Non-Heat Terminal Sterilization of Controlled Release Materials

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Sterilization – There's No Free Lunch

- A balance must be achieved between the need to maintain a safe, stable and efficacious product while providing sufficient lethality to attain a minimum level of sterility assurance.
- No sterilization method should be considered exempt.

Material Perspectives

- Sterilizing processes should be a compromise between the degradation effect on the materials and destruction of microorganisms.

- A sterilization process that destroys all microorganisms, but renders the item being sterilized unfit for use is of no value.

- The sterilization process and the specific product, formulation and container must all be suited to each other.

- There are few universal answers, and some of those that appear to be broadly applicable may be wrong.

Sterilization Methods (ranked by estimated material effect)

- Sterilization by Filtration
- Chemical Sterilization
  - Includes aldehydes, oxidizers, halides, acids, bases
- Gas Sterilization
  - Includes ETO, Chlorine Dioxide, Ozone
- Vapor Sterilization
  - Includes H_2O_2, and Peracetic acid Radiation Sterilization
- Steam Sterilization
- Dry Heat Sterilization

Sterilization Methods (effect & issue)

- Sterilization by Filtration
  - Must be a solution, likely requires aseptic processing to manufacture a dosage form.
- Chemical (Liquid phase) Sterilization
  - Strong acids / bases, post-process neutralization required, won't penetrate solids
- Chemical (Gas Phase) Sterilization
  - Potent chemicals, won't penetrate solids
- Vapor (BiPhasic) Sterilization
  - Poorly suited – prefer liquid or gas systems for ease of use / validation
- Radiation Sterilization
  - Method of choice?, penetration varies with method, new methods and ideas possible
- Steam Sterilization
  - Heat effects can be extreme, new ideas possible
- Dry Heat Sterilization
  - Heat effects are always extreme, few real opportunities
- (Emerging Methods)
  - Effective, but may require extensive support for implementation, material effects are largely unstudied.

Sterilization & Penetration

- Little or no penetration
  - Chemical Sterilization
  - Vapor Sterilization
- Some penetration
  - Gas Sterilization
  - Steam Sterilization
- Good Penetration
  - Dry Heat Sterilization
  - Radiation Sterilization

Contemporary TS Processes using Radiation

Sterilization by Irradiation

- All radiation sterilization processes (gamma, e-beam, X-ray, UV, etc.) rely on disruption of the cells metabolism – renders them unable to reproduce.
- Rapid radiation processes (e-beam & X-ray) may result in heating of the material.

Common & Key Elements

- Confirming that the irradiated materials are safe and that they are able to function as intended.
- The establishment of a proper radiation dose to assure the desired sterility assurance level.
- Confirmation that the system / equipment consistently delivers the prescribed dose.

Materials Compatibility

- Many materials are affected by exposure to radiation and the onset of these effects may not be immediate.
- Stability studies (accelerated and real-time) are needed at maximum exposure to demonstrate that essential material properties are not compromised
- Testing should address functionality, biocompatibility, and aesthetic properties.

Common Material Effects

- Changes in color, viscosity, loss of strength, embrittlement, odors, etc. are all possible.
- Plastics and rubbers are most affected, stabilized formulations are available.
- Color changes with glass are commonplace.
- Effects on various materials including some actives is available in the literature.

Sterilization by Irradiation

- All radiation sterilization processes (gamma, e-beam, UV, etc.) rely on disruption of the cells metabolism by the creation of free radicals to render them sterile.
- In some processes a concurrent heating of the material may provide a synergistic effect.

