Understanding Sterilization

- Sterilization basics
- Radiation Technology & Gas

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PDA Parenteral Drug Association

Sterigenics®
A Sotera Health company

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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

Coffee break

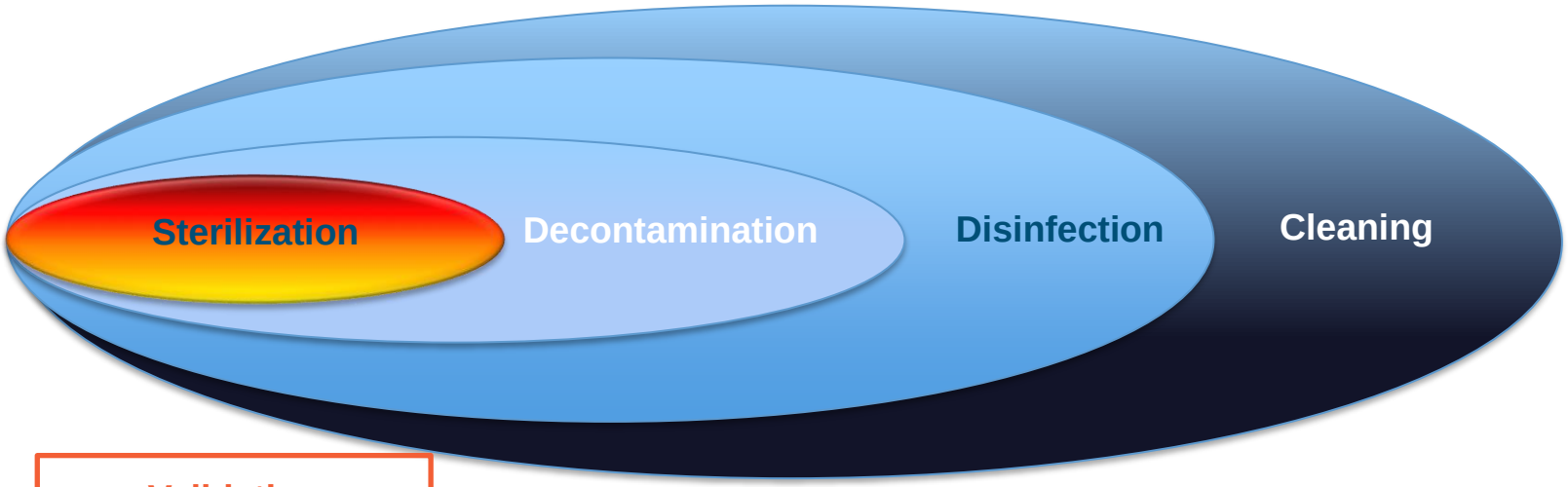
Content

- Sterilization by gas
  - Ethylene oxide
  - Novel technologies (NO_2)
- 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 !

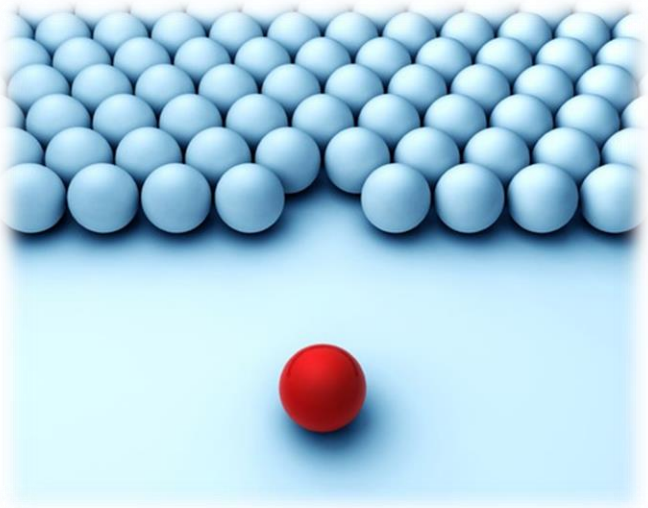
- 100% control of the batch is not possible
- No assurance that any microorganism can be detected during Sterility Test

Sterility 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



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

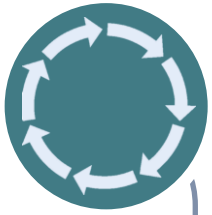
Equipment

- Control
- Maintenance
- Calibration

Product preservation

- Packaging
- Storage

Pharmaceutical Product Life Cycle



Think about sterilisation as soon as possible during product development

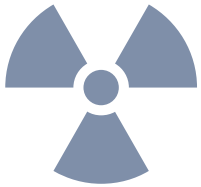
Sterile means : Safe Product **&** Functional product

Selection of the right sterilization method is critical !

Sterilization – Basics

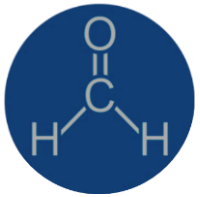
Heat

- Dry
- Moist Heat



Irradiation

- Gamma ray
- E-beam
- X-rays



Ethylene Oxide

- (EO) gas

Other

- VHP
- Gas plasma
- **Nitrogen Dioxide**

Traditional sterilization methods

Innovative methods

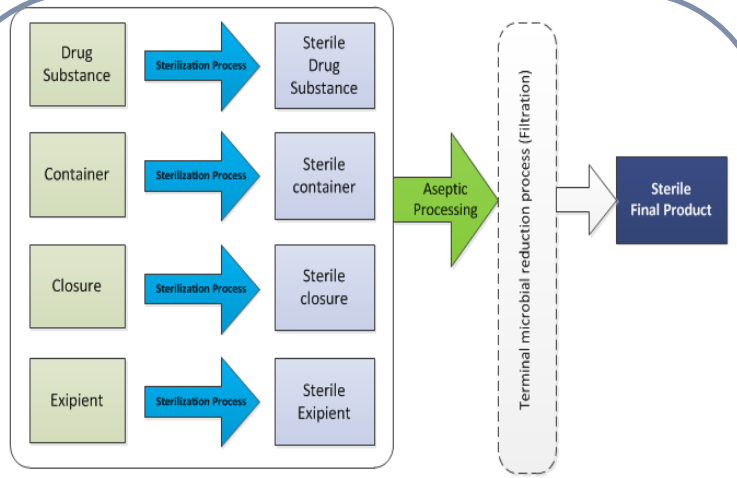
No single sterilization method will be compatible with every product on the market

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

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

Sterilization – Basics

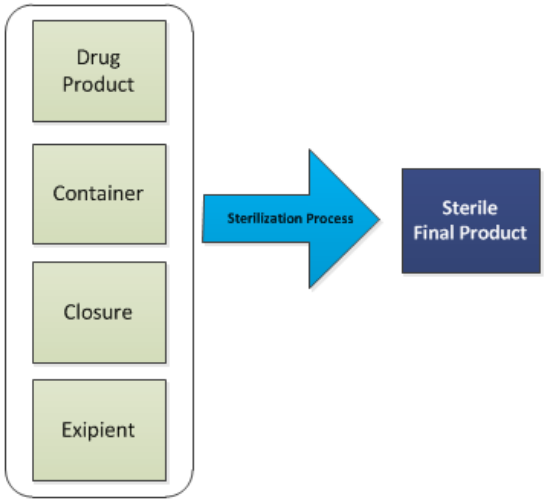
Aseptic Assembly



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

Sterile

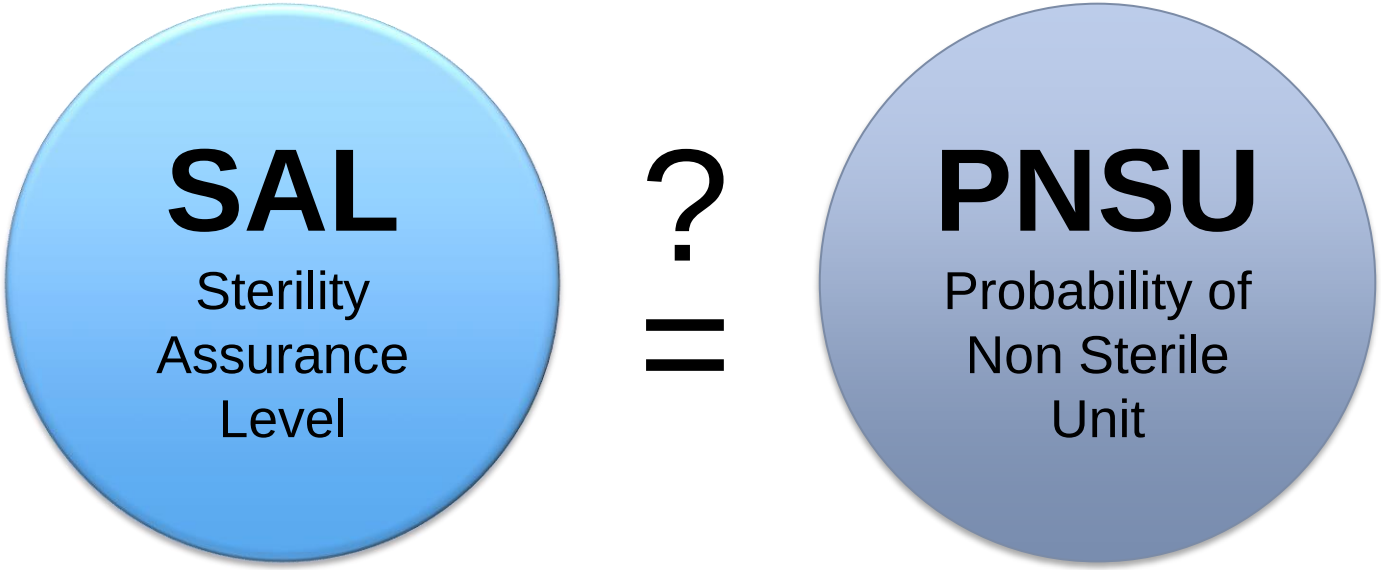
Terminal Sterilization



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

Sterilized

Is the effectiveness of a sterilization process assessed the same way for AA or TS products?



