

# Sterilization basics Radiation Technology & Gas

*A. Gillet, Technical Director Gas, Pharma - STERIGENICS*

# Introduction

Market Segments :

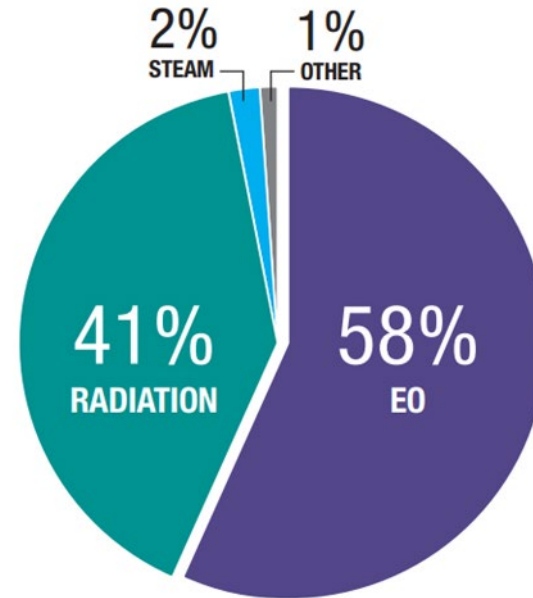
**Sterilization :**

- Medical Devices
- Drug/Pharmaceuticals

**Decontamination:**

- Vaccines & biologics
- Advanced Application
- Tissue
- Food
- Cosmetics

**Sterilization Methods Used to Sterilize Single-Use Medical Products**



Source: Global Industry Analysts. Sterilization Equipment and Supplies. A Global Strategic Business Report. MCP-3362. October 2011.

# Introduction

Where you probably do not expect us !



Spices decontamination



Gemstones colour change



Frog Leggs



Mail Anthrax decontamination



Cosmetic packaging



Physical properties change



Bioburden reduction

# Introduction

**SAL**

**Sterile**

**Aseptic  
Assembly**

**Decontaminated**

**Ionization**

**Terminal  
Sterilization**



**Clean**

**Radioactive**

# 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

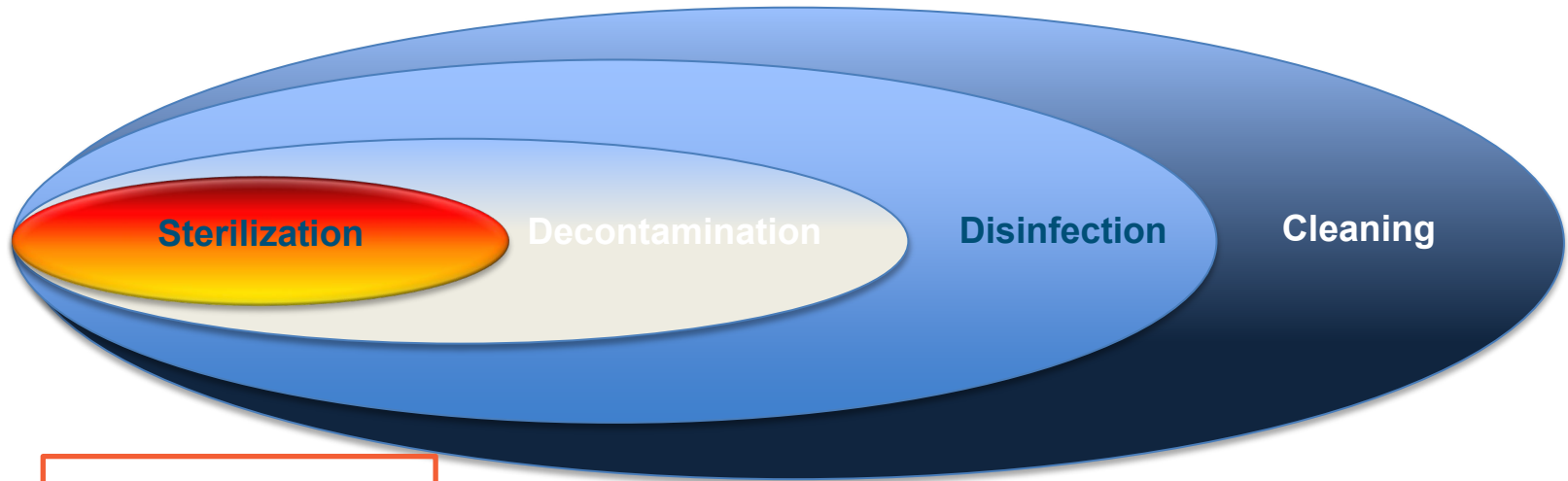
- Sterilization by gas
  - Ethylene oxide
  - Novel technologies ( NO<sub>2</sub> )
- Comparison between technologies

# Sterilization Basics

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

# Sterilization – Basics

## Decontamination Vs Sterilization

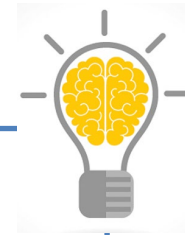


<b>Validation</b>			
<b>Sterilization</b>	<b>Decontamination</b>	<b>Disinfection</b>	<b>Cleaning</b>
<p>The application of a lethal sterilizing agent to finished product within a sealed container to achieve a predetermined <b>sterility assurance level (SAL)</b> of <math>10^{-6}</math> or better –</p>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



# Sterilization – Basics

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

# Sterilization – Basics

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

Sterile:  $SAL \leq 10^{-6}$

**SAL likelihood of surviving organisms**

$$10^{-1} = 1:10$$

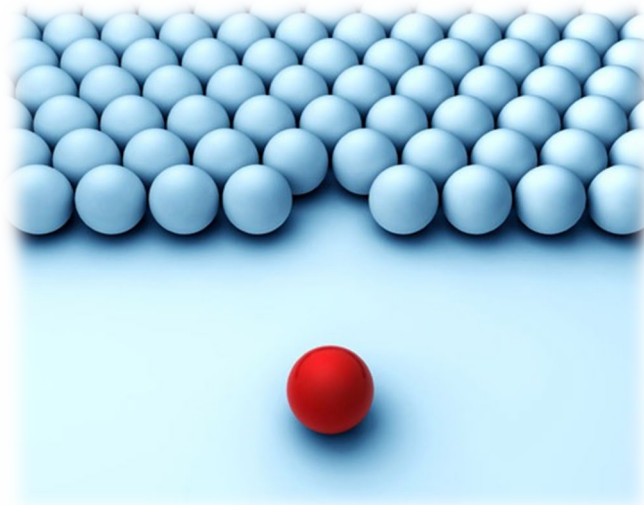
$$10^{-2} = 1:100$$

$$10^{-3} = 1:1,000$$

$$10^{-4} = 1:10,000$$

$$10^{-5} = 1:100,000$$

$$10^{-6} = 1:1,000,000$$



# Sterilization – Basics

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



# Sterilization – Basics

## Selection of the Sterilization Method

- **Think about sterilization process selection up front / early during product development**



# Sterilization – Basics

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



**Selection of the right sterilization method is critical !**

# Sterilization – Basics

## Regulatory update:

GMP EudraLex Volume 4 – Annex 1 – Aug 2022

ISO 11135:2014 -> FDIS under revision ( 2023)

# Sterilization – Basics

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

**Heat**

- Dry
- Moist Heat

In House /Low volume

**Irradiation**

- Gamma ray
- E-beam
- X-rays

**Gaseous (EO)**

- Alkylative

Industrial sterilization (large volume)

**Gaseous (NO<sub>2</sub>)**

- Oxidative

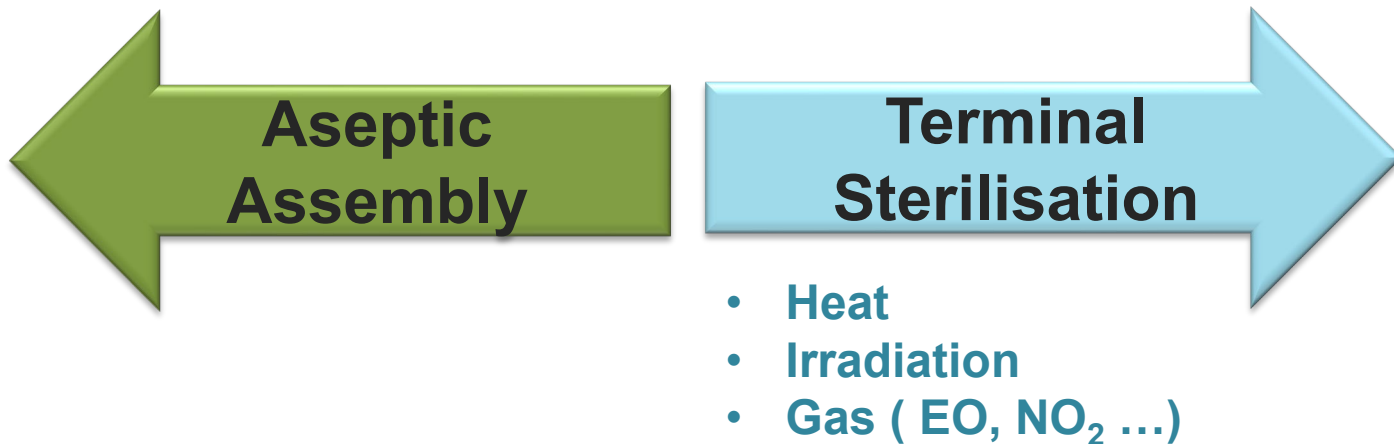
Innovative methods R&D

**New technologies**

- VHP
- Gas plasma
- Others

# Sterilization – Basics

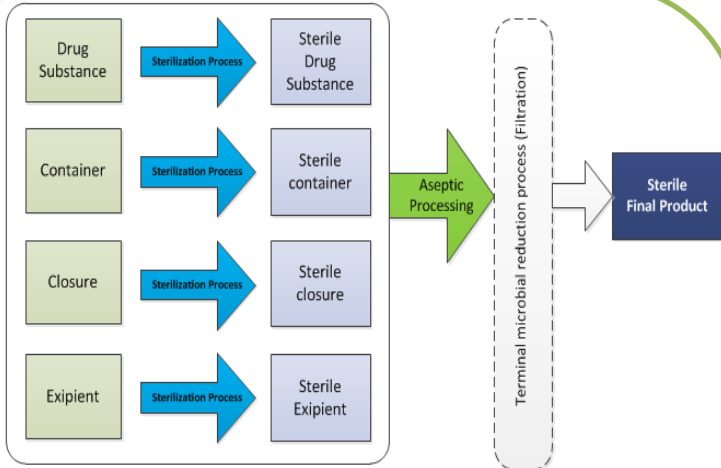
**There are two (2) methods to produce a sterile drug product:**