Irradiation Methods

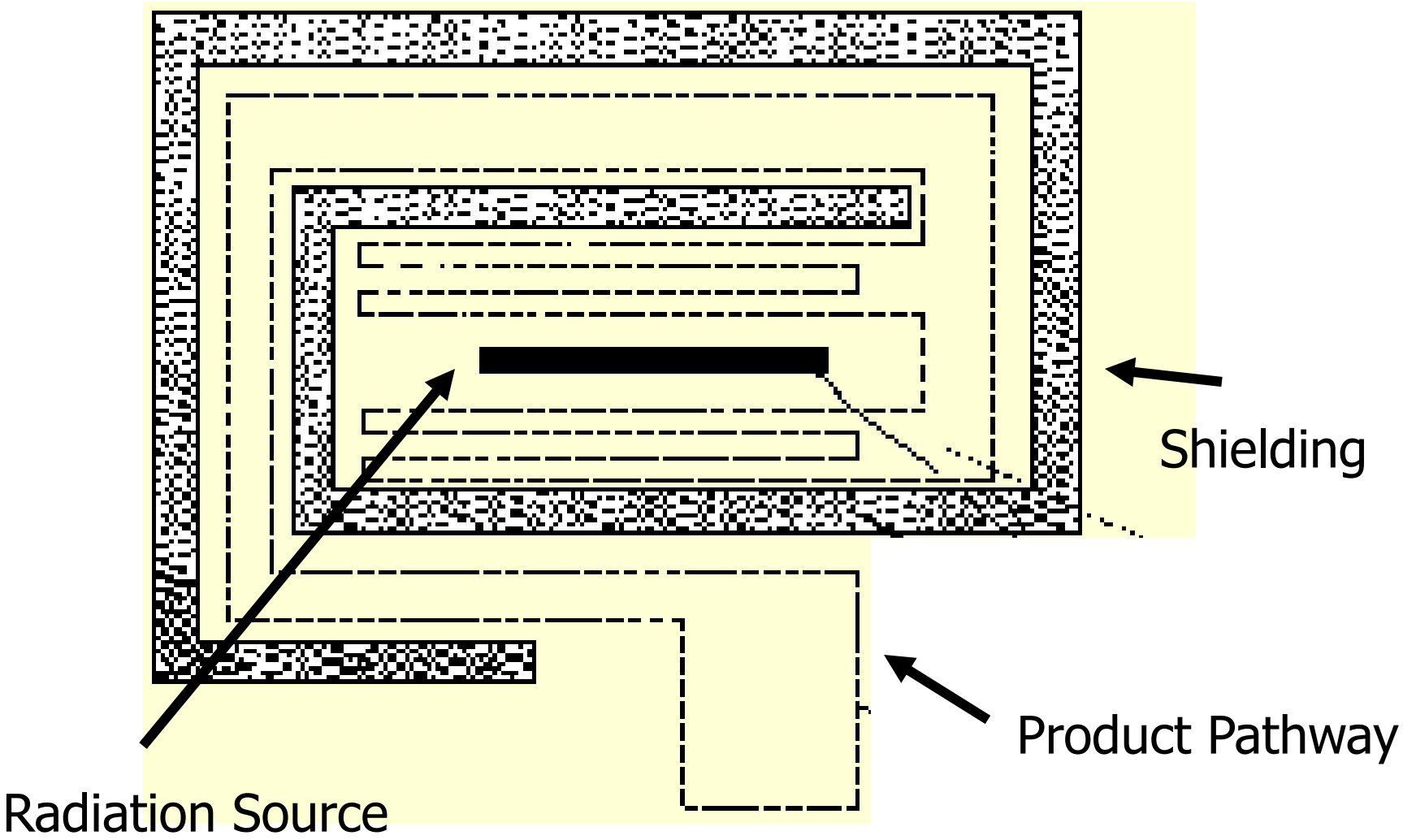
- Gamma rays - γ rays – most common
- Electron beam - β rays – growing use
- X-rays – emerging method (similar to electron beam with much greater power)

- All irradiation methods are similar in their approach & validation.

Gamma Sterilizer

- Nearly all facilities use Co^{60}
- Dose varies over time as source decays.
- Usually operate in a continuous manner with load items moving around the source
  - Individual containers on a conveyor
  - Multiple containers in a carrier
- Off carrier studies for fractional dose during development may give widely varying results.

