (SAL) of 10^{-6} or better – *GMP Annex 1 Draft*	A process that **eliminates viable bioburden** via use of chemical agents *GMP Annex 1 Draft*	The process by which **surface** bioburden is **reduced** to a safe level *GMP Annex 1 Draft*	Removal of **contamination** from an item to the extent necessary for further processing or for intended use *ISO 11139:2006*

A sterile product is one that is free of viable microorganisms

Absolute sterility can never be guaranteed !

- 100% control of the batch is not possible
- No assurance that any microorganism can be detected during Sterility Test

Sterility is much more than just a process!

Initial contamination level

- Microbiological status raw material and components
- Cleaning and disinfection procedures
- Environment control
- Personnel Hygiene

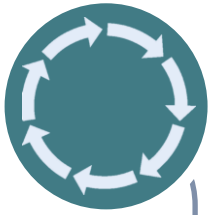
Equipment

- Control
- Maintenance
- Calibration

Product preservation

- Packaging
- Storage

Pharmaceutical Product Life Cycle



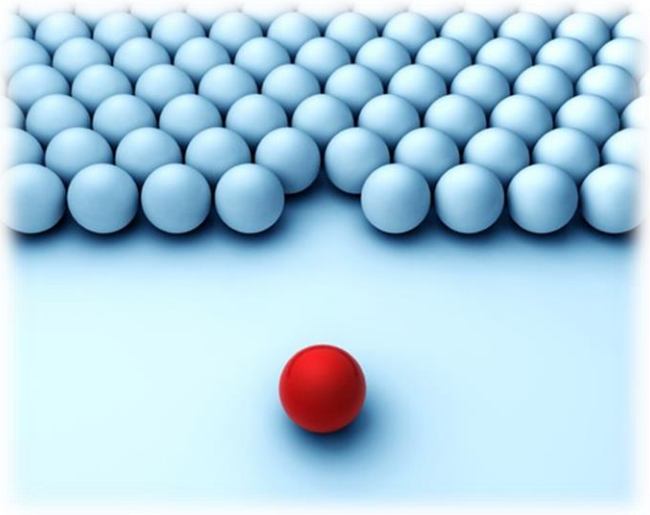
Think about sterilisation as soon as possible during product development

Sterility Assurance Level (SAL) = The **probability** of a single item in a batch being non-sterile after being subjected to a sterilization process.

Sterile: SAL ≤ 10^{-6}

SAL likelihood of surviving organisms

10^{-1} = 1:10
10^{-2} = 1:100
10^{-3} = 1:1,000
10^{-4} = 1:10,000
10^{-5} = 1:100,000
10^{-6} = 1:1,000,000



Sterile means : Safe Product **&** Functional product

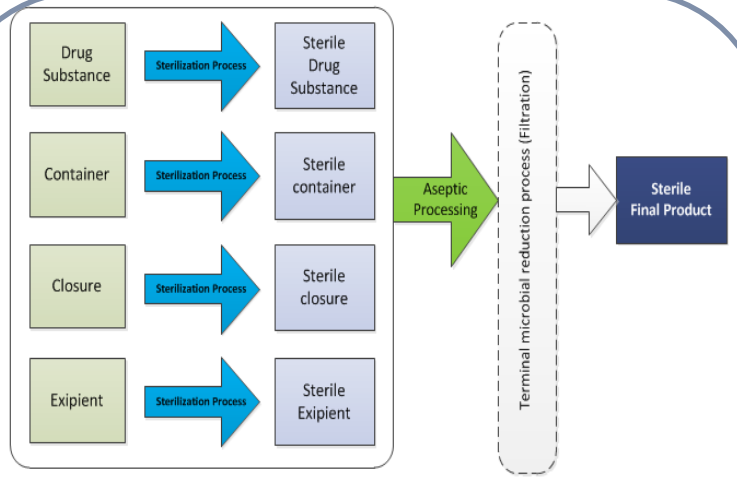
Selection of the right sterilization method is critical !

There are two (2) methods to produce a sterile drug product:

- Heat
- Irradiation
- Gas (EO, NO_2 …)

Sterilization – Basics

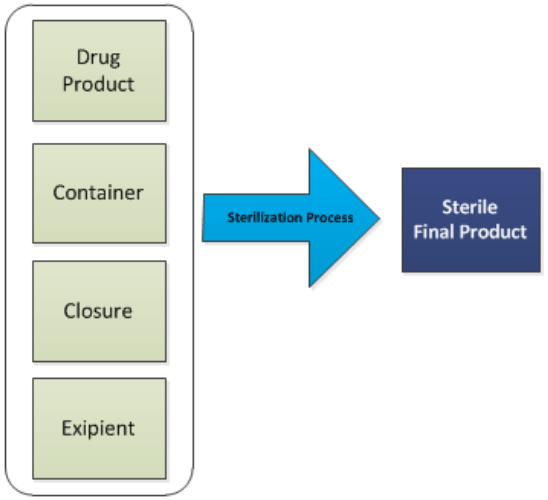
Aseptic Assembly



Maintain sterility of a product that is assembled from components, each of which has been previously sterilized

Sterile

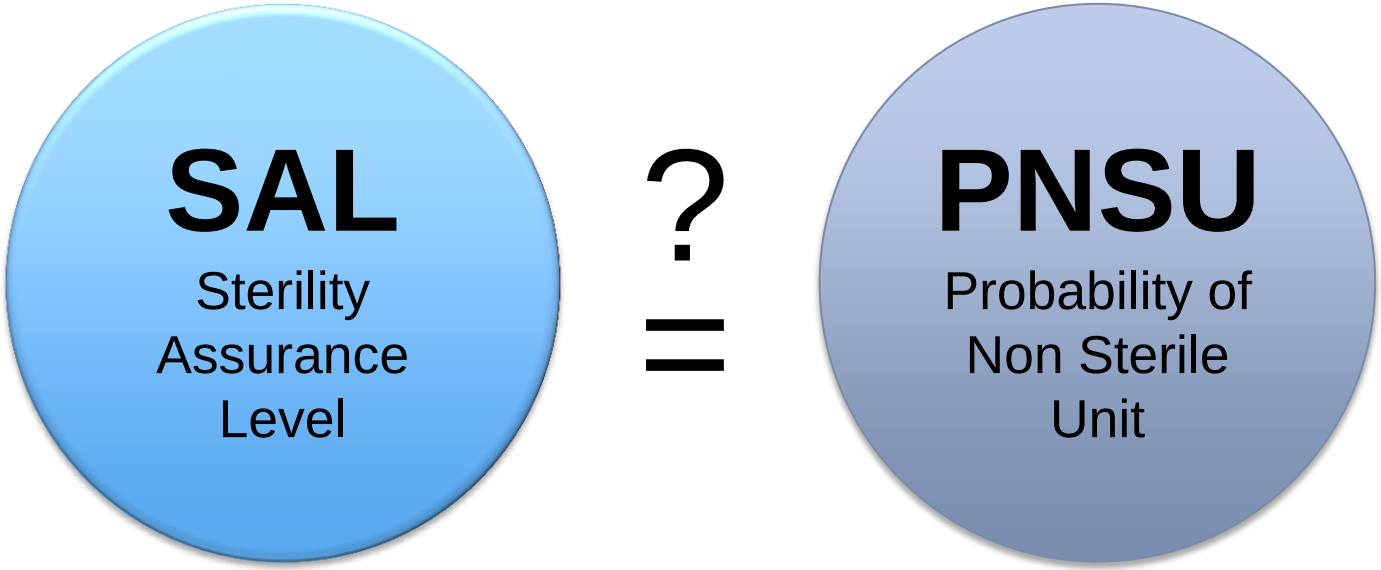
Terminal Sterilization



Exposure to a physical or chemical sterilizing agent for a predetermined extent of treatment

Sterilized

How to Assess the effectiveness of a sterilization process ?



Reference: ISO TS 19930:2017

PNSU

Probability of Non Sterile Unit (PNSU):

The probability of one or more microorganism being present on a product item in a population of items.

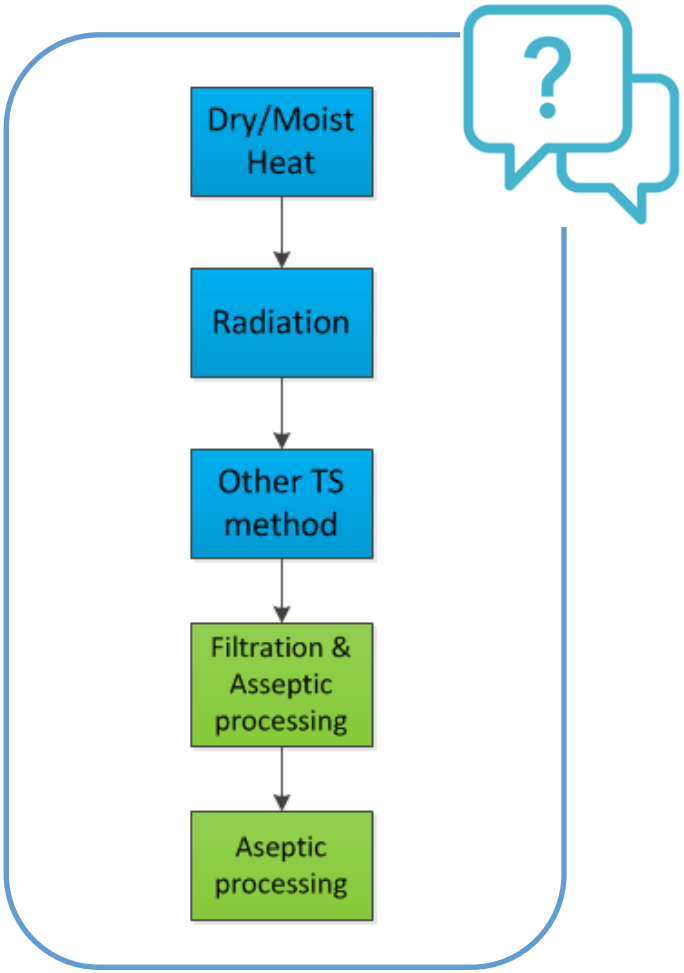
- No SAL can be calculated for aseptically assembled products (no killing kinetic)
- Rely on multiple factors
- Estimated by Media Fill Test (process simulation
- Bracketing approach (MFT before and after process)

Selection of the Sterilization Method:

“Wherever possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen”

European Pharmacopoeia 9.7

Per PDA 2017 Survey – 30% of Aseptically assembled product could be Terminally sterilized !



Based on EMA - *CPMP/QWP/054/98 Decision Tree for the selection of sterilisation methods*

Selection of the Sterilization Method:

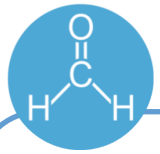
Use a **structured approach** to select the most appropriate sterilisation method

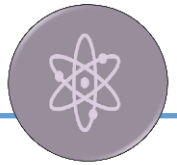
Prior to making your choice, consider mitigation options:

- Can your **formula** be adapted (limit degradation and impurities)?
- Can the **container** be adapted ?
- Can you select compatible **component** with selected sterilization process ?
- Can the **process** can be optimized (limit impact)?

CPMP/QWP/054/98 Decision Tree for the selection of sterilisation methods

Sterilization – Basics





Ethylene Oxide

- (EO) gas

Irradiation

- Gamma ray
- Accelerated electrons (E-beam)
- X-rays

Other

- Moist heat
- Dry heat
- Vaporized hydrogen peroxide (VHP)
- Gas plasma
- Low temp Steam Formaldehyde (LTSF)
- Nitrogen Dioxide (NO_2)

Most common methods
for terminal sterilization of single use medical devices

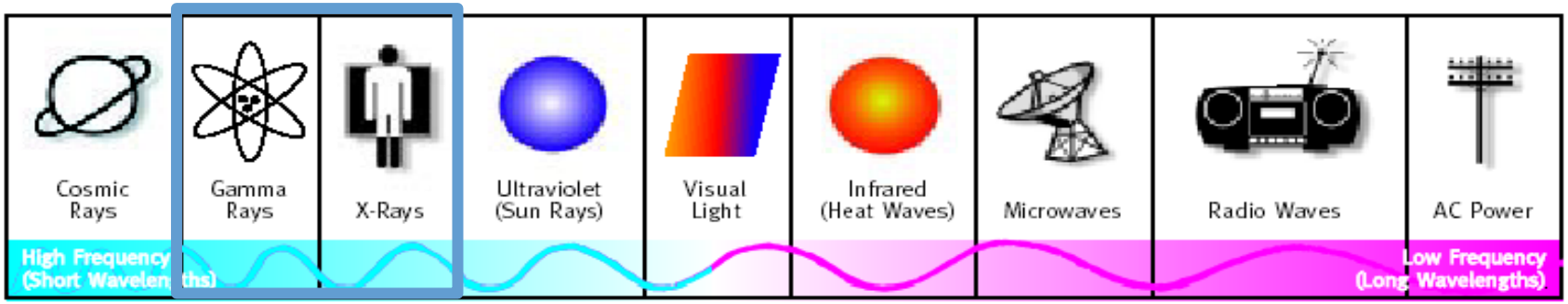
Radiation Technology

- General principles
- Gamma
- E-Beam
- Sterilization validation

General Terminology

Radioactivity:

Electromagnetic radiation (photons) produced by radioactive decay.