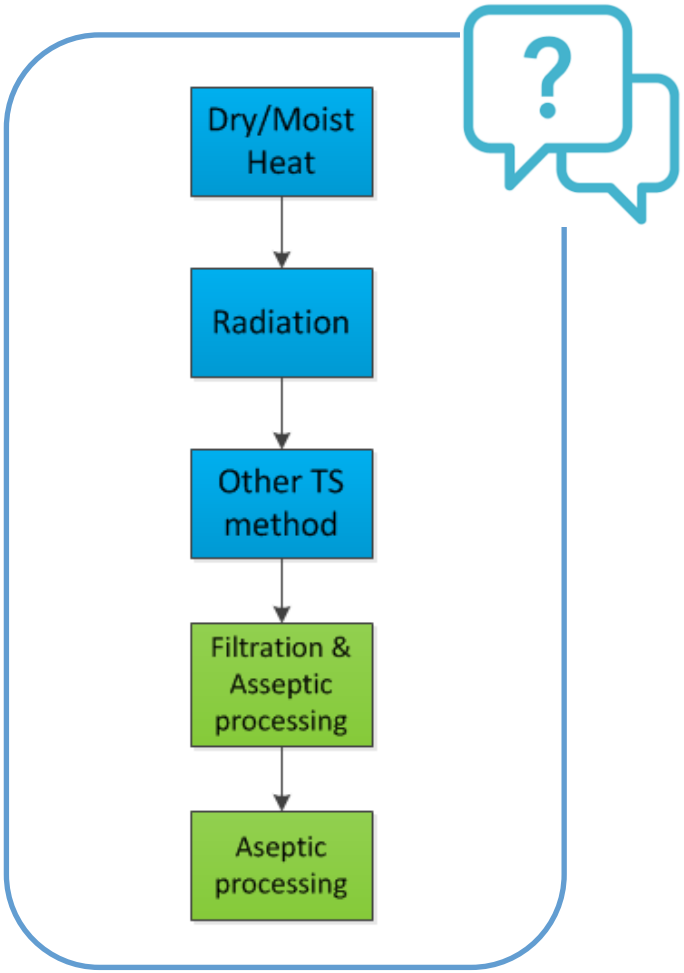
Reference: ISO TS 19930:2017

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

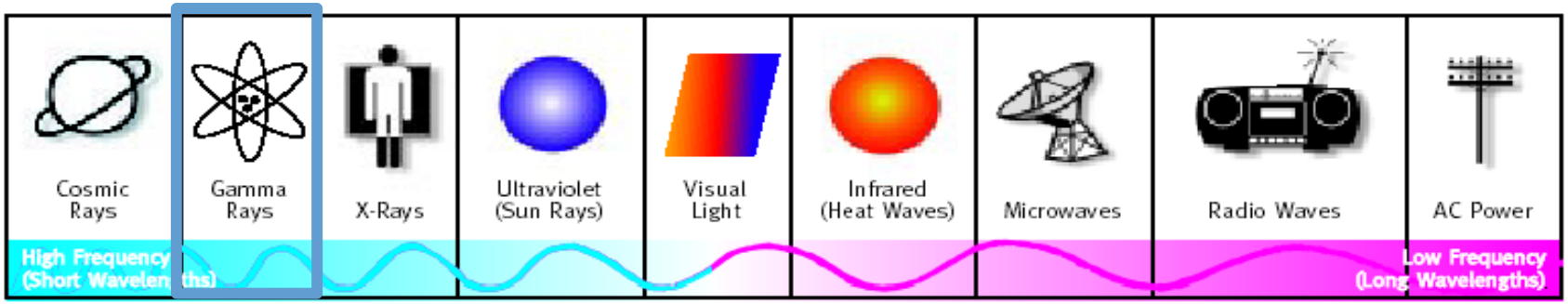
Radiation Technology

- 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

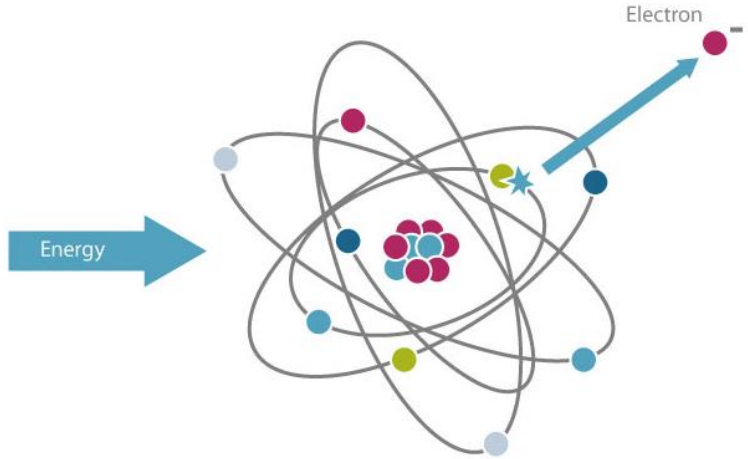
Radioactive

Substance emitting radiation

Irradiation

Exposure to radiation
≠ Making something radioactive

General Terminology



Ionising Radiation

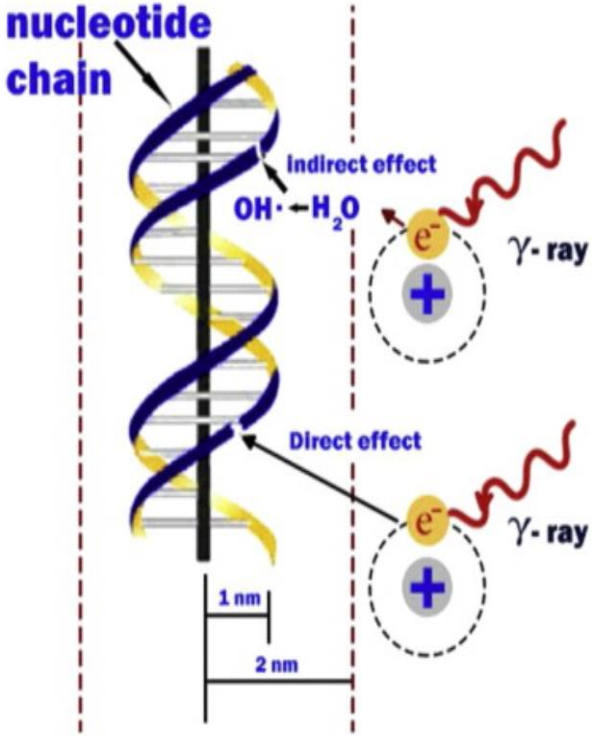
Radiation capable of knocking electrons out of their thermal orbits in atoms or molecules

(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**

How Radiation can be used to Damage DNA in Living Cells for Sterilization

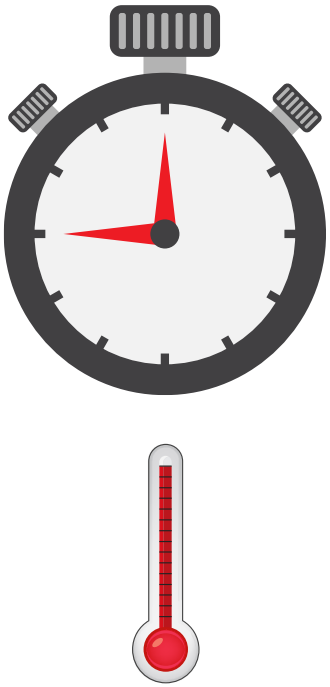


Direct action: the radiation hits the DNA molecule directly or via the ejected electron, disrupting the molecular structure leading to cell damage or cell death.

Indirect action: the radiation hits the water molecules, the major constituent of the cell, and other organic molecules in the cell, whereby **free radicals** such as hydroxyl are produced.Free radicals are very reactive.

Sterilization by Irradiation : General principles

Critical Parameters for Effective Radiation Treatment



Time !

Essentially a 1-step process – controlled by amount of time in the radiation field

Temperature typically not a factor – considered “cold sterilization” process. Typically 25-40 °C, but can be controlled!

Irradiation can take place under refrigerated or frozen conditions if necessary

Irradiation process monitoring:

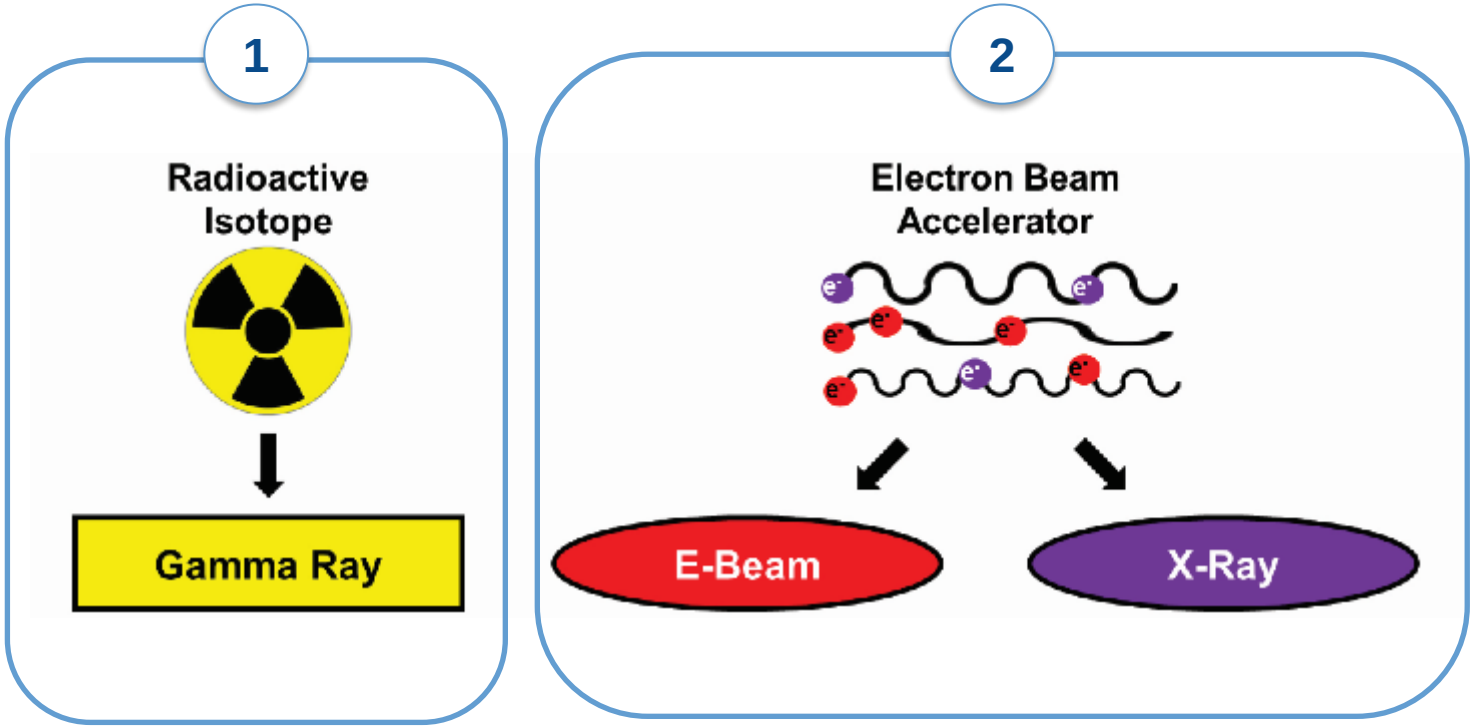
Dosimeter

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

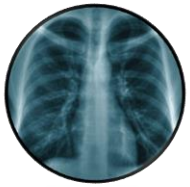
100

50

10

1

Typical chest X-Ray (0,1 mGy)

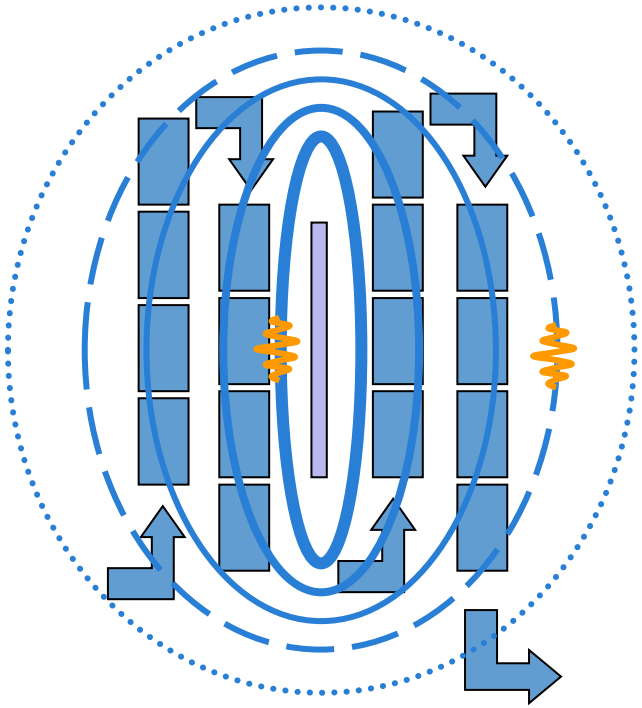


Sterilization by Irradiation: Gamma

Source: ^{60}Co (mostly)

