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Radiation sterilization of SVPP: RTU and fill/finished. Do not default to 25 kGy – 40 kGy

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NELSON SYMPOSIUM
MARCH 2022

Small Volume Parenteral Packaging: Radiation Sterilised*

Ready to Use (RTU)

Inj. stoppers

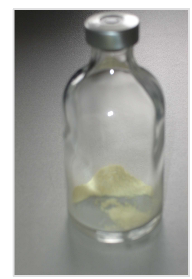
Plastic vials

Flip-off caps

Fill-finished

Solution

Suspension
(can also be aqueous)



*Illustrative purposes

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Agenda

Radiation Technology (Gamma, electron beam)

Establishing Product dose specification

Terminal Sterilization of fill finished product, examples

IRRADIATION TECHNOLOGY

General Introduction

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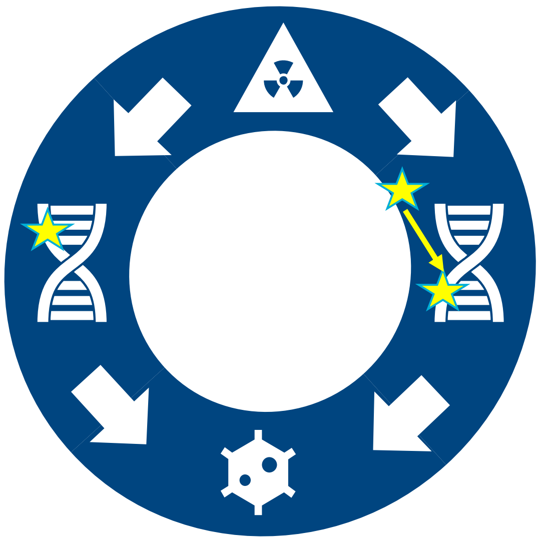
Ionizing Radiation: Lethality

DNA Damage

Ionizing Radiation

Direct DNA Damage

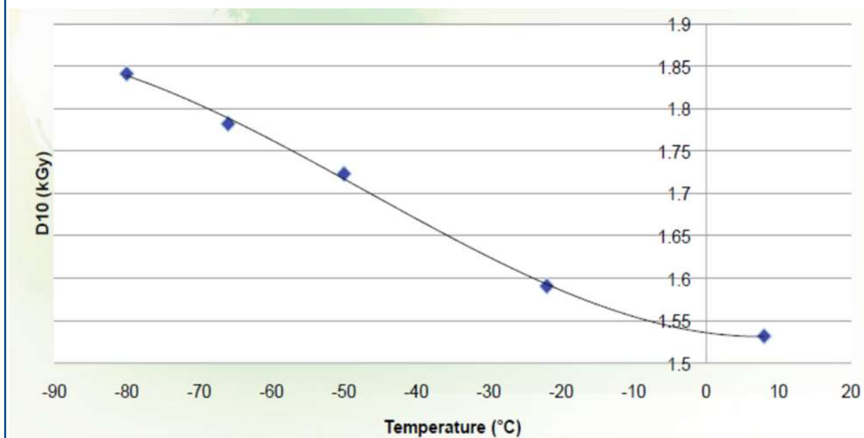


Indirect DNA Damage (radiolysis of water)

Death of Organism

Bacillus Pumilus D10 Values

Low Temperature Study



D10-value: energy absorbed (kGy) that reduces population by a factor of 10

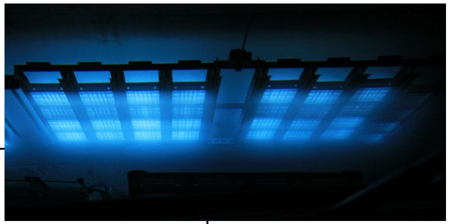
Source: E. Craven (MDS Nordion)

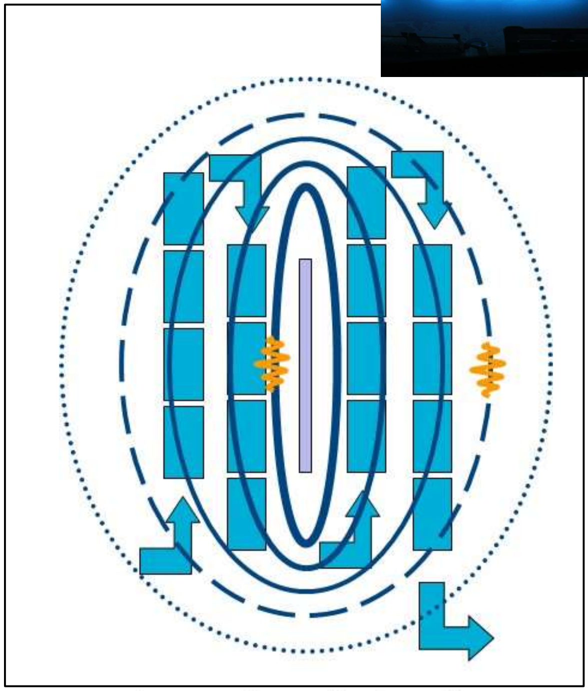
In essence only single process variable = dose (kGy)