# Sterilization – Basics

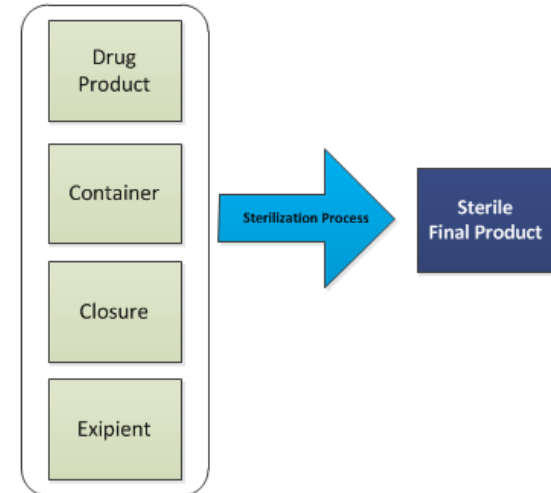
## Aseptic Assembly



**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**

# Sterilization – Basics

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 !*

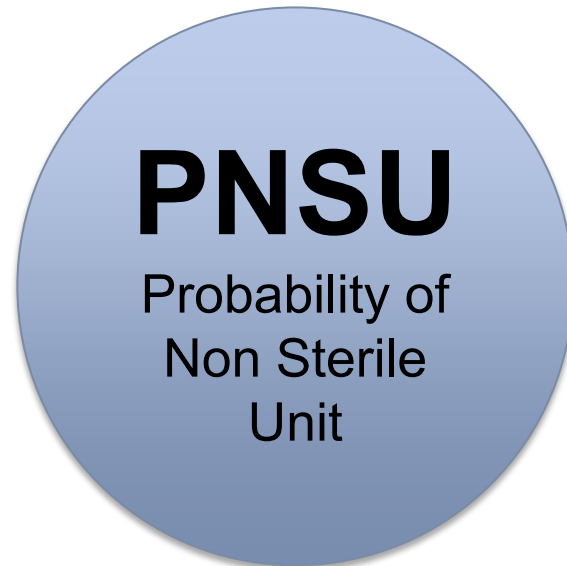
# Sterilization – Basics

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



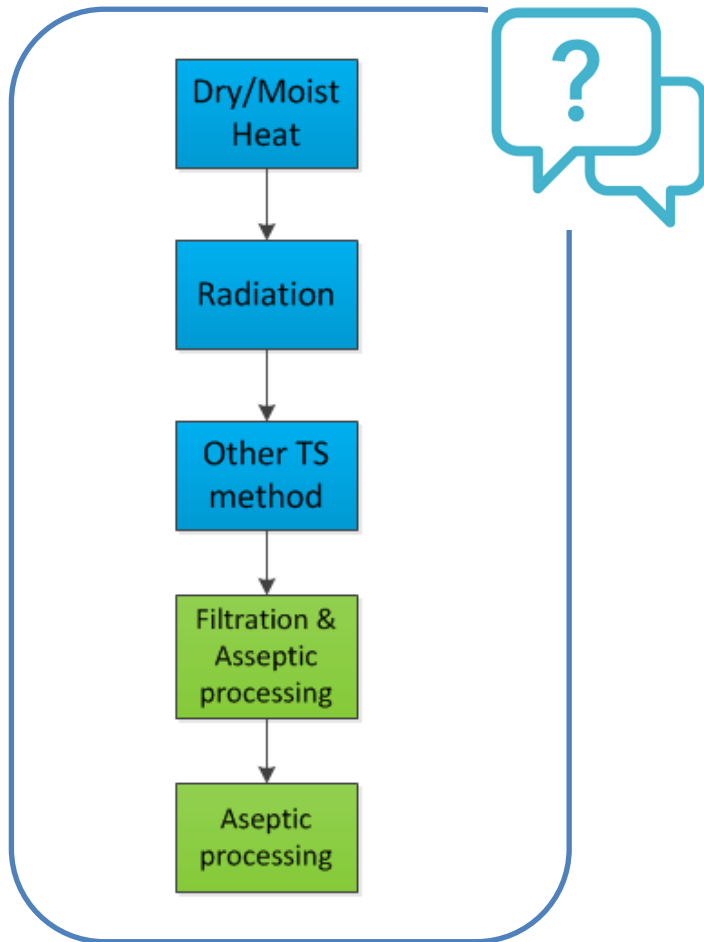
?

≡



*Reference: ISO TS  
19930:2017*

# Sterilization – Basics



## Selection of the Sterilization Method:

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

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

# Sterilization – Basics

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)?



# Radiation Technology

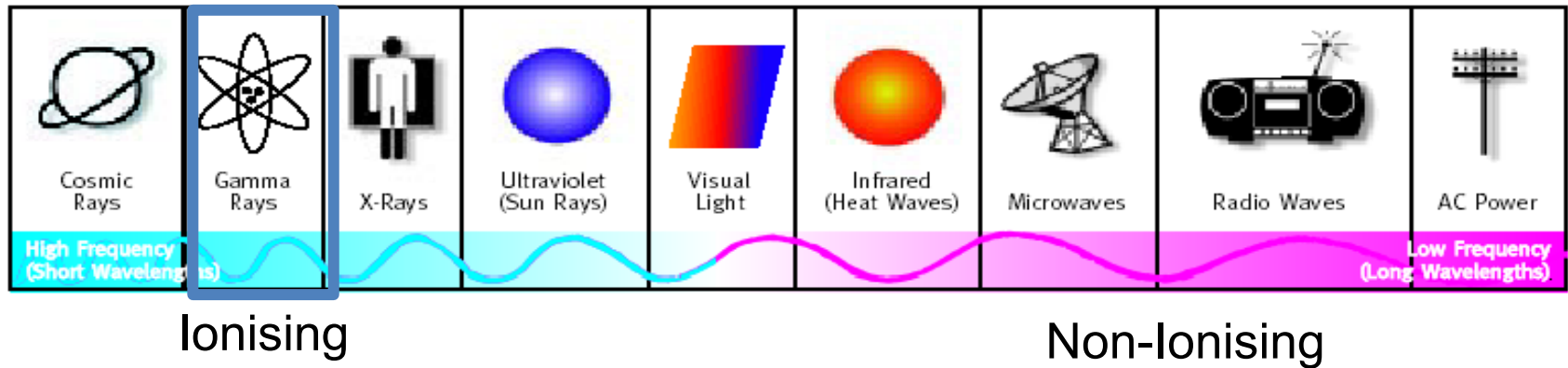
- General principles
- Gamma
- E-Beam
- Sterilization validation

# Sterilization by Irradiation

## General Terminology

### Radioactivity:

Electromagnetic radiation (photons) produced by radioactive decay.



**E-beam** = Electrons (with a mass)

# Sterilization by Irradiation

## General Terminology

### Radiation

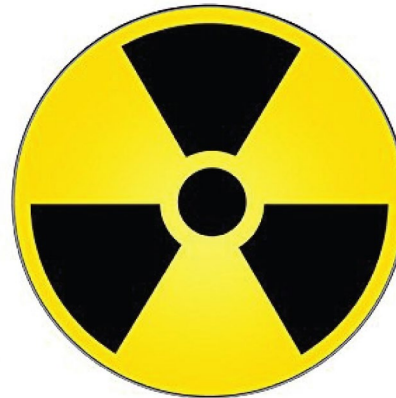
Energy in the form of waves or moving subatomic particles

### Radioactive

Substance emitting radiation

### Irradiation

Exposure to radiation  
≠ Making something radioactive





# Sterilization by Irradiation

## General Terminology

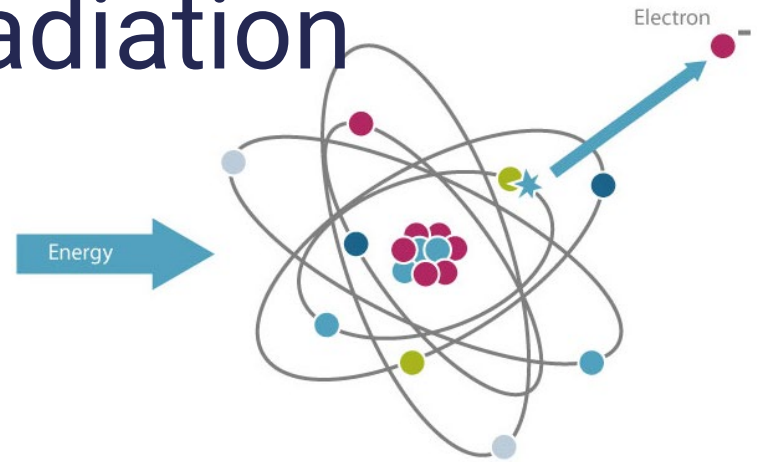
### **Ionising Radiation**

Radiation capable of knocking electrons out of their thermal orbits in atoms or molecules. It creates ions and free radicals. Breaks chemical bonds and may change material properties

### **(Absorbed) Dose**

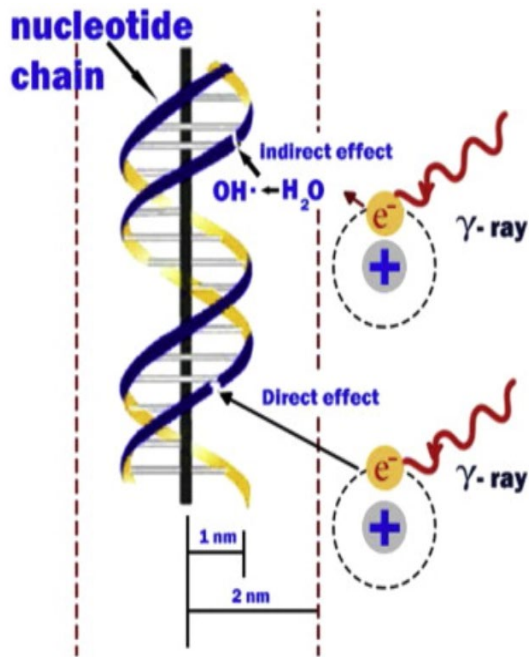
Measure of the amount of energy that is absorbed by the material while exposed to a radiation source.

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



# Sterilization by Irradiation

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



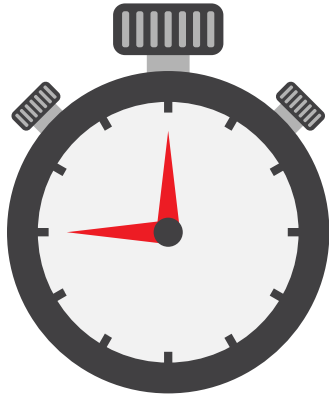
**Direct action:** the radiation hits the DNA molecule directly or via the ejected electron, disrupting the molecular structure leading to cell damage or cell death.

