Sterigenics®
A Sotera Health company

Sterilisation of your Medical device

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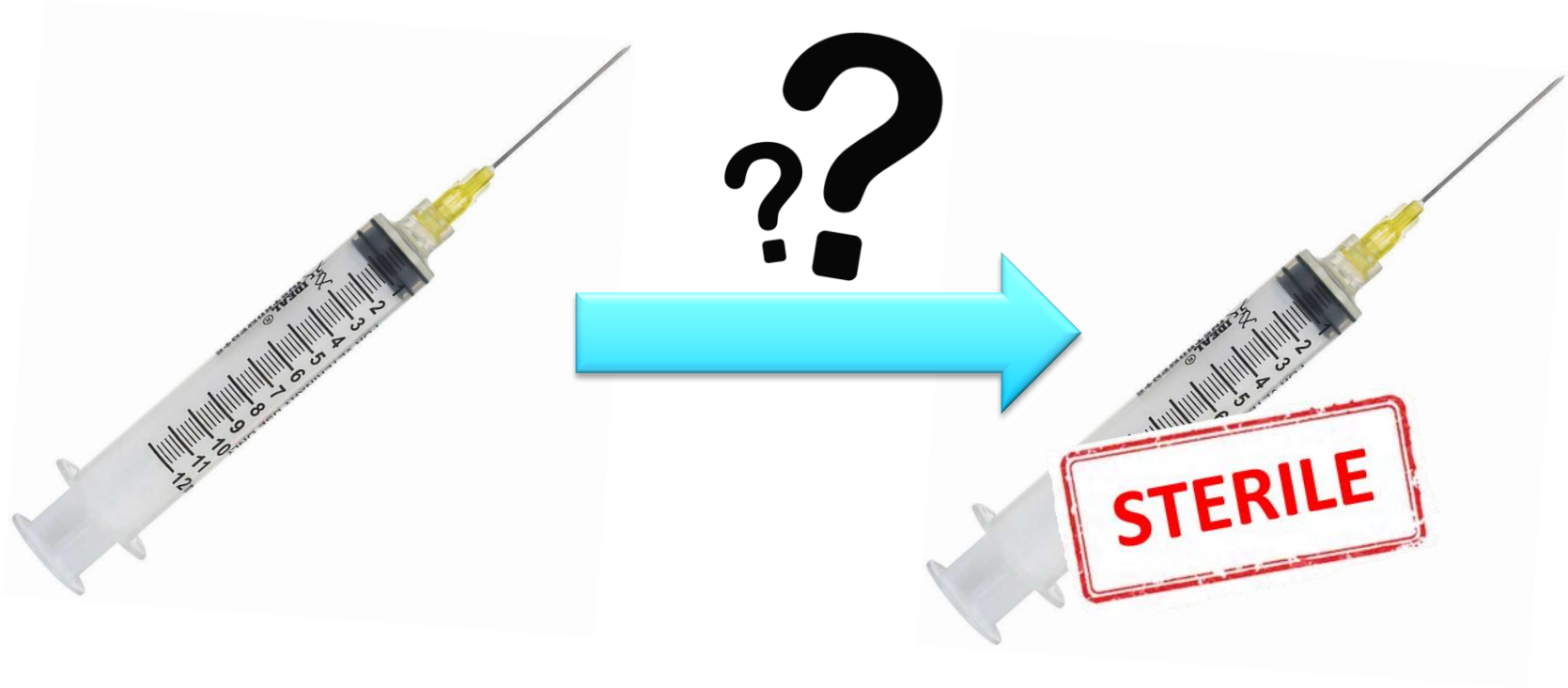
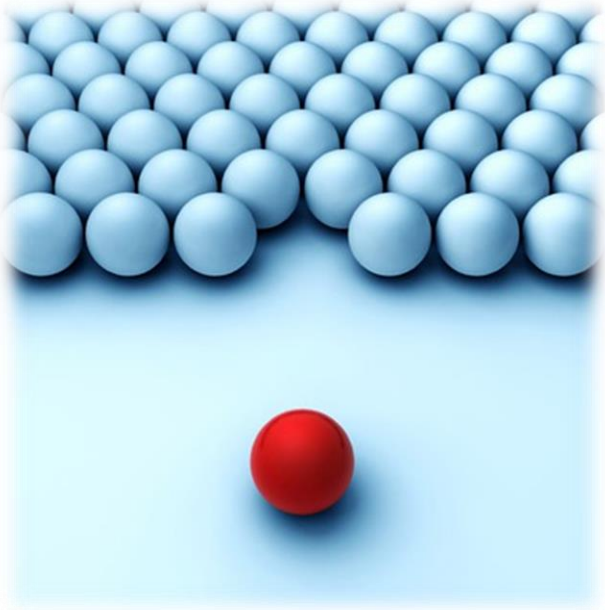
CONFIDENTIAL

What's the difference between these two devices ?



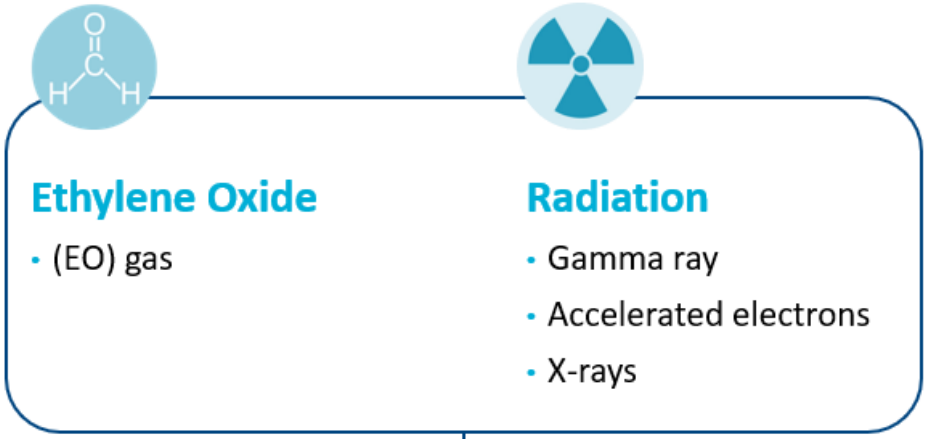
What is the meaning of sterility ?

- **Free from viable microorganisms**.
- Sterility is a **probability** as cannot be proven.
- Products can only be labelled ‘STERILE’ if the chance of an item remaining contaminated after sterilization is **less than to one chance in a million** (SAL $1x10^{-6}$ or less).



How can we obtain a sterile product ?