Type of radiation, generation and directionality of radiation field

Cobalt60 Gamma

Photons from
Radioactive decay





Isotropic radiation flux

Scale of decreasing intensity

Process Variables

- Irradiation Pathway
- Cycle time
- Load configuration in irradiation container
- Mixing of product in irradiator

Process Characteristics

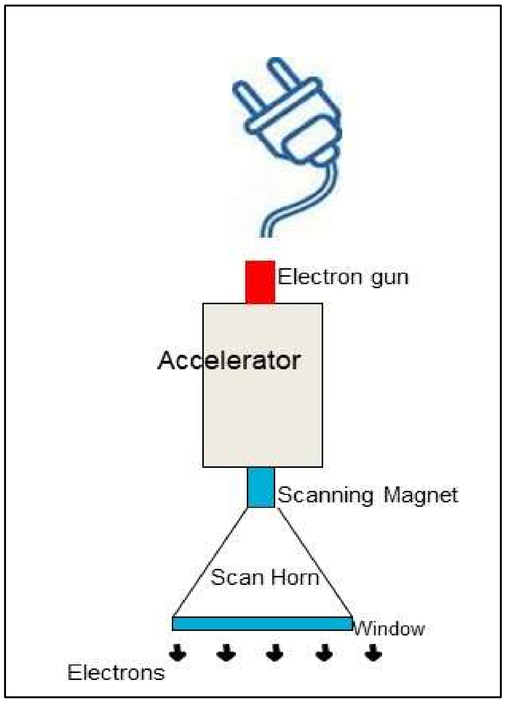
- Irradiation Time: order of several hours
- Heating: non-adiabatic
- Typically different product irradiated together (processing categories)

- *Dose magnitude and dose uniformity can generally be predicted reasonably well without PQ dose mapping*

Type of radiation, generation and directionality of radiation field

Electron Beam

10 MeV Electrons
from Particle accelerator



Directional radiation flux
<u>can be tailored to product needs</u>

<u>Process Variables</u>

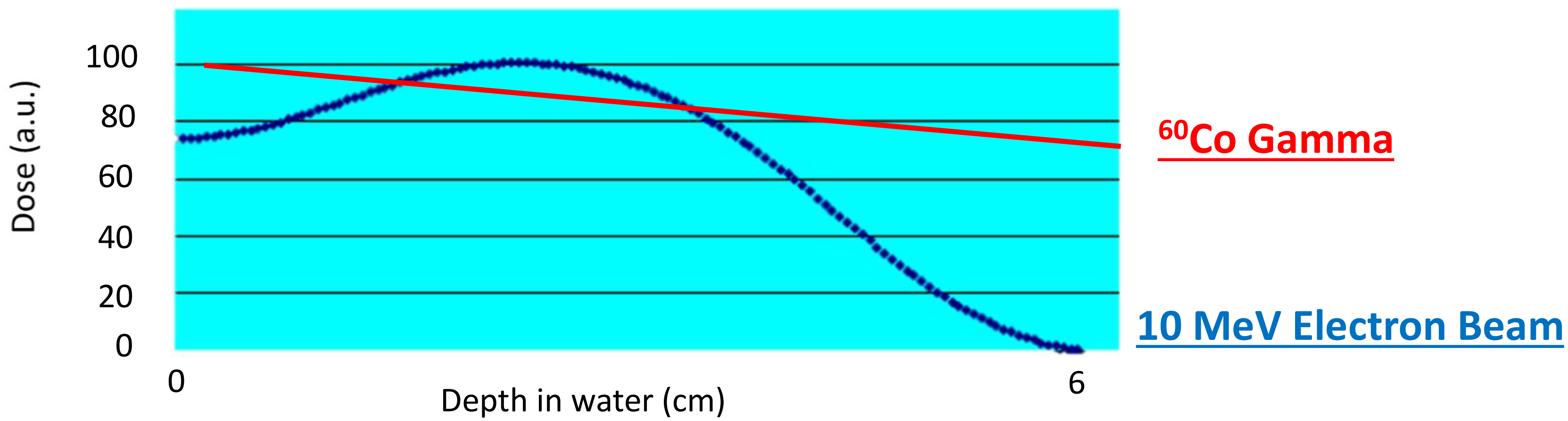
- Beam intensity
- Beam position/extent
- Speed of product through radiation field
- Irradiation pathway (single- or double-sided irradiation)
- Load configuration of irradiation container