Ionising Non-Ionising

E-beam = Electrons (with a mass)

General Terminology

Radiation

Energy in the form of waves or moving subatomic particles

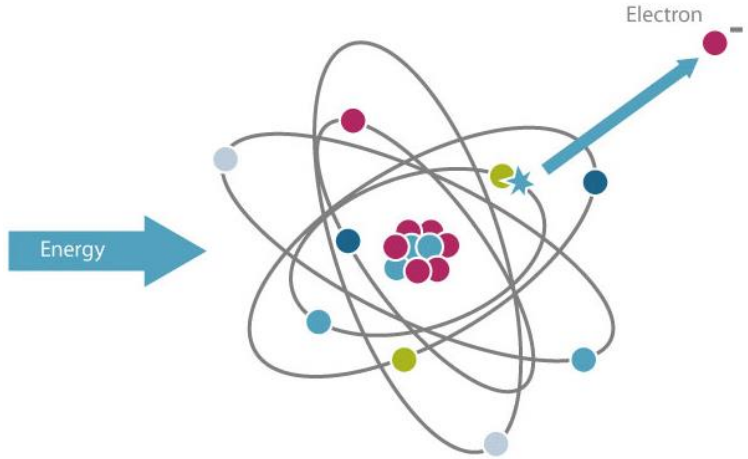
Radioactive

Substance emitting radiation

Irradiation

Exposure to radiation
≠ Making something radioactive

General Terminology



Ionising Radiation

Radiation capable of knocking electrons out of their thermal orbits in atoms or molecules

(Absorbed) Dose

Measure of the amount of energy that is absorbed by the material while exposed to a radiation source.

Unit: Gray **1 Gy = 1 Joule per Kg material**

Irradiation process monitoring:

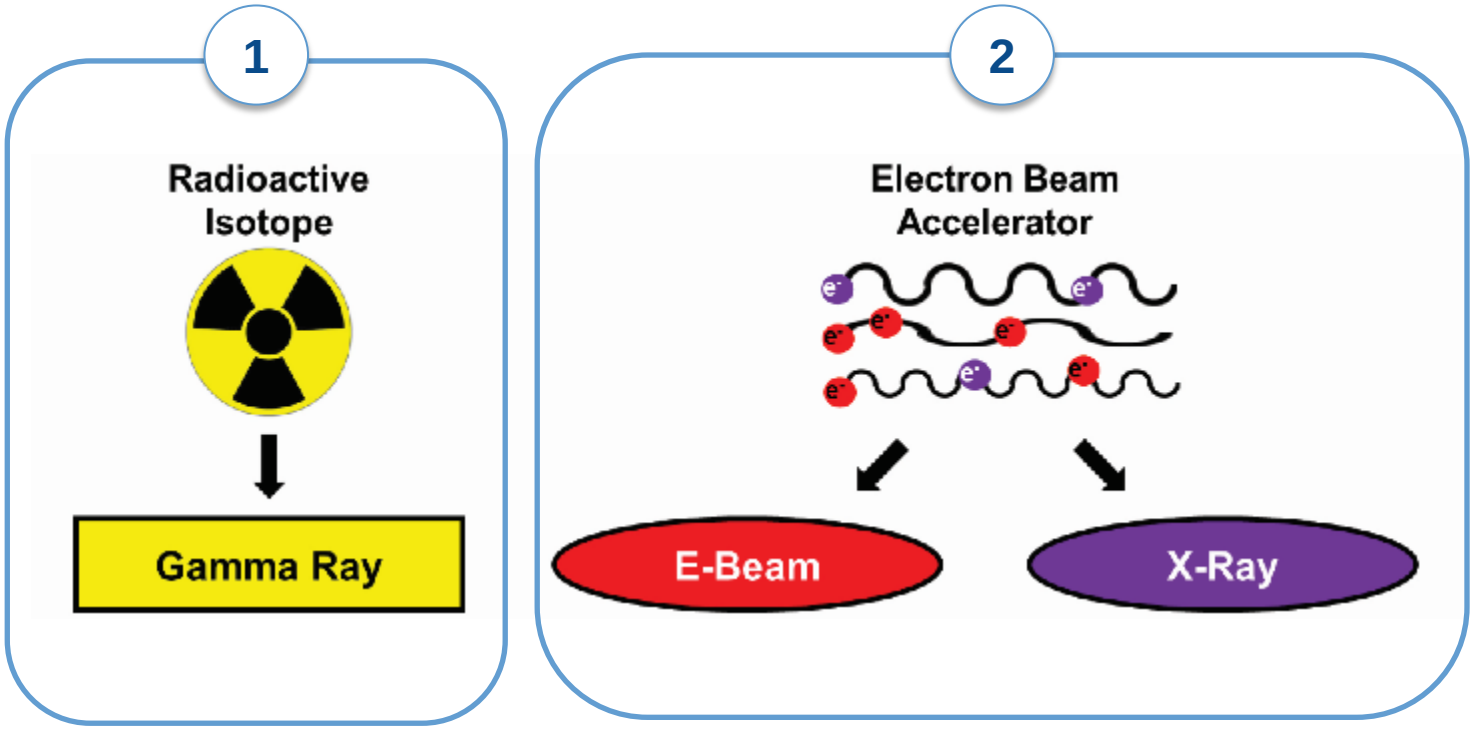
Dosimeter

Device having a reproducible, measurable response to radiation, which can be used to measure the obsorbed dose in a given system.

0 kGy 12 kGy 25 kGy 50 kGy 0kGy

Sterilization by Irradiation – General principles

Two methods to generate irradiation :



Gamma Irradiation

Sterilization by Irradiation : Gamma

Scale of irradiation :

Sterilization Dose
10.000 – 40.000 Gy

Dose that may cause symptoms of radiation sickness (1000 mGy)

1000

500

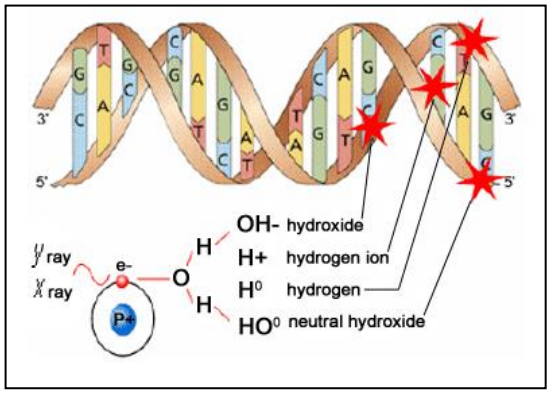
100

Typical chest X-Ray (0,1 mGy)

50

10

1



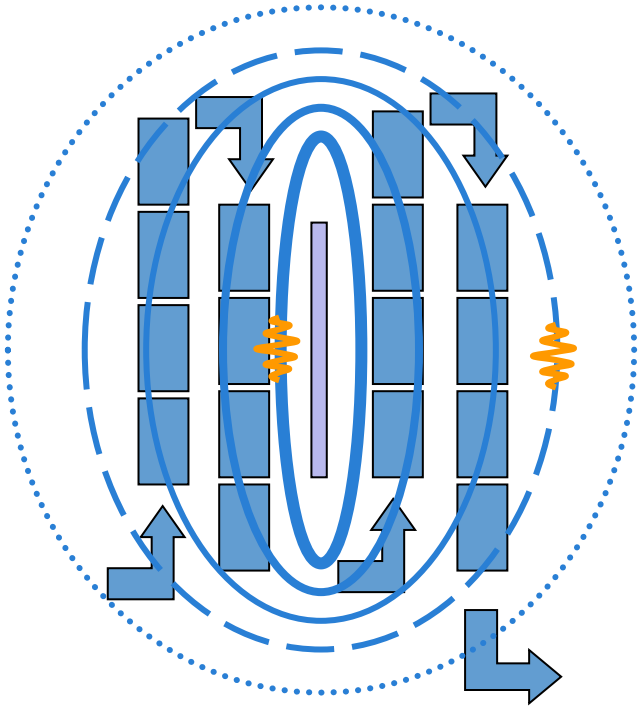
Effects of ionizing Radiation on DNA

Sterilization by Irradiation: Gamma

Source: ^{60}Co (mostly)

Decay rate: 12% per year (Half life 5,3 years)

