Sterility Assurance & Quality Risk Management Conference

PDA®
Parenteral Drug Association
Midwest Chapter

PDA Parenteral Drug Association Midwest Chapter

Sterility Assurance & Quality Risk Management Conference

October 25th & 26th

Terminal Sterilization of Drug Products

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Sterigenics®
A Sotera Health company

Gain an understanding of…..

- Difference between Aseptic Assembly and Terminal Sterilization
- Concept of a Sterility Assurance Level and how it is determined
- Different Modalities of Terminal Sterilization Available
- Process Definition steps for a Radiation Sterilization Process
- Examples of Drug/Pharma Product Terminally Sterilized
- Understand how Sterility of a product is a holistic process and not just “Sterilization”

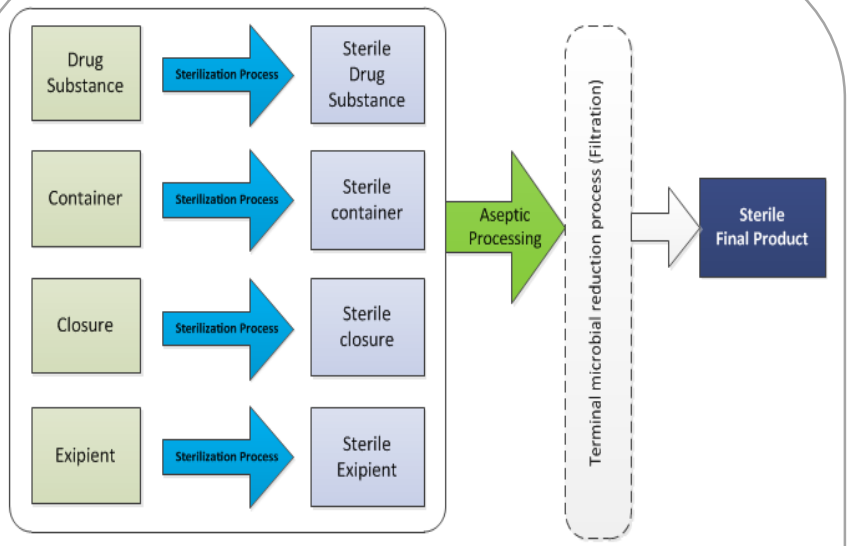
There are two (2) strategies to produce a sterile drug product:

Aseptic Assembly

Terminal Sterilization

- Heat
- Radiation
- Gas (EO, NO_2 …)

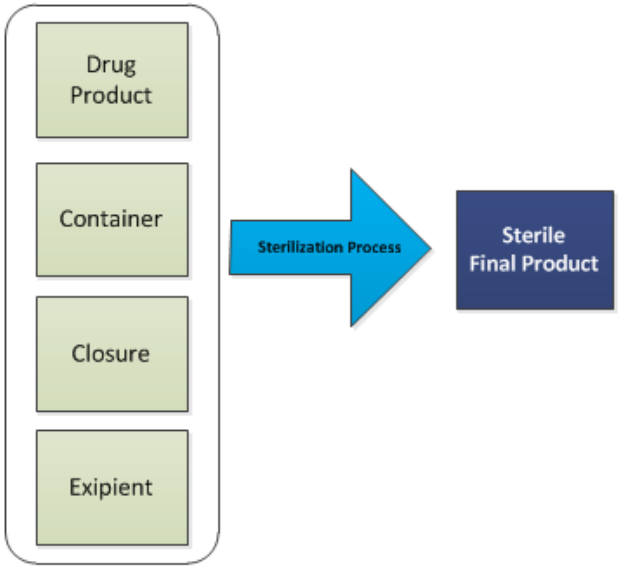
Aseptic Assembly



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

Sterile

Terminal Sterilization



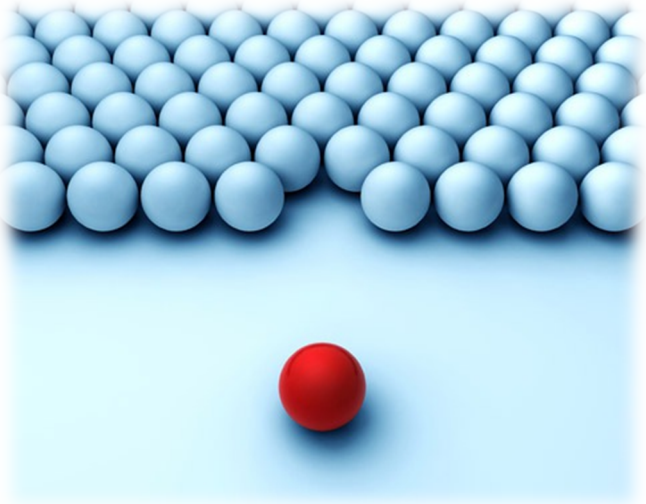
Exposure to a physical or chemical sterilizing agent for a predetermined extent of treatment