<u>Process Characteristics</u>

- Time: Irradiation time only seconds
- Heating: Adiabatic (polymer approx. 0.7 °C per kGy)
- *Dose magnitude and dose uniformity for product difficult to predict in general*

Penetration and uniformity of dose delivery

Penetration



Dose uniformity (experimental data irradiator qualification)

*DUR = Dose Uniformity Ratio = Max dose/Min dose

10 MeV Electron Beam

40 cm box
0.15 g/cm^3 (density of 6 cm water)

DUR* 2.83
(Double sided irradiation)

^{60}Co Gamma

Industrial Pallet (100 cm × 120 cm × 180 cm)
0.15 g/cm^3 (density of 15 cm water)

DUR* 1.66
(Double sided irradiation)

PRODUCT DOSE SPECIFICATION

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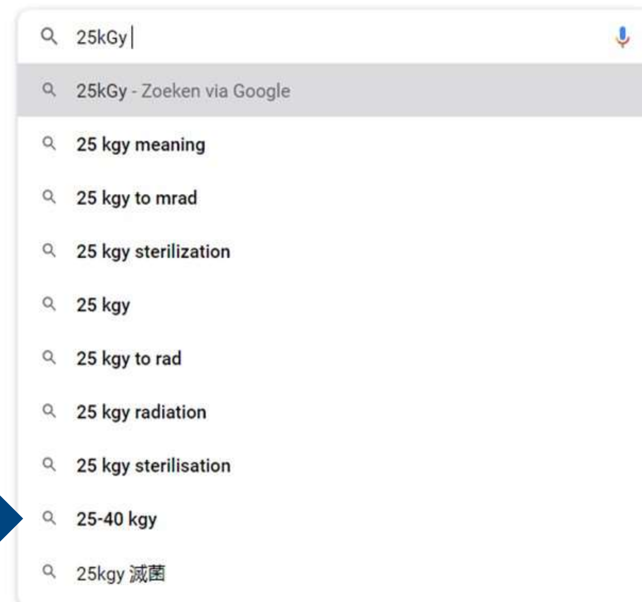
Background to “default” product specification of 25 kGy – 40 kGy

25 kGy – 40 kGy

Ratio 40 kGy / 25 kGy = 1.6

Google



“Overkill” dose,
selected and in place for decades

“Belief” of a dose that an irradiator operator “needs” when running at a minimum of 25 kGy

This is a specification NOT based on product nor on “standard” irradiator capabilities

Uniformity of dose delivery

Dose uniformity (experimental data irradiator qualification)

*DUR = Dose Uniformity Ratio = Max dose/Min dose

10 MeV Electron Beam	^{60}Co Gamma
40 cm box	Industrial Pallet (100 cm × 120 cm × 180 cm)
0.15 g/cm^3 (density of 6 cm water)	0.15 g/cm^3 (density of 15 cm water)
DUR* 2.83	**DUR* 1.66**
(Double sided irradiation)	(Double sided irradiation)

Not possible to irradiate product as defined within 25 kGy – 40 kGy (ratio 40 kGy / 25 kGy = 1.6)

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Possible gain of a properly widened dose specification

Supply chain

More options for irradiating product

- In the desired irradiator
- In other irradiators of the same modality
- In irradiators with other modality

TOTAL addressable Market

More options for using the packaging

- Terminal sterilisation of fill finished product

Methods for sterilization dose establishment (Healthcare product)

- Method 1, Method 2
  - Methods 1 and 2 ***set*** a product-specific dose for obtaining a defined SAL level

    (SAL = Sterility Assurance Level)

- Method VD_{max}^{SD}

  Method VD_{max}^{SD} ***substantiates*** a selected sterilization dose
  - Initially applied to substantiation of 25 kGy as a sterilization dose
  - Subsequently expanded to other doses
  - Only SAL 10-6

Method VDmaxSD

Avg. Bioburden Range (Colony Forming Units)	Sterilization Dose SD (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 23000	30.0
≤ 1.0 to 100000	32.5
≤ 1.0 to 440000	35.0