**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.

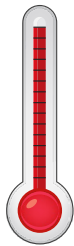
# Sterilization by Irradiation

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

# Sterilization by Irradiation

Irradiation process monitoring:

## Dosimeter

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



0 kGy

12 kGy

25 kGy

50 kGy

0kGy



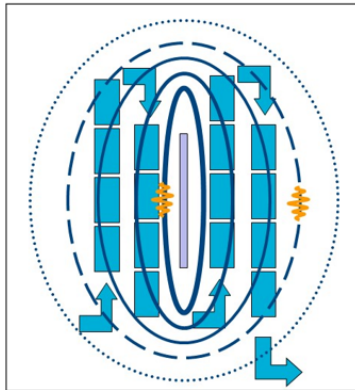
# Sterilization by Irradiation

Type of radiation, generation and directionality of radiation field

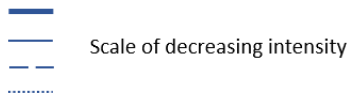
## $^{60}\text{Co}$ Gamma

Photons  
from

Radioactive decay



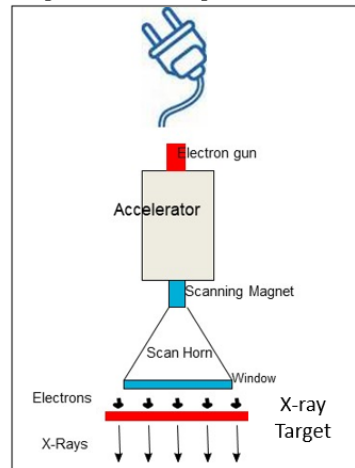
Isotropic radiation flux



## X-ray

Photons  
from

Particle accelerator  
(by high energy electrons  
hitting material with high atomic number)

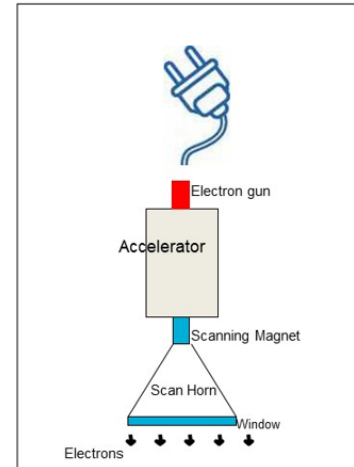


Directional radiation flux  
can be tailored to product needs

## Electron Beam

10 MeV Electrons  
from

Particle accelerator



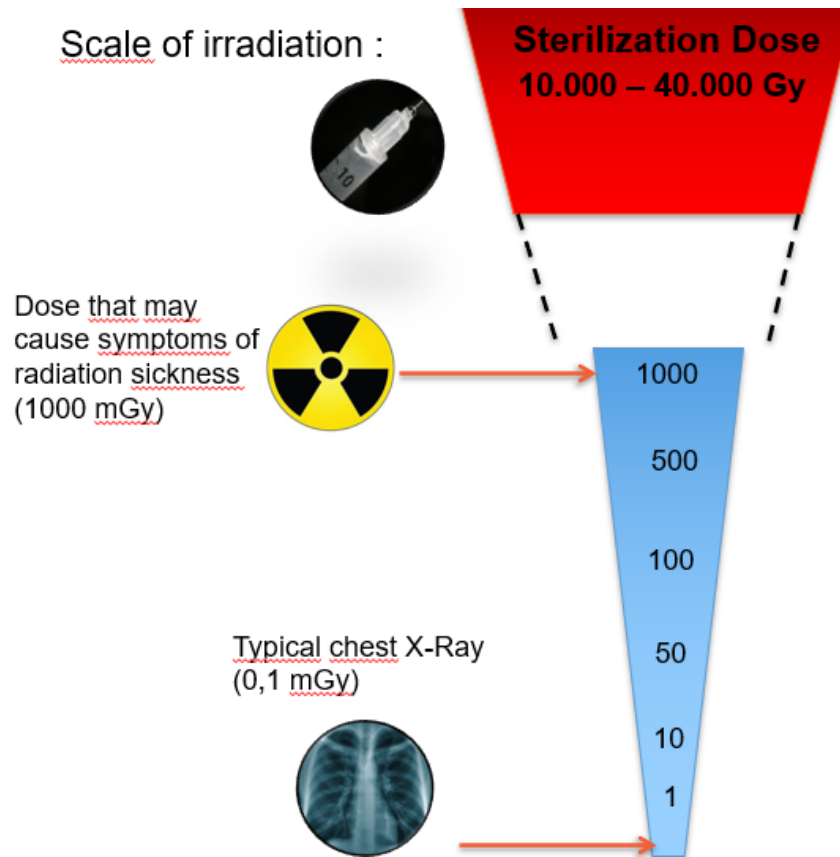
Directional radiation flux  
can be tailored to product needs

# Sterilization by Irradiation

## Gamma Irradiation



# Sterilization by Gamma

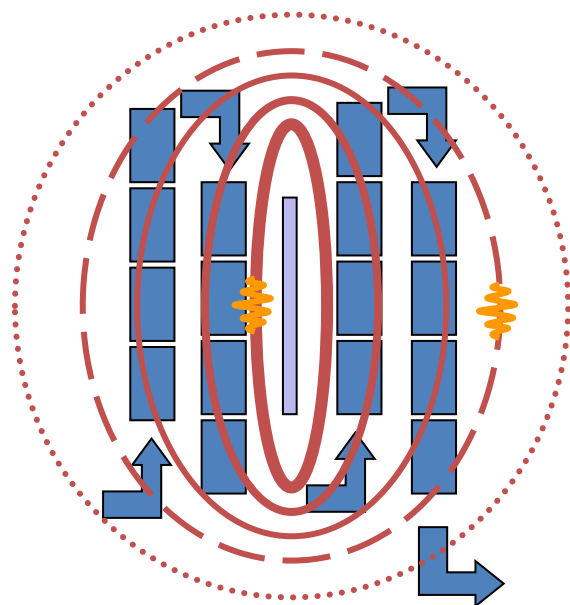


# Sterilization by Gamma

**Source:**  $^{60}\text{Co}$  (mostly)

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

**Source Activity:** Several Million Ci



Isotropic radiation flux

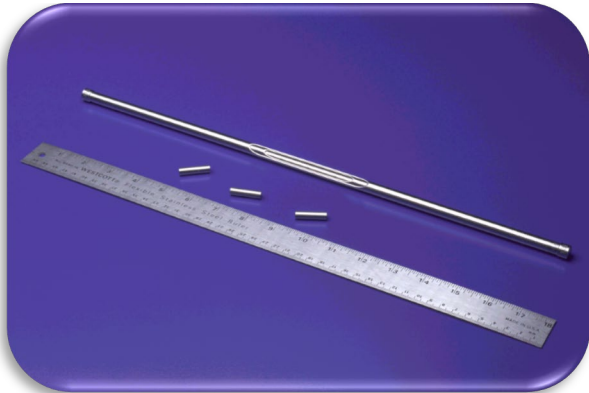




# Sterilization by Gamma

## Source Rack

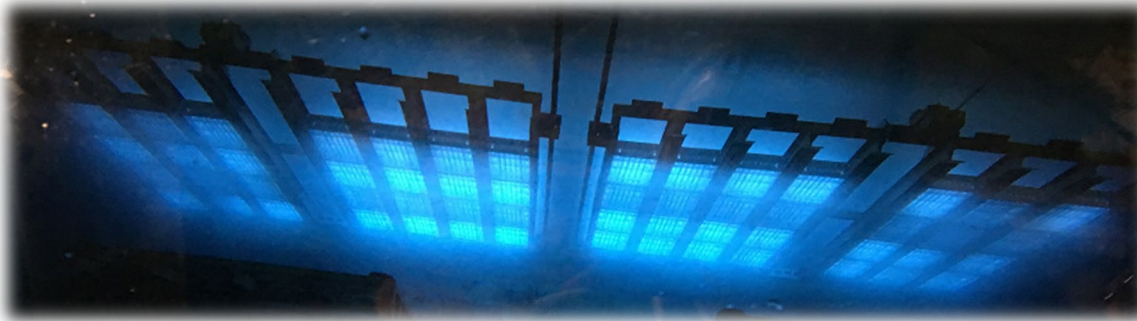
Cobalt-slugs in a source pencil



Source module

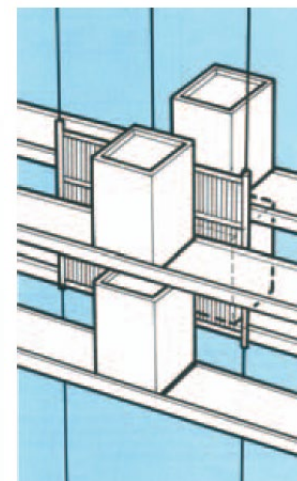
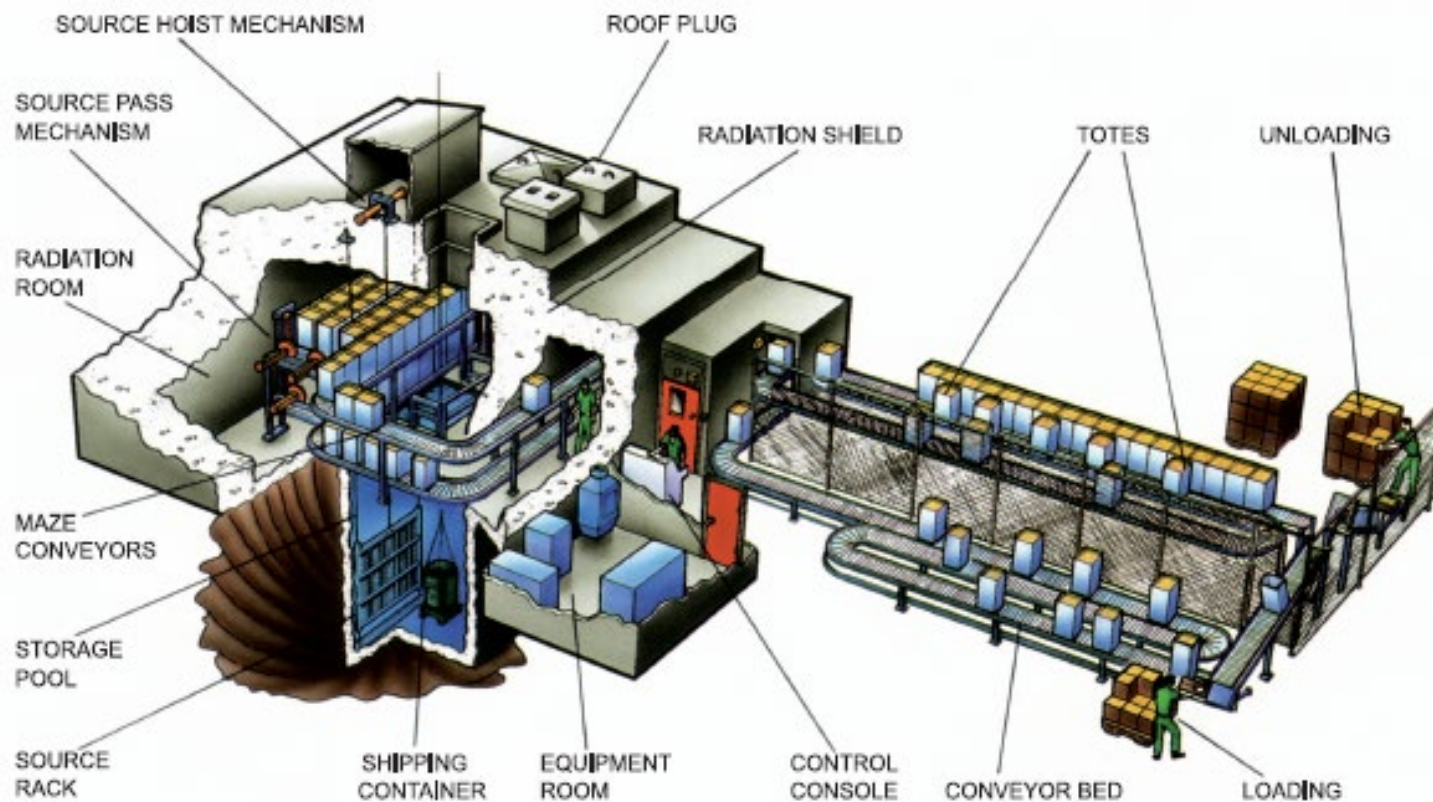