Sterilized

Sterile = Sterility Assurance Level (SAL) ≤ 10^{-6}

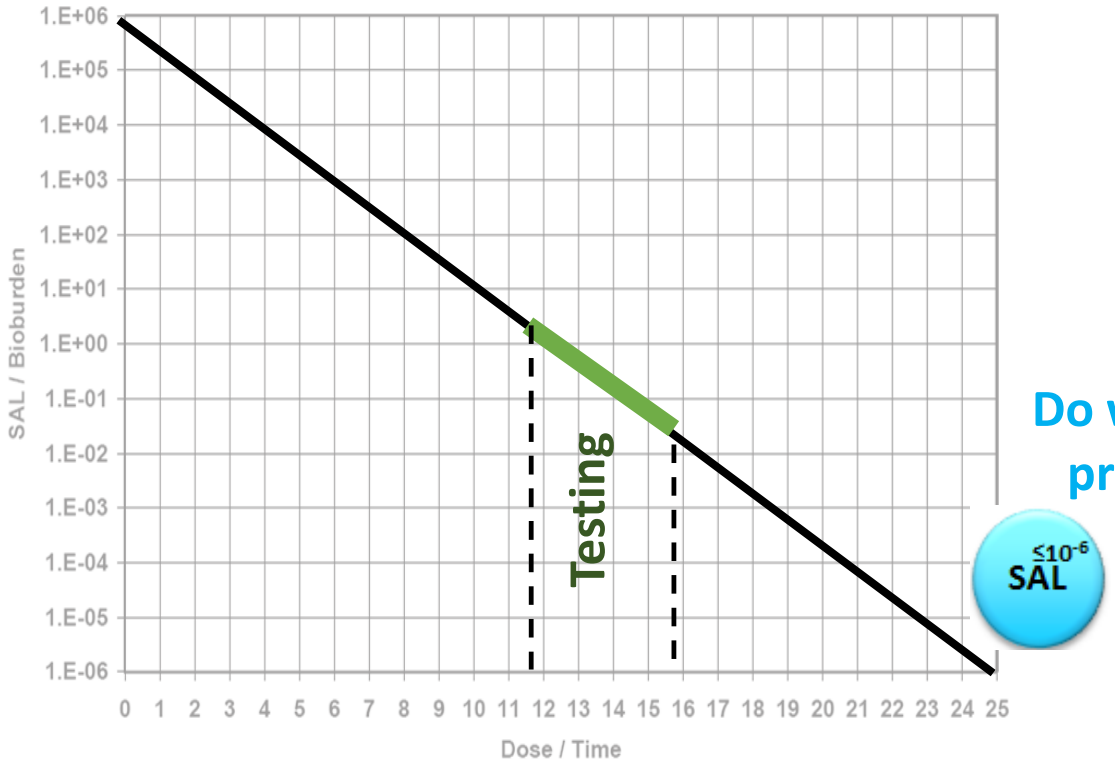
SAL likelihood of surviving organisms

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



- Is there any magic regarding 1 in 1 million?
- Why selected?
  - Some background in food processing perhaps
  - Nordic Pharmacopeia 1970 selected 10^{-6}
  - NASA selected 10^{-4} in 1960s for spacecraft
  - Scientific rationale for the 10^{-6} value?
    - **None!**
- Srun, *et al* in 2012 : At 10^{-3} and 10^{-4} generally no potential impact to patients

Terminal Sterilization



Do we ever test product here?

The Terminal Sterilization cycle is **validated** to achieve an SAL equal to or less than a specified value

Sterility Assurance

is NOT:

- A product sterility test result
- A sterilization cycle
- A BI or dosimetry test result

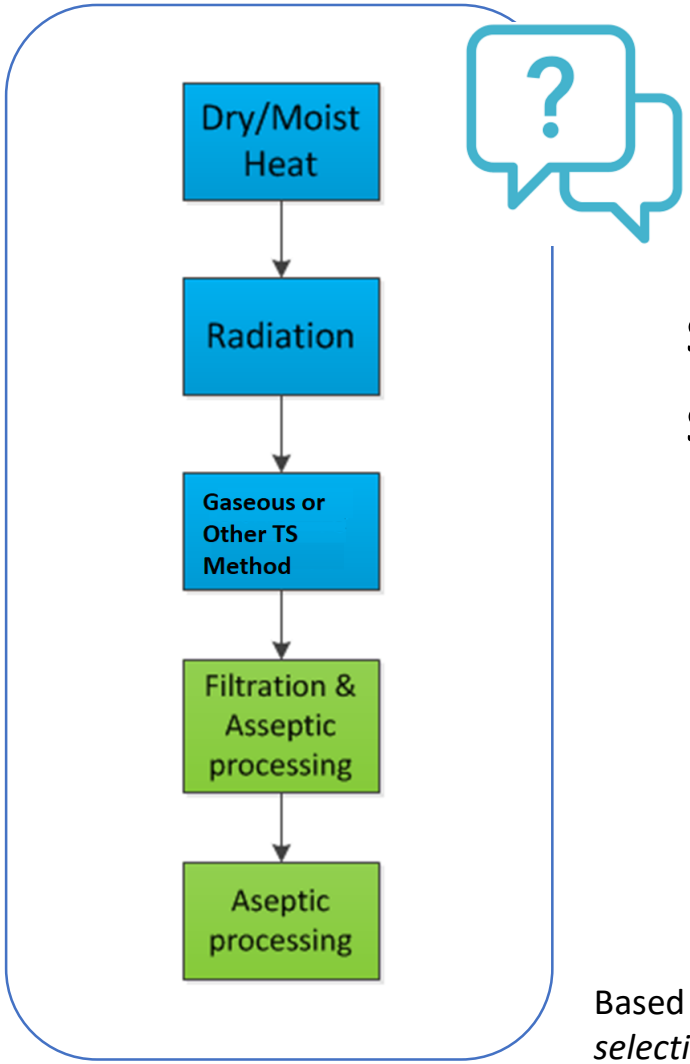
IS:

- Product design
- Manufacturing
- Packaging
- Sterilization
- Process and associated testing

Components of Sterility Assurance

ISO TS 19930 definition:

"Assurance of sterility: qualitative concept comprising all activities that provide confidence that product is sterile"



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

Based on *CPMP/QWP/054/98 Decision Tree for the selection of sterilization methods*

Ethylene Oxide

- (EO) gas

Irradiation

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

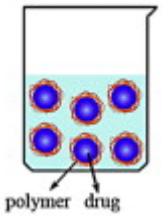
Other

- 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

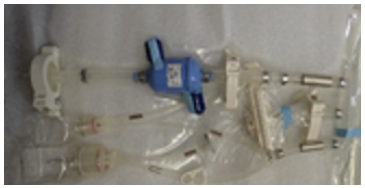
Radiation



Nanosuspensions

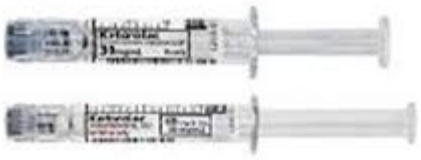
Lyophilized product

Dry Powder/ API



Single Use Systems

Ethylene Oxide



Prefilled syringes (external)

Auto-Injector (external)

API

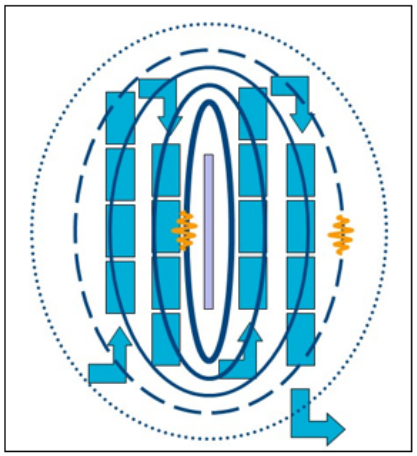
Sterilization by Irradiation – General principles

Two methods to produce radiation:

1

^{60}Co Gamma

Photons
from
Radioactive decay



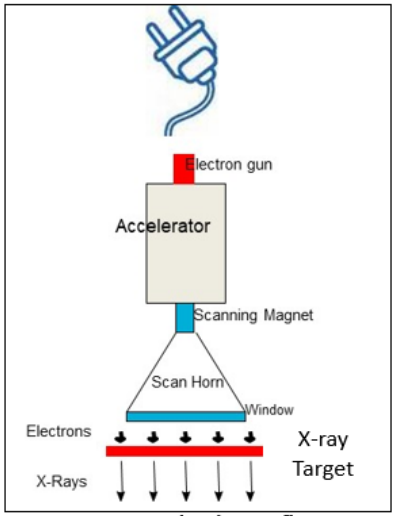
Isotropic radiation flux

Scale of decreasing intensity

2

X-ray

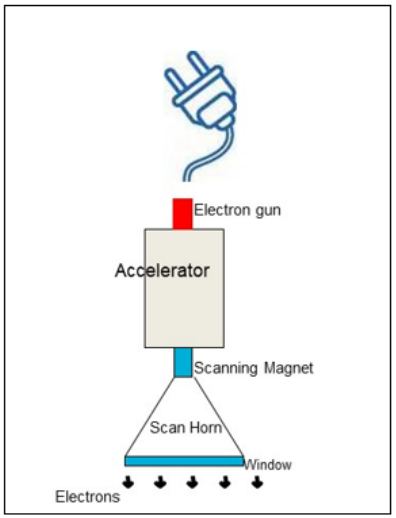
Photons
from
Particle accelerator
(by high energy electrons
hitting material with high atomic number)