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

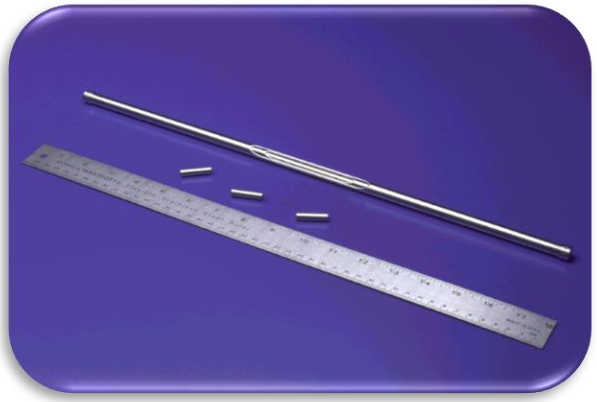
Source Activity: Several Million Ci



Isotropic radiation flux

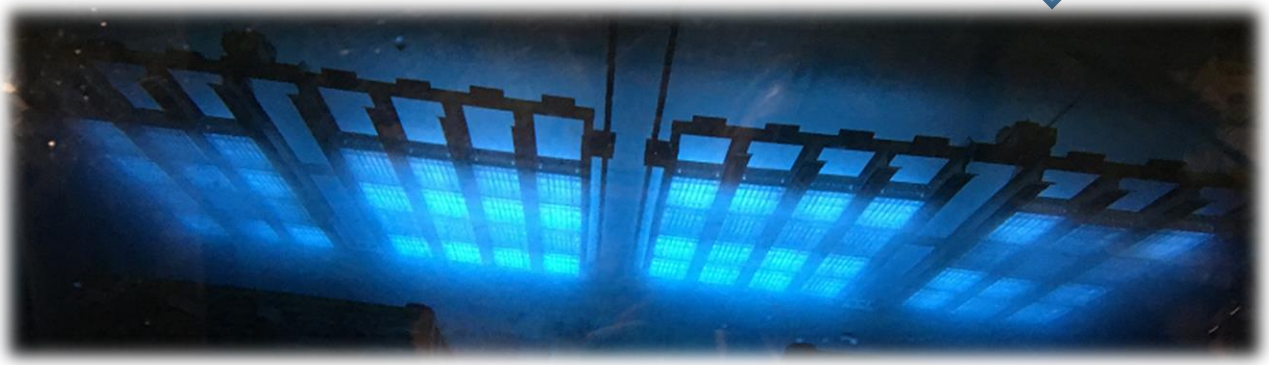
Source Rack

Cobalt-slugs in a source pencil



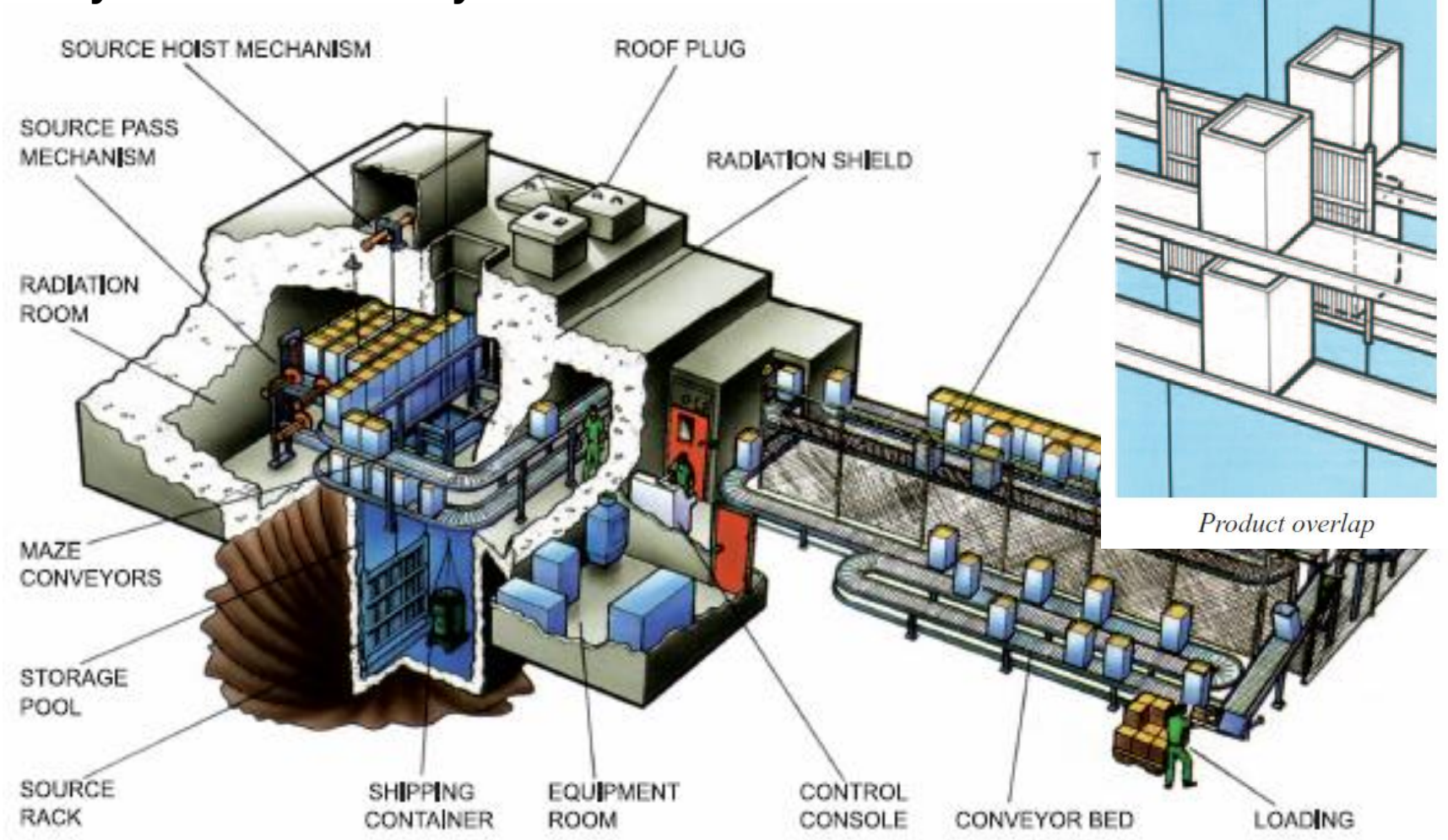
Source module

Source rack



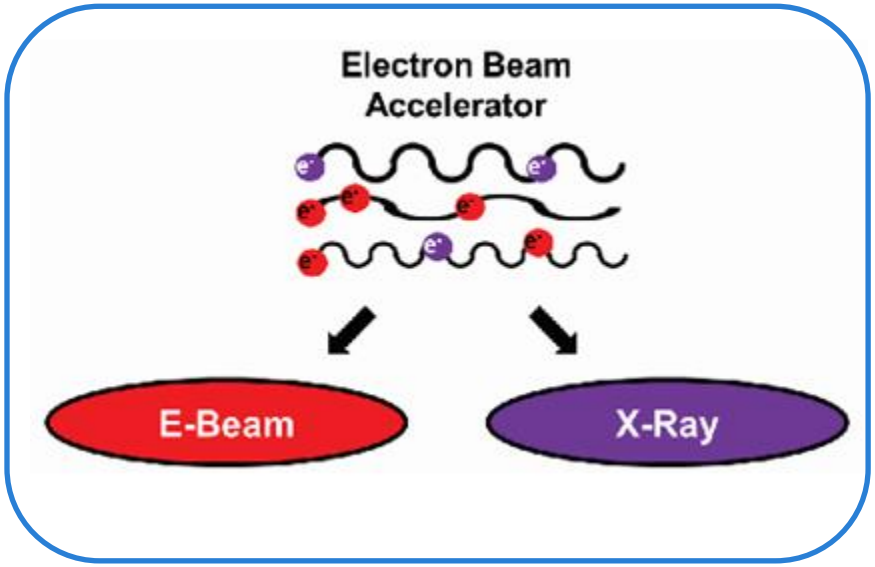
Sterilization by Irradiation : Gamma

Layout Gamma facility



Product overlap

E- Beam irradiation



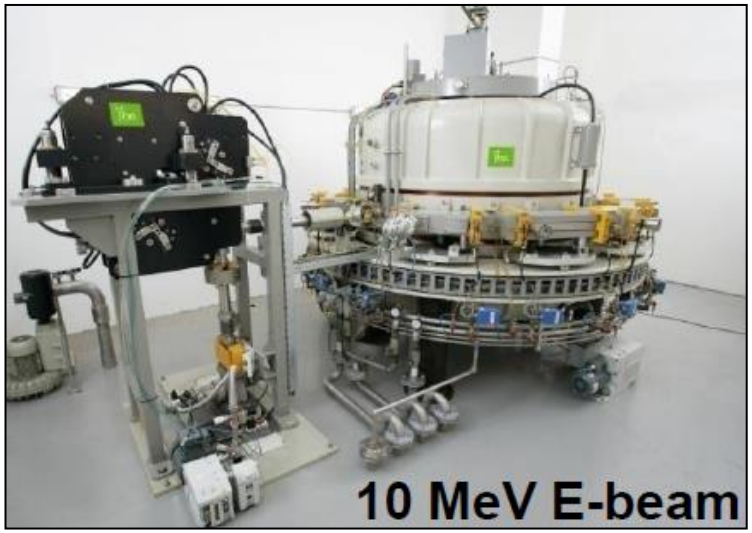
Electron Beam

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

Beam energy

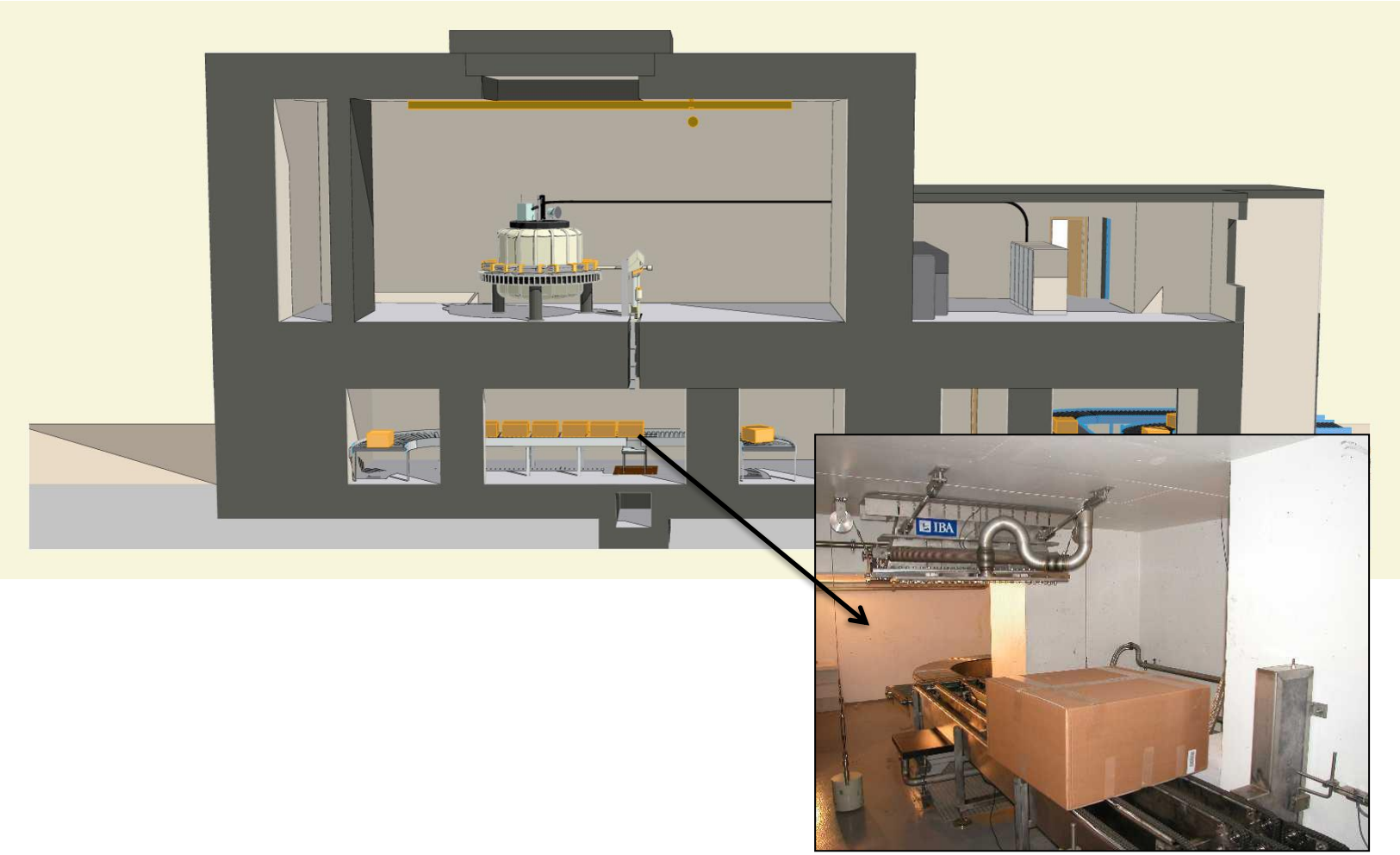
Speed of the electrons. Parameter related to depth of penetration

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

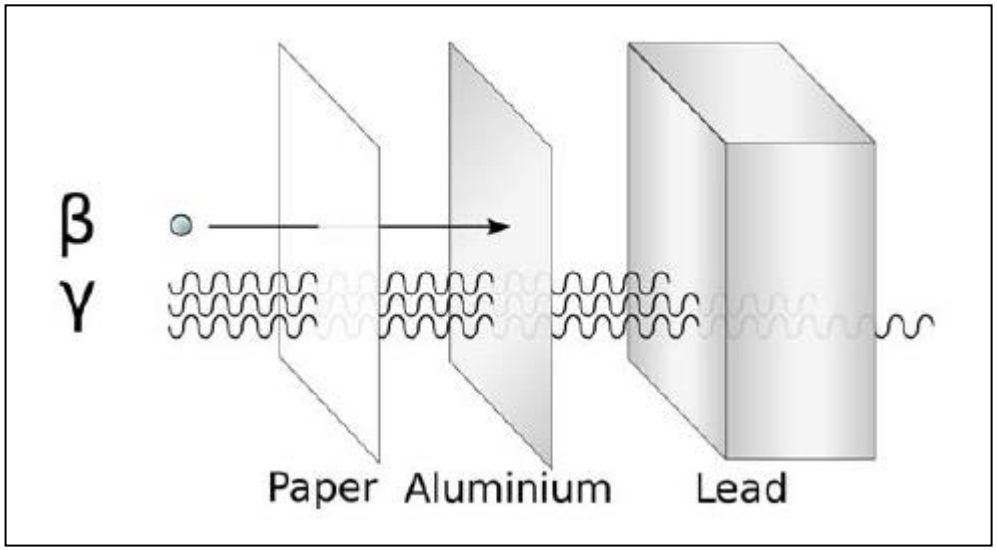


IBA Rhodotron