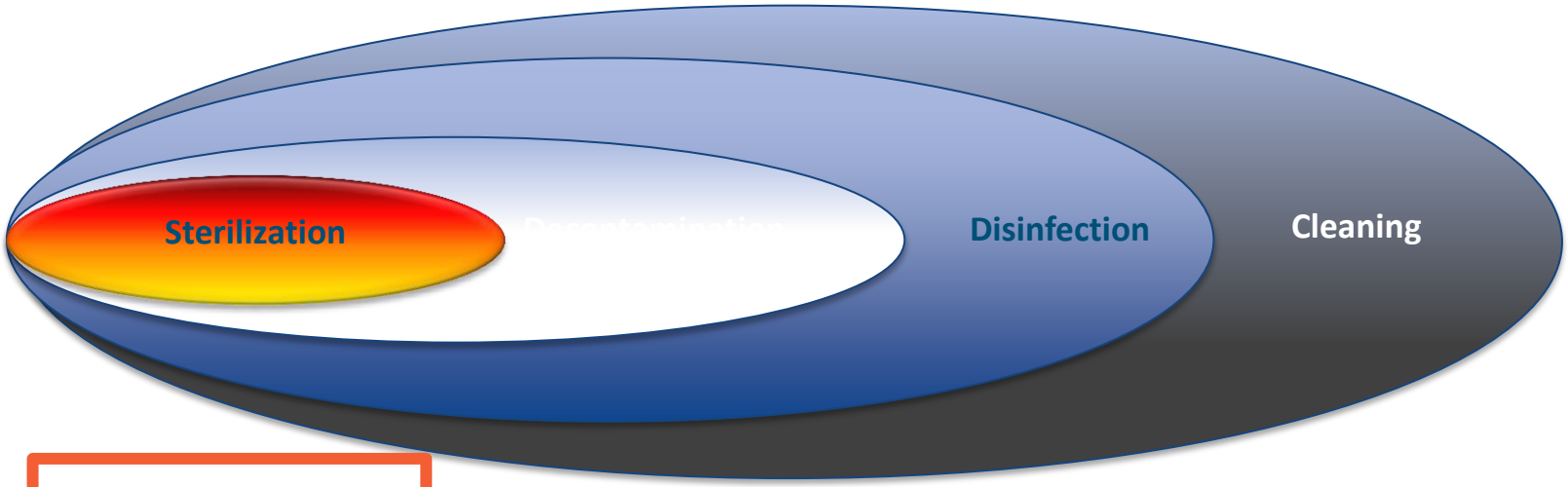
- **Different possibilities**
- The method depends about **the nature of the product** (material, temperature sensitivity …Etc.) and **intended use** (e.g. external, injectable, ophthalmic …Etc.)
- **Heat sterilization** is the most popular method.



Sterilization methods

Sterilization by **Radiation** and by **Ethylene Oxide gas** are the most common methods for **industrial** sterilization of Medical Devices