Directional radiation flux

Electron Beam

10 MeV Electrons
from
Particle accelerator

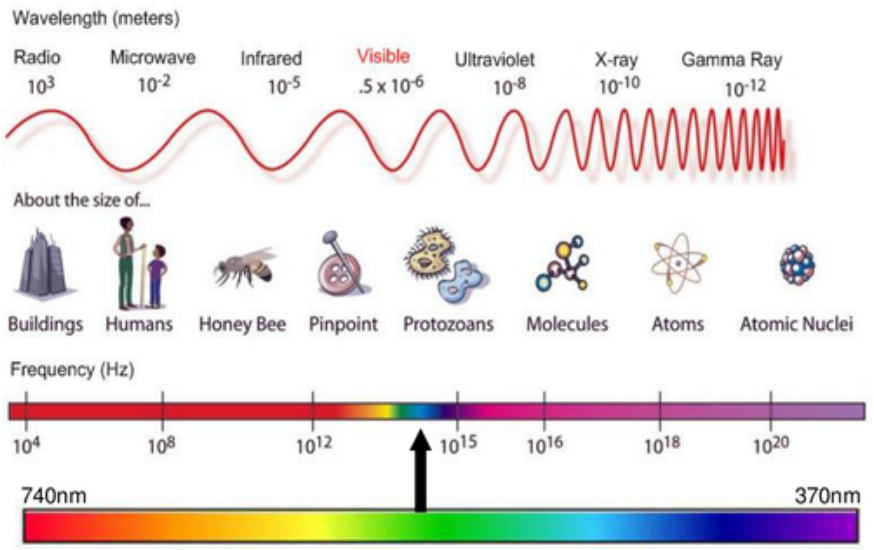


Directional radiation flux

Sterilization by Irradiation – General principles

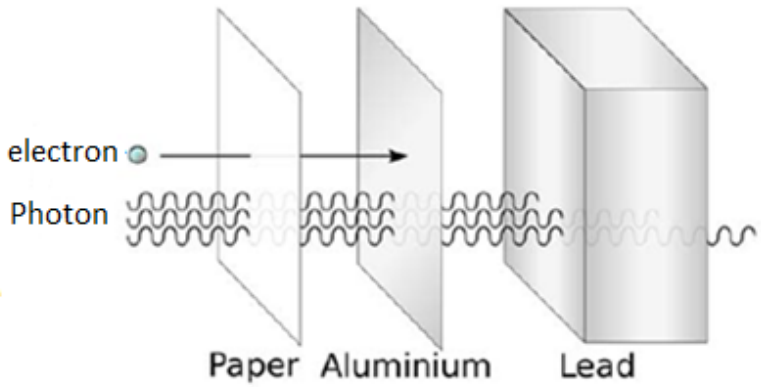
Gamma and X-Ray Radiation

Electromagnetic Spectrum



Passing Through Matter

Penetration Capabilities

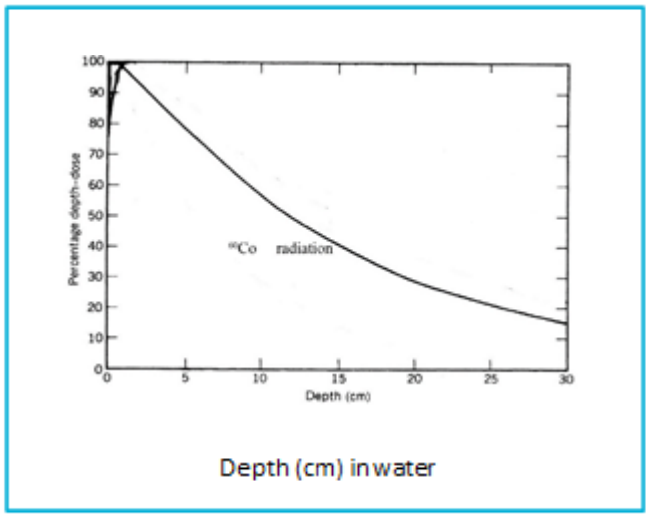


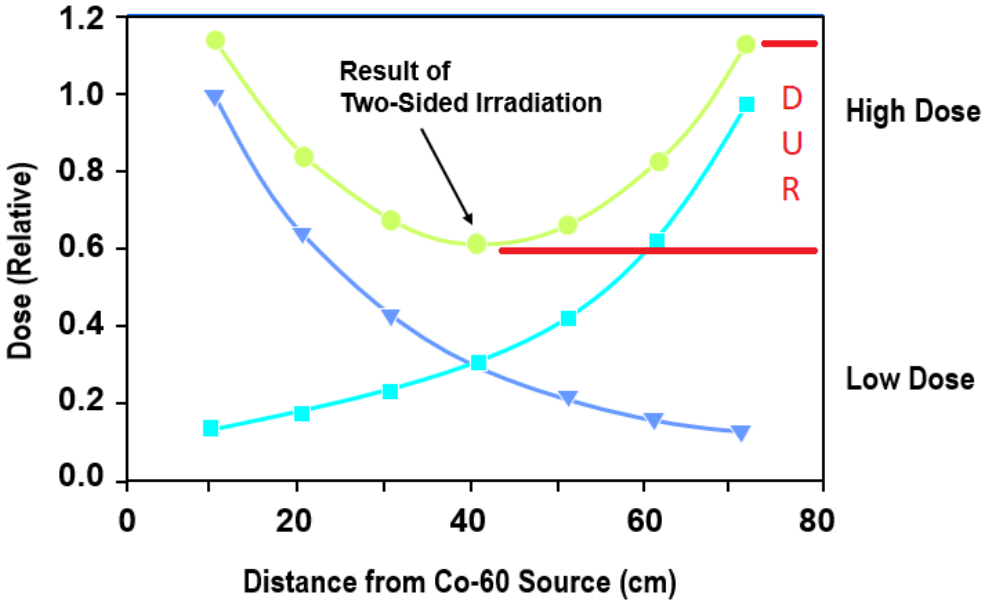
Photon Radiation - γ or X-Ray

Absorbed Dose in kGy → 1 Gray (Gy) = 1 Joule/kg → 1 kGy = 1000 Gy

Terminal Sterilization Using Gamma Radiation

Penetration

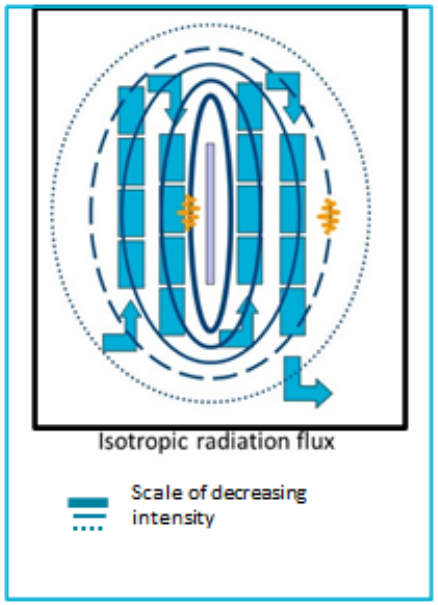




Dose Uniformity Ratio (DUR) → Ratio Maximum dose absorbed to minimum dose absorbed

Terminal Sterilization Using Gamma Radiation

Isotropic radiation flux



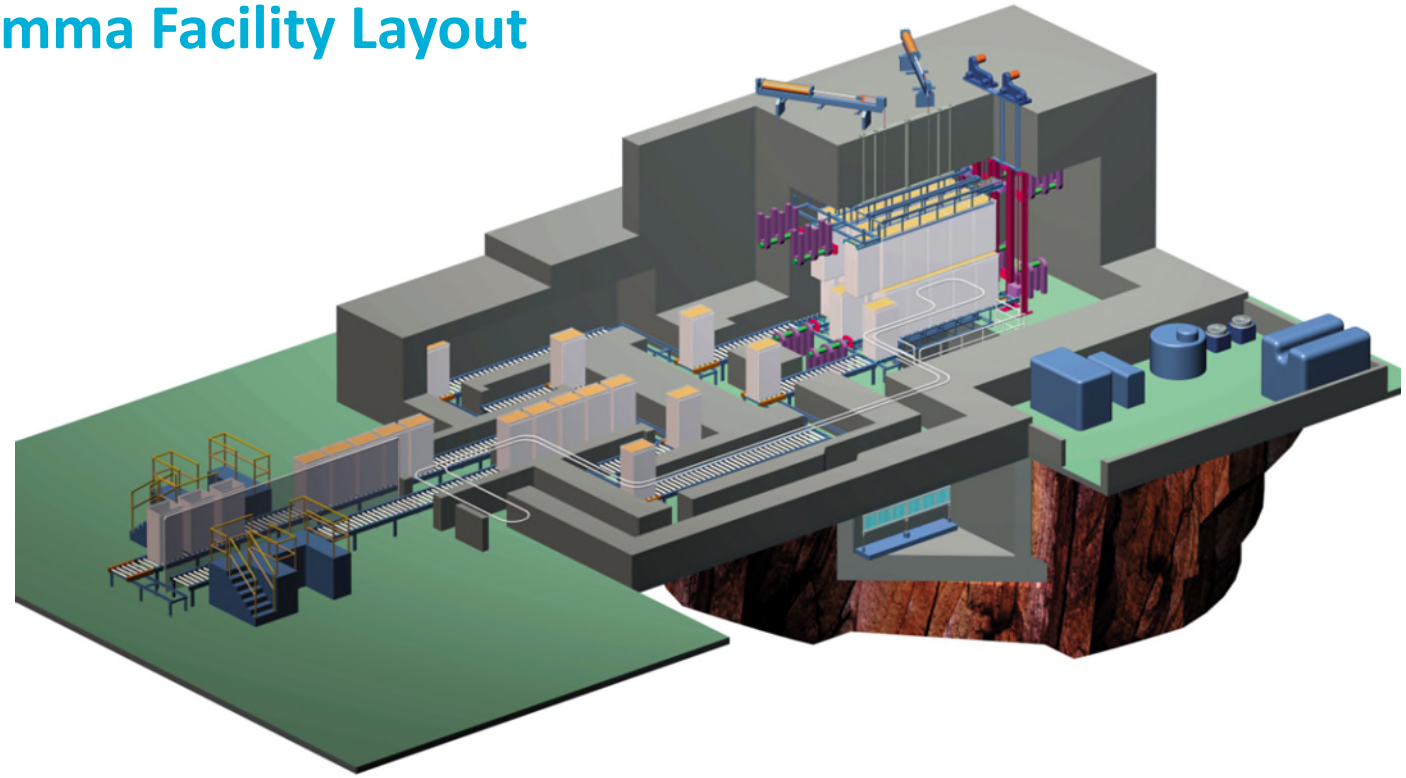
Process Variables

- Irradiation Pathway
- Cycle time
- Load configuration

Process Characteristics

- Time: order several hours
- Heating: non-adiabatic
- Typically different product irradiated together