Layout E-Beam facility



Electron Beam & Gamma, Penetration



Sterilization by Irradiation : comparison

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

Sterilization by Irradiation : comparison

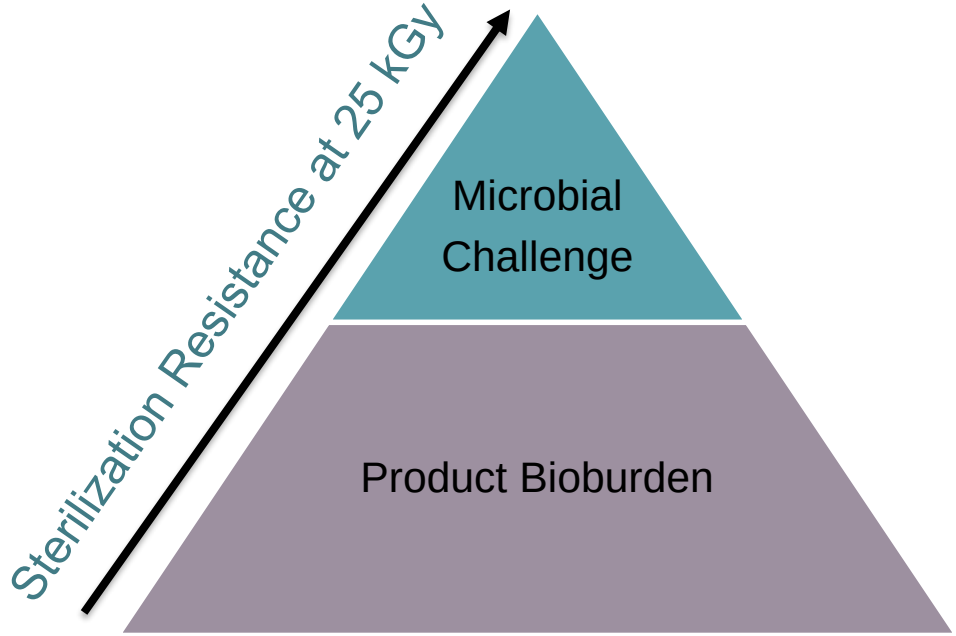
Parameter	Gamma	E-Beam
Product Treatment	Pallet/Tote	Boxes
Dose Rate (Dmin 25KGy)	Hours	Seconds
Dose uniformity ration (DUR)	Low sensitivity to product thickness	sensitivite to product thickness
On/Off Technology	No	Yes
Flexible Target Dose	No	Yes
Process validation	Straightforward	Potentially complicated

Relevant Standards:

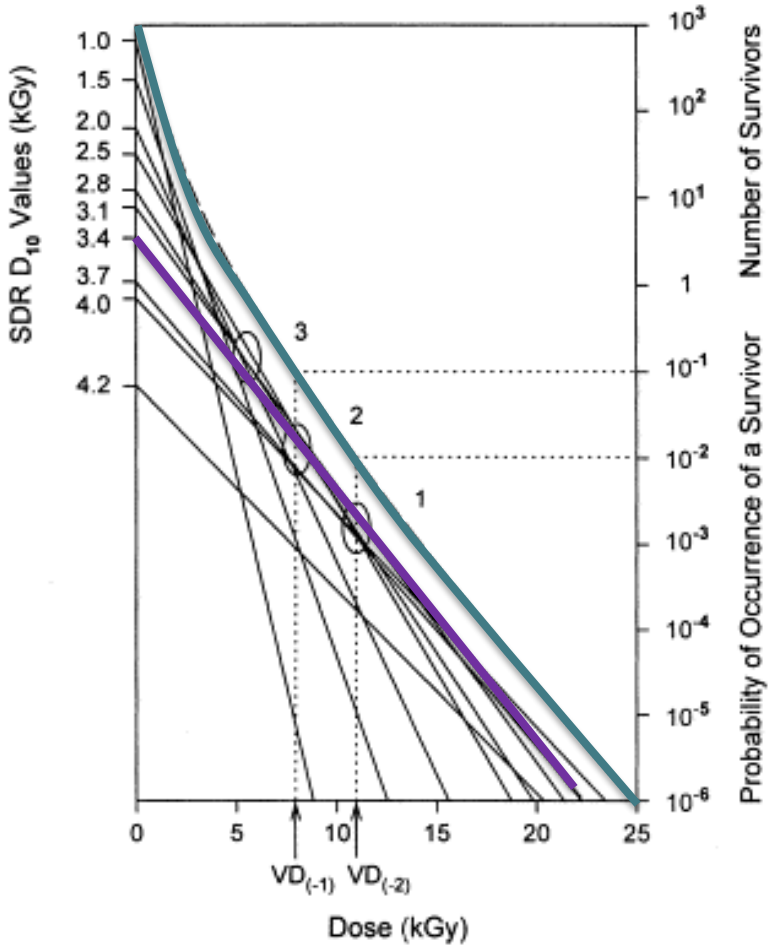
ISO 11137-1:2015	ISO 11137-2: 2015	GMP – Annex 12
Sterilization of health care products – Radiation – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization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