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*

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

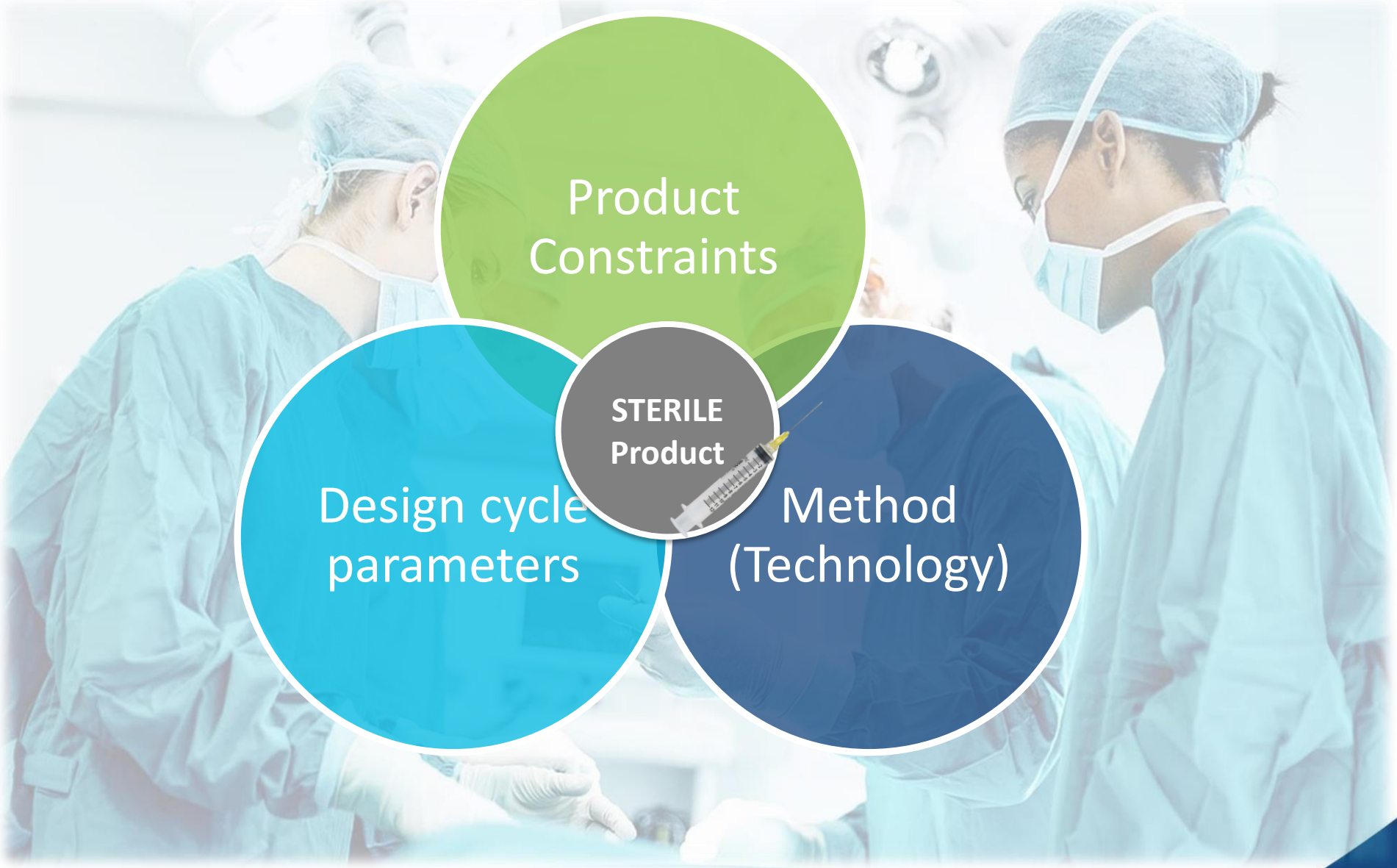
Equipment

- Control
- Maintenance
- Calibration

Product preservation

- Packaging
- Storage

Selection of the Sterilization Method

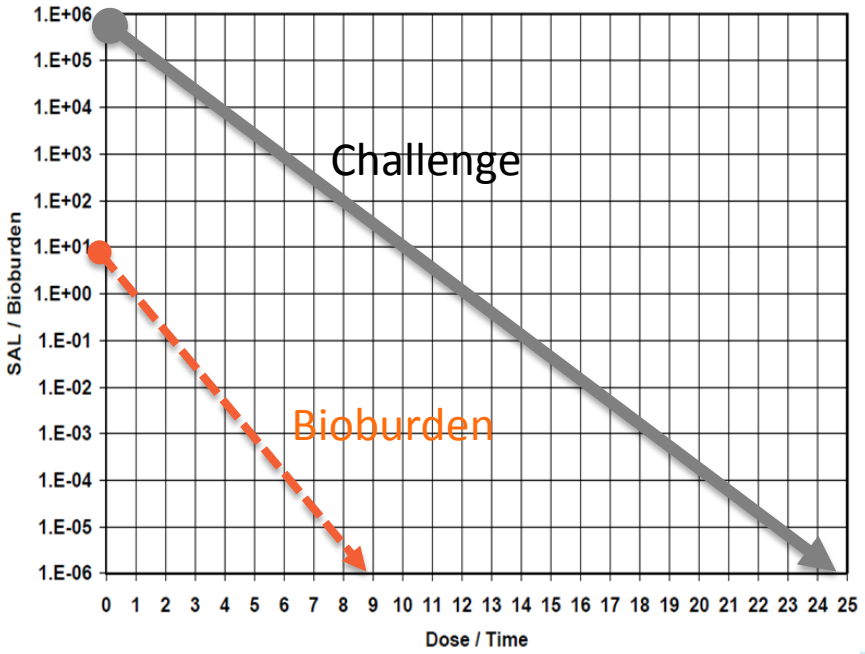


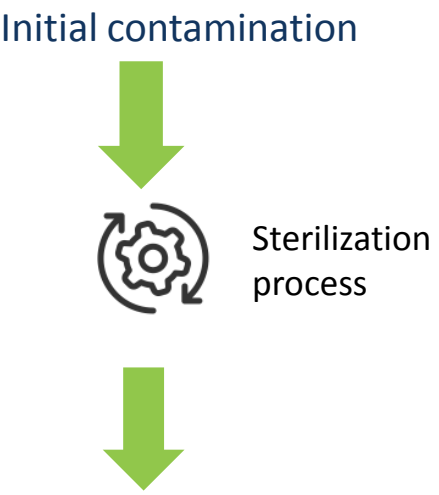
Selection of the Sterilization Method

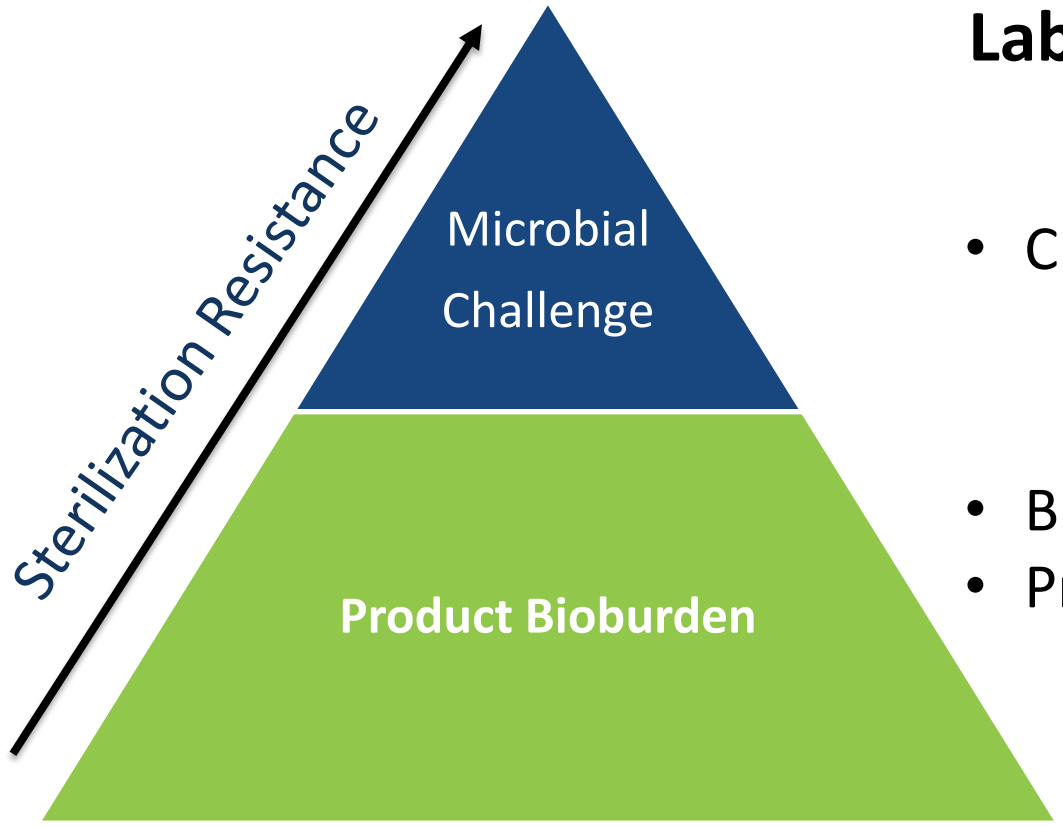
Think about sterilisation process selection up front / early during product development

Terminal Sterilisation

- Linear relationship bioburden/ treatment applied (dose or exposure time)
- Any terminal sterilization process is **validated** based on that assumption
- You can **predict** the required time/dose to achieve a defined SAL







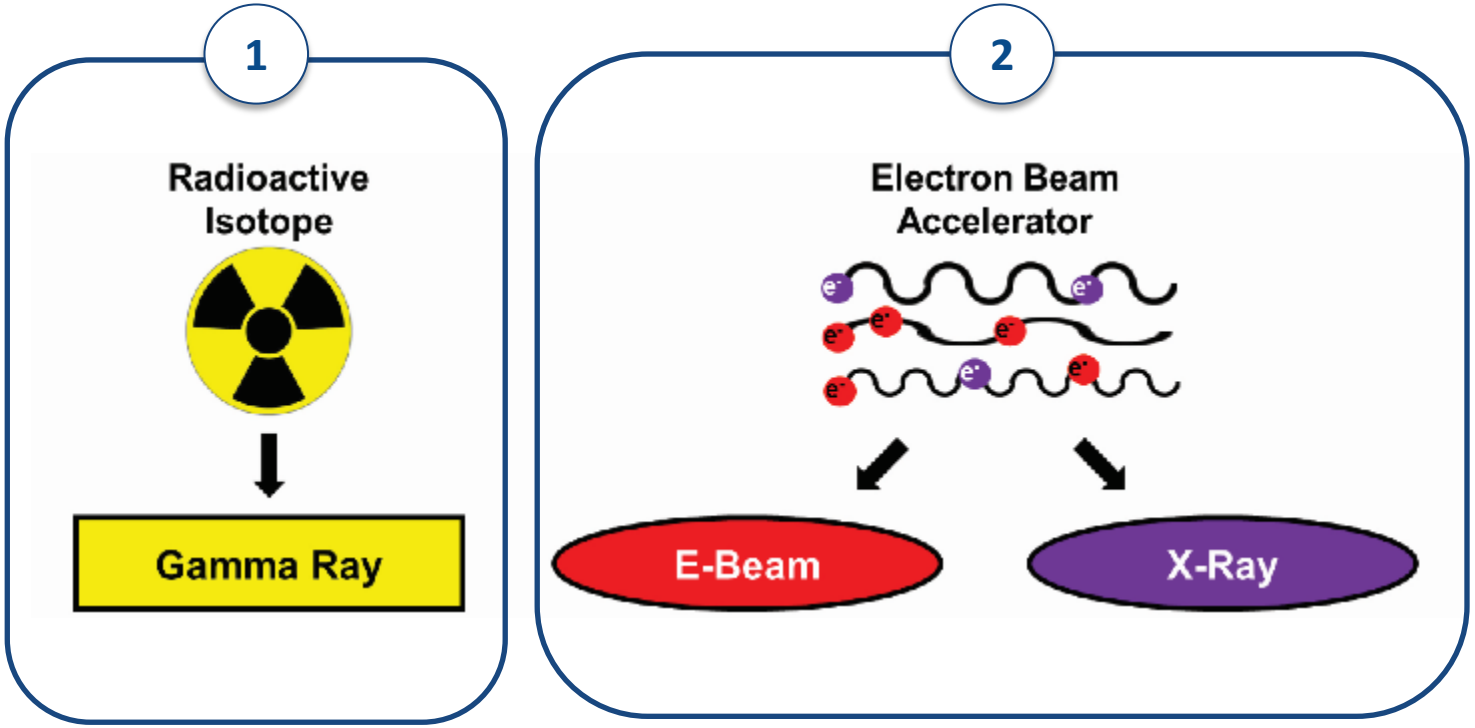
Laboratory Tests:

- Challenge (BI) Sterility test

- Bioburden test
- Product Sterility test

Sterilization by Irradiation

Two methods to generate 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

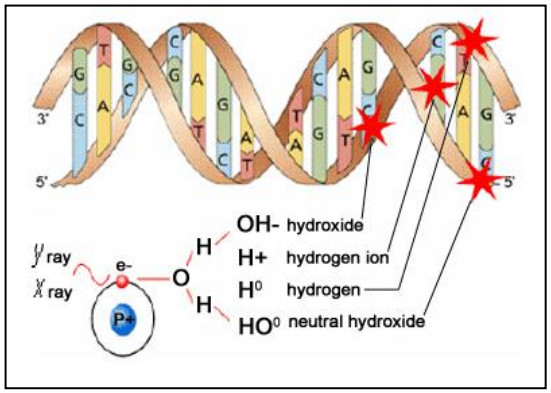
100

Typical chest X-Ray (0,1 mGy)

50

10

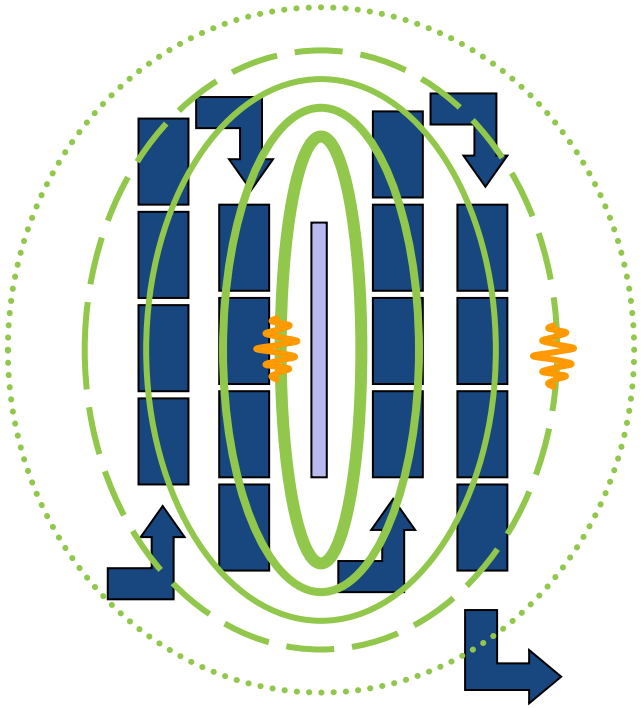
1



Effects of ionizing Radiation on DNA

Sterilization by Irradiation: Gamma

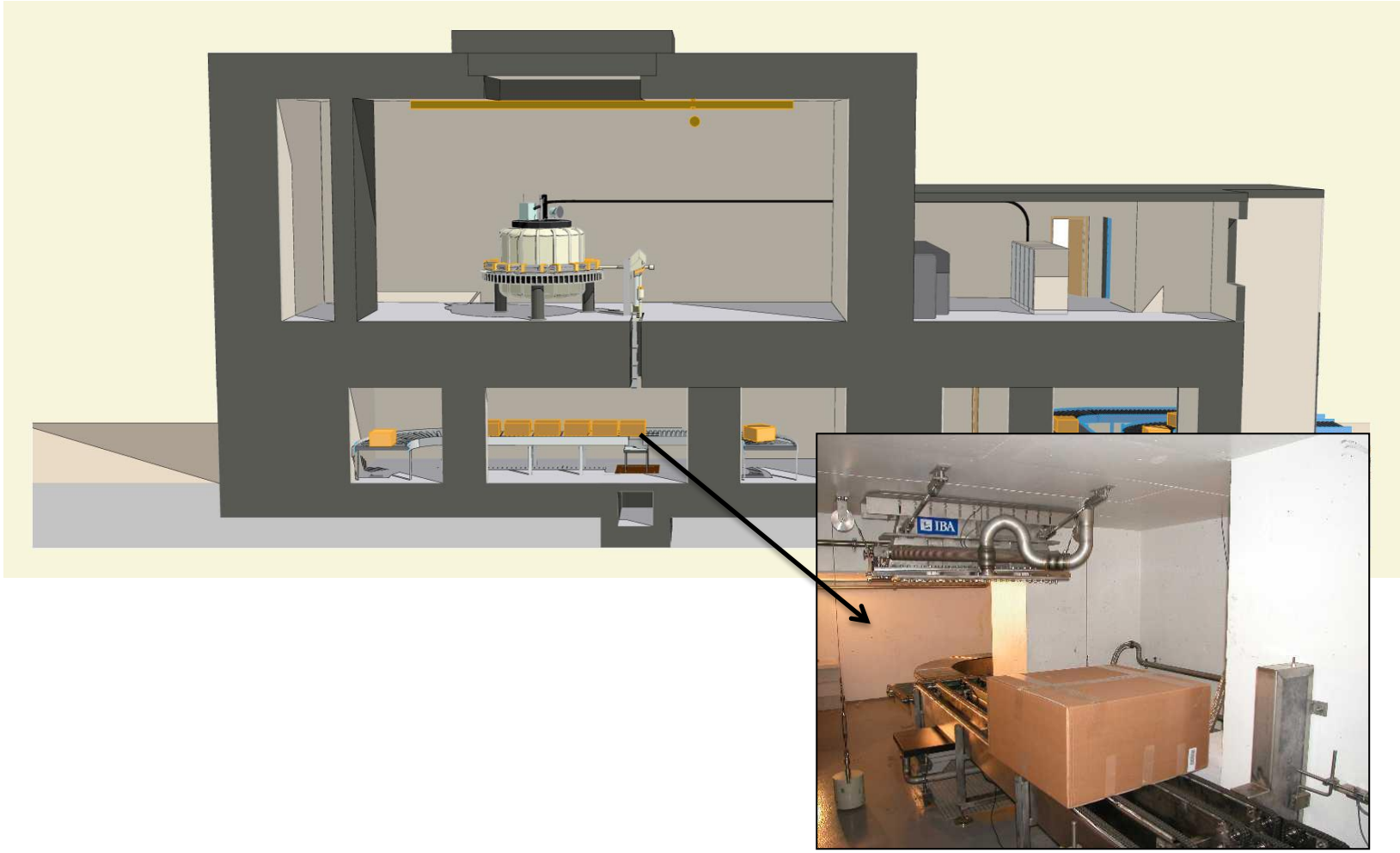
Source: ^{60}Co (mostly)