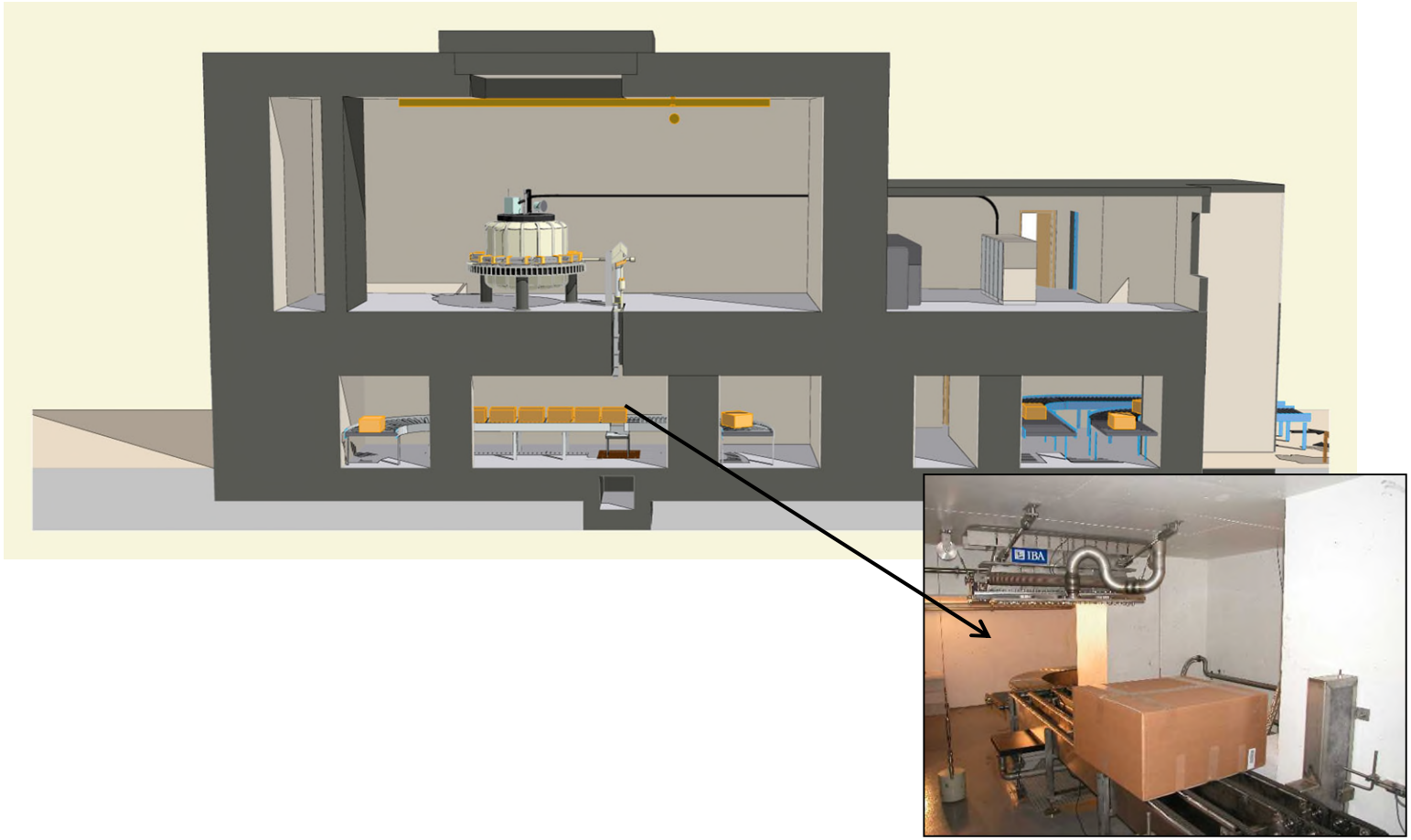
Gamma Facility Layout



In the irradiator above each irradiation container is the size of half an industrial pallet