Source rack



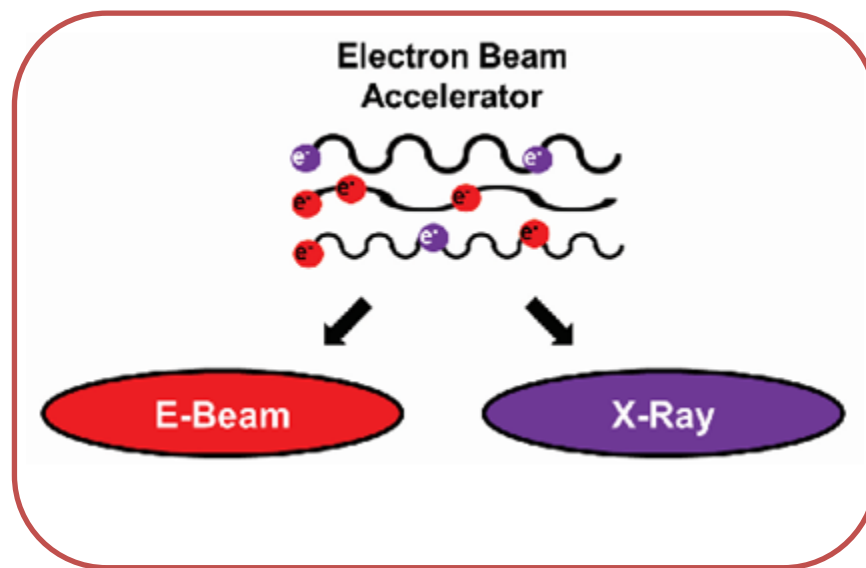
# Sterilization by Gamma

## Layout Gamma facility



*Product overlap*

# Sterilization by E-Beam



# Sterilization by E-Beam

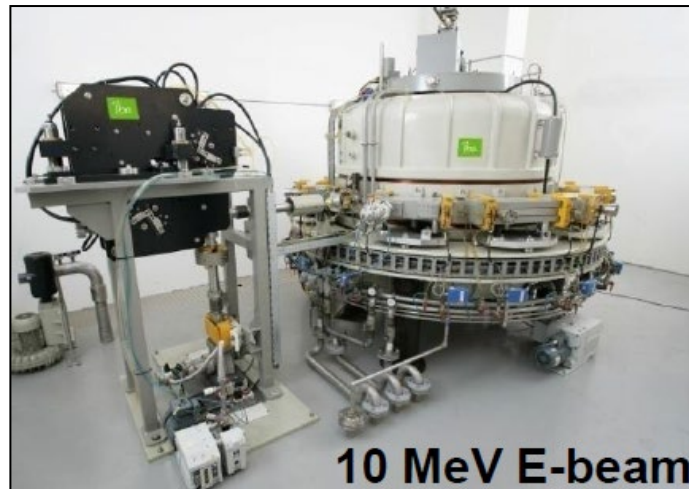
## Electron Beam

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

## Beam energy

Speed of the electrons. Parameter related to depth of penetration

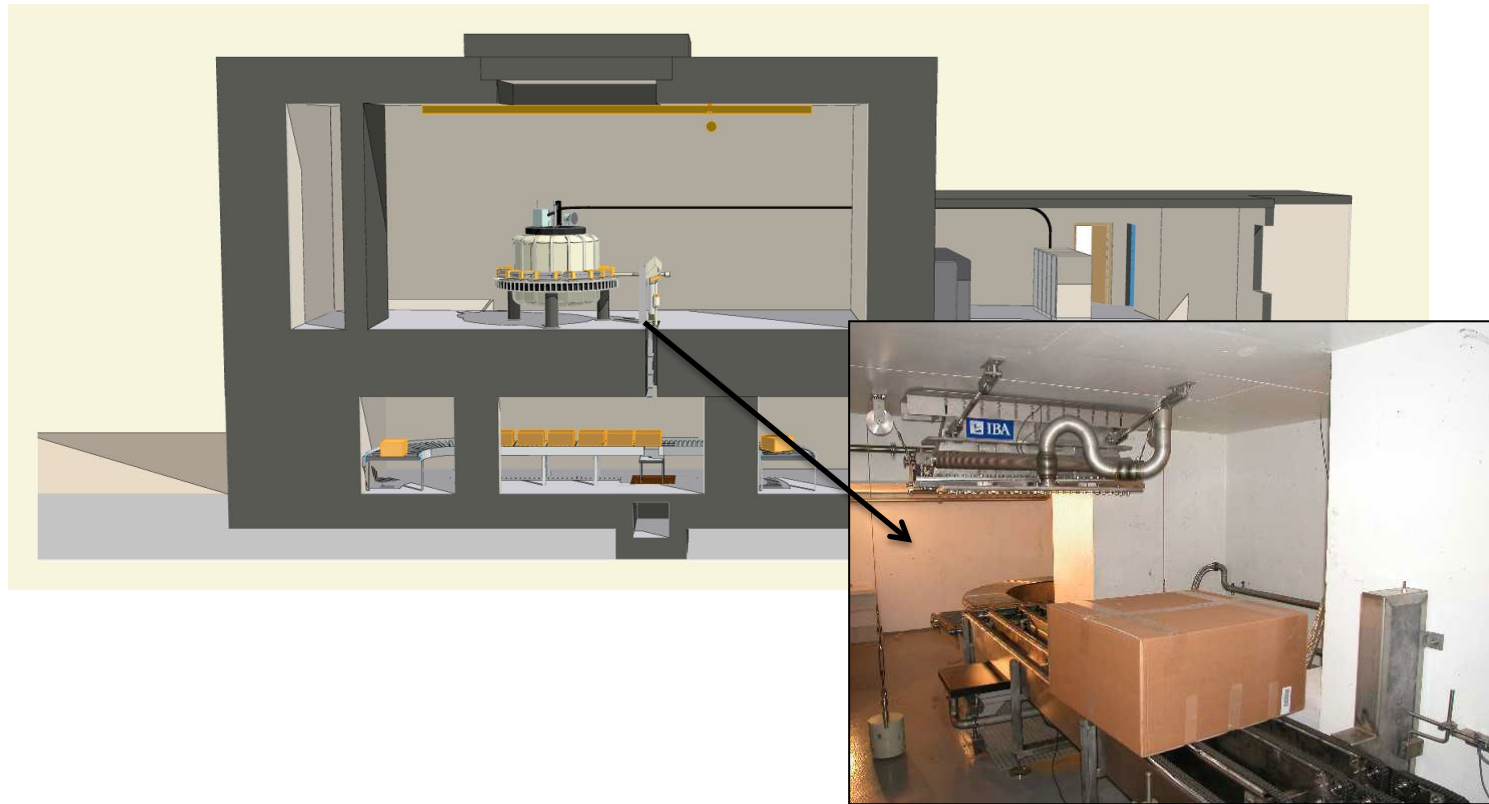
Limited to 10 MeV for medical device sterilisation (ISO 11137-1) to avoid radioactivity induced in product