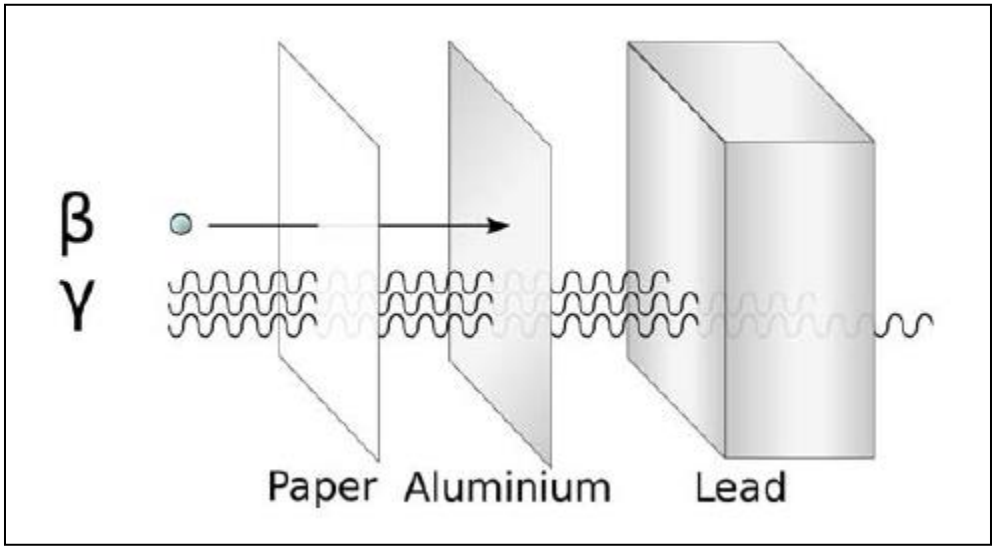
Isotropic radiation flux

Sterilization by Irradiation : E-beam

Layout E-Beam facility

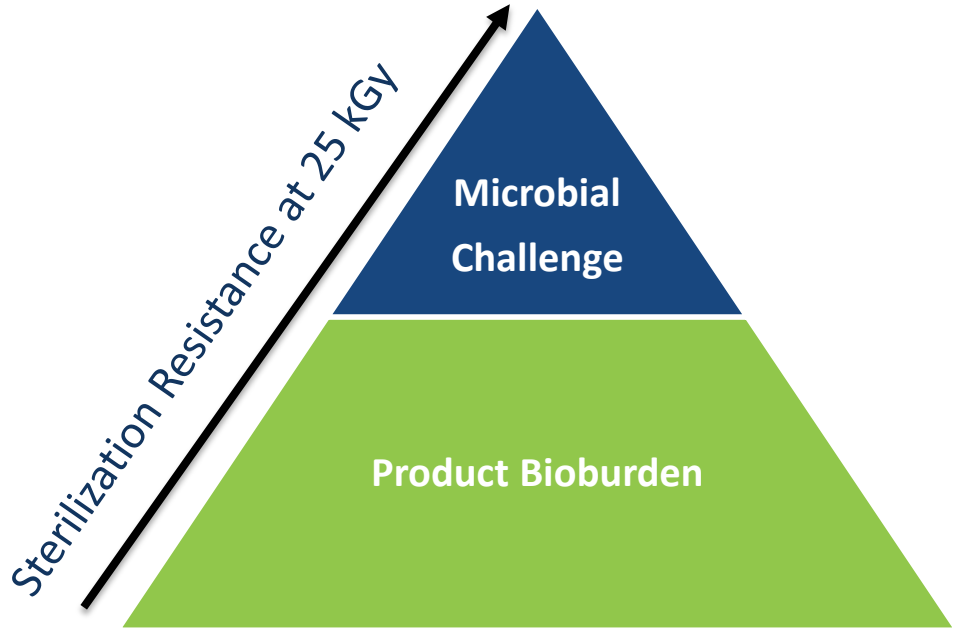


Electron Beam & Gamma, Penetration

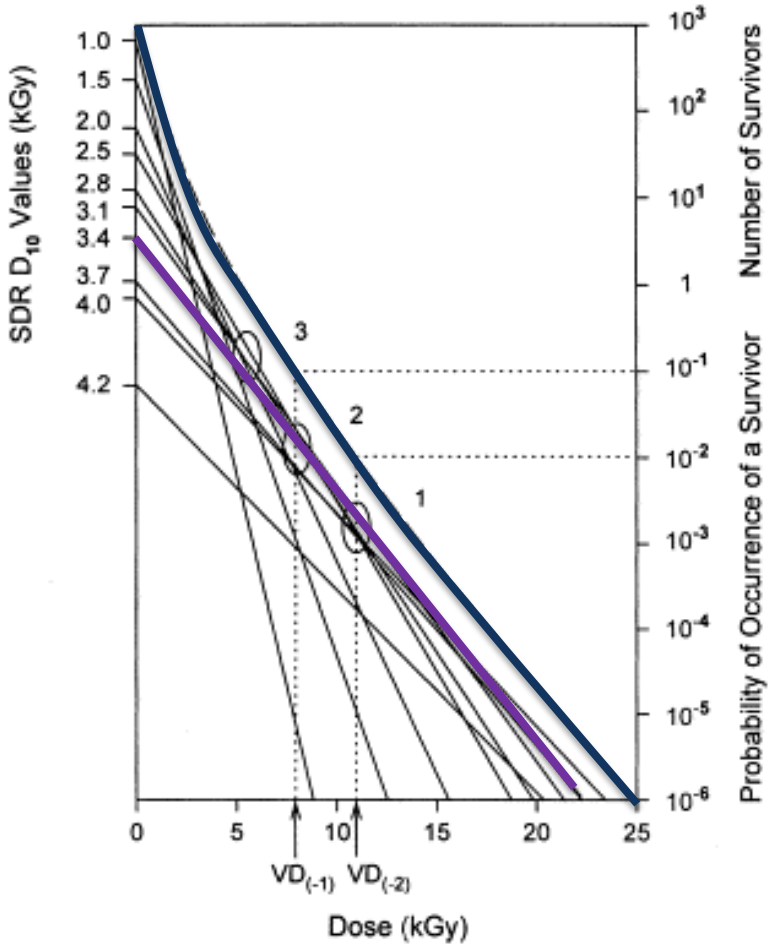


Sterilization by Irradiation

Method VD_{max}



Standard Distribution of resistances (SDR)