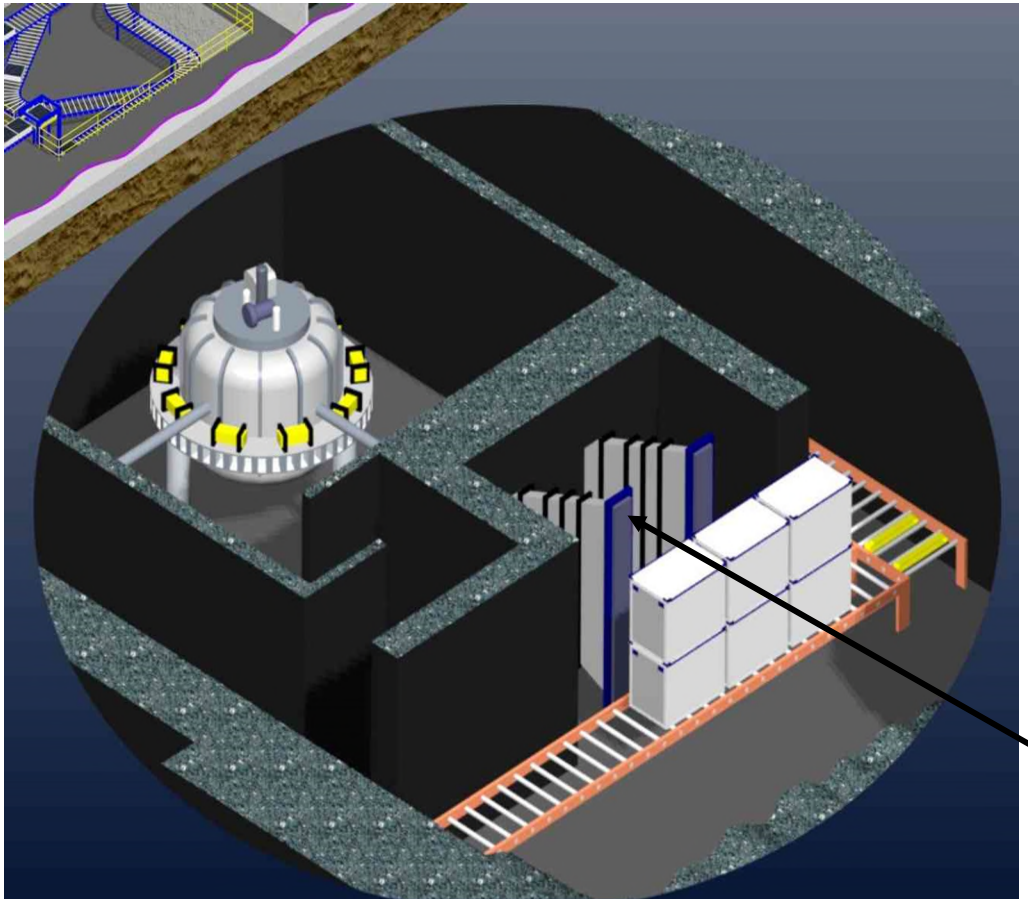
Courtesy MDS Nordion

E-Beam Facility Layout



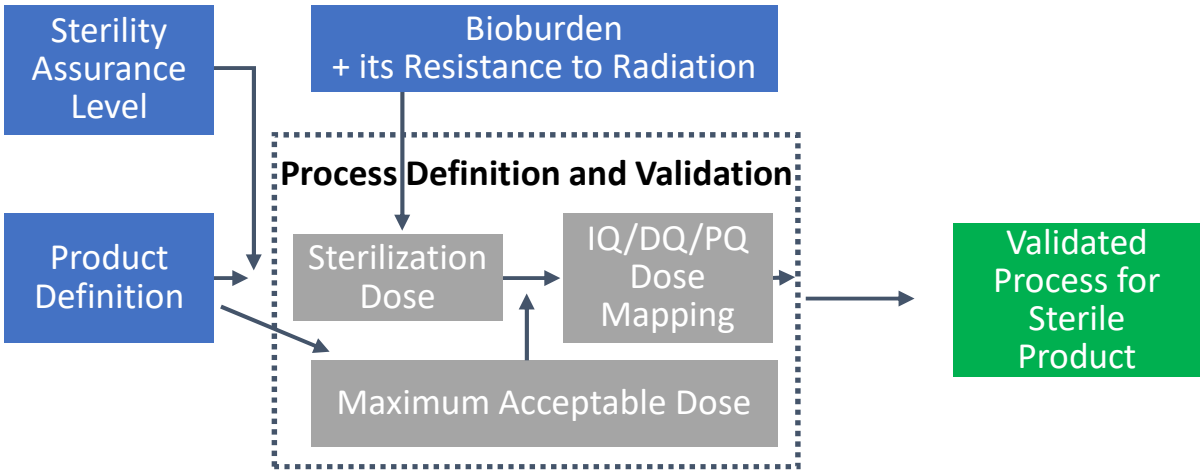
X-Ray Facility

Sterigenics Bridgeport Facility (2001)



Accelerate Electrons → Strike a Target → Create X-Rays

Process Definition and Process Validation (ISO 11137-1*)



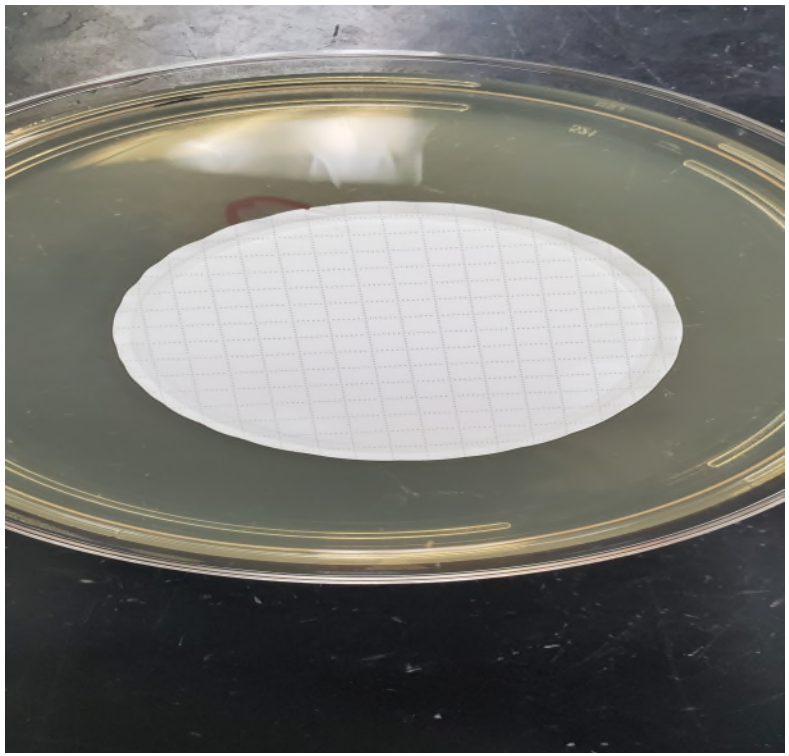
Process Definition
Establishing dose specification for product (Sterilization dose and maximum acceptable dose)

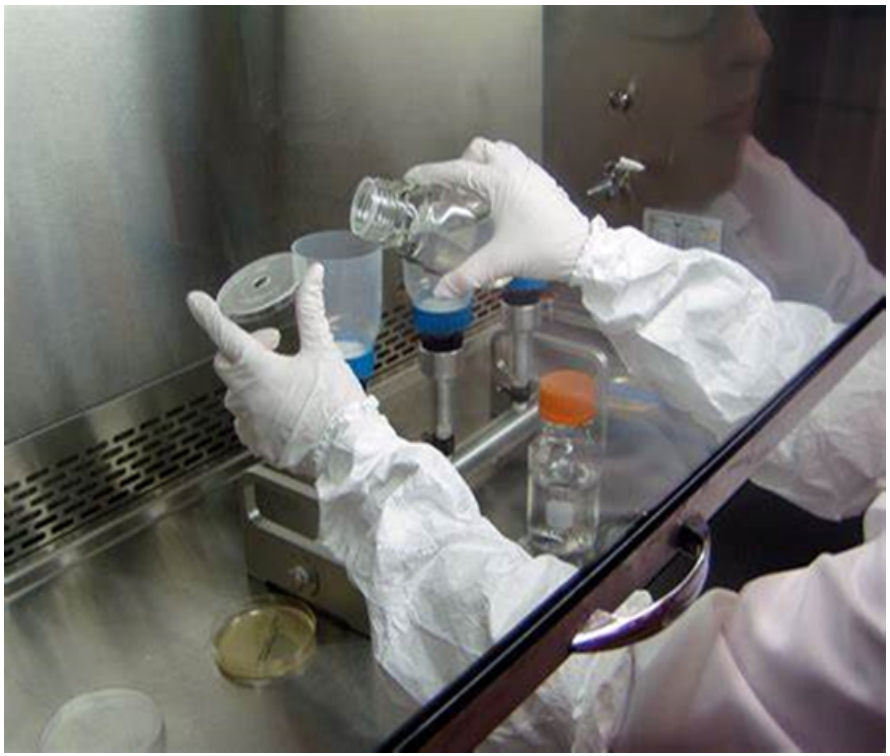
Process Validation
Establishing irradiation process that will render product within its dose specification