IBA Rhodotron

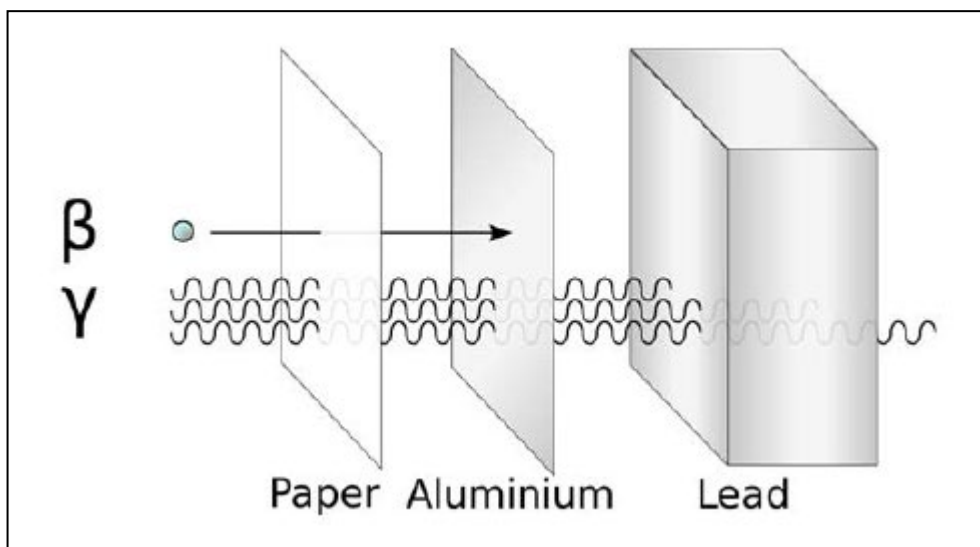
# Sterilization by E-Beam

## Layout E-Beam facility



# Sterilization by E-Beam

## Electron Beam & Gamma, Penetration



# Sterilization by irradiation

## Comparison

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

# Sterilization by Irradiation

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



# Sterilization by E-Beam

## Validation principles

### Relevant Standards:

#### ISO 11137-1:2015

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: 2015

Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose

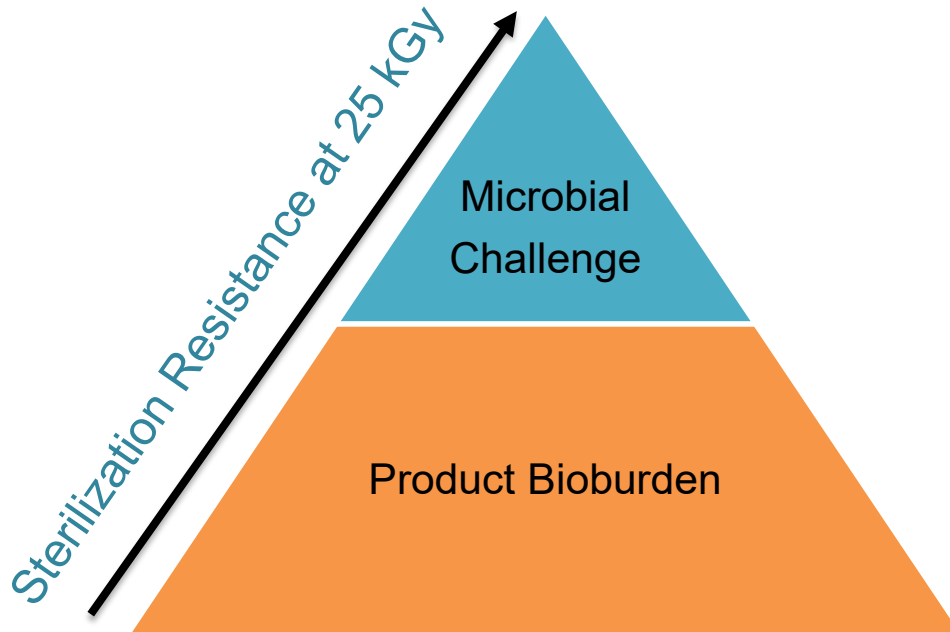
#### GMP – Annex 12

Use of ionising radiation in the manufacture of medicinal products

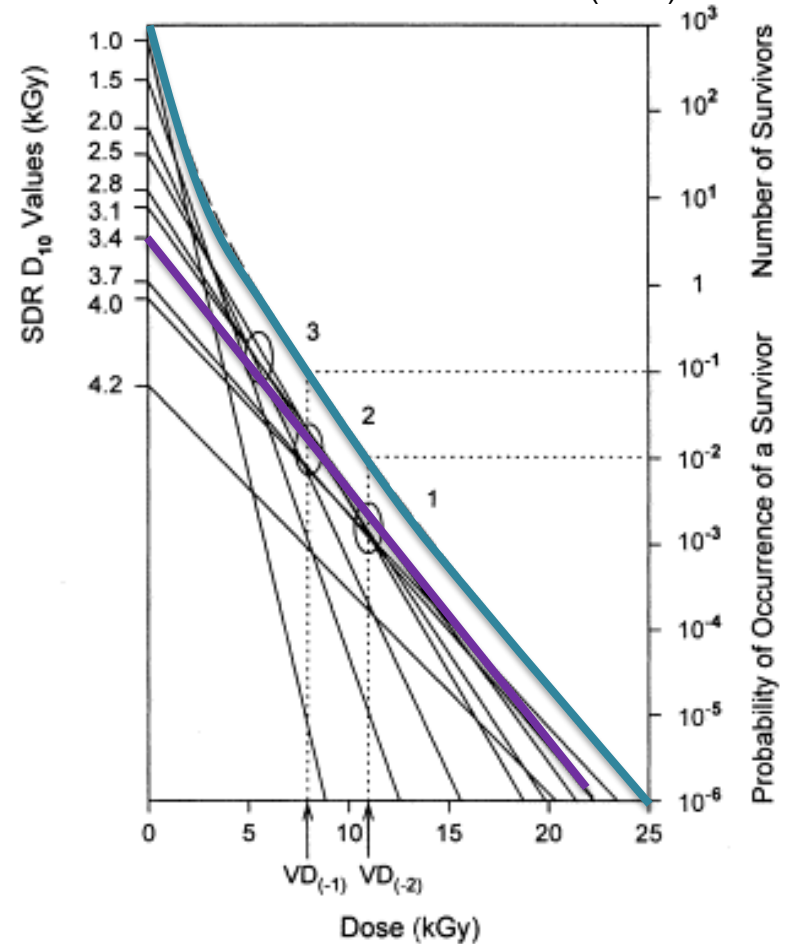
# Sterilization by E-Beam

## Validation principles

Method  $VD_{max}$

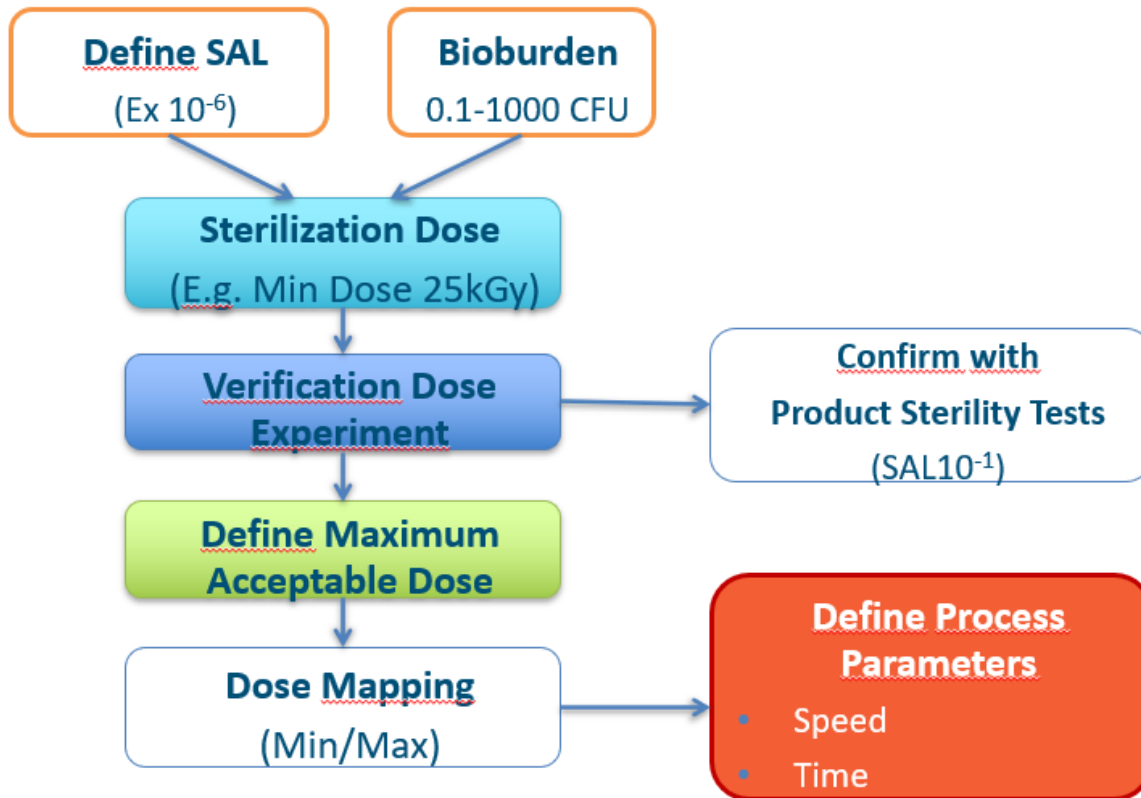


Standard Distribution of resistances (SDR)



# Sterilization by E-Beam

## Validation principles



# Sterilization by Irradiation

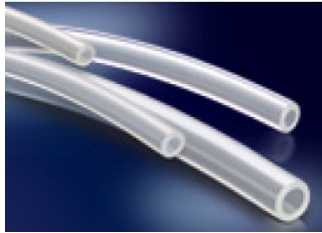
Bioburden is critical parameter in Irradiation technology

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 (implants)



# Sterilization by Radiation

## Validation principles

### Select Sterilization Dose

Method  $VD_{max}$

Example minimum  
Dose to apply related  
to bioburden

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

# Sterilization by Radiation

## Validation principles

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

Bioburden	Verification Dose (kGy)
40	8.6
<b>45</b>	<b>8.7</b>
50	8.8
55	8.9

Verification is conducted at an SAL of  $10^{-1}$  with 10 product items irradiated.