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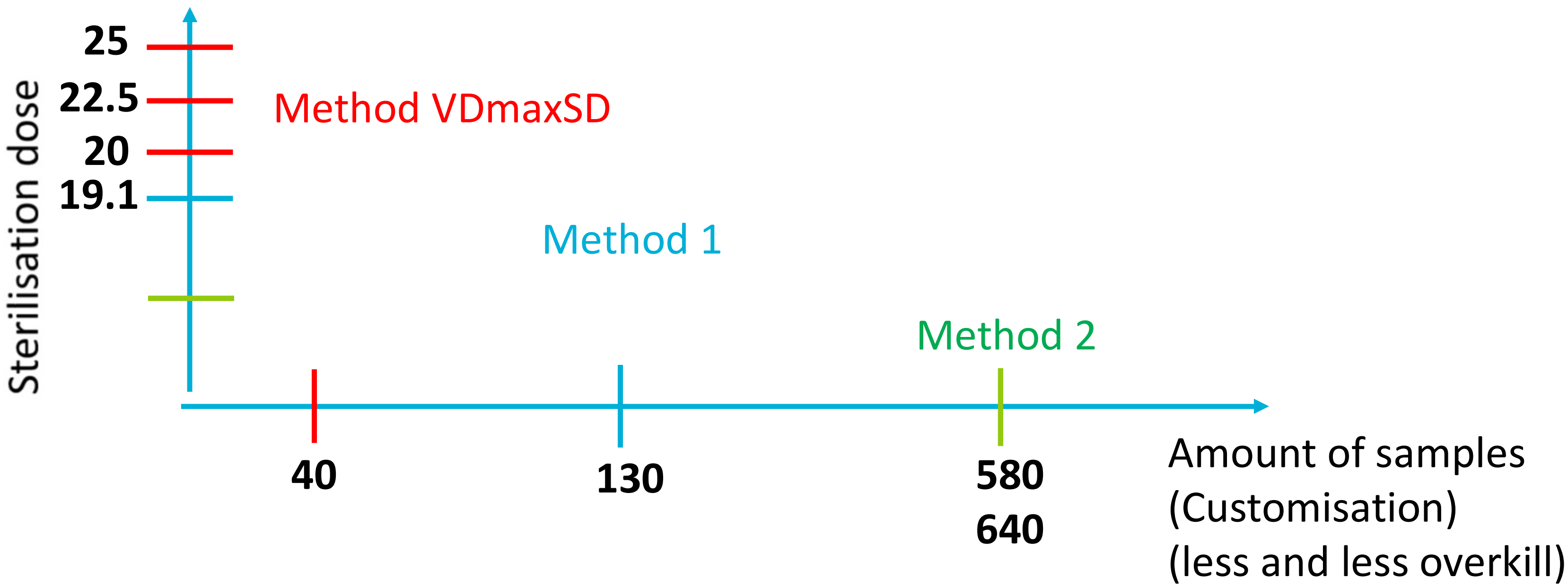
Methods for sterilization dose establishment (Healthcare product)

For a defined product (SAL 10-6), example average bioburden 25 CFU



Method VDmaxSD	Selected dose and level of conservativeness of “Standard Distribution of Resistances”
Method 1	conservativeness of “Standard Distribution of Resistances”
Method 2	Purely based on resistance of organisms residing on defined product

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Numerical examples

For a defined product with average bioburden (dose achieving SAL 10^{-6})

Avg. Bioburden	Method VDmaxSD	Method 1
1000 CFU	25.0 kGy	25.0 kGy
100 CFU	22.5 kGy	21.2 kGy
10 CFU	20.0 kGy	17.6 kGy
1 CFU	15.0 kGy	14.2 kGy
≤ 0.1 CFU	15.0 kGy	11.0 kGy

Selection of sterilization doses (kGy) established for customers with SVPP at Sterigenics

Method VDmaxSD   Method 1   Method 2

9.6 12.2 12.5 13.6 14.8 **15** 15.6 16.2 16.6 16.7 17.0 **17.5** 17.6 18.0 18.3 18.7 19.3 **20** 20.6 **25**

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Establishing maximum acceptable dose

1) Irradiate samples in a uniform way at selected doses

- Might be more complicated to irradiate uniformly in e-beam than gamma
- On the other hand, likely specialized irradiator needed in gamma to obtain selected doses

2) Evaluation based on performance attributes e.g. Appearance, E&L, sealant properties etc

Left: no irradiation
Middle: 15 kGy
Right: 30 kGy

Glass vials

Penetration test

TERMINAL STERILIZATION OF FILL FINISHED PRODUCT

Examples of terminal sterilization using ionizing radiation at Sterigenics

1) Terminal sterilization of **aseptically** manufactured biologic

   → Double sterilization of packaging components (?!)

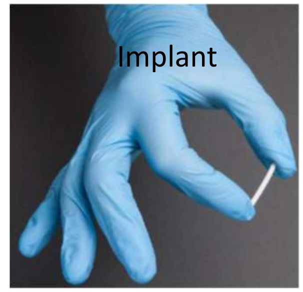
2) Terminal sterilization of pre-filled syringe under **deep-frozen condition**

3) Terminal sterilization powder filled vial using e-beam (**50 kGy** maximum acceptable dose)

Key take-aways

- Irradiation technology can be applied for more than sterilization of packaging components



Suspension
(can also be aqueous)

- Inherent possibility to irradiate in a substantially more uniform manner using Gamma than when using electron beam

- Do not default to 25 kGy – 40 kGy; but customize...