*Radiation sterilization standard for medical device product

Bioburden Determination

- Determine amount and types of viable microorganisms present on the product (during manufacturing and packaging)
- Measured in Colony Forming Units (CFU)





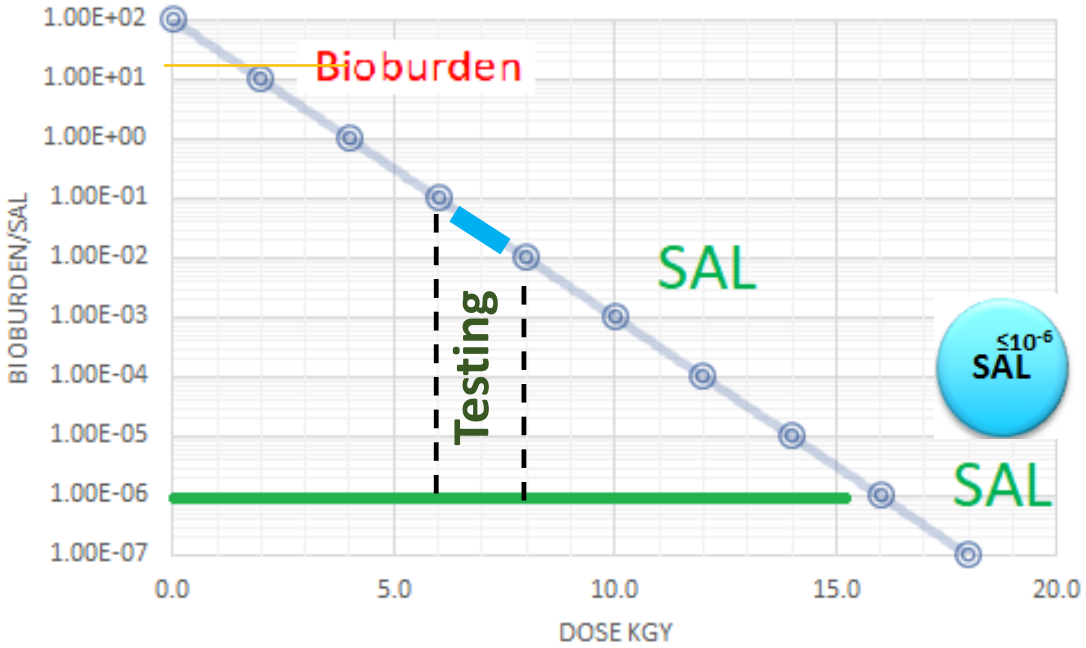
Sterility Assurance Level (SAL)

- 'Sterile' usually implies an SAL (Sterility Assurance Level) of 10^{-6}, meaning, at maximum, 1 in 1,000,000 manufactured and sterilized products is non-sterile

- A D_{10} value describes the amount of dose required to reduce our bioburden by 90% (or to reduce by 1 Log)

- This value allows us to extrapolate the sterilization dose from high SAL levels (say 10^{-1} or 10^{-2}) to the required level for sterilization

Example D_{10} = 2.0 kGy



Dose (kGy)	CFU	SAL
0.0	100	n/a
2.0	10	n/a
4.0	1	n/a
6.0	0.1	10^-1
8.0	0.01	10^-2
10.0	0.001	10^-3
12.0	0.0001	10^-4
14.0	0.00001	10^-5
16.0	0.000001	10^-6
16.7	4.47E-07	10^-6.35

Standard distribution of resistance

D_{10} (kGy)	1.0	1.5	2.0	2.5	2.8	3.1	3.4	3.7	4.0	4.2
Probability (%)	65.487	22.493	6.302	3.179	1.213	0.786	0.350	0.111	0.072	0.007

Methods of Minimum Dose Establishment (D_{ster})

ISO 11137-1

8.2 Establishing the sterilization dose

8.2.1 The sterilization dose shall be established for product

Methods typically used are per ISO 11137-2

- Method VD_{max}
- Method 1
- Method 2

Methods of Minimum Dose Establishment (D_{ster})

Method VD_{max}

Advantages

- Least number of samples needed
- Samples for dose establishment = 48
- Shorter turn time than Method 2

Disadvantages

- Lowest possible sterilization dose is 15 kGy
- Only an SAL 10^{-6} is possible

Method 1

Advantages

- Alternative SAL's possible
- Minimum dose can be as low as 11.0 kGy
- Based on specific product bioburden – Could have lower sterilization minimum dose than for Method VDmax
- Shorter turn time and fewer samples than Method 2

Disadvantages

Larger number of samples needed than for Method VD_{max}

Standard distribution of resistance (SDR) used in Method VDmax and Method 1

D_{10} (kGy)	1.0	1.5	2.0	2.5	2.8	3.1	3.4	3.7	4.0	4.2
Probability (%)	65.487	22.493	6.302	3.179	1.213	0.786	0.350	0.111	0.072	0.007

Methods of Minimum Dose Establishment (D_{ster})

Method 2

Resistance of the microorganisms sets a product-specific dose **– Essentially establish D_{10} for the bioburden present on the specific product**

Advantages

- Possible to set a low minimum dose of 8.3 kGy for SAL 10^{-6} (Possibly even 6.4 kGy for "Zero Bioburden" Pharma product that is aseptically packaged)
- Alternate SAL's possible
- Validate products that have failed VD_{max} and Method 1

Disadvantages

- Large number of samples needed for testing
- Approximately 500 to 800 samples for dose establishment
- Long turn time for completion of the validation (12-16 weeks)

Maximum Dose Establishment ($D_{max,acc}$)

ISO 11137-1

8.1 Establishing the maximum acceptable dose

8.1.1 The maximum acceptable dose for product shall be established. When treated with the maximum acceptable dose product shall meet its specific functional requirements throughout its defined lifetime

Example: 25-40 kGy Dose Range, Max. dose testing done **at or above 40 kGy**

- Several dose points should be tested in order to determine $D_{max,acc}$
- Keep in mind the difference between a specification of 25 – 37kGy (Max to min specified dose ratio of 1.48) is significantly more difficult to achieve in routine than a specification of 25-40 kGy (Max to min specified ratio of 1.60). It could mean the difference between a “capable” process and a process that is “not capable”. Even better to get 42 kGy or 43 kGy.
- A few kGy “extra” in either the minimum or maximum dose can be significant!