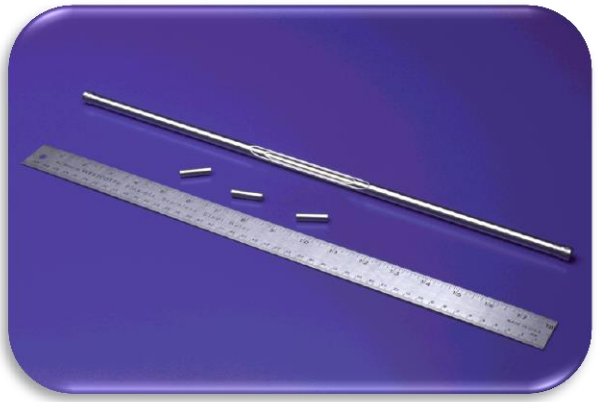
Source Activity: Several Million Ci



Isotropic radiation flux

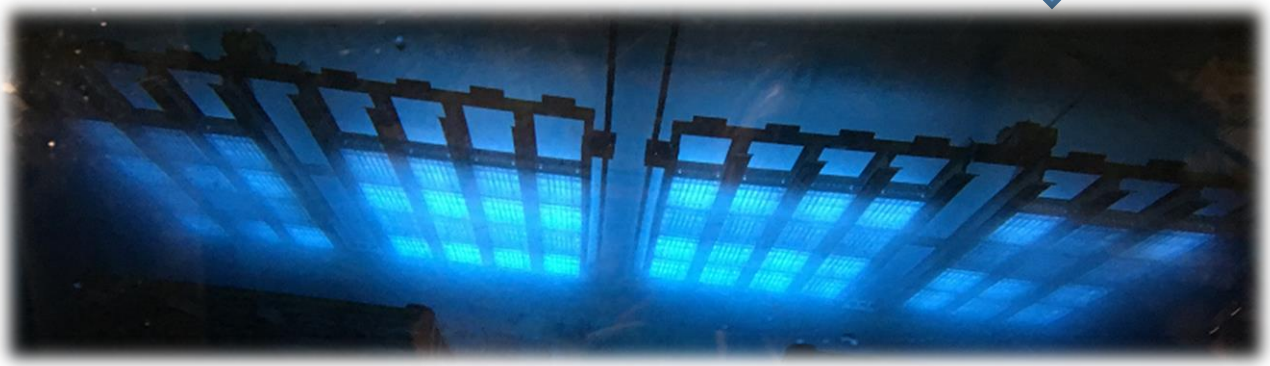
Source Rack

Cobalt-slugs in a source pencil



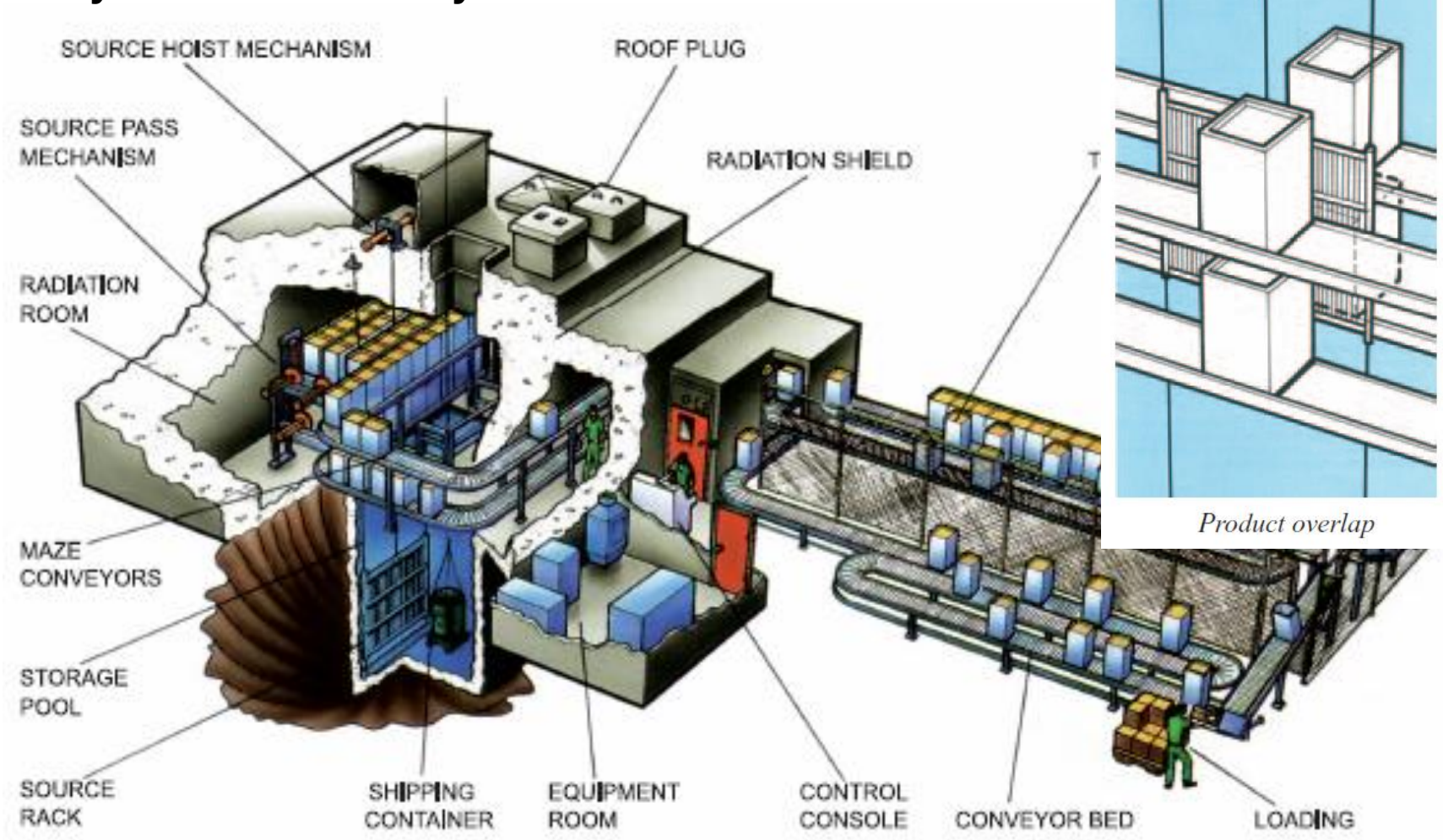
Source module

Source rack



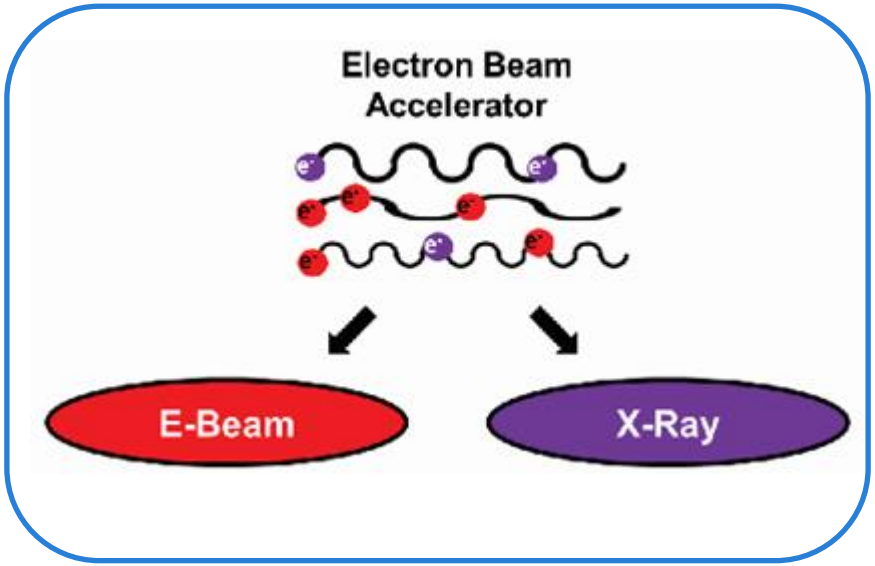
Sterilization by Irradiation : Gamma

Layout Gamma facility



Product overlap

E- Beam irradiation



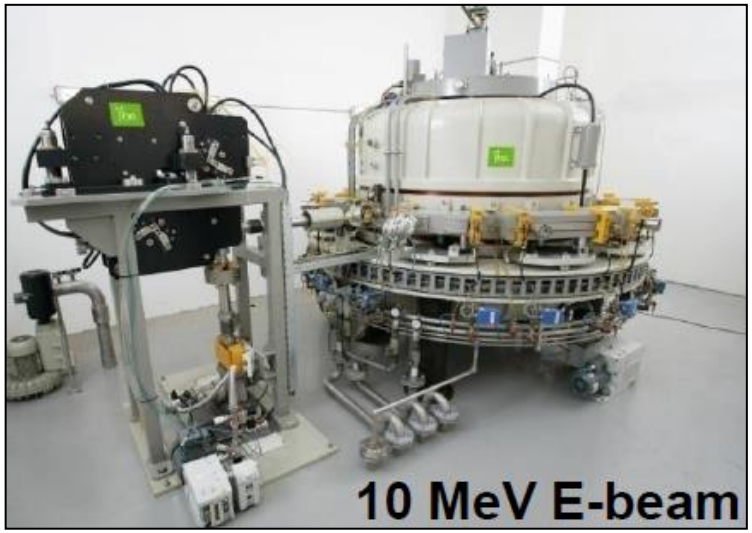
Electron Beam

Directed stream of electrons (B radiation) produced by a particle accelerator

Beam energy

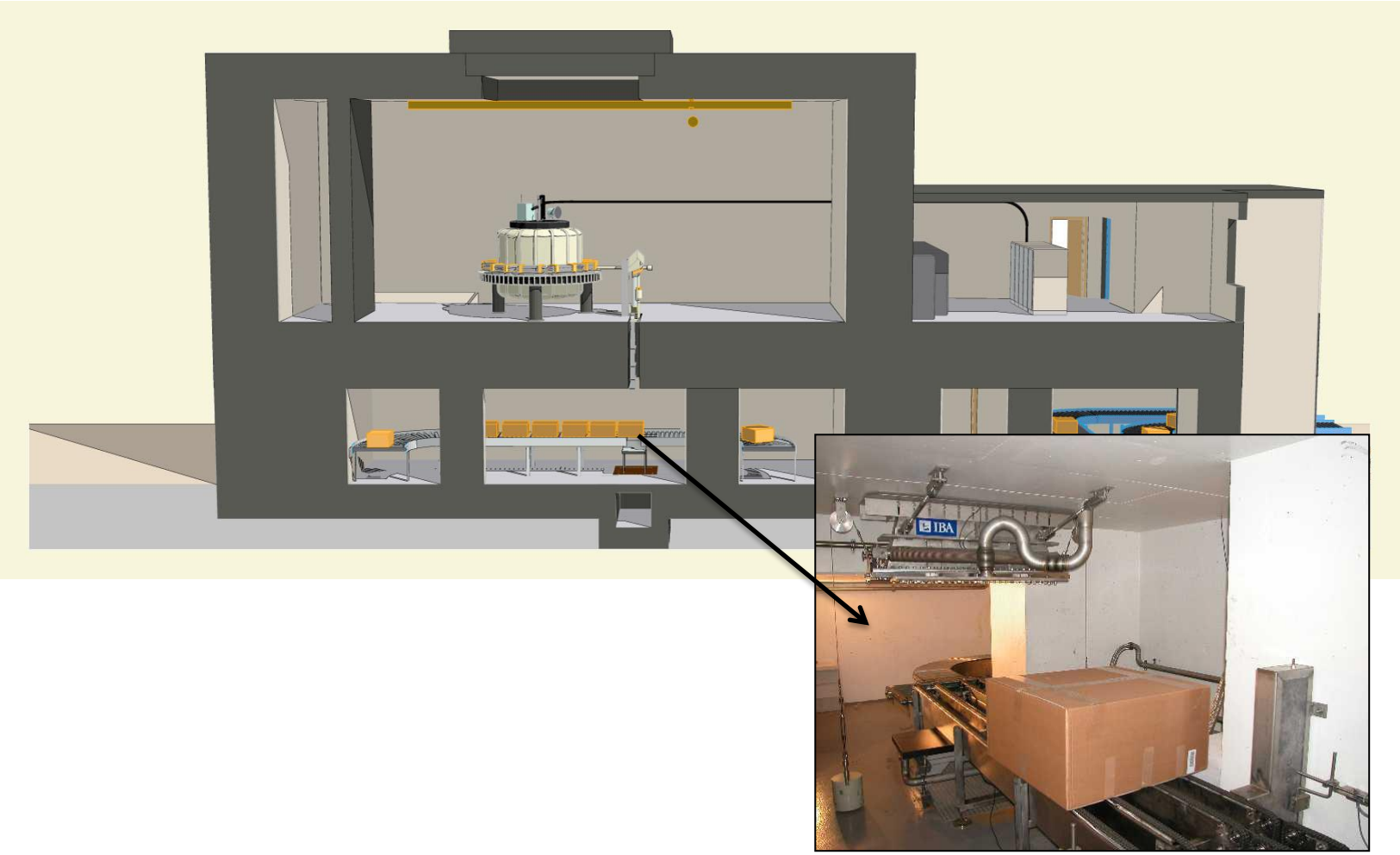
Speed of the electrons. Parameter related to depth of penetration

Limited to 10 MeV for medical device sterilisation (ISO 11137-1) to avoid radioactivity induced in product

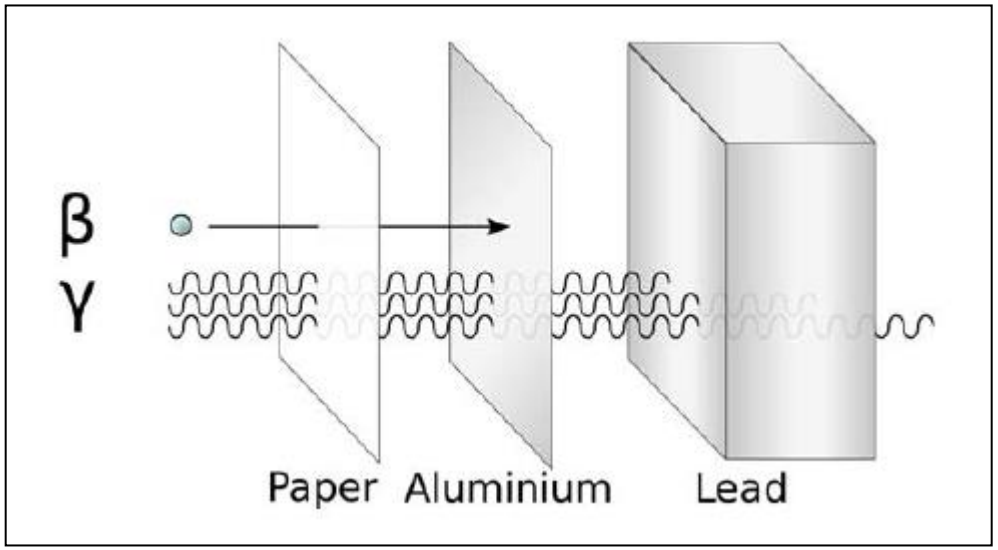


IBA Rhodotron

Layout E-Beam facility



Electron Beam & Gamma, Penetration



Sterilization by Irradiation : comparison

Parameter	Gamma	Xray	E-Beam
Irradiation parameter	Cycle Time Density	Conveyor speed Density Scan width Beam energy	Conveyor speed Density Scan width Beam energy
Radiation Field	Isotroptic	Highly directional	Highly directional
Geometry of material and heterogeneity of Product	Important to consider	Important to consider	Critical

Sterilization by Irradiation : comparison

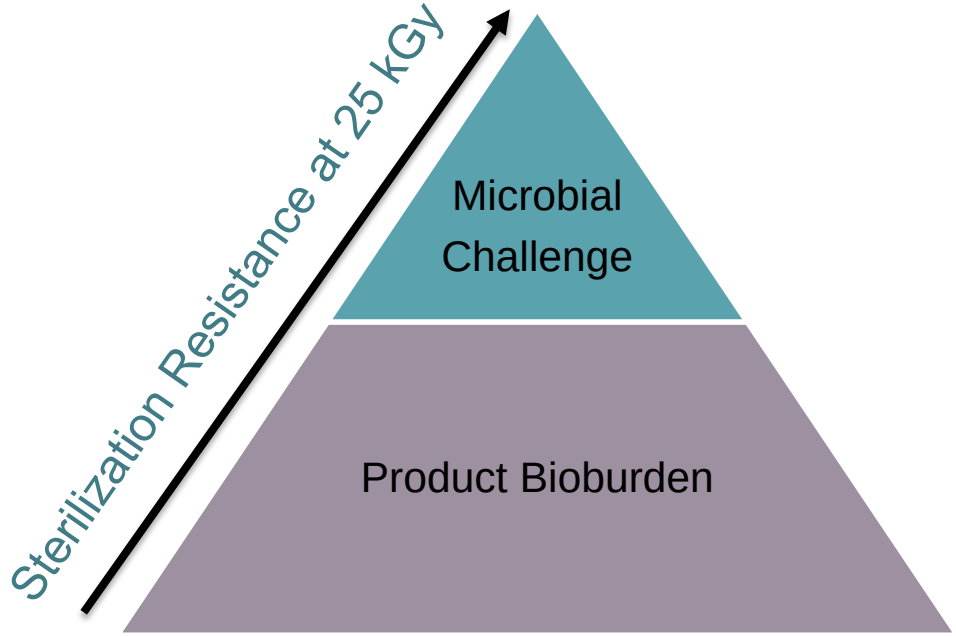
Parameter	Gamma	Xray	E-Beam
Product Treatment	Pallet/Tote	Pallet/Tote	Boxes
Dose Rate (Dmin 25KGy)	Hours	Minutes	Seconds
Dose uniformity ration (DUR)	Low sensitivity to product thickness	Low sensitivity to product thickness	sensitivite to product thickness
On/Off Technology	No	Yes	Yes
Flexible Target Dose	No	Yes/No	Yes
Process validation	Straightforward	Straightforward	Potentially complicated

Relevant Standards:

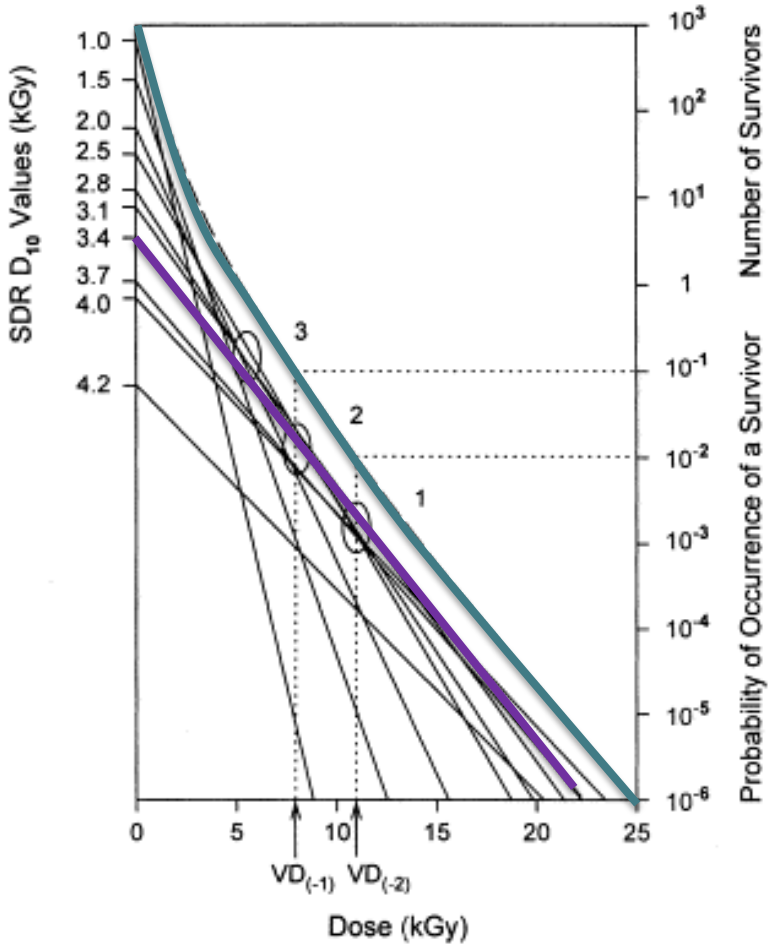
ISO 11137-1:2015	ISO 11137-2: 2015	GMP – Annex 12
Sterilization of health care products – Radiation – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose	Use of ionising radiation in the manufacture of medicinal products