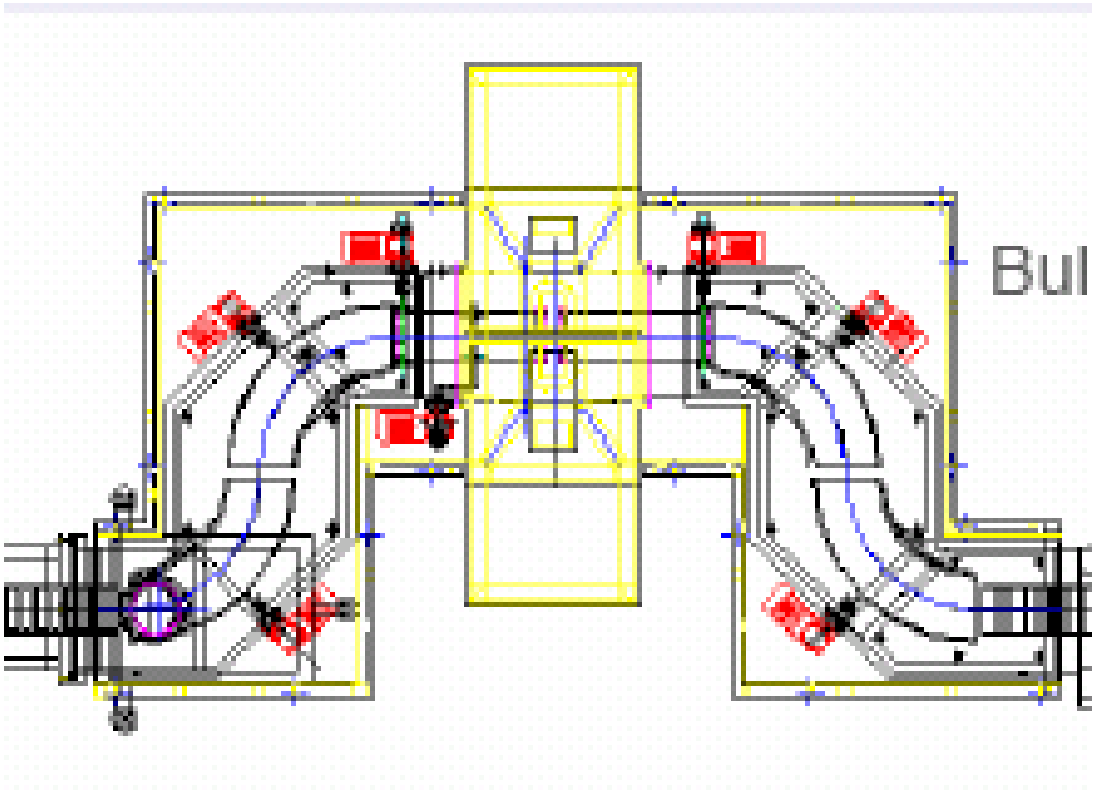
Typical Gamma Irradiator Layout



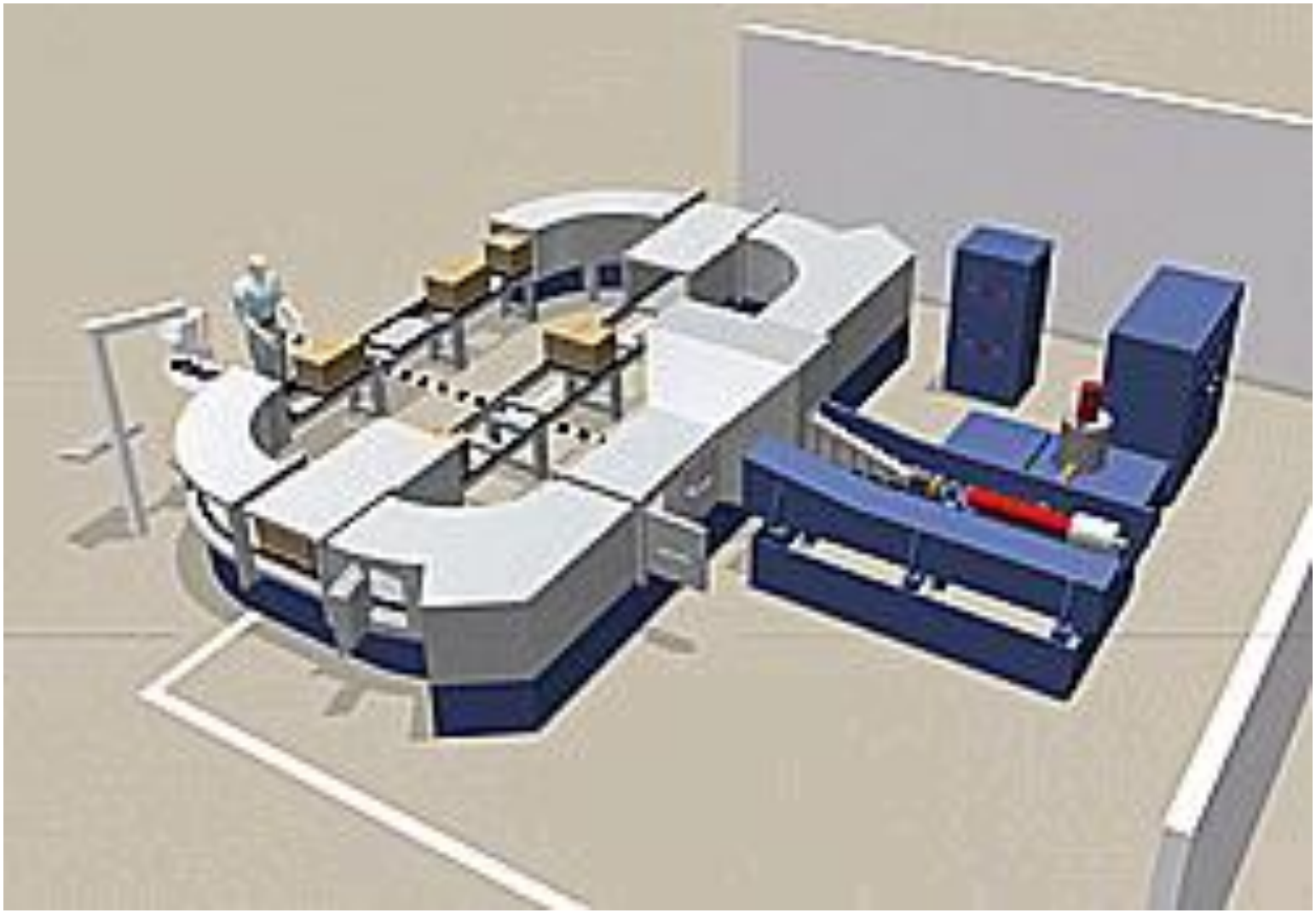
E-Beam Sterilizer

- Use accelerated & focused electrons to sterilize a limited volume.
- No change in dose over time.