# Sterilization by Radiation

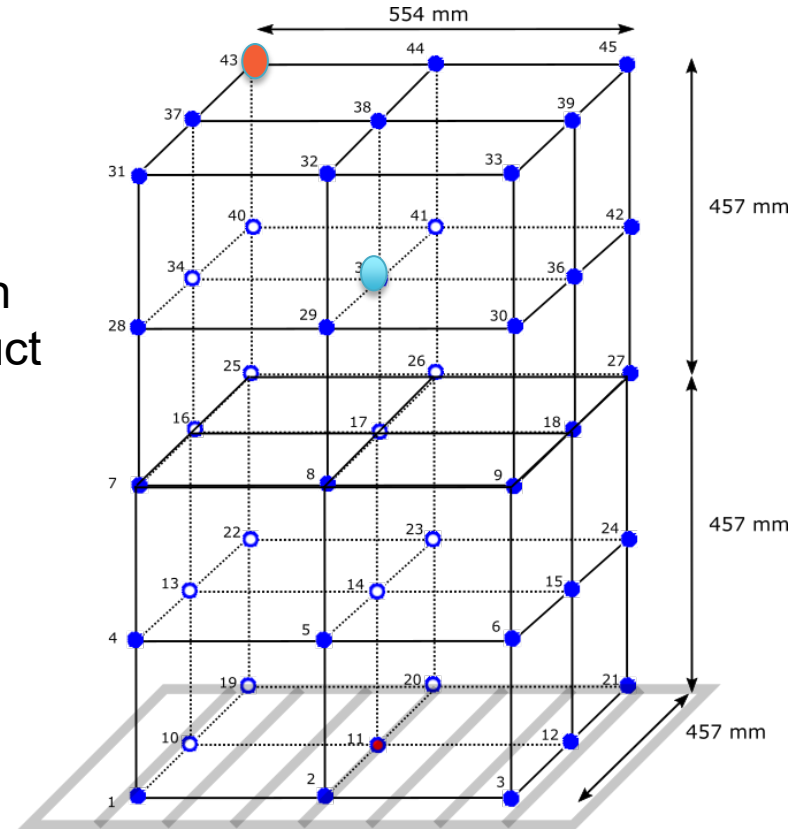
## Validation principles

### 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

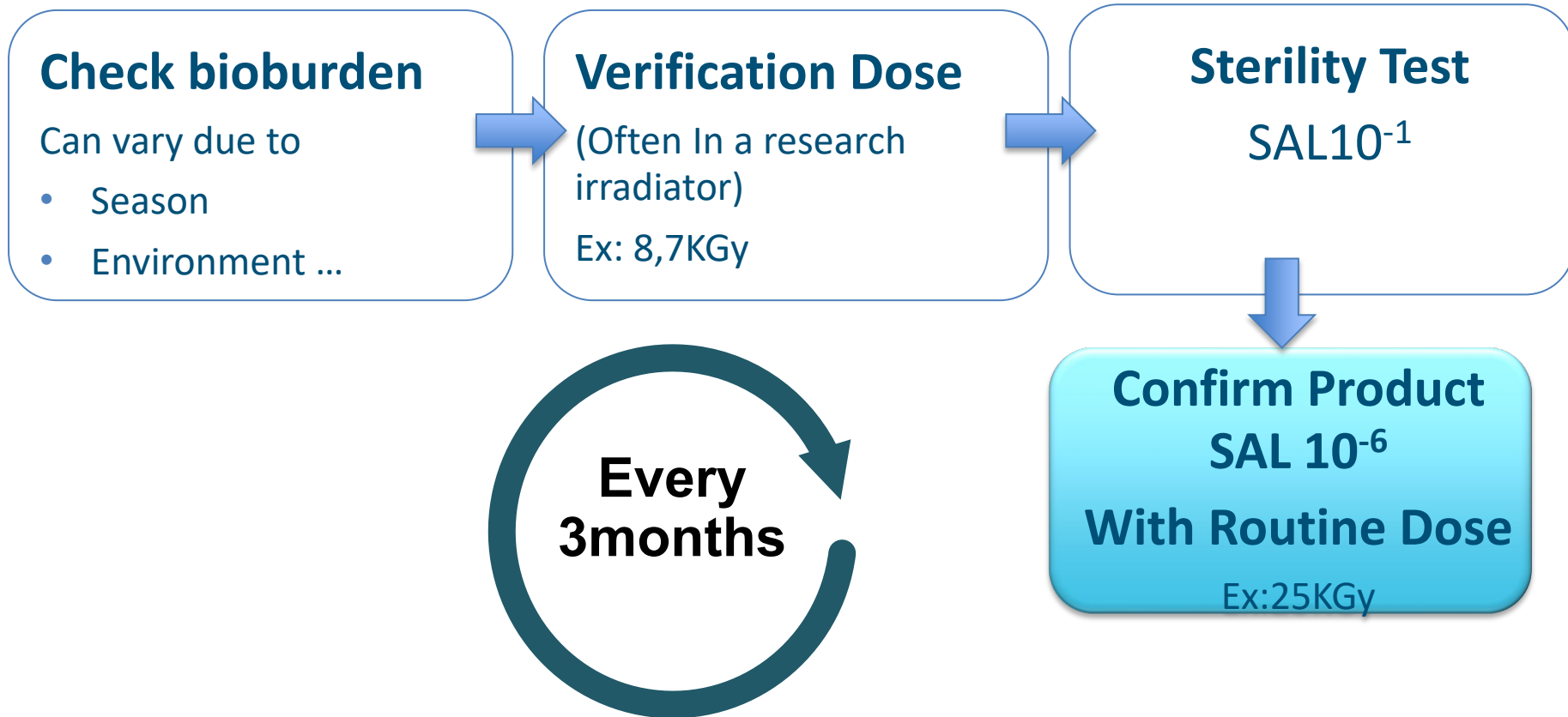
- Min Dose = 28KGy
- Max Dose = 37KGy



# Sterilization by Radiation

## Validation principles

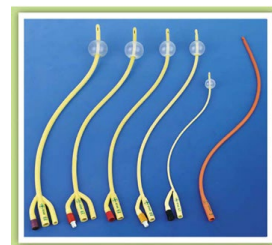
### Quarterly Dose Audit (QDA)





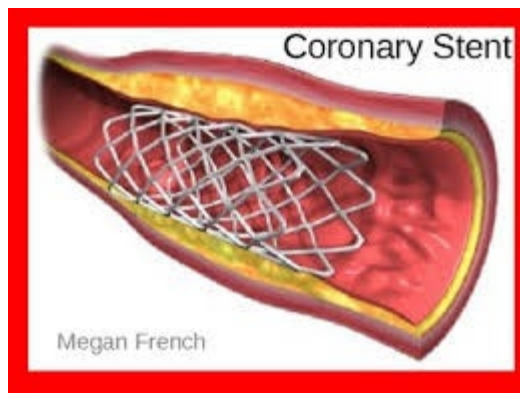
# Sterilization by Radiation

## Examples



# Sterilization by Radiation

... But also



Grafts



API

# Sterilization by Radiation

## Summary

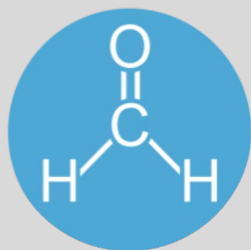
**Minimum & Maximum dose to product shall be defined**

**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



Ethylene Oxide discovered

Charles Wurz

1859



First production of Ethylene Oxide

Union Carbide Chemicals

1925



Patent for sterilization of spices

Lloyd Hall

1938



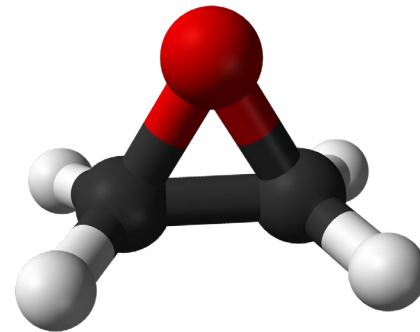
Use in sterilization of materials

1940

# Sterilization by Ethylene Oxide

## Mode of Action

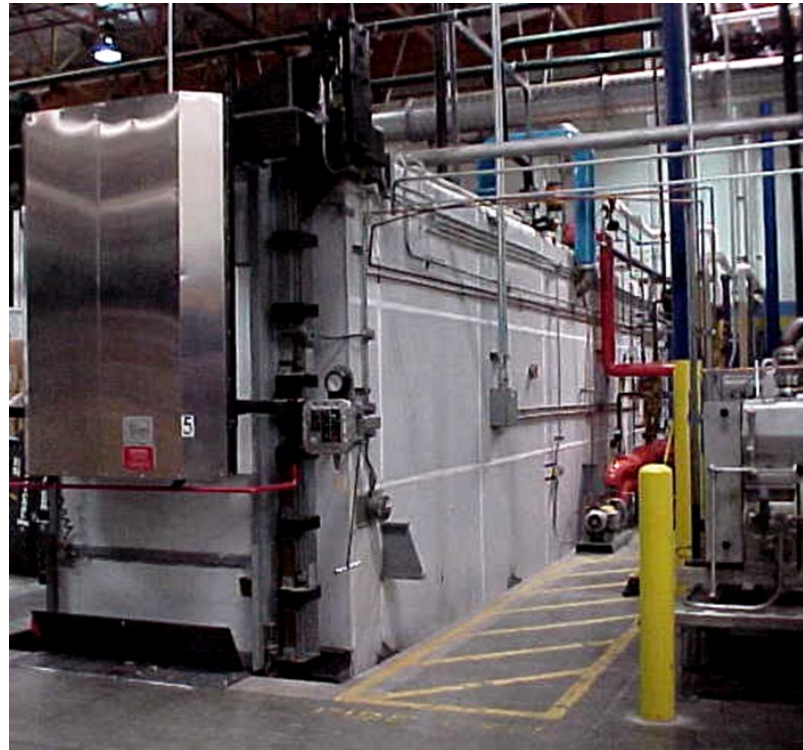
- Extremely reactive
- Irreversible reaction with DNA and proteins (alkylation)
  - The molecule is loses function
  - Replication stops
  - The cell dies



# Sterilization by Ethylene Oxide

## Mainly used to sterilize:

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



# Sterilization by Ethylene Oxide

## 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)





# Sterilization by Ethylene Oxide

## Customer Needs To Define

Product  
Families/Processing  
Categories

Finalize Packaging

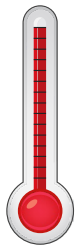
Load Configuration

Bioburden

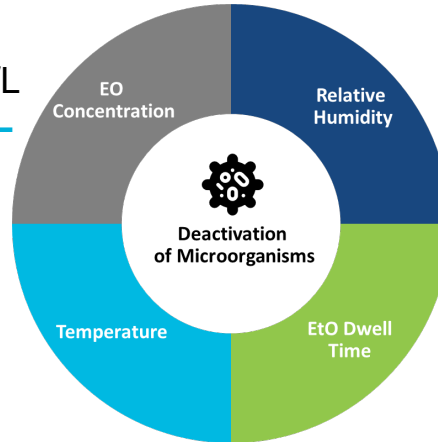
Internal PCD

# Sterilization by Ethylene Oxide

## Key Parameters



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



Necessary for **alkylation reaction**  
EO is most effective at **RH > 30%**



**Microbiological deactivation**  
is more effective with longer  
gas dwell phase (**Industry cycles** typically 3-4 hours)

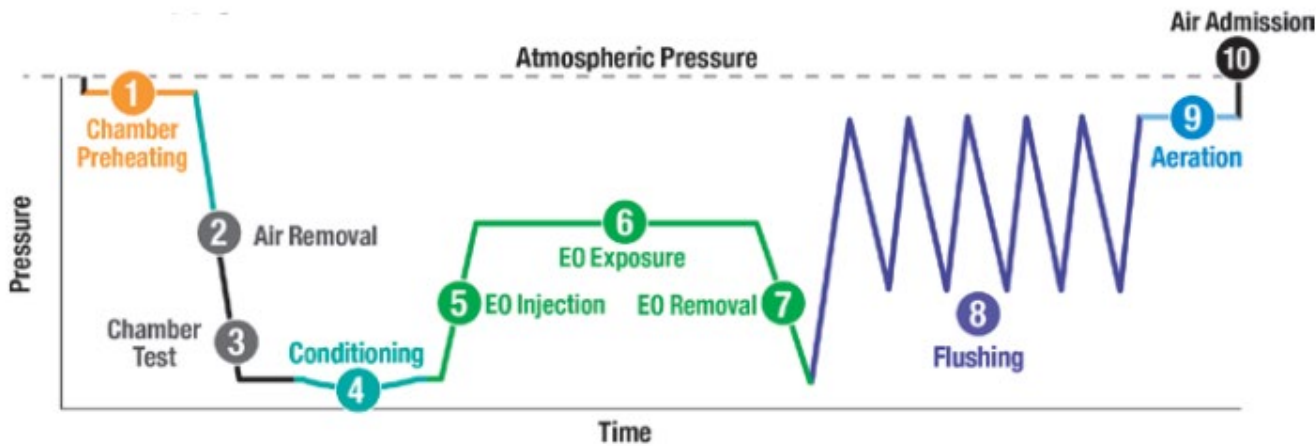


## 3-Step Process



# 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



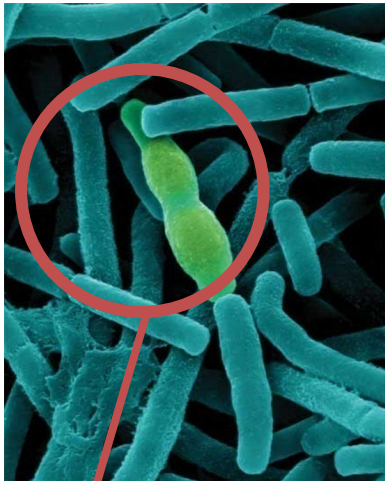
We have set a goal to reduce the amount of EO by

} **↓50%**

# Sterilization by Ethylene Oxide

## Monitoring EO Sterilization - Biological Indicators

- Usually, the BI contains at least a million spores (>10<sup>6</sup>) of an organism that is highly-resistant to the EO process (*Bacillus atrophaeus*)
- Growth is very characteristic (orange ring)