Sterilization by Irradiation: validation principles

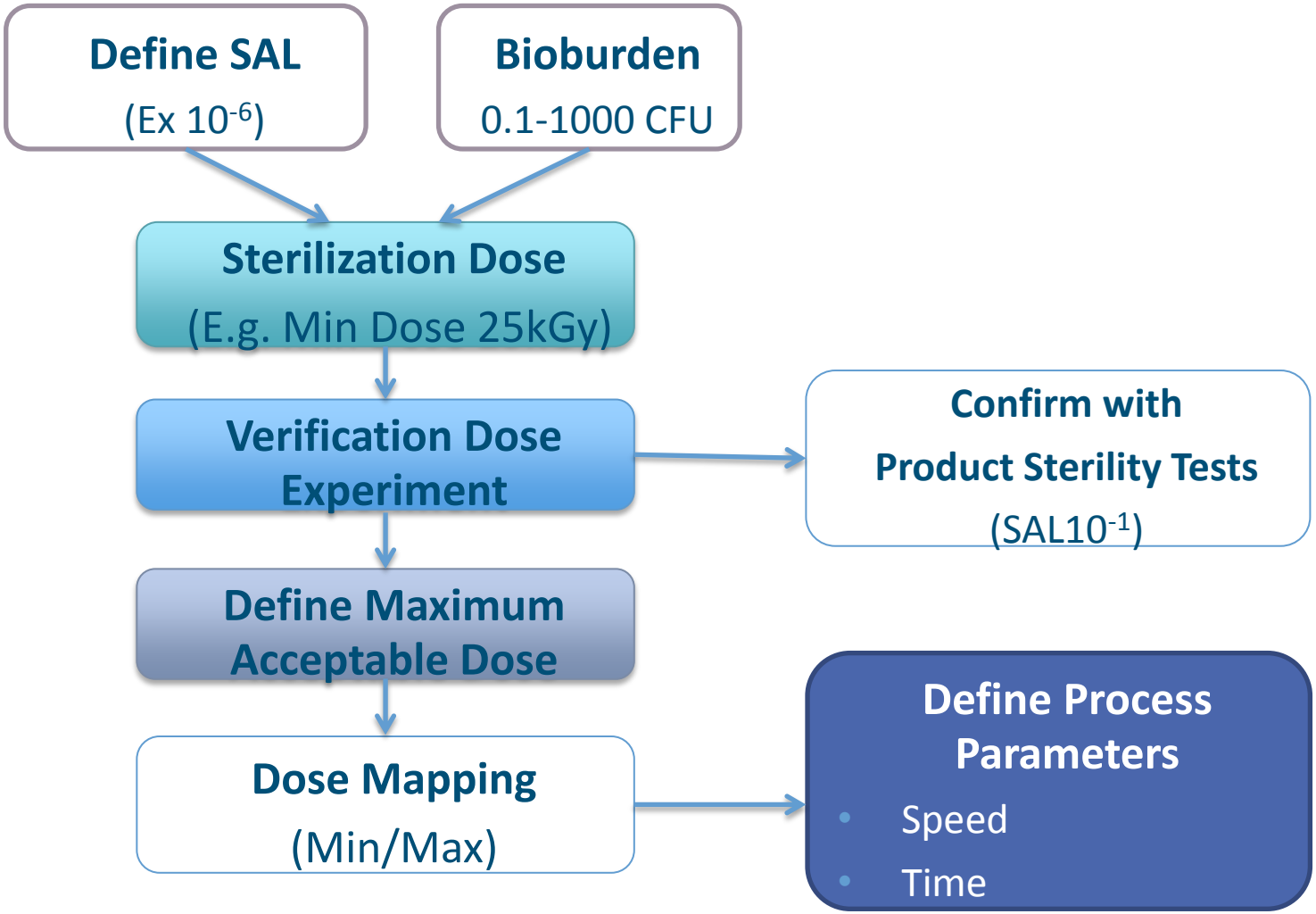
Method VD_{max}



Standard Distribution of resistances (SDR)



Sterilization by Irradiation: validation principles



Sterilization by Irradiation: validation principles

Bioburden is critical parameter in Irradiation technology

Sample Item Portion (SIP) is frequently used for bioburden evaluation .
Basis for SIP can be:

Length

- Consistent diameter tubing

Mass

- Powders
- Gowns
- Absorbable implants

Volume

- Fluid

Surface Area

- Non-absorbable implants
- Variable diameter tubing

Select Sterilization Dose

Method VD_{max}

Example minimum Dose to apply related to bioburden

Bioburden Range	Dose (kGy)
≤ 0.1 to 1.5	15.0
≤ 0.1 to 9.0	17.5
≤ 0.1 to 45	20.0
≤ 0.1 to 220	22.5
≤ 0.1 to 1000	25.0
≤ 1.0 to 5000	27.5
≤ 1.0 to 23,000	30.0
≤ 1.0 to 100,000	32.5
≤ 1.0 to 440,000	35.0

- Select Verification Dose: VD_{max}^{25}

Bioburden	Verification Dose (kGy
40	8.6
45	8.7
50	8.8
55	8.9

Verification is conducted at an SAL of 10−1 with 10 product items irradiated.

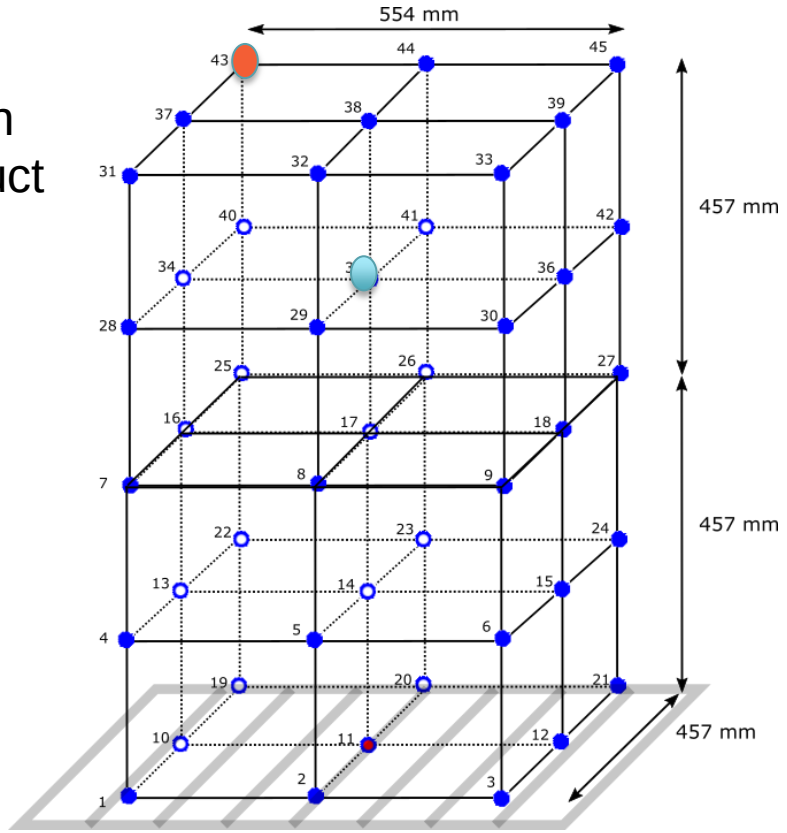
Dose Mapping

Establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration

- Min and Max limits of absorbed Dose
- Define cycle time
- Establish monitoring points

Min Dose = 28KGy

Max Dose = 37KGy



Quarterly Dose Audit (QDA)

Check bioburden

Can vary due to

- Season
- Environment …

Verification Dose

(Often In a research irradiator)

Ex: 8,7KGy

Sterility Test

$SAL10^{-1}$

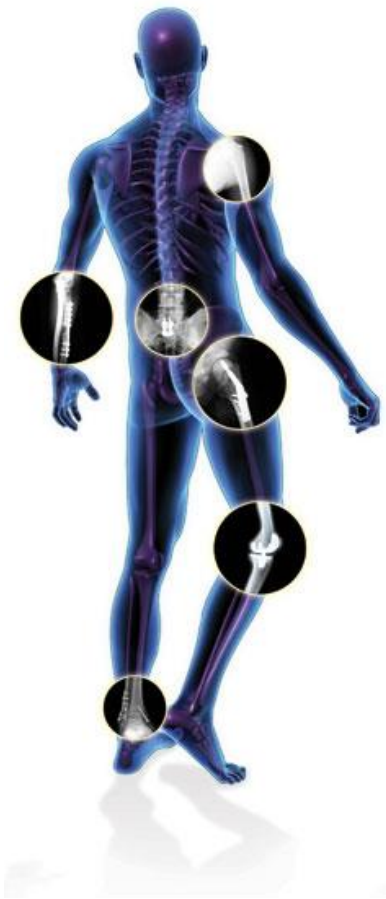
Confirm Product
$SAL\ 10^{-6}$
With Routine Dose

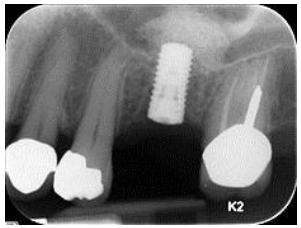
Ex:25KGy

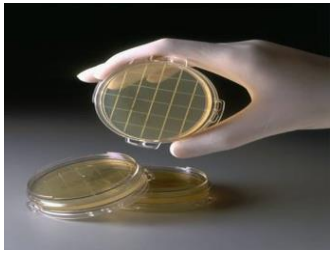
Summary

- Minium & Maximum dose to product shall be defined
- Methods 1, 2, VDmax, “equivalent method”
- Based on natural product bioburden
- Routine process monitored with dosimeters
- Quarterly Dose Audit (QDA) required

Sterilization by Irradiation: examples



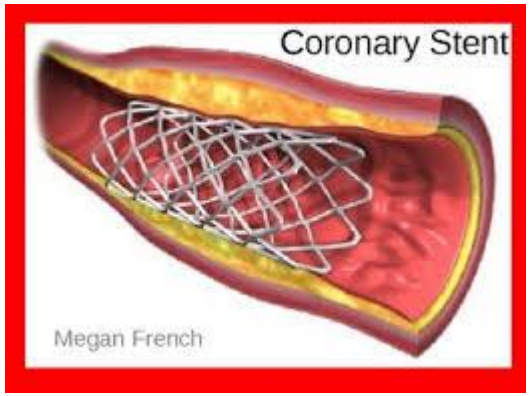


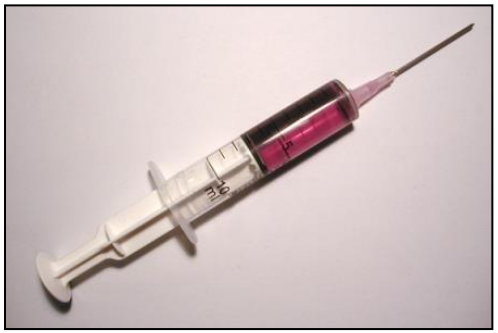


Sterilization by Irradiation: examples

… But also

Grafts





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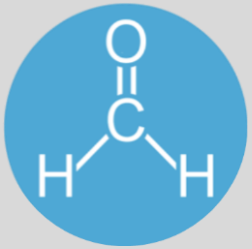


Ethylene Oxide Sterilization

Introduction

Sterilization by Ethylene Oxide : History

1859 — Ethylene Oxide discovered
Charles Wurz

1925 — First production of Ethylene Oxide
Union Carbide Chemicals

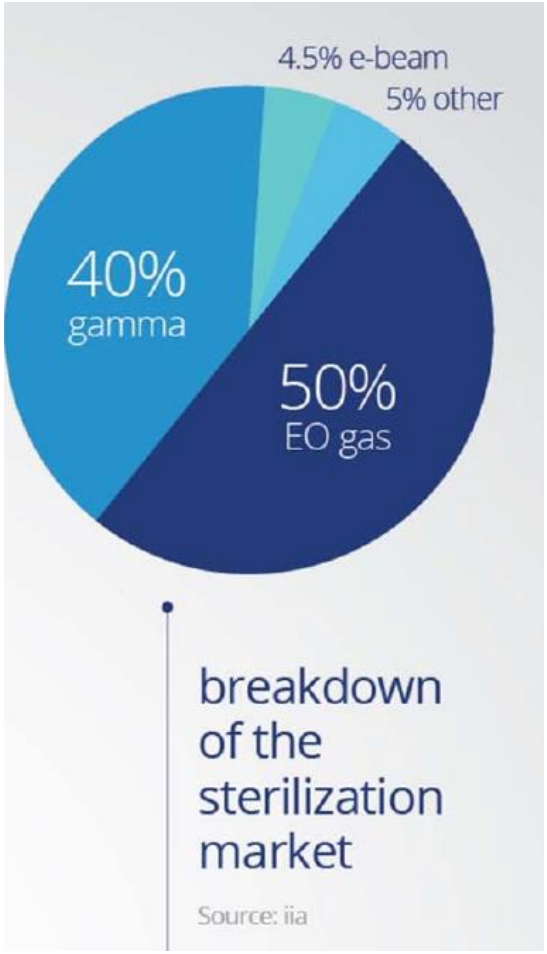
1938 — Patent for sterilization of spices
Lloyd Hall

1940 — Use in sterilization of materials

Dr. Lloyd Augustus Hall, a food scientist, while working for Griffith Laboratories, devised a process known as the Ethylene Oxide Vacugas treatment to control the growth of molds and bacteria. Griffith and Hall received US Patent 2,189,949 in 1940.