Dose Mapping

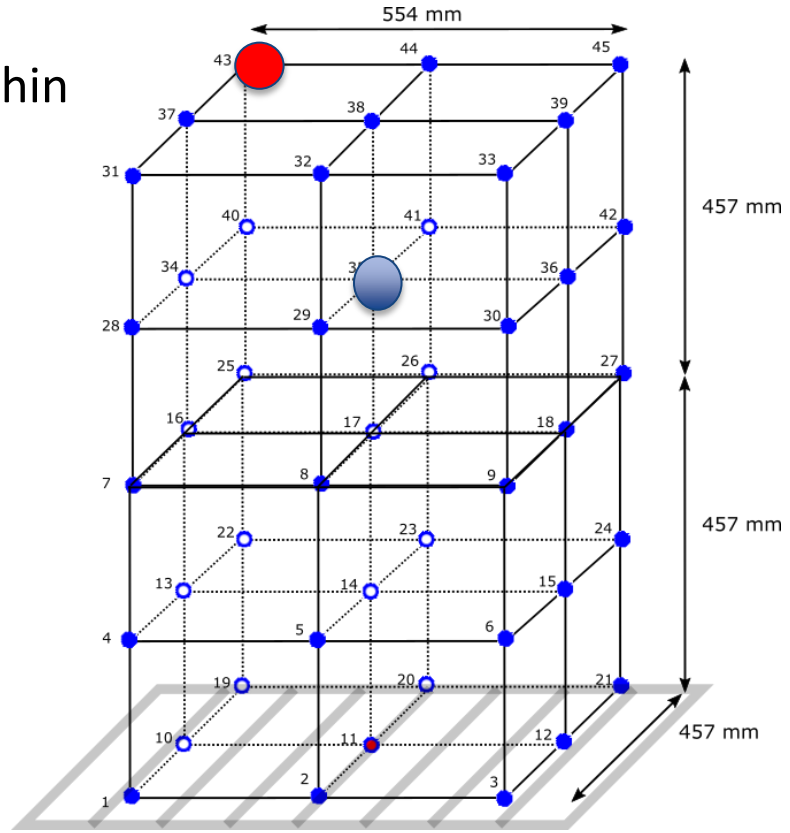
Establish the **distribution of absorbed dose** within the irradiation container when packed with product in a defined configuration

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

Min Dose

Max Dose

Fig.1 Dosimeter



Quarterly Dose Audit (QDA)

Check bioburden

Can vary due to

- Season
- Environment …

Verification Dose

(Often In a research irradiator)

Ex: 8,7KGy

Sterility Test

$SAL10^{-1}$

Every 3 months

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

Ex:25KGy

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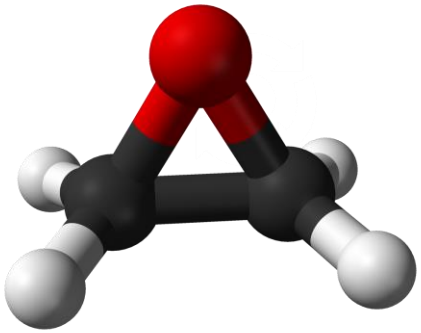
The Ethylene Oxide Sterilization Process

Ethylene Oxide is an **extremely reactive gas** creating irreversible reaction with cells DNA and proteins.

Due to its toxicity and difficulty, this makes this method the **last choice**.

Anyway in regards of modern product complexity, it's still one of the **most commonly used industrial method** for medical devices sterilization.



Sterilization by Ethylene Oxide

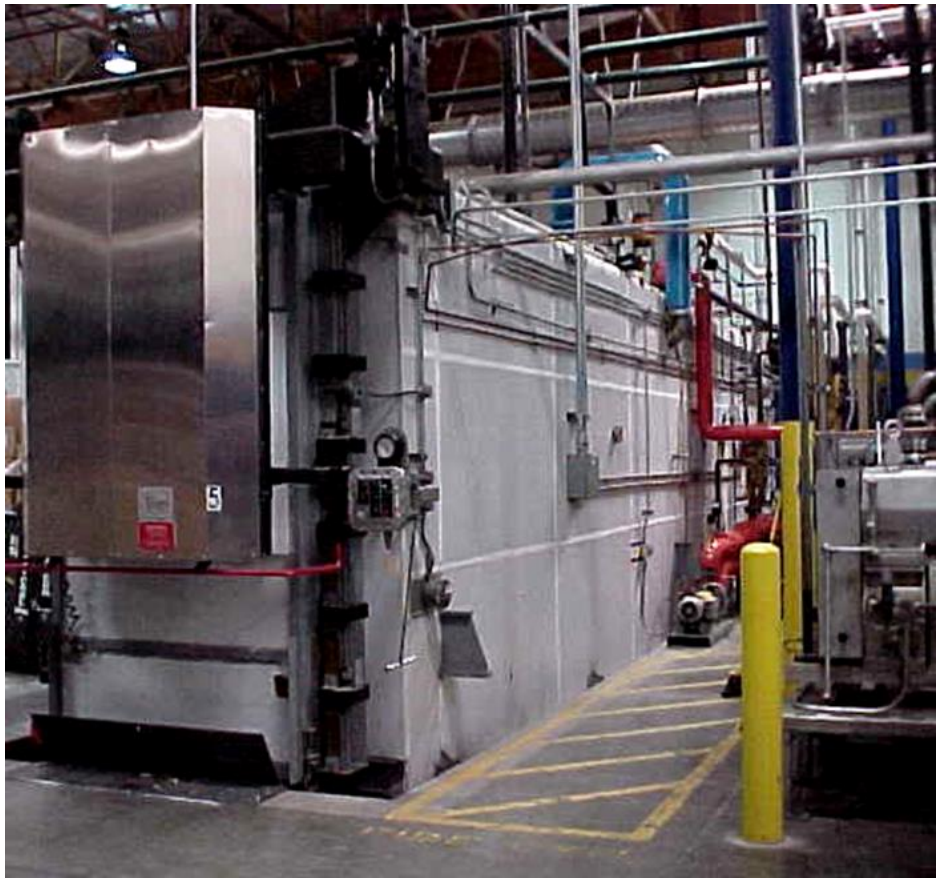


Fig.1 Eto Sterilization Chamber

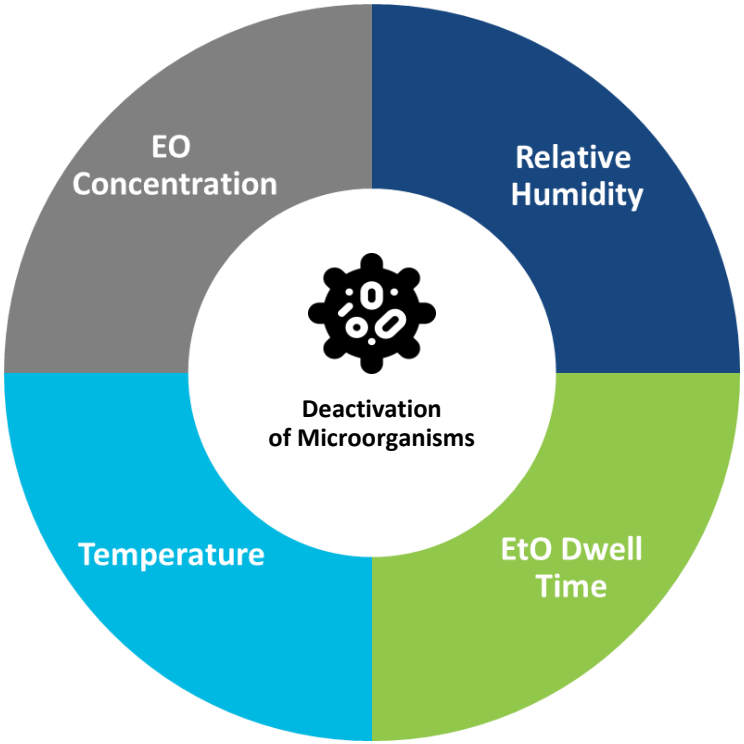
- Product sterilized on pallet
- Different capacity (1 to 32 PL)
- Gouped by family/category

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

There are **4 key parameters** to monitor the process:



A standard cycle is typically running at 50°C, with an exposure time of 3 hours at a concentration of 600mg/L with a humidity around 50%.