Sterilization by Irradiation: validation principles

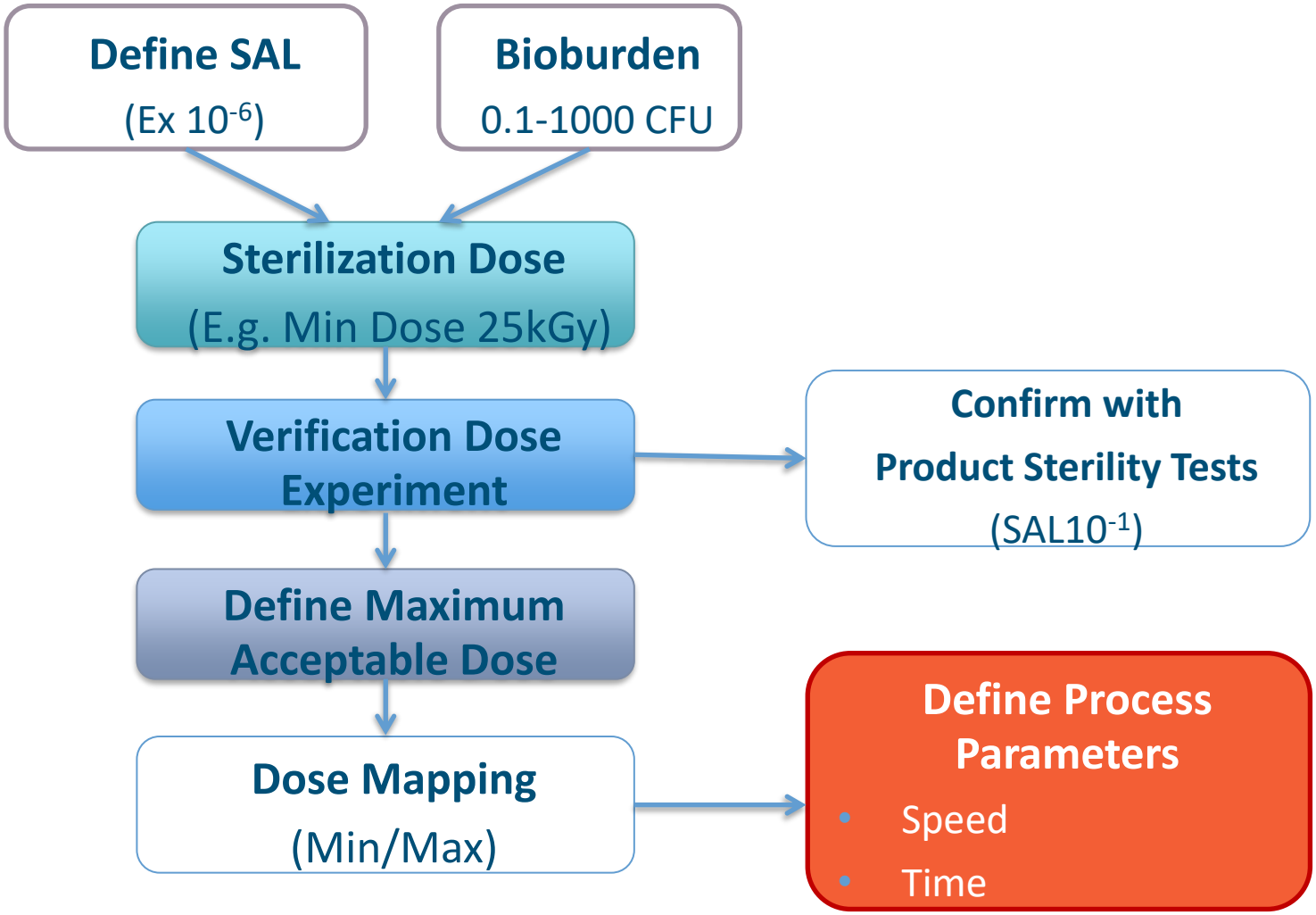
Method VD_{max}



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.

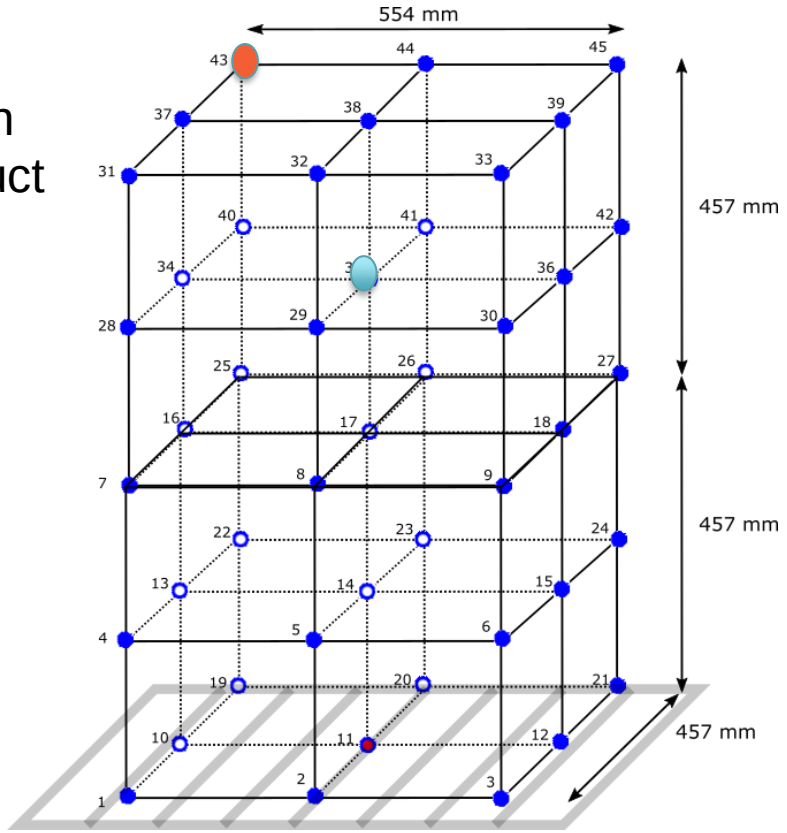
Dose Mapping

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

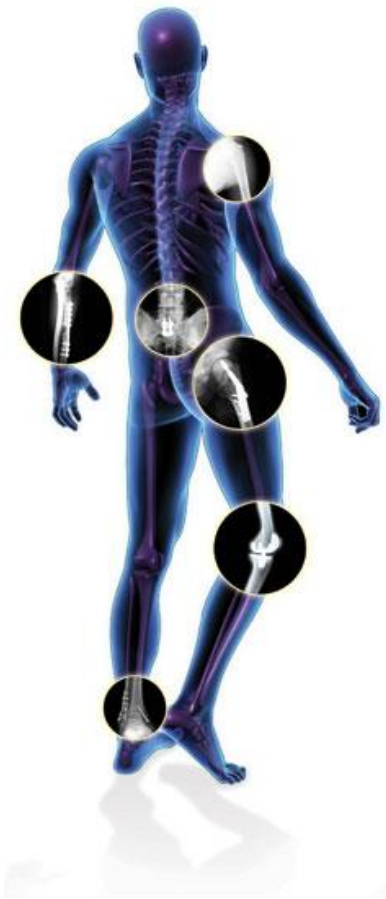
Sterility Test

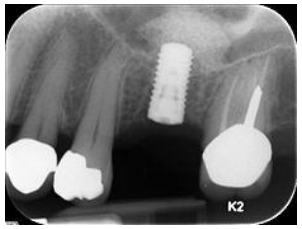
$SAL10^{-1}$

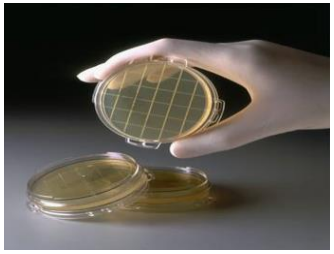
Confirm Product
$SAL\ 10^{-6}$
With Routine Dose

Ex:25KGy

Sterilization by Irradiation: examples



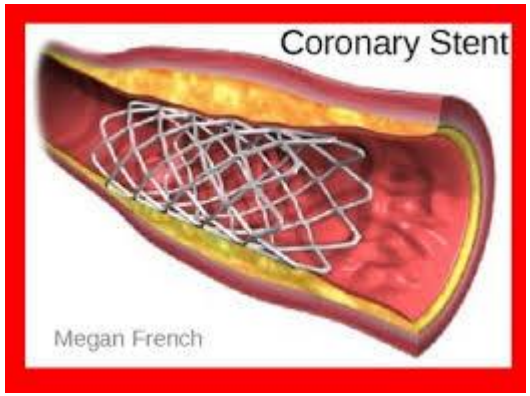


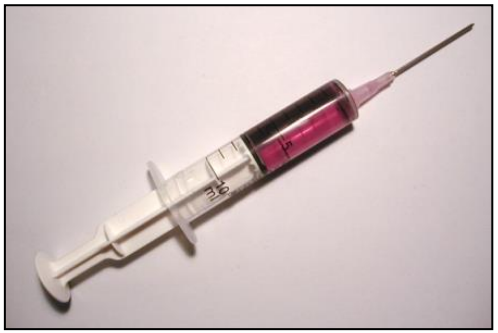


Sterilization by Irradiation: examples

… But also

Grafts





API

Summary

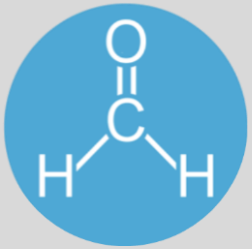
Minium & Maximum dose to product shall be defined

Methods 1, 2, VDmax, “equivalent method”

Based on natural product bioburden

Routine process monitored with dosimeters

Quarterly Dose Audit (QDA) required



Ethylene Oxide Sterilization

Introduction

Sterilization by Ethylene Oxide : History

1859 — **Ethylene Oxide discovered**
Charles Wurz

1925 — **First production of Ethylene Oxide**
Union Carbide Chemicals

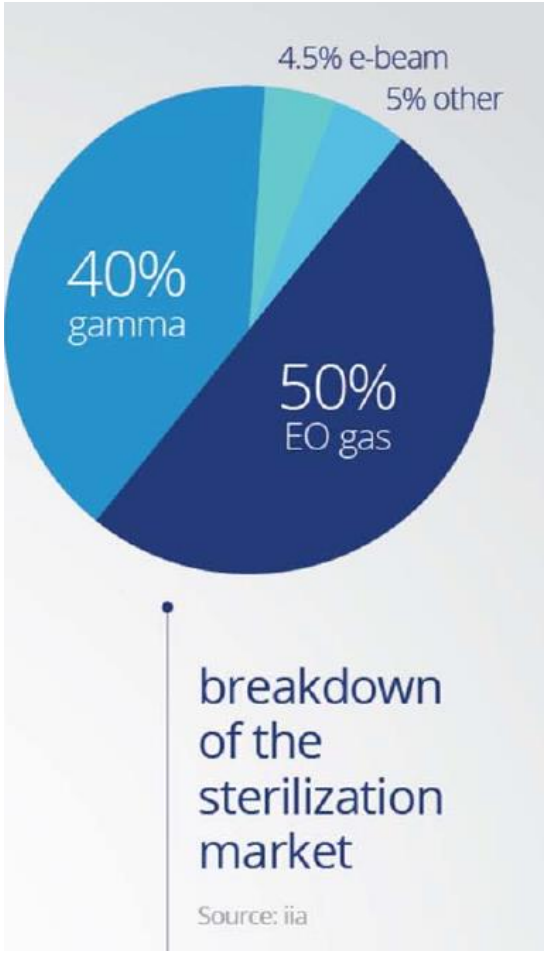
1938 — **Patent for sterilization of spices**
Lloyd Hall

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

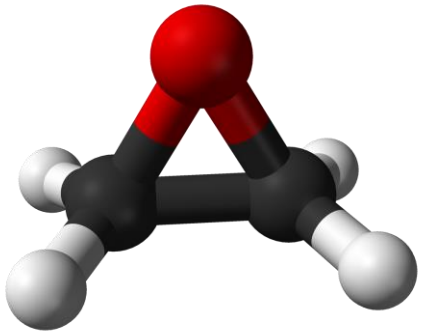
- Toxic gas
- “Sweet smell” from ca. 500 ppm concentration
- Forms with air explosive mixtures (2.6 %)
- Oncogenic by inhalation
- Irritating for skin and respiratory system
- Mutagenic for animals and very likely for humans



Last choice but sometimes the only one !