Properties

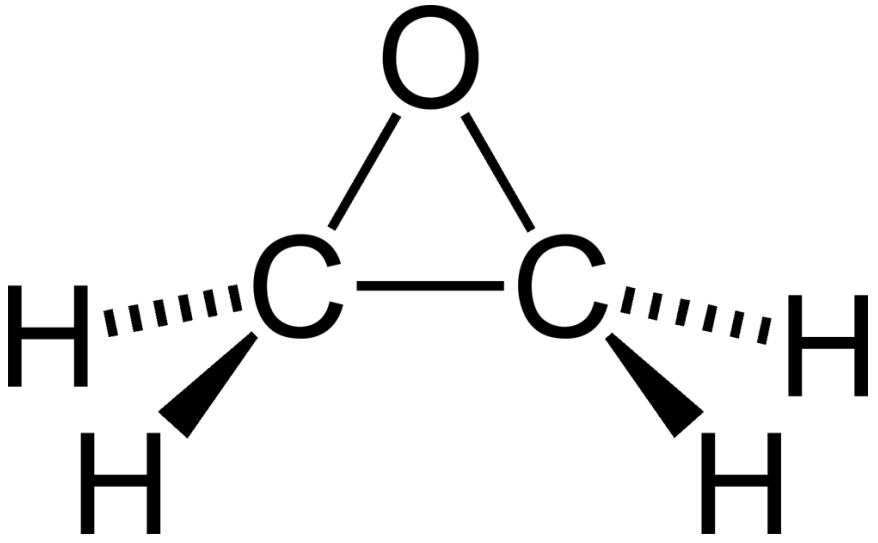
- Toxic gas
- “Sweet smell” from ca. 500 ppm concentration
- Forms with air explosive mixtures (2.6 %)
- Oncogenic by inhalation
- Irritating for skin and respiratory system
- Mutagenic for animals and very likely for humans



Last choice but sometimes the only one !

Mode of Action

- Extremely reactive
- Irreversible reaction with DNA
  and proteins (alkylation)
  - The molecule is loses function
  - Replication stops
  - The cell dies



Sterilization by Ethylene Oxide

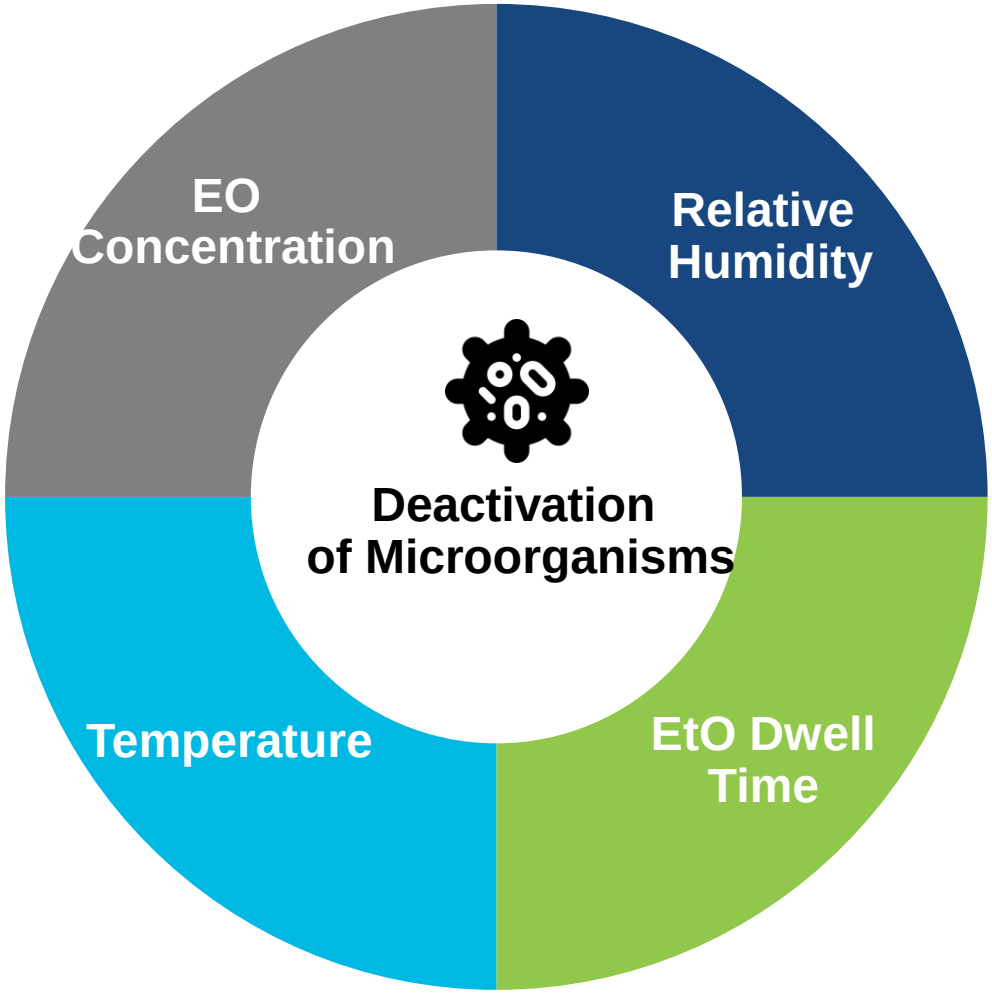
Mainly used to sterilize:

- Heat-sensitive material
- Material sensitive to ionizing radiation
- High Volumes
- Packs with multiple components

Device/packaging must be permeable to the gas

- No aqueous substances
- No protein-type materials
- Powders, batteries, electronic circuits have to be assessed (risk of explosion)
- Vacuum/heat can have adverse impact on some packaging (bubble wrap packaging, polystyrene)

Critical Parameters for Effective EO Treatment



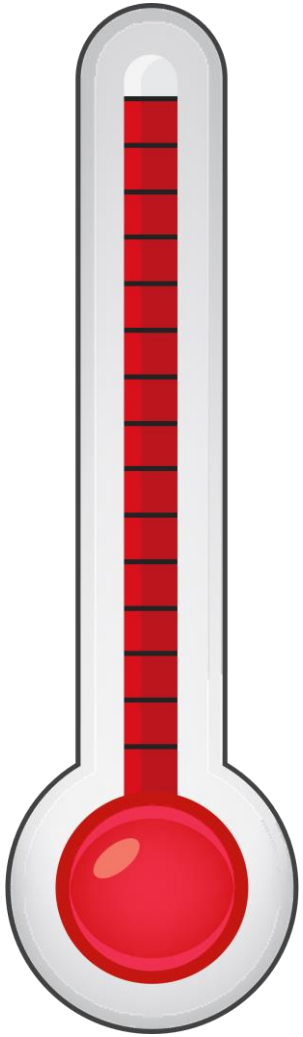
Temperature (T)

EtO kills microorganisms even at temperatures below 10°C (50oF)

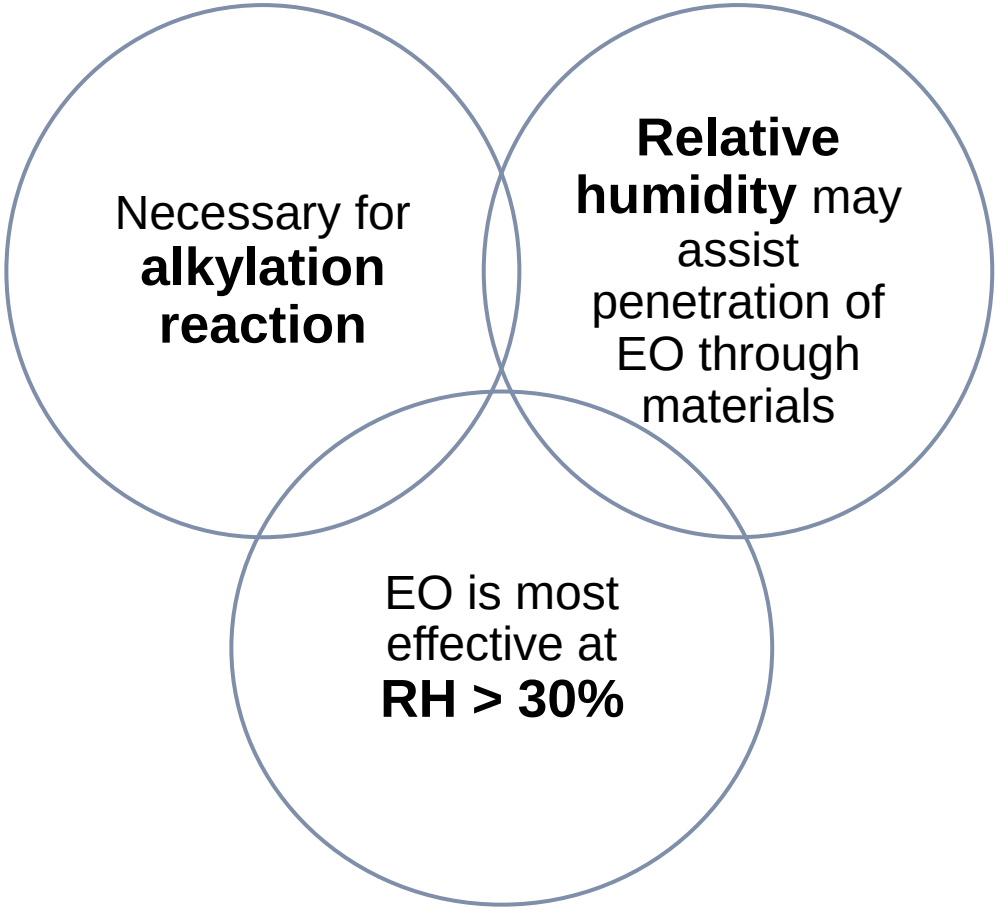
Industrial sterilization performed in 40-60 °C (104–140oF) temperature range

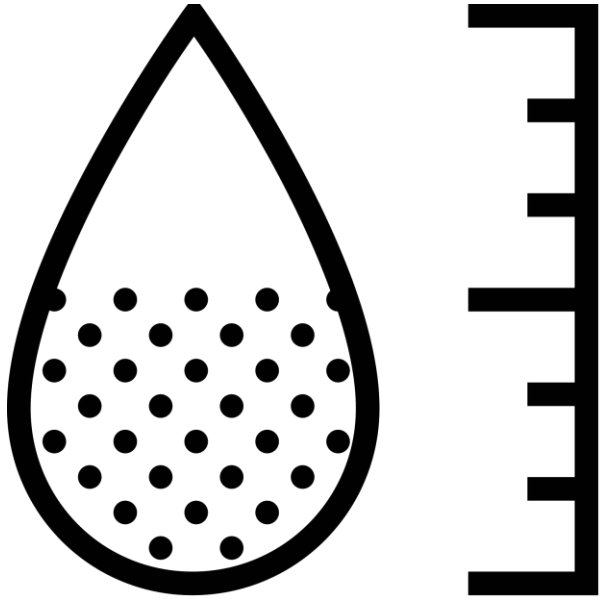
Q10 Effect increase by 10°C (18°F) = 2x Deactivation Rate

Temperature increase may increase of permeability of gases through materials



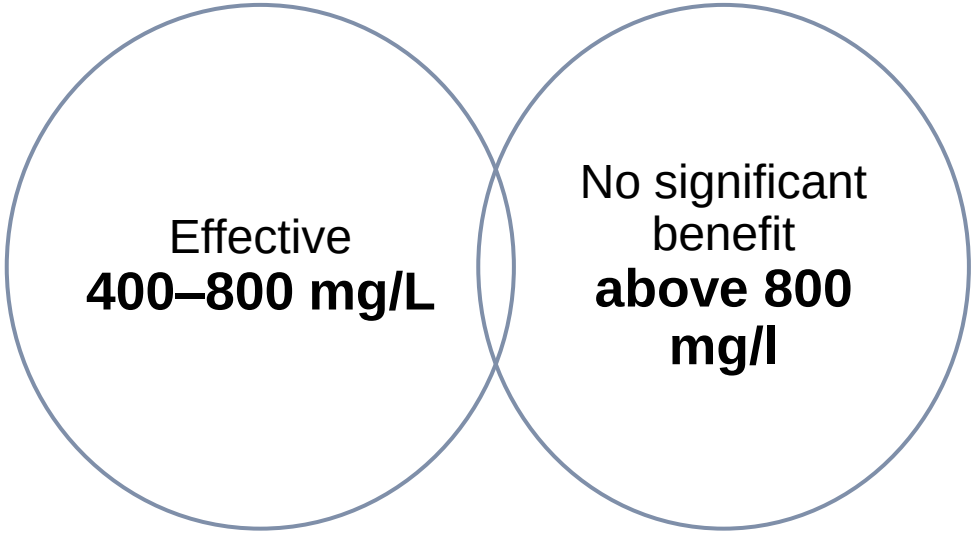
Relative Humidity (RH)

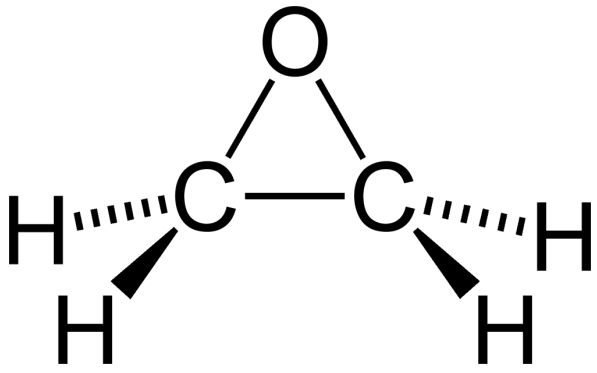




Sterilization by Ethylene Oxide

EO-Concentration





At constant T and RH – if EO concentration increases microbiological Deactivation is more effective - up to c. 800 mg/l