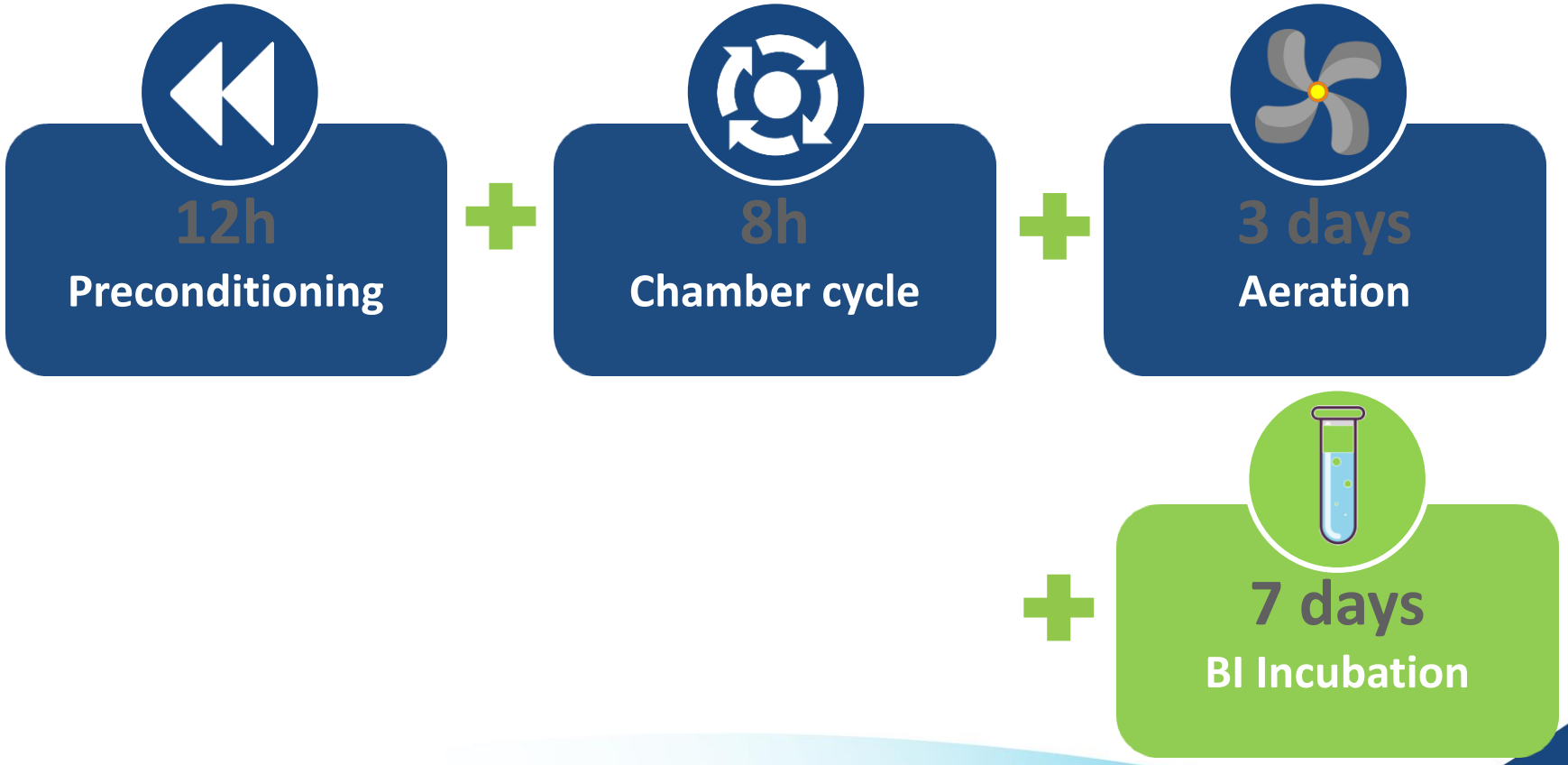
The cycle parameters are **optimized** for each type of product to sterilize.

Sterilization by Ethylene Oxide

The sterilization process has 3 key phases:

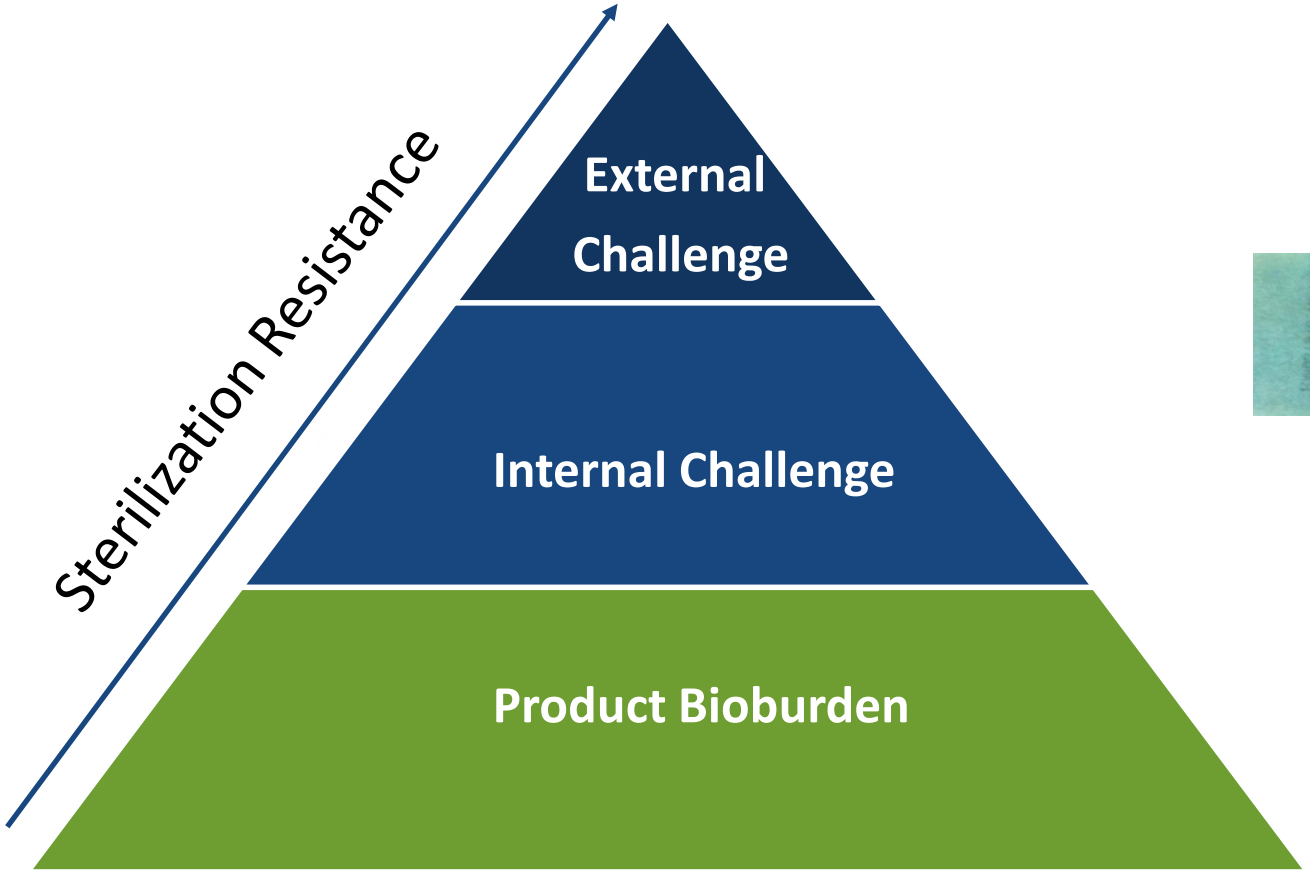
The main challenge is getting the product **sterile**, **effective** with an acceptable level of **EO gas residues**