Mode of Action

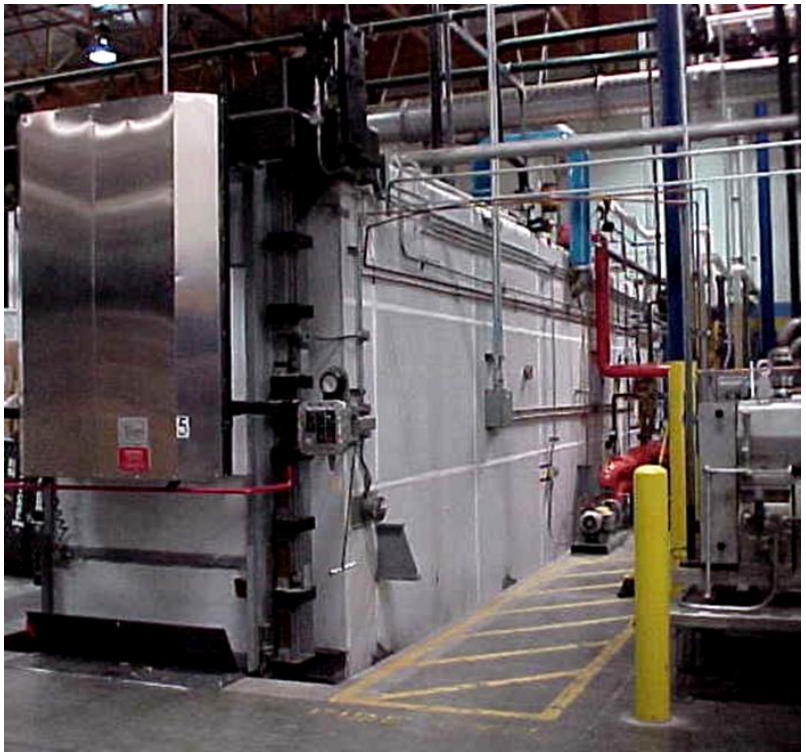
- Extremely reactive
- Irreversible reaction with DNA and proteins (alkylation)
  - The molecule is loses function
  - Replication stops
  - The cell dies



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

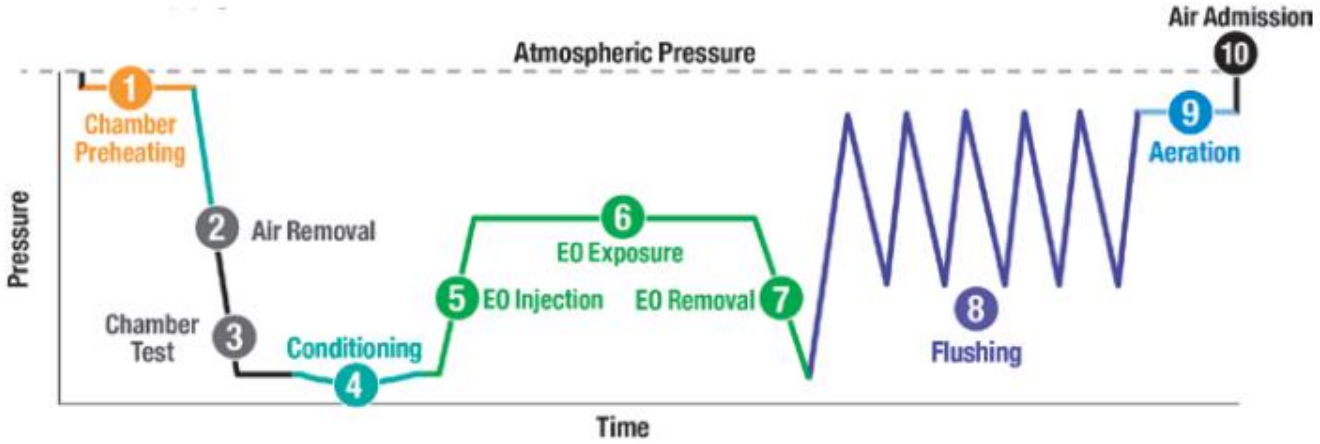
- No aqueous substances
- No protein-type materials
- Powders, batteries, electronic circuits have to be assessed (risk of explosion)
- Vacuum/heat can have adverse impact on some packaging (bubble wrap packaging, polystyrene)

Customer Needs To Define

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

Sterilization by Ethylene Oxide

Typical EO Cycle Design



The 3Rs of EO Sterilization

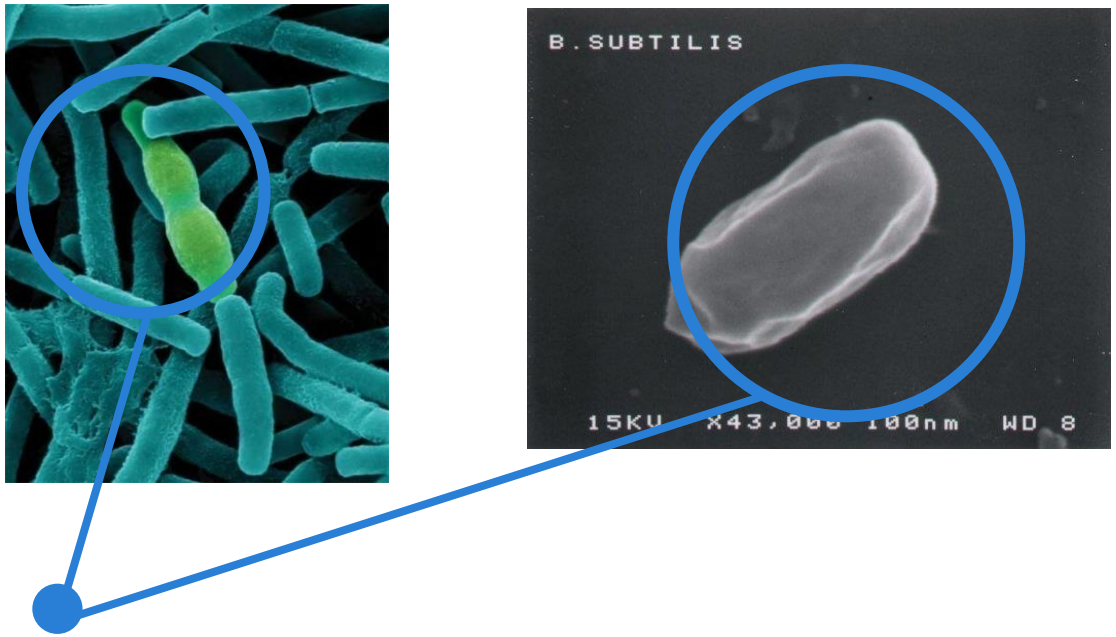
REDUCE
REUSE
RECLAIM™

✓Optimize the EO sterilization process
✓Enhance the safe and sustainable use of EO

We have set a goal to reduce the amount of EO by ↓50%

Monitoring EO Sterilization - Biological Indicators

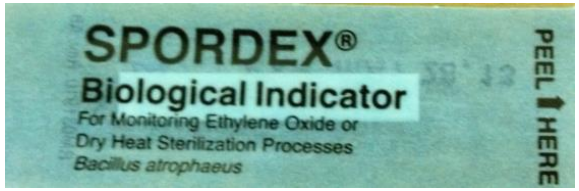
- Usually, the BI contains at least a million spores (>10Exp6) of an organism that is highly-resistant to the EO process (*Bacillus atrophaeus)*
- Growth is very characteristic (orange ring)



Process Challenge Device (PCD)

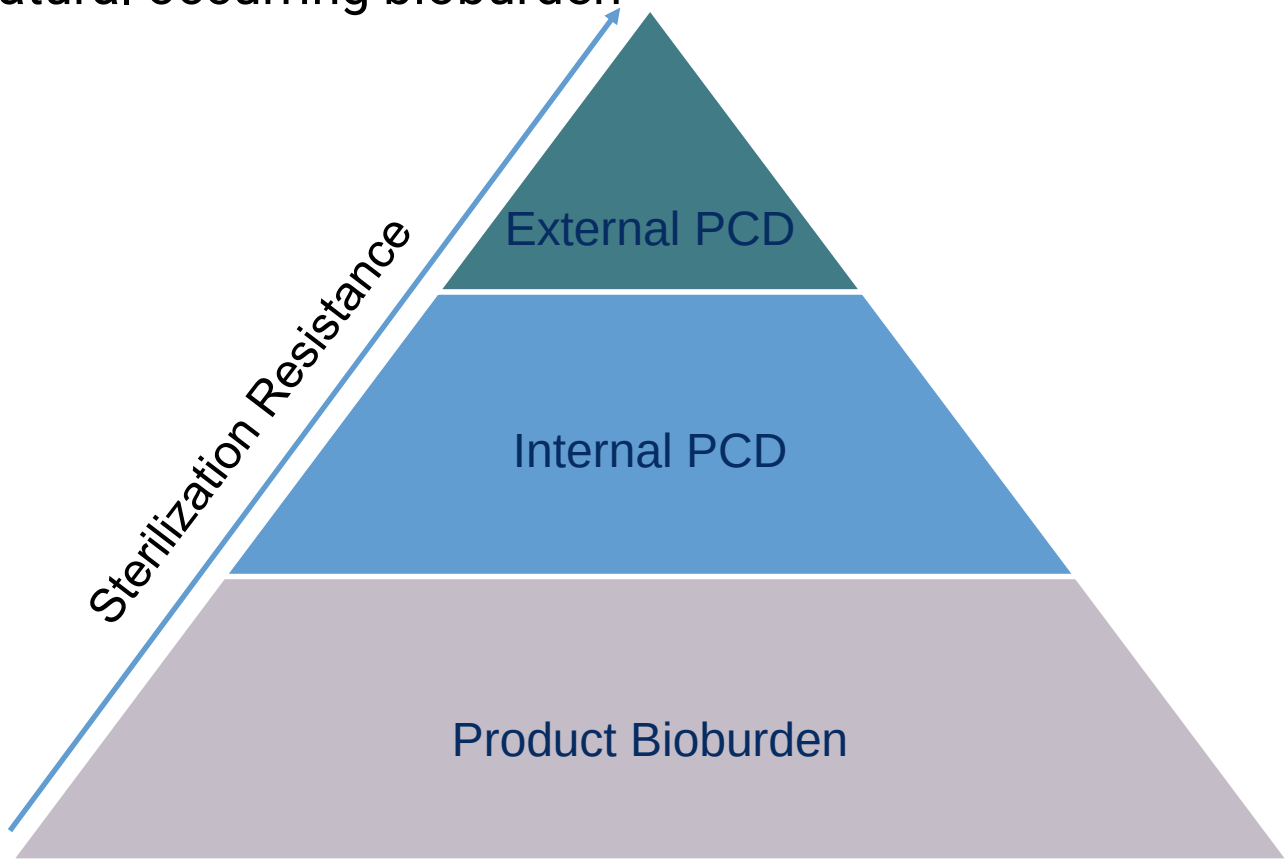
Item designed to constitute a defined resistance to the sterilization process and used to assess performance of the process