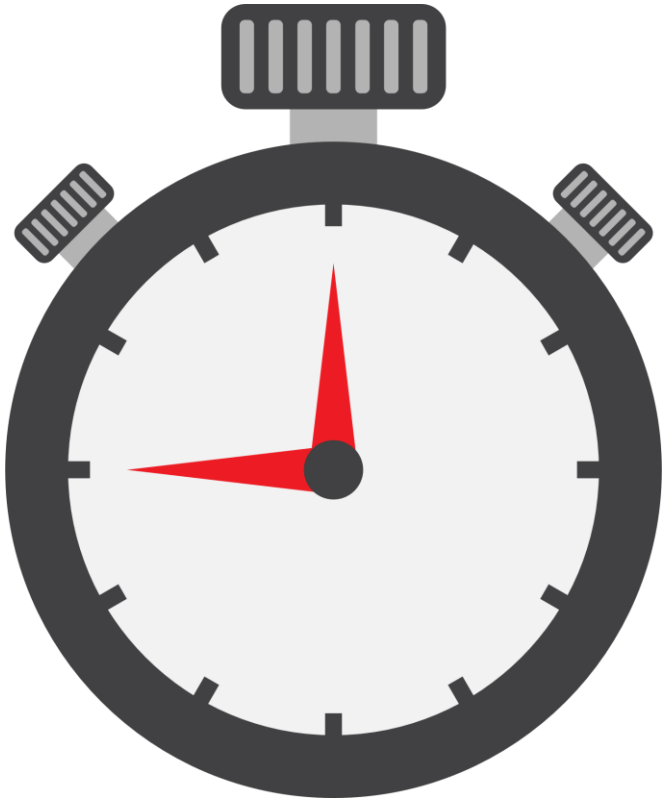
- ~ 500 mg/L @ 131°F
- ~ 800 mg/L @ 86°F

Sterilization by Ethylene Oxide

Time

Microbiological deactivation
is more effective with longer gas dwell phase

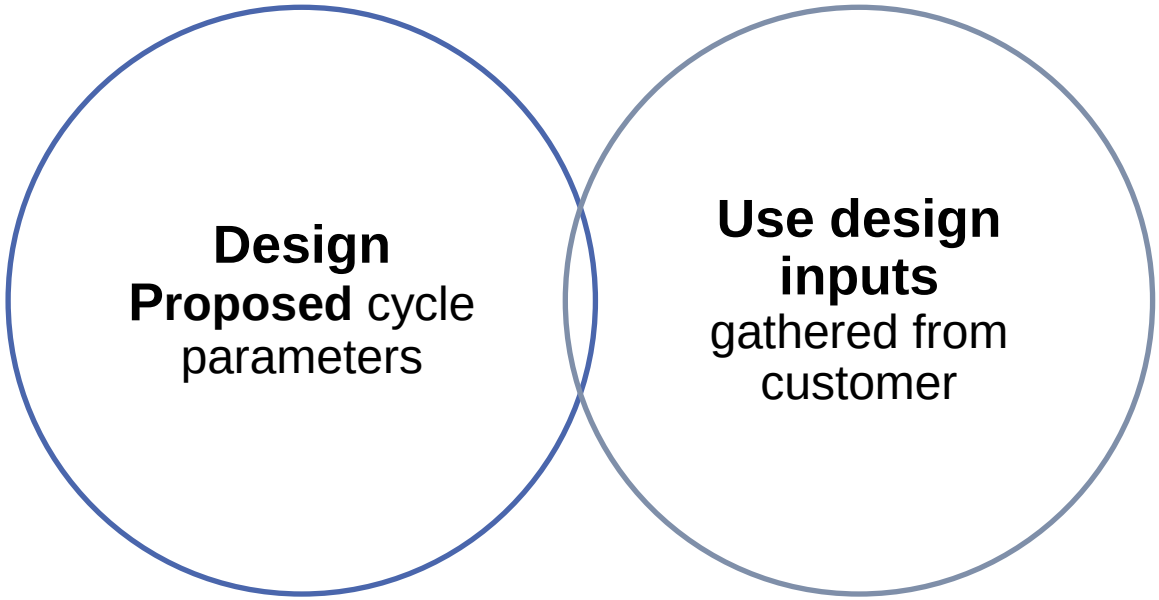
Industry cycles
2 to 10 hours gas dwell phase
Typically 3-4 hours



Customer Needs To Define

- Product Families/Processing Categories
- Finalize Packaging
- Load Configuration
- Bioburden
- Internal PCD