In total the sterilization process takes approximatively **4 days** in parallel with **7days** incubation for the BI:



Monitoring EO Sterilization – Biological Indicators

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



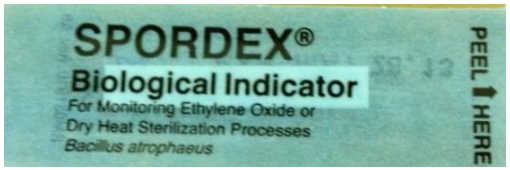


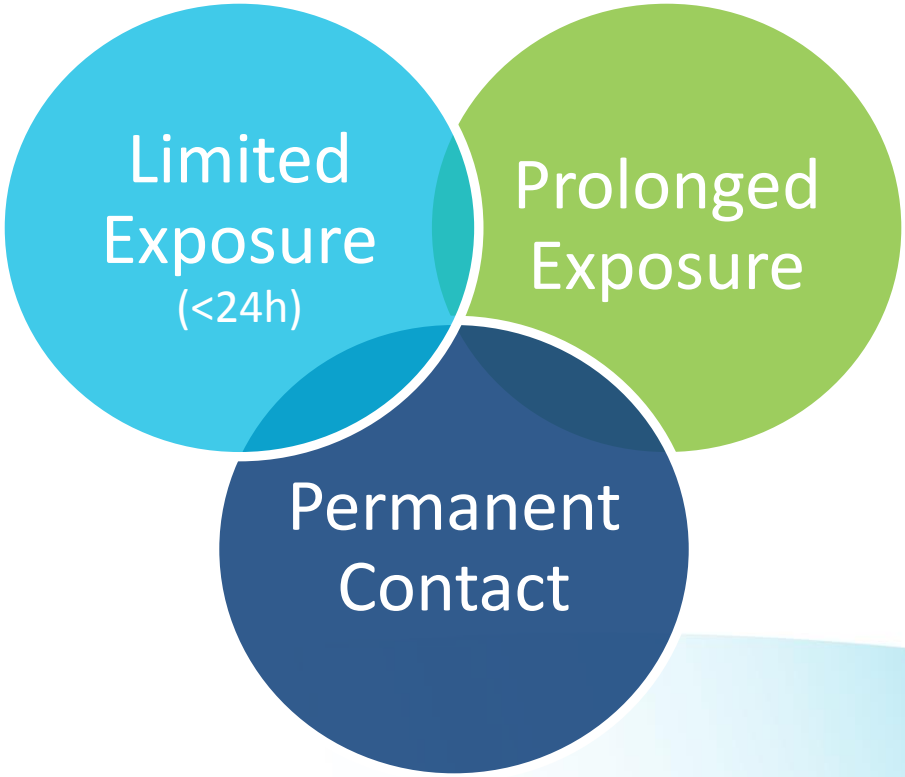
Fig.1 Biological indicator

Sterilization by Ethylene Oxide

Compounds that remain on product after EO sterilization:

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

There are Three Patient Exposure Categories:



Sterilization by Ethylene Oxide : Product examples

Medical Devices

Surgery packs

Catheters

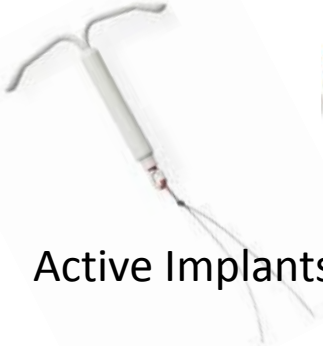
vials

Bandages

Drug products

API

Prefilled syringes (external)



Active Implants

Auto-Injector (external)

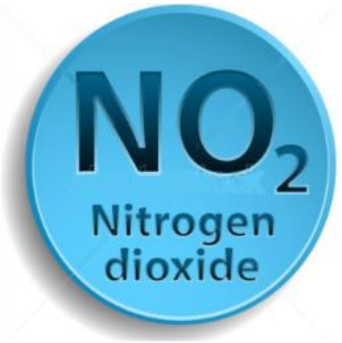
Sterilization : Comparison Radiation & Ethylene Oxide

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

Sterilization : Comparison Radiation & Ethylene Oxide

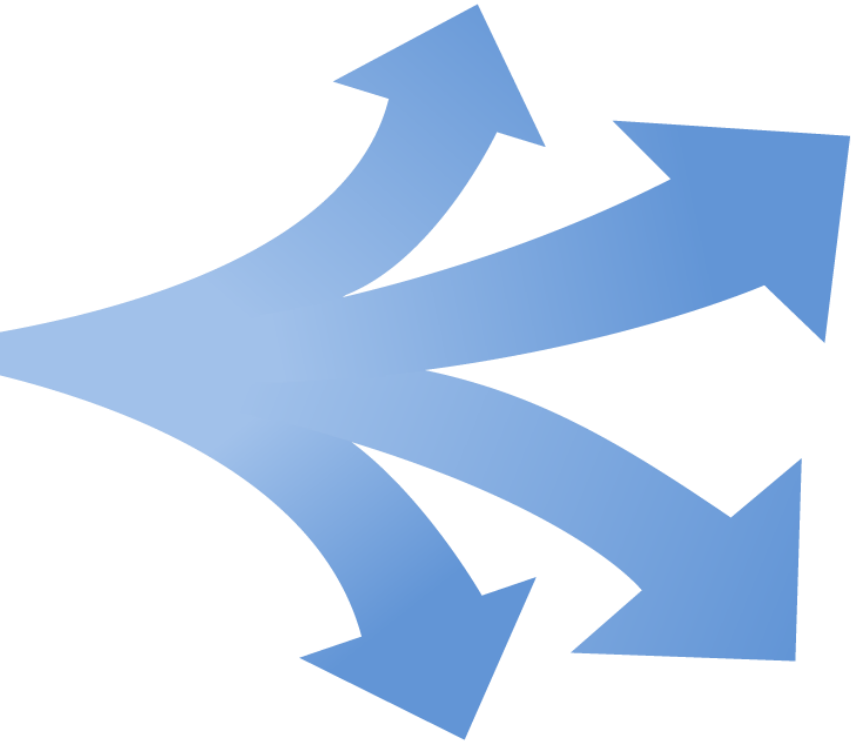
Parameter	Gamma	E-Beam	EO
Tolerance for density variation	High	Low	Medium
Routine monitoring	• Only a few parameters (Time, Size, density) • Dosimeter	• Higher Nb of parameters • Dosimeter	• Multiple cycle parameters • BI (unless parametric release)
Residues	None	None	ETO,ECH,(EG)
Volumes	High	Limited	High
Turn time	Fast (<24 hours)	Very Fast (<8 hours)	Long (1 week)

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
- Low residuals
- Small volume – Scale up ?

Different ways to get there !



Sterilization:

The invisible crucial process!

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