- 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

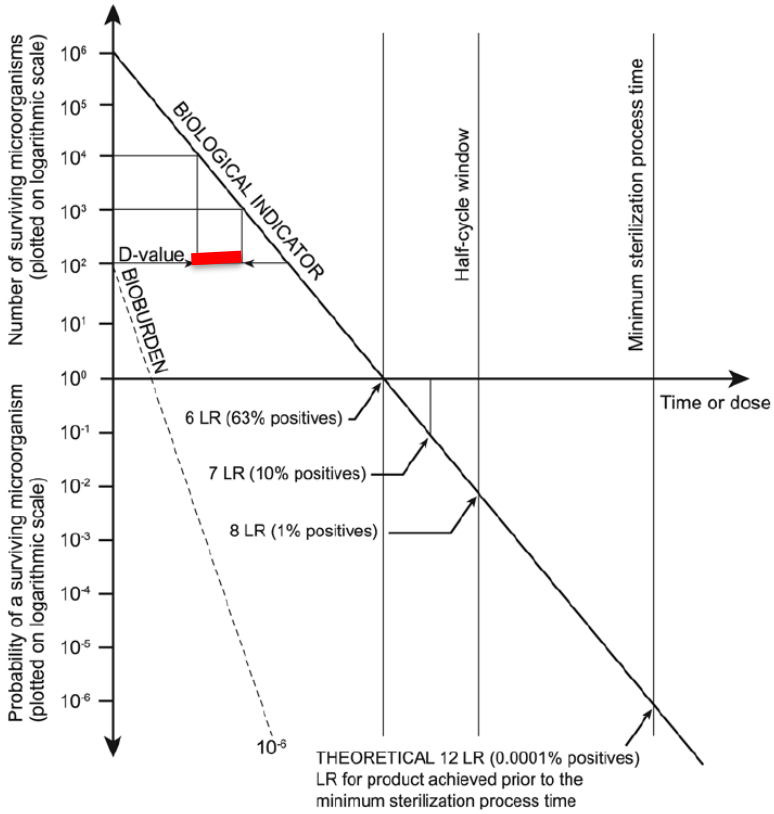


D Value

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)*

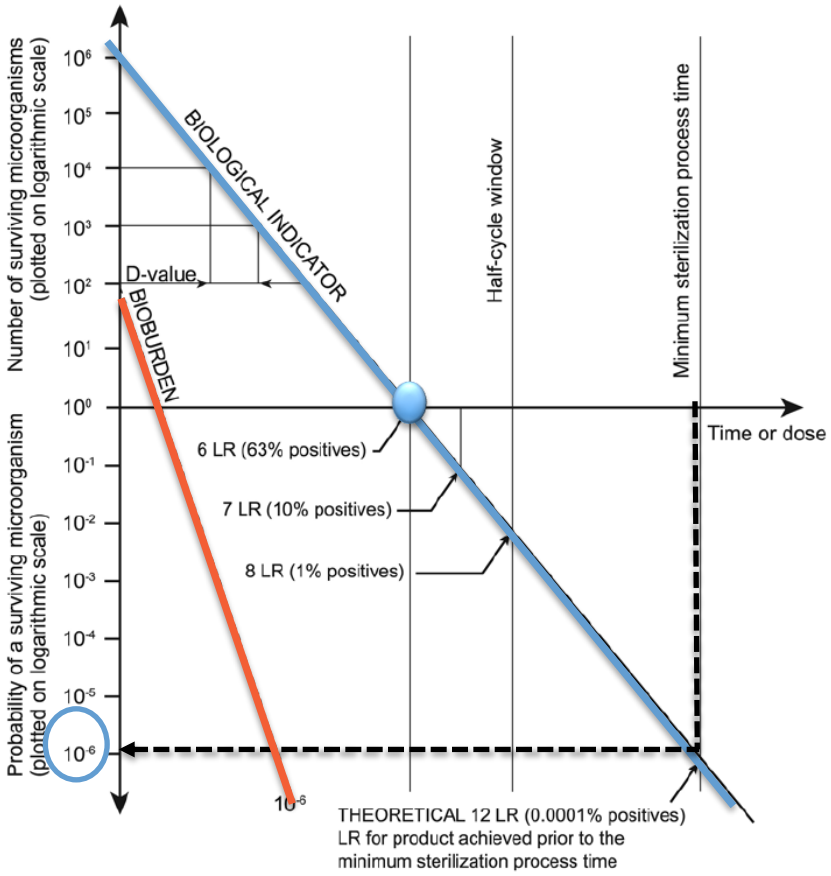


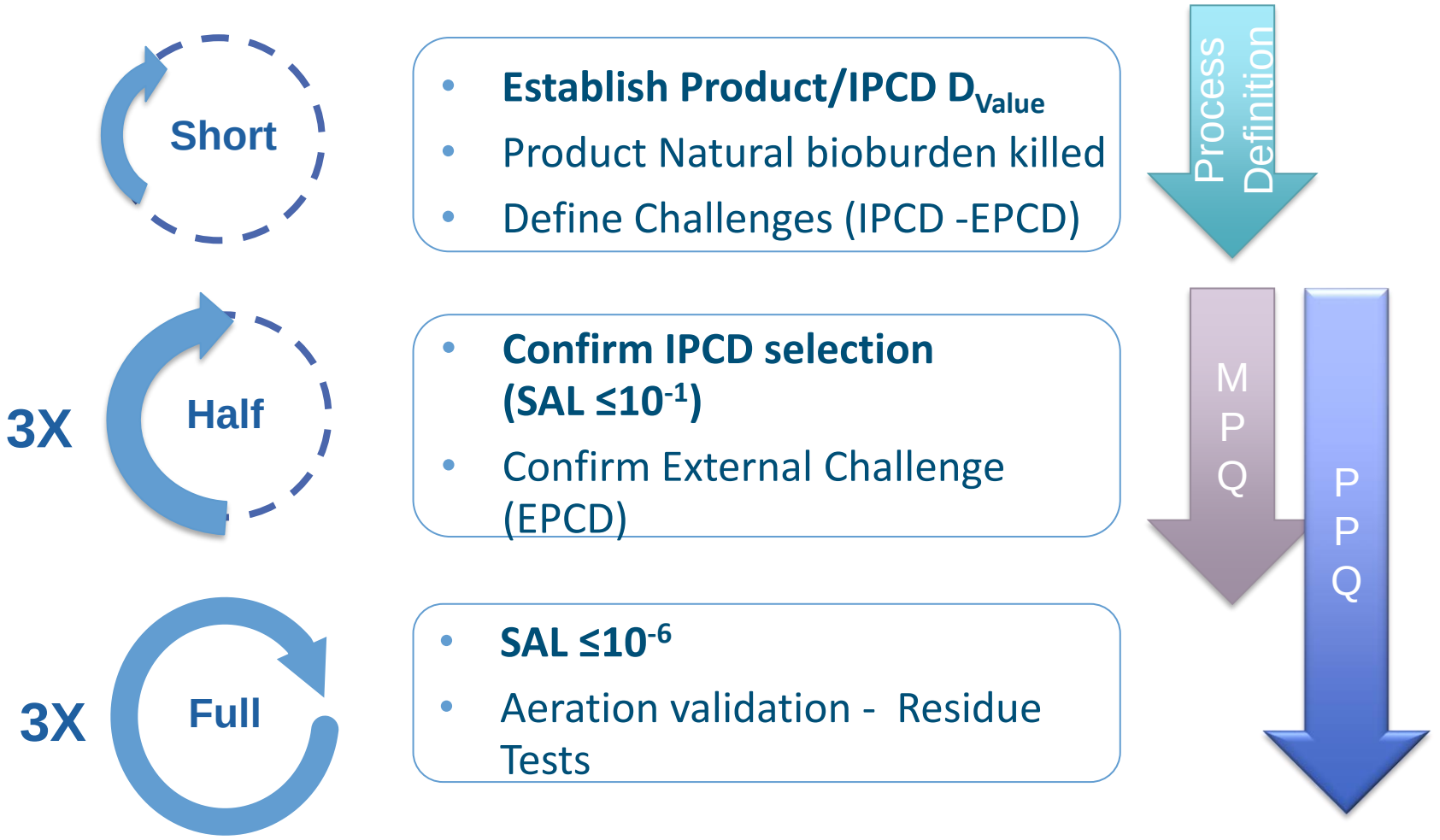
Level of Sterility Assurance

Example:

D_{value} IPCD = 15min = 1LR

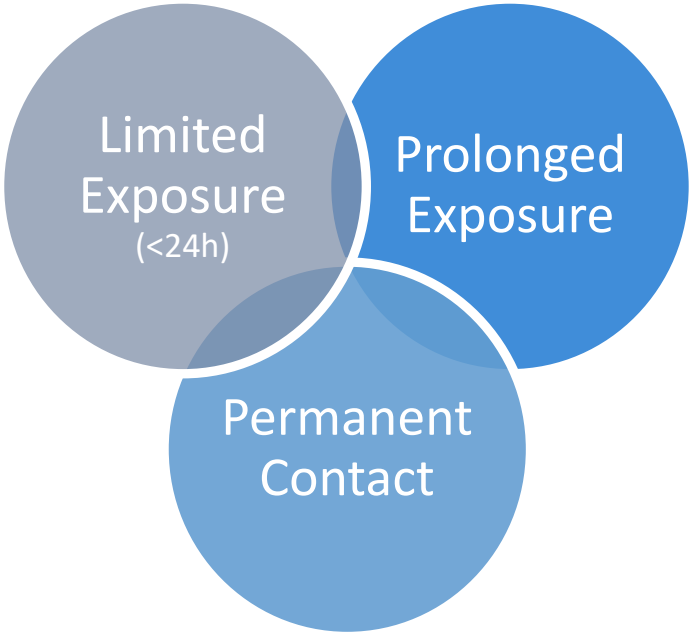
6 LR = 90 min (Half cycle)
12 LR =180 min (Full cycle)




Short
Half
3X
Full
3X
Establish Product/IPCD D_{Value}
Product Natural bioburden killed
Define Challenges (IPCD -EPCD)
Confirm IPCD selection (SAL ≤10^{-1})
Confirm External Challenge (EPCD)
SAL ≤10^{-6}
Aeration validation - Residue Tests
Process Definition
MPQ
PPQ

Sterilization by Ethylene Oxide

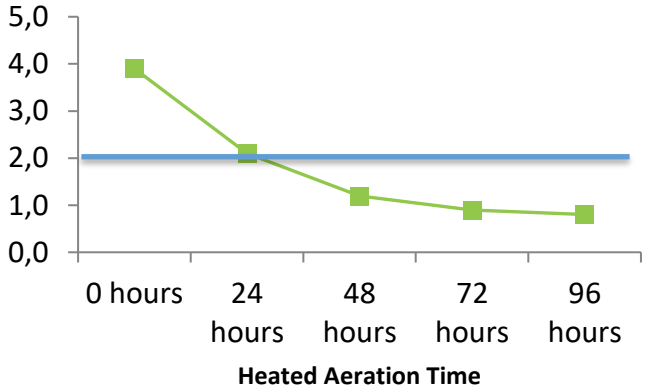
There are Three Patient Exposure Categories (Medical devices/combo)



Compounds that remain on product after EO sterilization:

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

Reference : **ISO 10993-7:2008** "Biological Evaluation Of Medical Device Part 7: Ethylene Oxide Sterilization Residuals"



Residue Limits for Pharma

Raw materials /Finished product

- Ethylene oxide: 1 µg/g
- Ethylene chlorohydrin (or any other halogenated ethylenehydrine): 50 µg/g.

If the residual ethylene oxide originates from its use in the raw starting material, its content must be limited in the raw starting material.

Containers

Specification (based on simulated use):

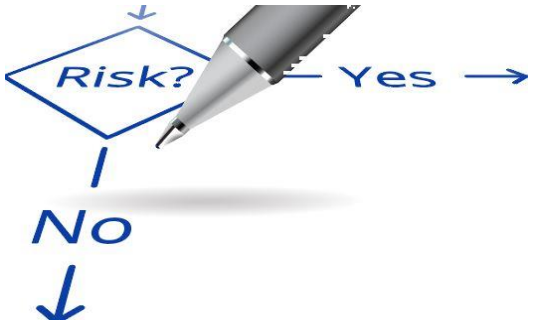
- Ethylene oxide: 1 µg/ml (container volume)
- Ethylene chlorohydrin (or any other halogenated ethylenehydrine): 50 µg/ml (container volume).