Sterilization by Ethylene Oxide

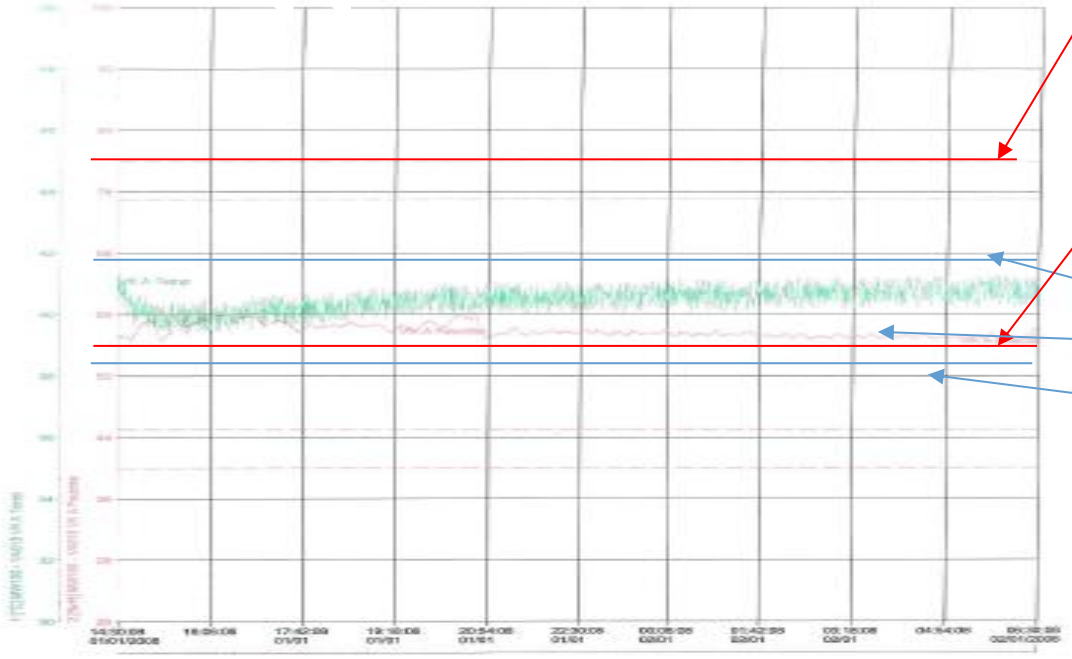


Sterilization Process

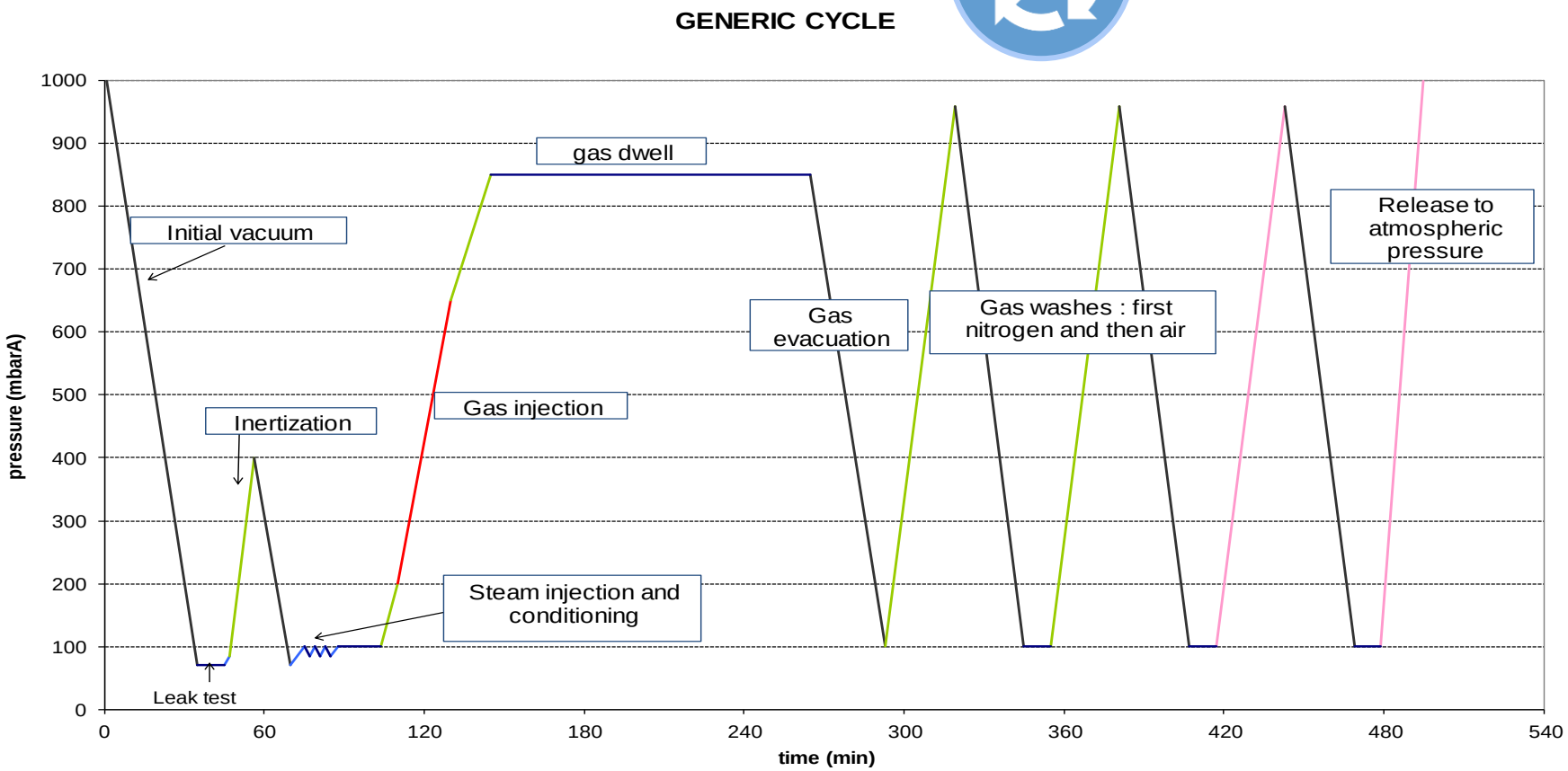
3 key phases

Preconditioning

- 40-45°C
- 45–75 %RH
- 10-24 hours

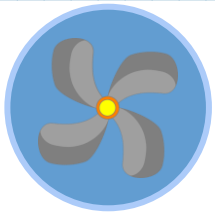


Typical EO Cycle Design – Deep Vacuum



Sterilization by Ethylene Oxide

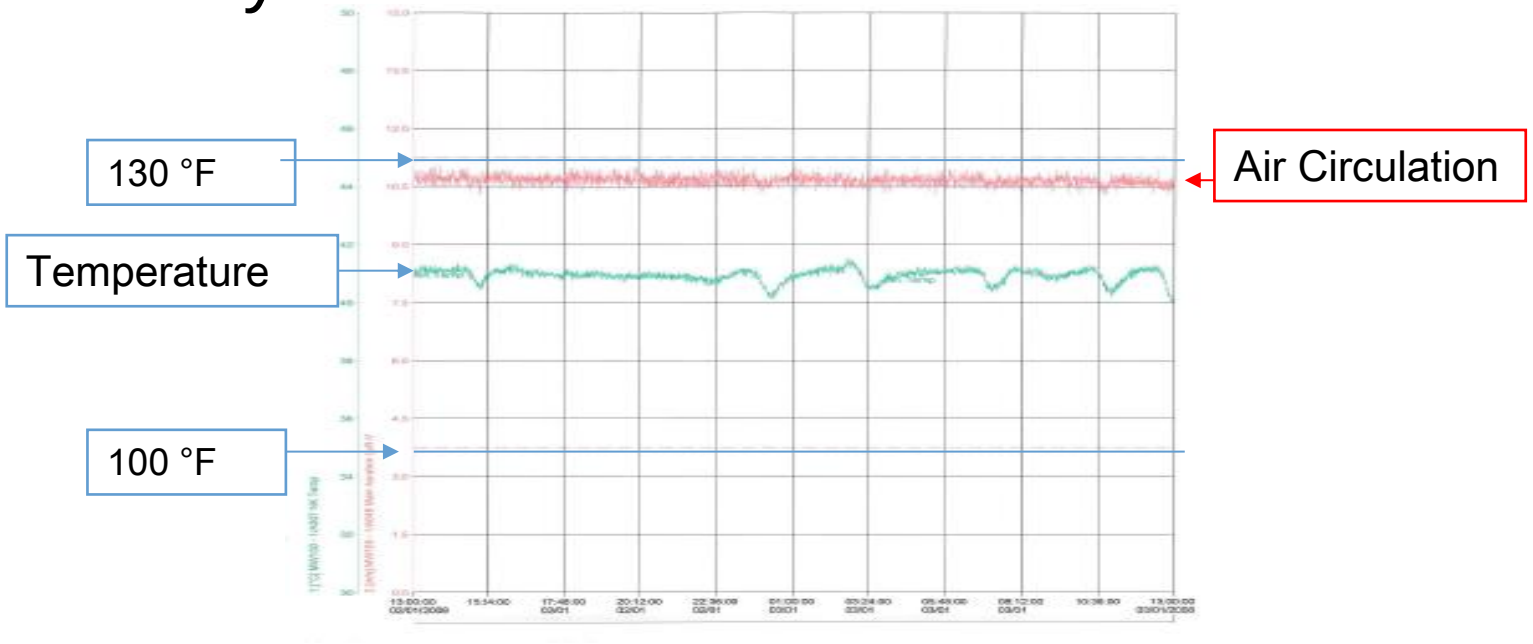
Aeration



– 45°C

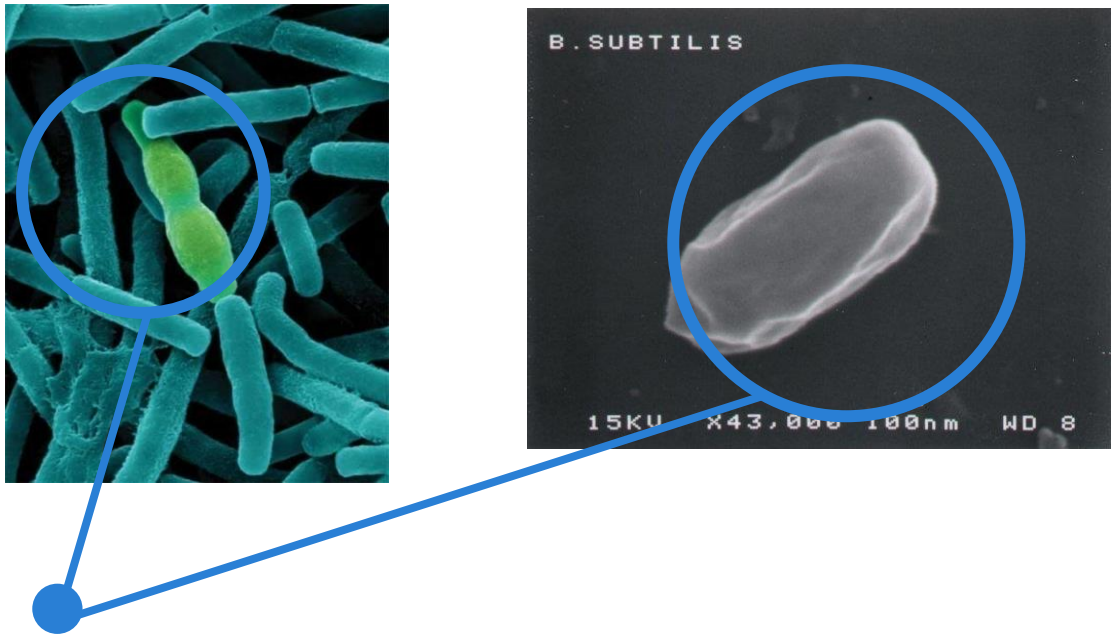
– Forced circulation

– 1-3 days



Monitoring EO Sterilization - Biological Indicators

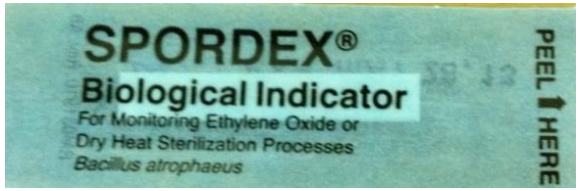
- Usually, the BI contains at least a million spores (>10Exp6) of an organism that is highly-resistant to the EO process (*Bacillus atrophaeus)*
- Growth is very characteristic (orange ring)



Process Challenge Device (PCD)

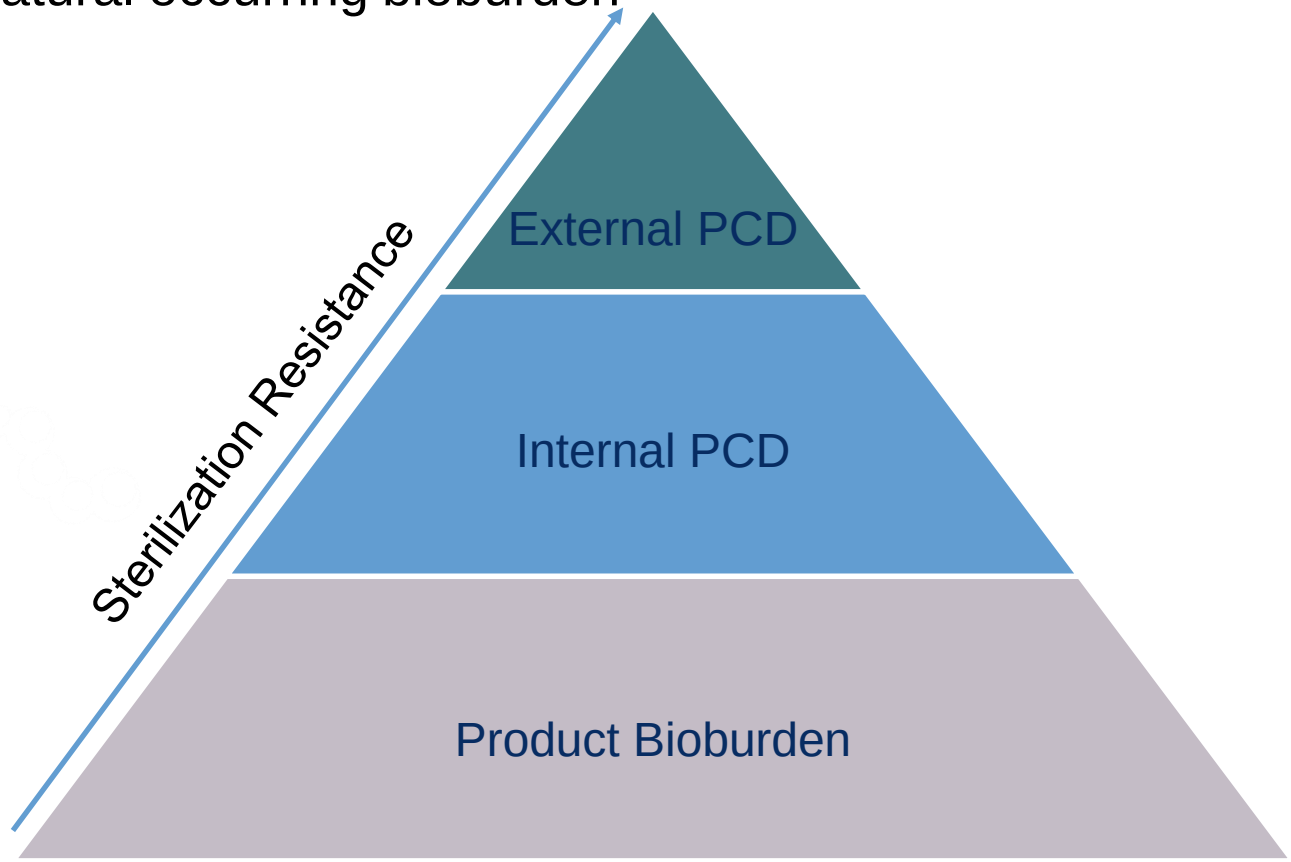
Item designed to constitute a defined resistance to the sterilization process and used to assess performance of the process

- Internal PCD (IPCD)
- External PCD (EPCD)



Monitoring EO Sterilization – Biological Indicators

We design the validation to show that the **BI** is more difficult to kill than natural occurring bioburden

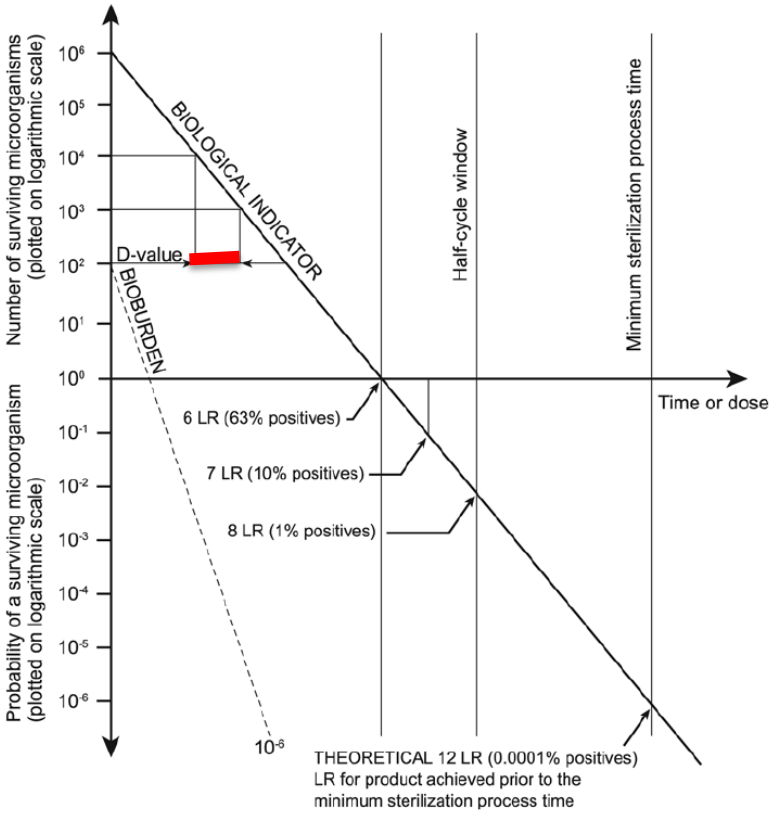


D Value

The Time needed to deactivate 90% of population of microorganisms (or 1 Log Reduction)

SAL $\leq 10^{-6}$

*The sterilization cycle is **validated** to predict achievement of an SAL equal to or less than a specified value (≥12LR)*

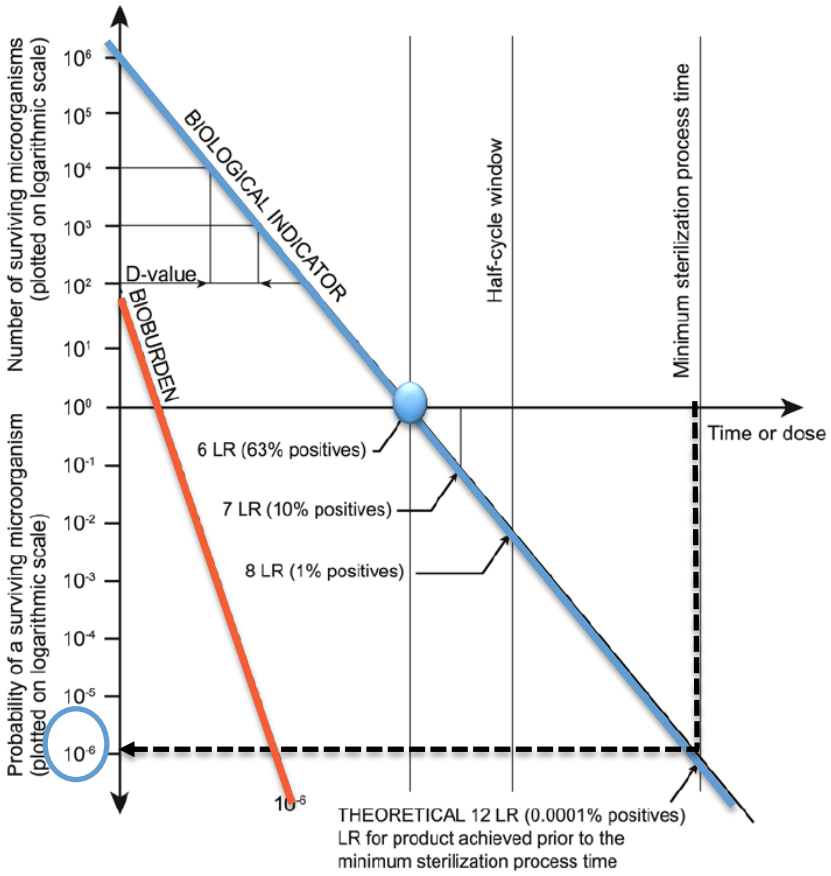


Level of Sterility Assurance

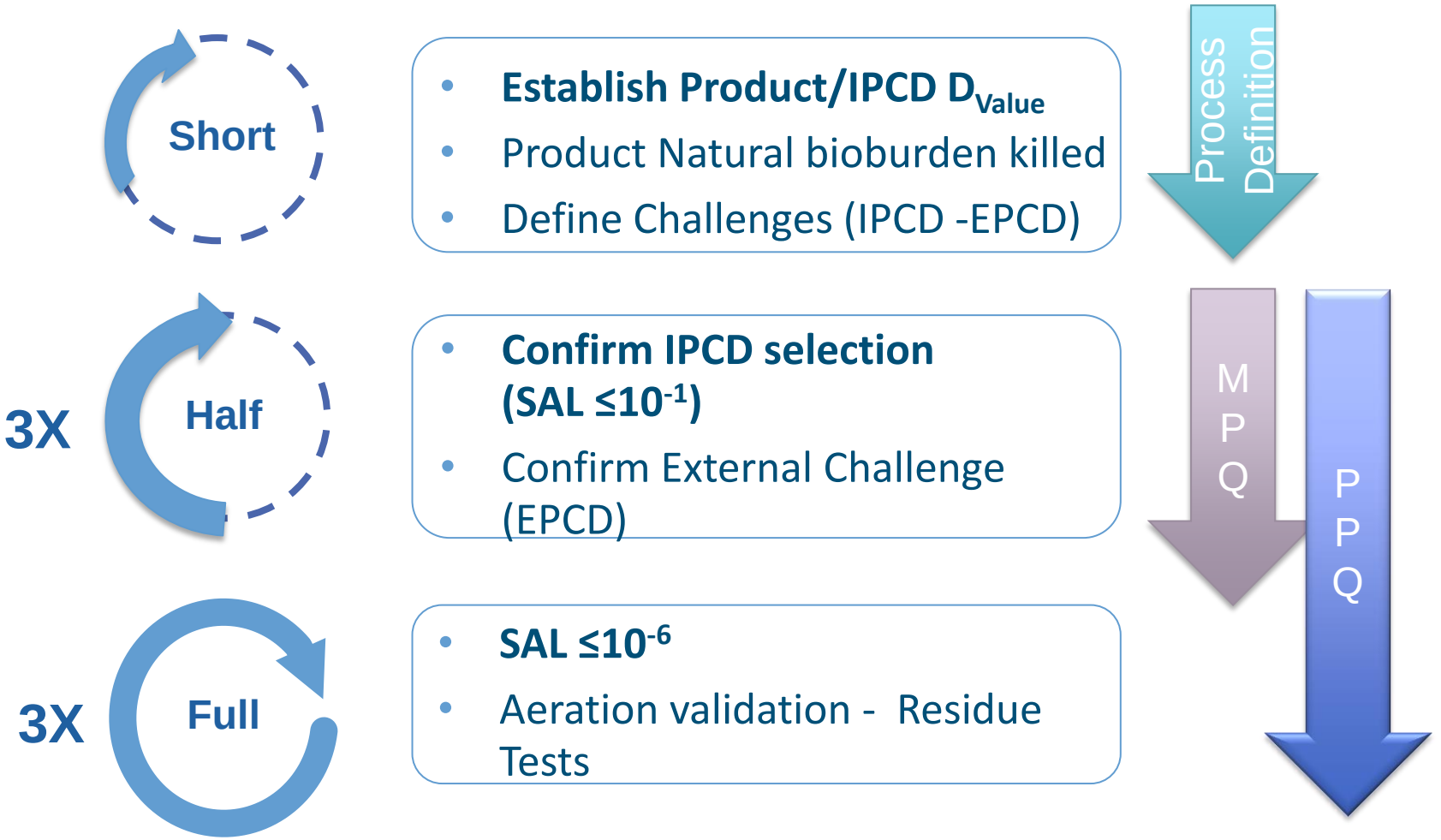
Example:

D_{value} IPCD = 15min = 1LR

6 LR = 90 min (Half cycle)
12 LR =180 min (Full cycle)



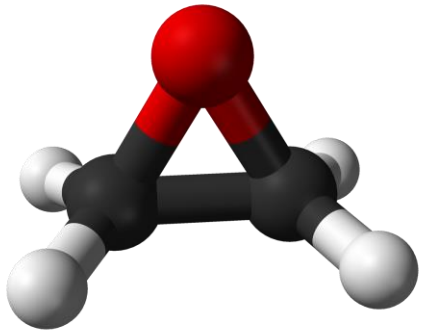
Sterilization by ETO: validation principles



Sterilization by Ethylene Oxide: Validation principle

Compounds that remain on product after EO sterilization

- Ethylene Oxide (EO)
- Ethylene Chlorohydrin (ECH) = EO + HCL
- Ethylene Glycol (EG) = EO + H2O



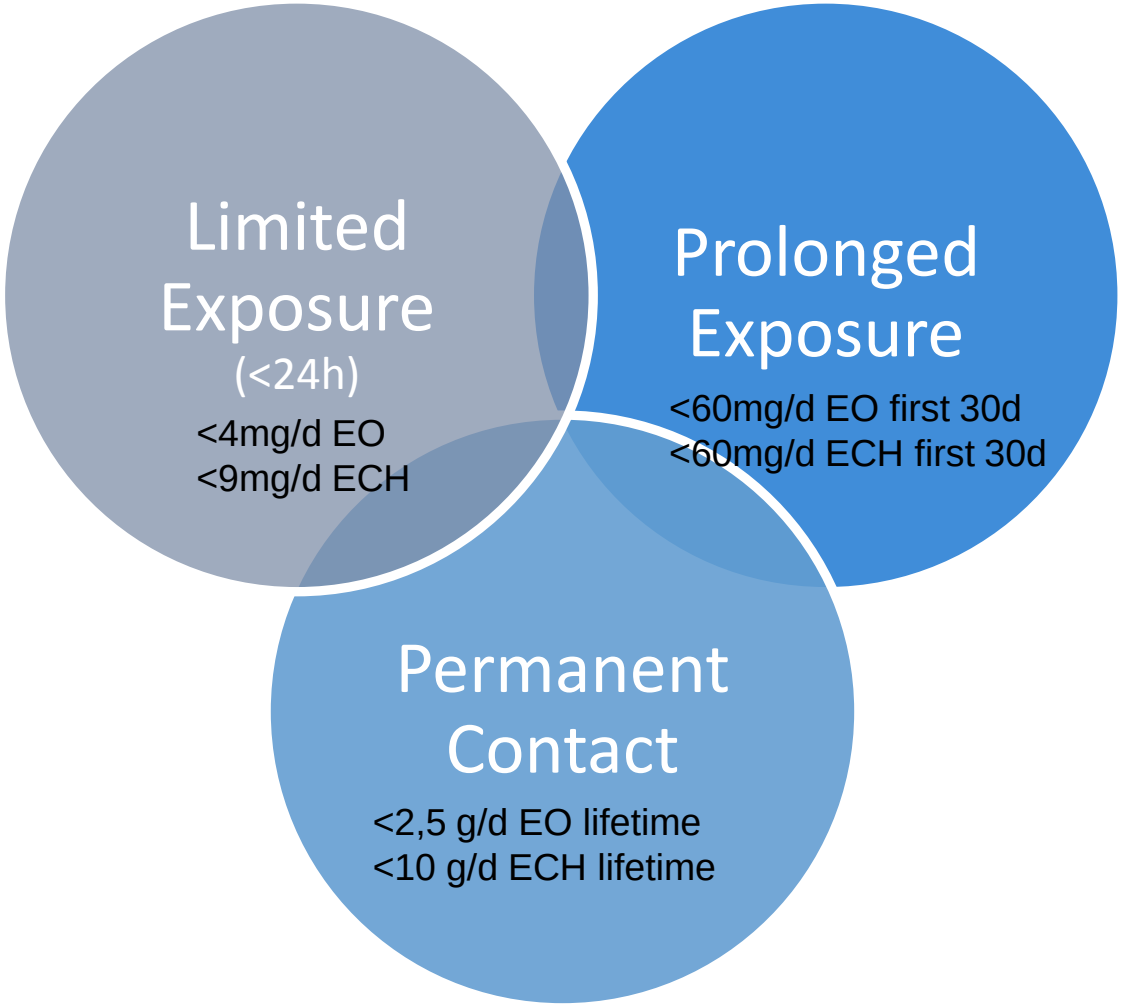
ISO 10993-7:2008

“Biological Evaluation Of Medical Devices-

Part 7: Ethylene Oxide Sterilization Residuals”

Sterilization by Ethylene Oxide: Validation principle

There are Three Patient Exposure Categories



Sterilization by Ethylene Oxide

ISO 11135:2014

Sterilization of medical devices – Requirements for the development; validation and routine Control of a Sterilization Process for Medical Devices – Ethylene Oxide

ETO Residuals

ISO 10993-7:2008 (R) 2012

Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals

GMP – Annex 1 (Draft)

- Manufacture of Sterile medicinal Products

Bioburden

ISO 11737-1:2018

Sterilization of medical devices (Microbiological methods) Part 1: Determination of a population of microorganisms on products

Sterilization by Ethylene Oxide

Product Sterility

- *ISO 11737-2:2009 (R) 2014*

Sterilization of medical devices (Microbiological methods) Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

- *United States Pharmacopeia* (USP) Chapter <71> Sterility Tests
- *European Pharmacopeia* (EP) Chapter 2.6.1 Sterility
- *Japanese Pharmacopeia* (JP) Chapter 54. Sterility Test

Biological Indicator Tests

- *ISO 11138-1:2017*

Sterilization of health care products (Biological indicators) Part 1: General requirements

- *ISO 11138-2:2017*

Sterilization of health care products (Biological indicators)Part 2: Biological indicators for ethylene oxide sterilization processes

- *ISO 14161: 2009 (R) 2014*

Biological indicators. Guidance for the selection, use and interpretation of results

Sterilization by Ethylene Oxide : Product examples

Medical Devices

Surgery packs

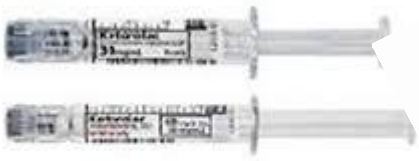
Catheters

vials

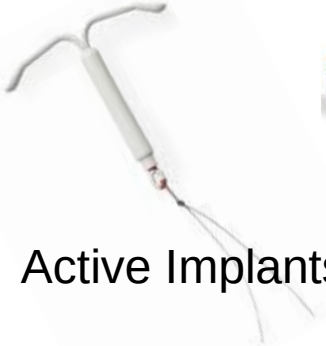
Bandages

Drug products

API



Prefilled syringes (external)



Active Implants

Auto-Injector (external)

Sterilization : Comparison Radiation & Ethylene Oxide

Parameter	Gamma	E-Beam	EO
Process	Individual product, box, tote, pallet	Boxes	Pallets
Material compatibility	Not compatible with some type of polymers (PTFE and PVC affected)	Wider polymer compatibility compared to Gamma	Very good No liquid/proteins Low Temperature (40-55°C)
Validation	Straightforward	Straightforward	Complicate
Validation principle	Based on bioburden	Based on bioburden	Based on Bio Indicators
Requalification	Every 3 months (QDA)	Every 3 months (QDA)	Every 2 years (1 cycle)
SAL	<10exp6	<10exp6	<10exp6
Residues	None	None	ETO,ECH,(EG)

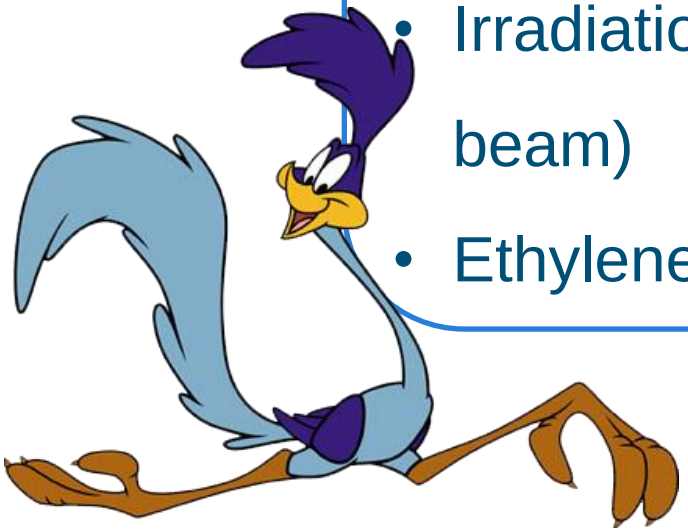
Sterilization : Comparison Radiation & Ethylene Oxide

Parameter	Gamma	E-Beam	EO
Process	Individual product, box, tote, pallet	Boxes	Pallets
Material compatibility	Not compatible with some type of polymers (PTFE and PVC affected)	Wider polymer compatibility compared to Gamma	Very good No liquid/proteins Low Temperature (40-55°C)
Tolerance for density variation	High	Low	Medium
Routine monitoring	• Only a few parameters (Time, Size, density) • Dosimeter	• Higher Nb of parameters • Dosimeter	• Multiple cycle parameters • BI (unless parametric release)
Volumes	High	Limited	High
Turn time	Fast (<24 hours)	Very Fast (<8 hours)	Long (1 week)

Sterilization – Conclusions

You should now feel better at ease with the following concepts :

- What is sterilization Vs decontamination
- Aseptic Assembly Vs Terminal sterilization
- Irradiation sterilization (Gamma and E-beam)
- Ethylene Oxide sterilization



agillet@eu.sterigenics.com

Reference Slide

- *ISO 11135:2014* Sterilization of medical devices – Requirements for the development; validation and routine Control of a Sterilization Process for Medical Devices – Ethylene Oxide
- *ISO 10993-7:2008 (R) 2012* Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals
- *ISO 11137-1* Sterilization of health care products – Radiation – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices
- ISO 11137-2 Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose
- *ISO 11737-1:2018* Sterilization of medical devices (Microbiological methods) Part 1: Determination of a population of microorganisms on products
- *ISO 11737-2:2009 (R) 2014*
- Sterilization of medical devices (Microbiological methods) Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
- *ISO 11138-1:2017*
- Sterilization of health care products (Biological indicators) Part 1: General requirements
- *ISO 11138-2:2017*
- Sterilization of health care products (Biological indicators)Part 2: Biological indicators for ethylene oxide sterilization processes
- *ISO 14161: 2009 (R) 2014*
- Biological indicators. Guidance for the selection, use and interpretation of results

Reference Slide

- *ISO 11737-2:2009 (R) 2014*
  Sterilization of medical devices (Microbiological methods) Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
- *ISO TS 19930:2017 Guidance on aspects of a risk-based approach to assuring sterility of a terminally-sterilized, single use health care product unable to withstand processing to achieve maximally a sterility assurance level of 10-6*
- *AAMI TIR 33* Sterilization of health care products—Radiation—Substantiation of a selected sterilization dose — Method Vdmax
- *United States Pharmacopeia* (USP) Chapter <71> Sterility Tests
- *Eudralex Volume 4* – GMP Annex 1
- *Eudralex Volume 4* – GMP Annex 12
- *European Pharmacopeia* (EP) Chapter 2.6.1 Sterility
- The *Aseptic and Sterile Processing: Control, Compliance and Future Trends* - Edited by Tim Sandle, Edward Tidswell PDA – 2017
- *PDA Survey*: 2017 PDA Aseptic Processing
- A comparison of Gamma, E-beam, X-Ray and ETO technologies for the indsutrial Sterilization of MD and Health care products – GIPA, IIA – 31 Aug 2017