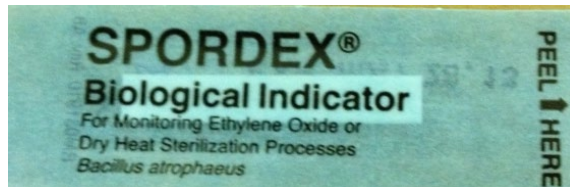
Spore

# Sterilization by Ethylene Oxide

## Process Challenge Device (PCD)

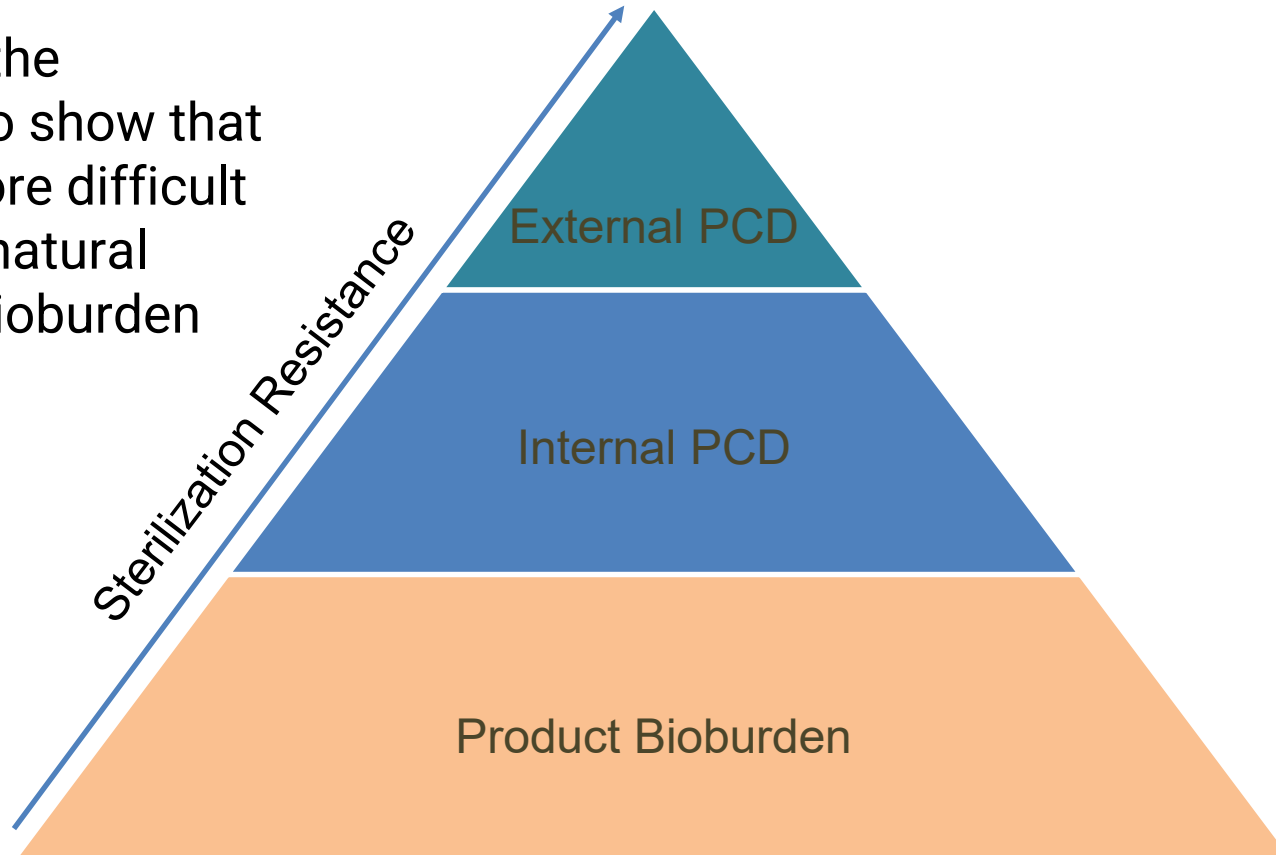
**Item designed to constitute a defined resistance to the sterilization process and used to assess performance of the process**

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



# Sterilization by Ethylene Oxide

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



# Sterilization by Ethylene Oxide

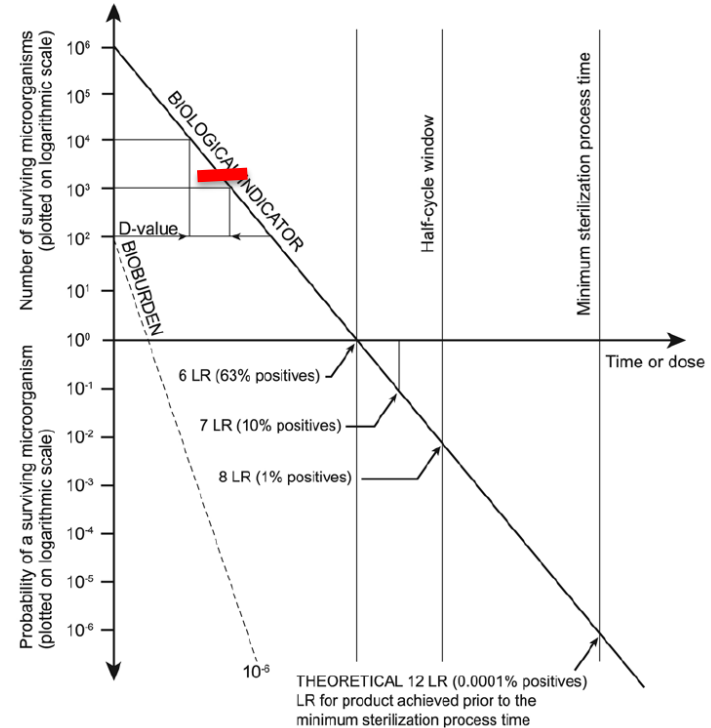
## D Value

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



$$\leq 10^{-6}$$

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



# Sterilization by Ethylene Oxide

## Validation principle

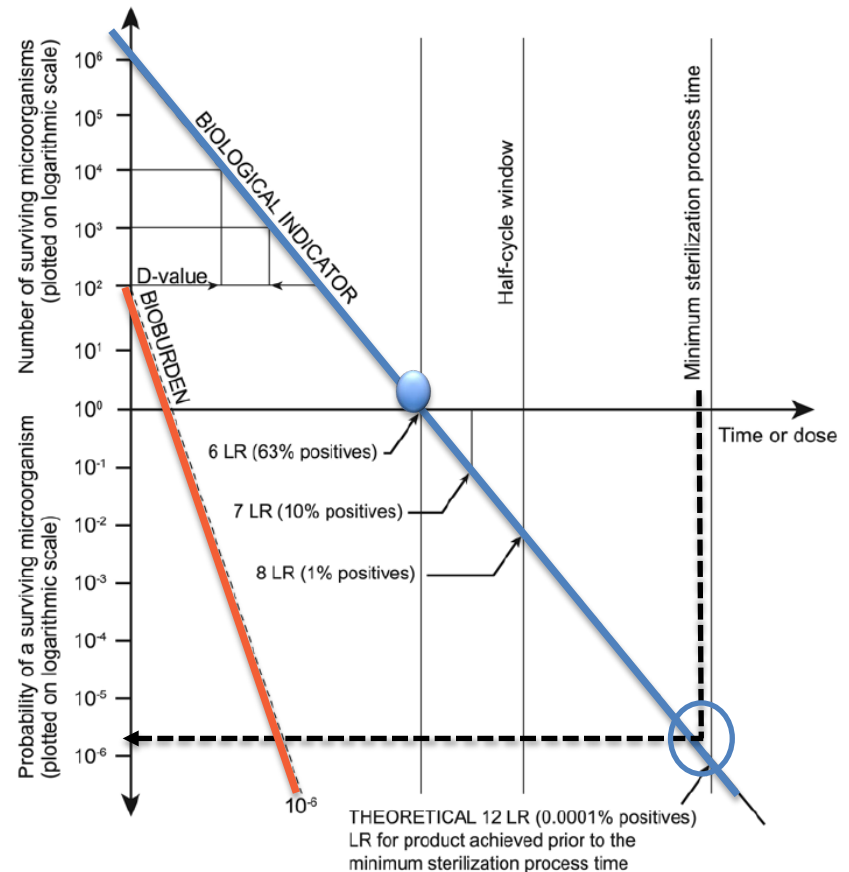
## Level of Sterility Assurance

*Example:*

$$D_{value} \text{ IPCD} = 15 \text{ min} = 1 \text{ LR}$$

$$6 \text{ LR} = 90 \text{ min (Half cycle)}$$

$$12 \text{ LR} = 180 \text{ min (Full cycle)}$$





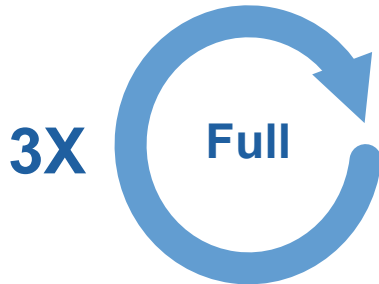
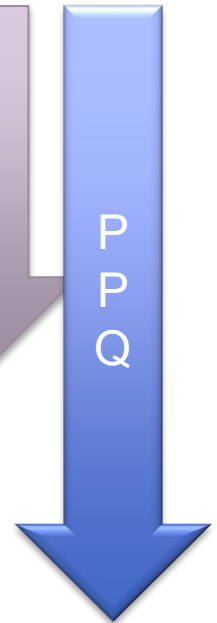
# Sterilization by Ethylene Oxide



- Establish Product/IPCD  $D_{\text{Value}}$
- Product Natural bioburden killed
- Define Challenges (IPCD -EPCD)

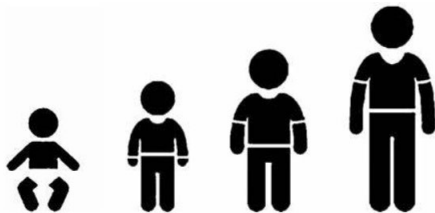
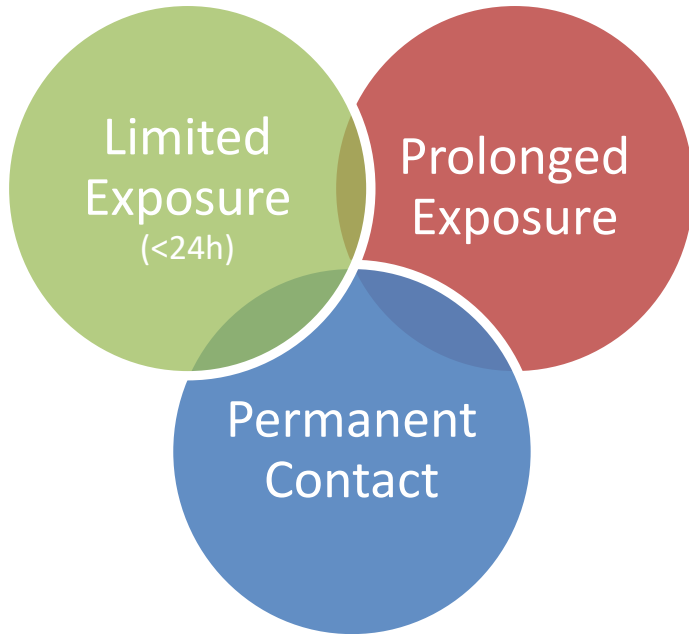


- Confirm IPCD selection ( $SAL \leq 10^{-1}$ )
- Confirm External Challenge (EPCD)