Reference : EMEA/CVMP/271/01 Note for guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products

Sterilization by Ethylene Oxide:

Residue Limits for Pharma

Other limits can be established based on



- Risk analysis
- Toxicological data
- Product intended use

Note : In a prefilled syringe, the syringe is both the injector device and the primary packaging !

Reference : ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

Sterilization by Ethylene Oxide : Product examples

Medical Devices

Surgery packs

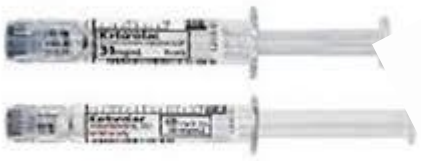
Catheters

vials

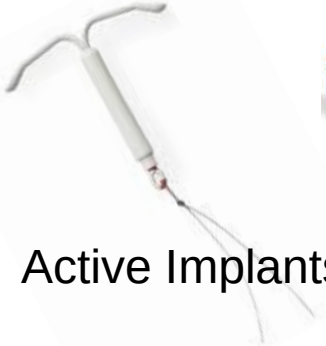
Bandages

Drug products

API



Prefilled syringes (external)



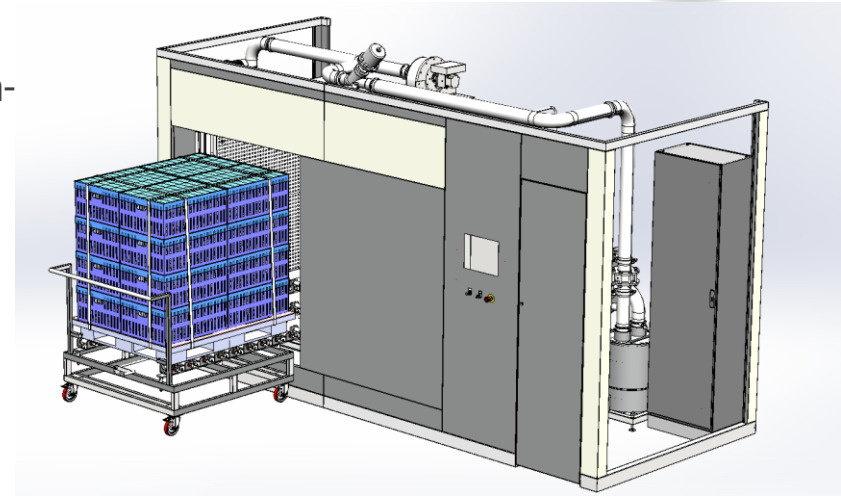
Active Implants

Auto-Injector (external)

Nitrogen Dioxide Sterilization

An alternate possibility ?

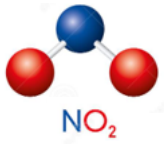
- **Surface sterilization** (Drug-delivery devices, Orthopaedic implants, implantable sensors)
- **Short** process time (2-4hours).
- **Safe** and simple to use: non-flammable, non-explosive and non-carcinogenic
- Wide variety of **compatible materials** (if not cellulose based)
- Allows processing of moisture/temperature **sensitive materials**
- Validation with the NO_2 Sterilization method follows **ISO 14937**
- **Low residuals**
- Small volume – Scale up ?



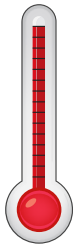
FDA Innovation Challenge 2 to promote the development of new strategies to reduce EO emissions

Nitrogen Dioxide Sterilization

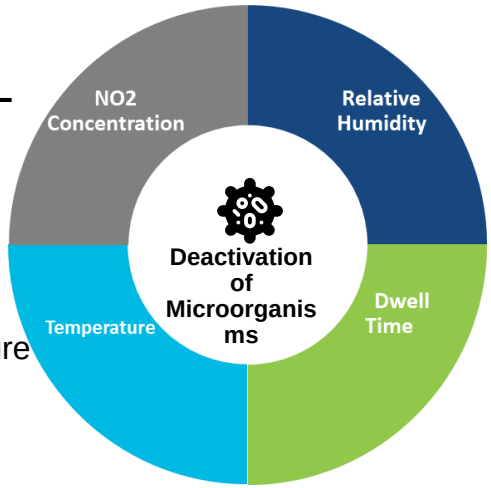
Key Parameters



Typical range **6-15 mg/L**



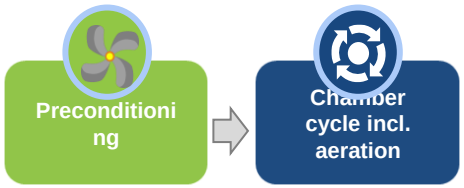
Industrial sterilization
performed in 20-25°C temperature range



Necessary for **oxidation reaction** effective at **60-80 RH %**

Microbiological deactivation
is more effective with longer gas dwell phase (**Total Cycle time = 4-8h**)

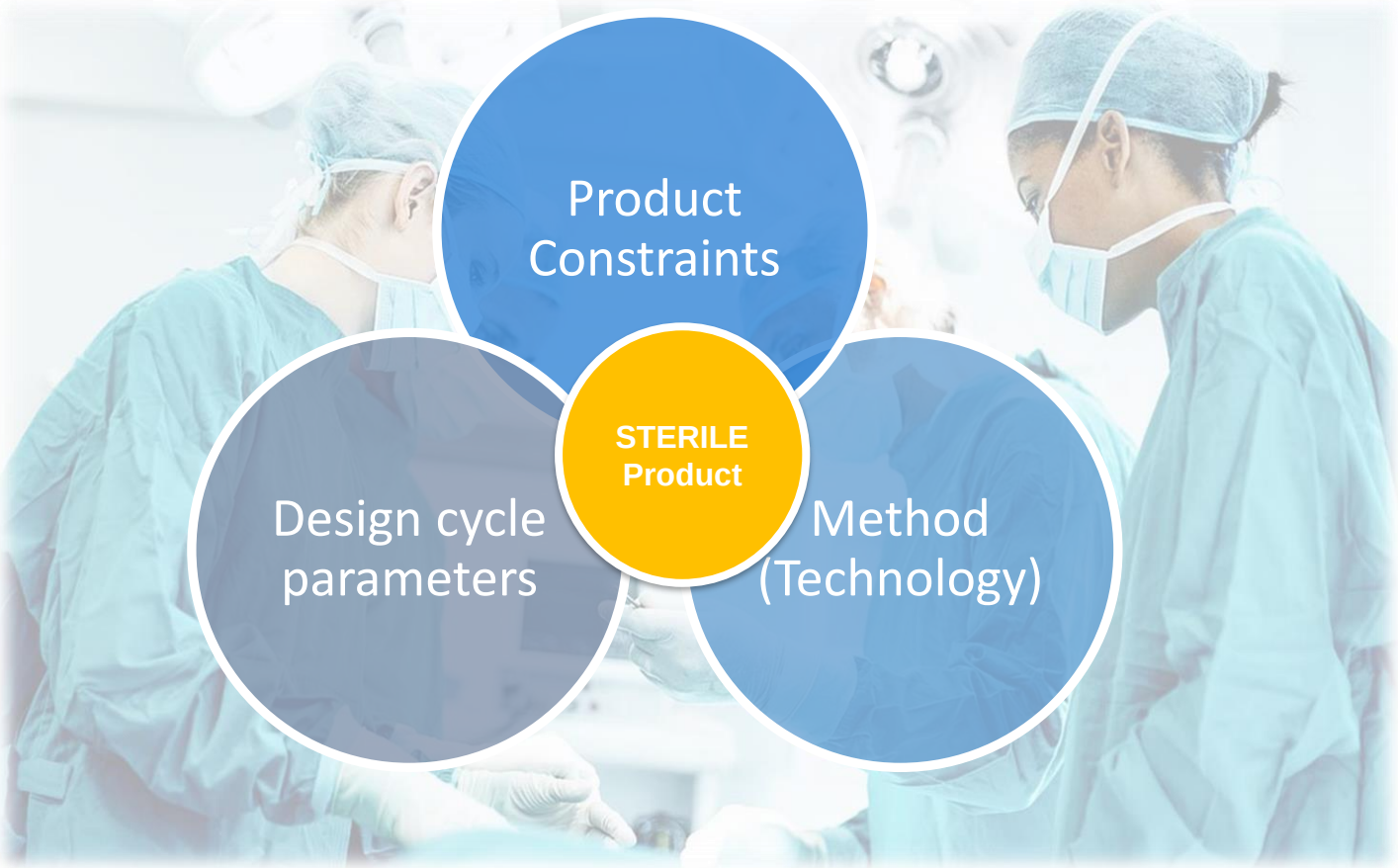
2-Step Process



Sterilization – Comparing Radiation and Gas sterilization

Parameter	Gamma or X-Ray	E-Beam	EO	NO2
Process	Individual product, box, tote, pallet	Boxes	Pallets – High Volume	Plastic Tote 1 pallet
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)	Good No Cellulose (paper/carton) No liquid/proteins Very Low Temperature (25°C)
Validation	Straightforward	Straightforward	Complicated	Complicated
Validation principle	Based on bioburden	Based on bioburden	Based on Bio Indicators or bioburden	Based on Bio Indicators
Requalification	Every 3 months (QDA)	Every 3 months (QDA)	Every 2 years (1 cycle)	Every 2 years (1 cycle)
SAL	<10exp6	<10exp6	<10exp6	<10exp6
Residues	None	None	ETO,ECH,(EG)	NO2,NO3

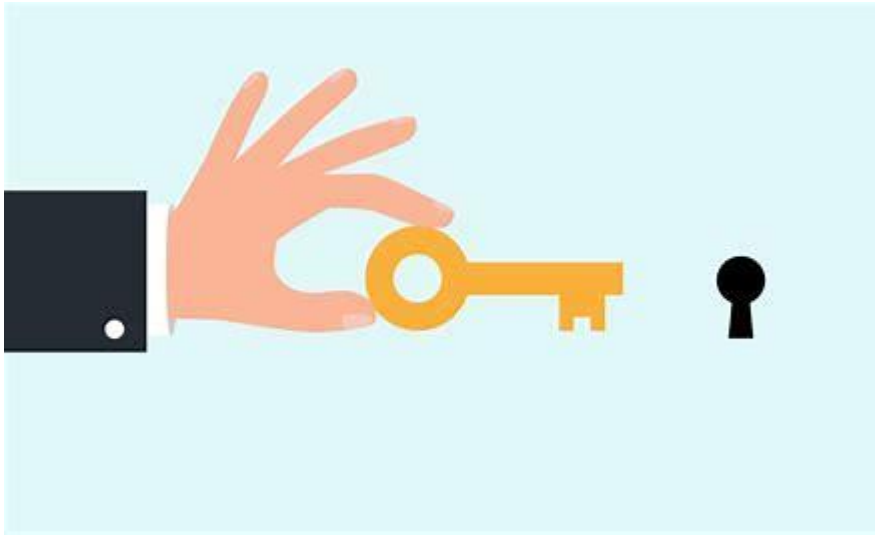
Sterilization – Conclusions



Selecting the Right Technology is Key !

There are multiple Terminal Sterilization possibilities

Key is to select the most appropriate technology to **YOUR product** !



Thank you !

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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