D_{ster} and $D_{max,acc}$ are related

Radiation Sterilization mitigation possibilities

D_{ster} other than 25 kGy Exist!

- Lower Sterilization dose (11 kGy/8 kGy)
- Establishing a Lower D_{ster} can result in lower maximum dose to the product
- Freeze (impede diffusion of reactive species in product)
- Inert atmosphere inside package (reduce oxidation effects)

Example of dose delivery characteristics for powder filled vial

PQ Example: Powder Filled Vials (Gamma or X-Ray)

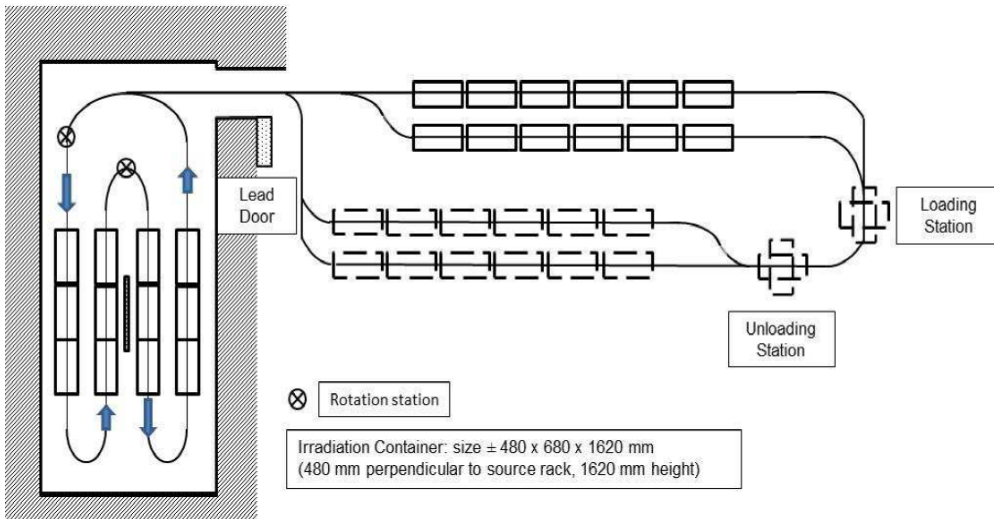
Gamma

- Glass vial with powder
- Cold chain management (temperature ≤ -20 °C)
- Dose uniformity requirement $D_{max,acc}/D_{ster}$= 1.50

- Product trays able to be loaded to design specification
- Several 1000 vials per irradiation container
- Able to achieve D_{max} / D_{min} approximately **1.20**

Irradiation Using Gamma (Co-60): Example Irradiator For Pharma Product

Sterigenics Fleurus Facility – Batch Irradiator



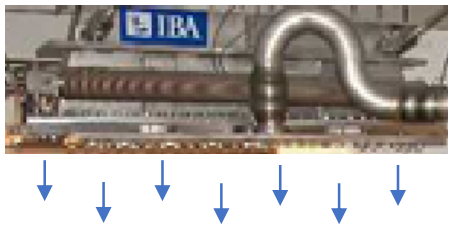
Dedicated processing, per batch

- Process can be customized

Example: Powder Filled Vials (Electron Beam)

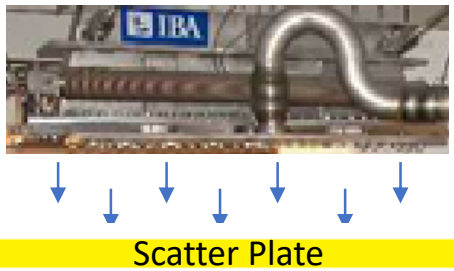
Monte Carlo calculation of dose distribution in single vial (electron beam irradiation)

- 10 MeV electrons
- 1 cm fill height inside the vial
- 1.50 DUR Required



(★) Dmax / (★) Dmin

= 3.5



(★) Dmax / (★) Dmin

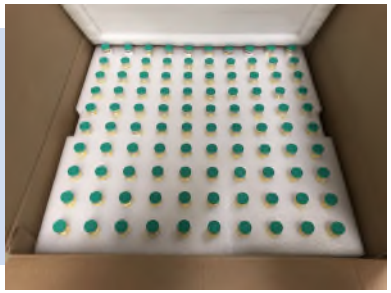
= 1.4

Example: Powder Filled Vials (Electron Beam)

From single vial to product tray + **From calculation to experiment**

Dosimetry:
average ratio of maximum dose to minimum dose = 1.40

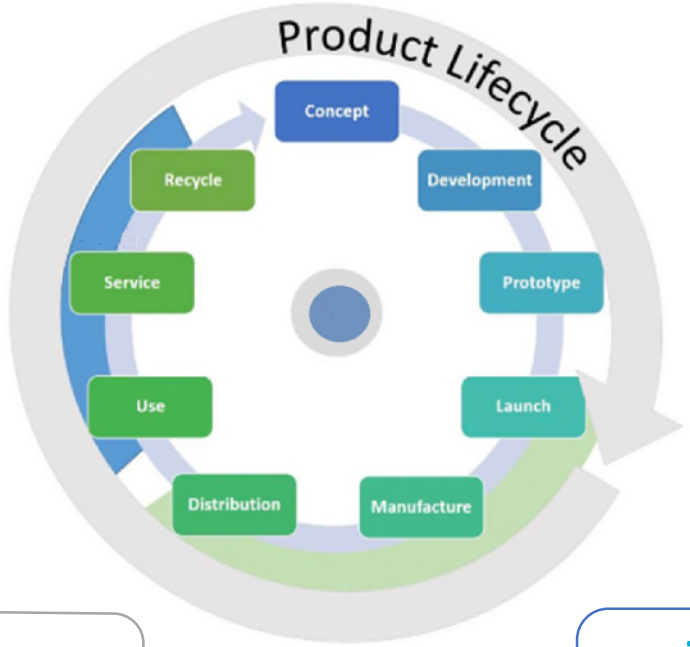
Product tray with sufficient spacing between vials so they can be considered as individual



Gamma or X-Ray

- Several 1000 vials per irradiation container in Gamma example
- No spacing between vials required
- Dosimetry: average ratio of maximum dose to minimum dose = 1.20

Think about Sterilization as soon as Possible During Product Development



Aseptic Assembly

Terminal Sterilization

Takeaways…..

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