- $SAL \leq 10^{-6}$
- Aeration validation - Residue Tests

# Sterilization by Ethylene Oxide Residues

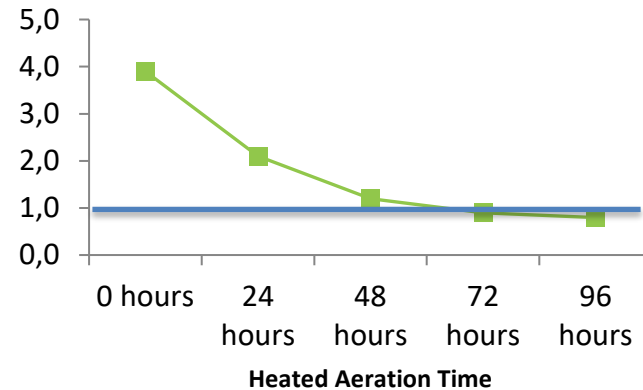


Body mass to consider (Amd1:2019)

Compounds that remain on product after EO sterilization:

- Ethylene Oxide (EO)
- Ethylene Chlorohydrin (ECH) = EO + HCL
- Ethylene Glycol (EG) = EO + H<sub>2</sub>O

Reference : **ISO 10993-7:2008** “Biological Evaluation Of Medical Devices-Part 7: Ethylene Oxide Sterilization Residuals”



# Sterilization by Ethylene Oxide

## Residue Limits for Pharma

### Raw materials /Finished product

- Ethylene oxide: 1 µg/g
- Ethylene chlorohydrin (or any other halogenated ethylenehydride): 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 ethylenehydride): 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*

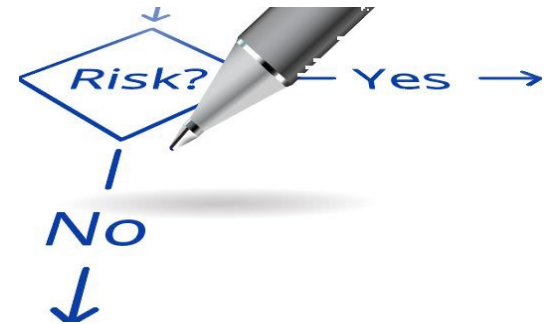


# Sterilization by Ethylene Oxide

## 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

## Medical Devices



Surgery packs



Catheters



vials



Bandages

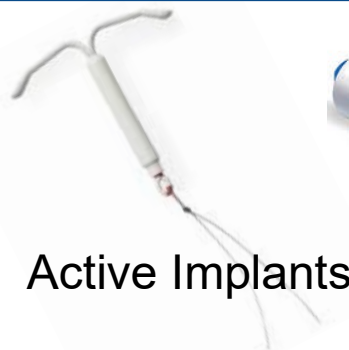
## Drug products



API



Prefilled syringes  
(external)



Active Implants

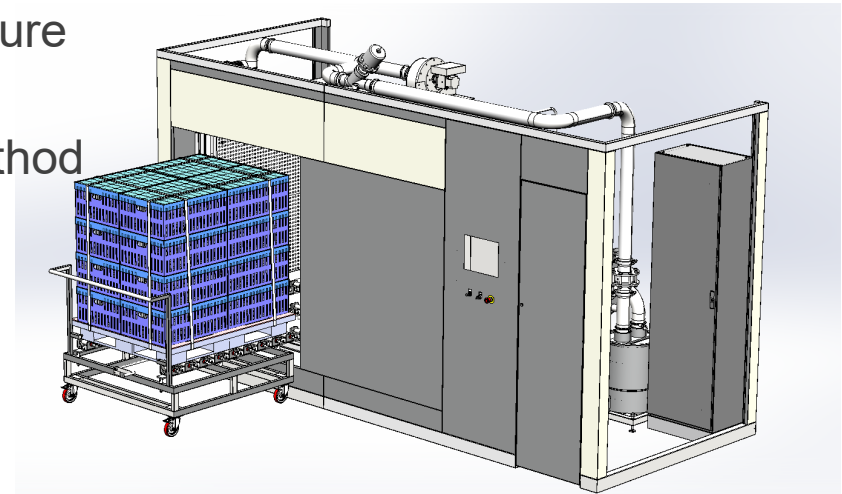


Auto-Injector  
(external)

# NO<sub>2</sub> Sterilization

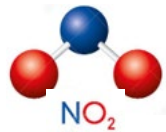


- **Surface sterilization** (Drug-delivery devices, Orthopaedic implants, implantable sensors )
- **Short** process time (2-4hours).
- **Safe** and simple to use: non-flammable, non-explosive and non-carcinogenic
- Wide variety of **compatible materials** (if not cellulose based)
- Allows processing of moisture/temperature **sensitive materials**
- Validation with the NO<sub>2</sub> Sterilization method follows **ISO 14937**
- **Low residuals**
- Small volume – Scale up ?

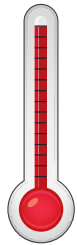


# NO<sub>2</sub> Sterilization

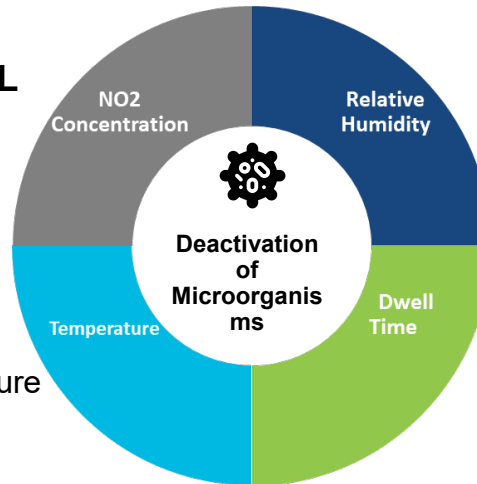
## Key Parameters



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



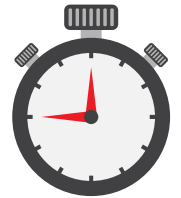
**Industrial sterilization**  
performed in 20-25°C temperature  
range



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



# Comparison

## Radiation and Gas sterilization

Parameter	Gamma or X-Ray	E-Beam	EO	NO2
<b>Process</b>	Individual product, box, tote, pallet	Boxes	Pallets – High Volume	Plastic Tote 1 pallet
<b>Material compatibility</b>	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)
<b>Validation</b>	Straightforward	Straightforward	Complicated	Complicated
<b>Validation principle</b>	Based on bioburden	Based on bioburden	Based on Bio Indicators or bioburden	Based on Bio Indicators
<b>Requalification</b>	Every 3 months (QDA)	Every 3 months (QDA)	Every 2 years (1 cycle)	Every 2 years (1 cycle)
<b>SAL</b>	<10exp6	<10exp6	<10exp6	<10exp6
<b>Residues</b>	None	None	ETO,ECH,(EG)	NO2,NO3



# Selection of the method

Ideas to allow Terminal sterilization:

From:

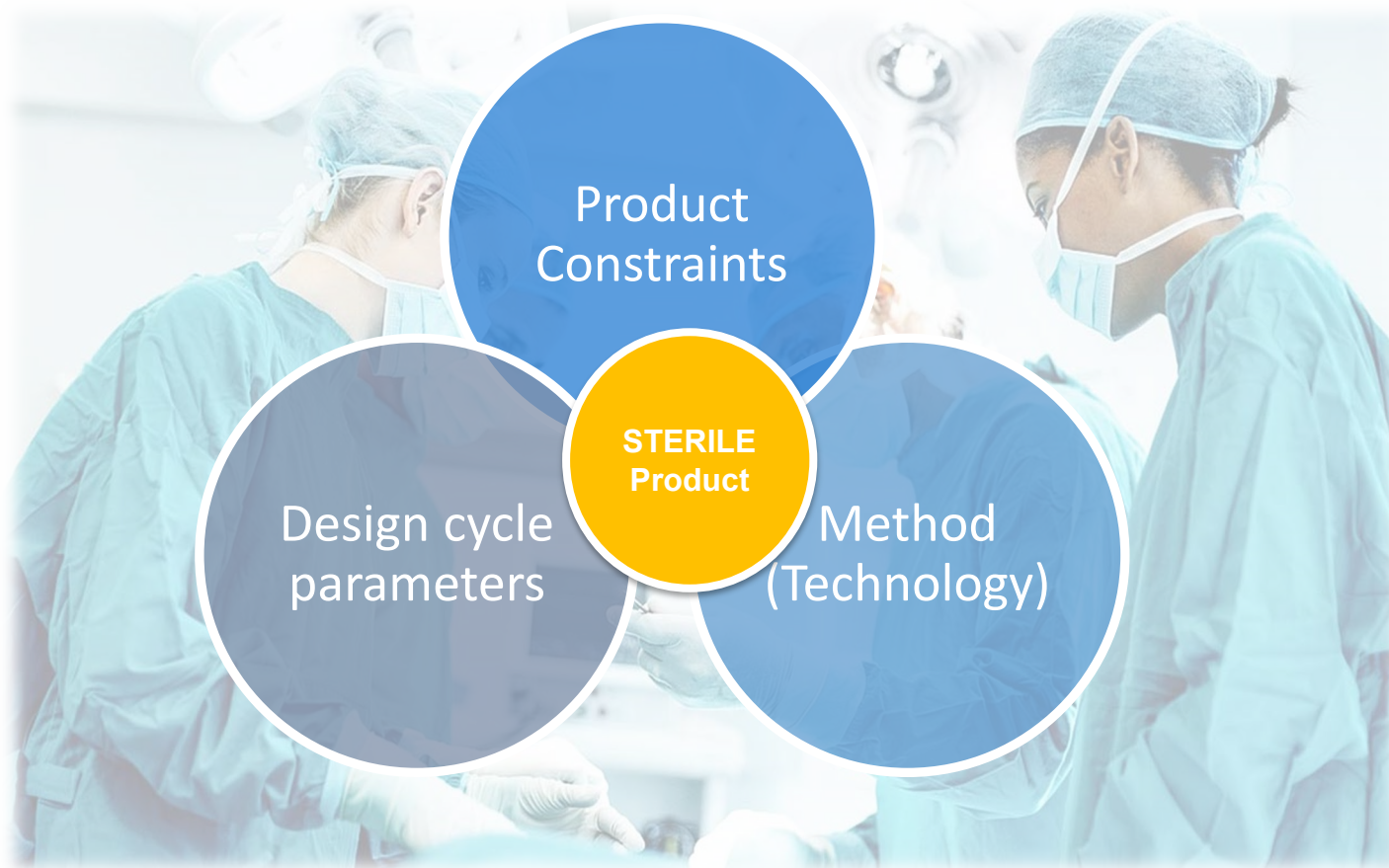
- Steam sterilization  $\geq 121$  °C,  $\geq 15$  min / Dry heat  $\geq 160$  °C,  $\geq 2$  hours
- High sterilisation doses and wide specs (e.g. 25 kGy – 50 kGy)
- “Overkill” approach for EO



To:

- Lower sterilisation doses/exposure based on bioburden
- Steam : F0  $\geq 8$  minutes
- Irradiation under Inert atmosphere
- Irradiation in cryotainers with dry ice
- shallow vacuum cycle in EO
- Higher SAL ( $10^{-4}$ )
- New sterilization technology (NO<sub>2</sub>)?

# Conclusions



# 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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- *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 Amd1 (2019)* 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

- *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<sup>-6</sup>*
- *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 industrial Sterilization of MD and Health care products – GIPA, IIA – 31 Aug 2017*