- Containers are brought into the chamber intermittently.
- Heat input to materials can be substantial given the speed of the process.

E-Beam Sterilizer Material Flow



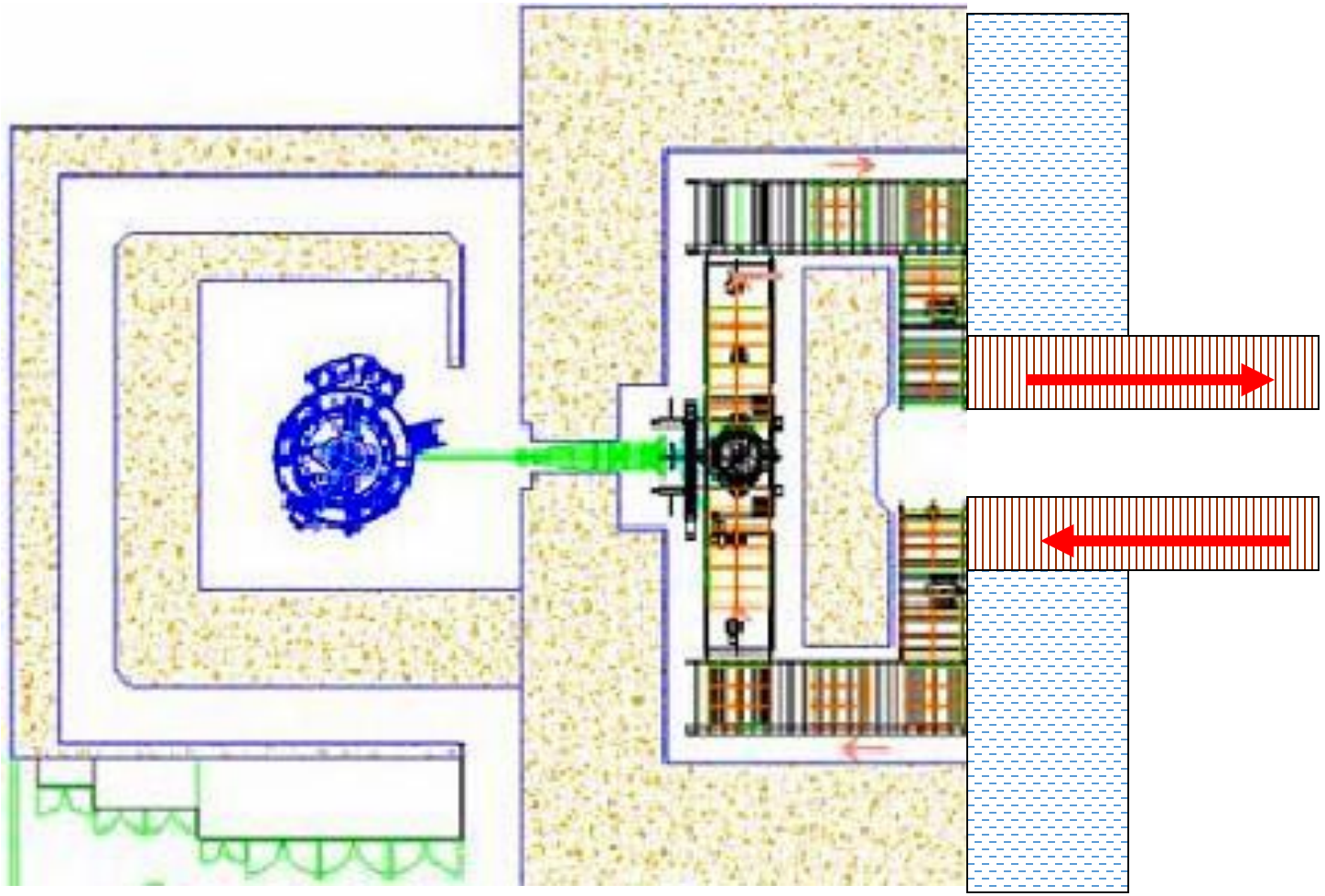
E-Beam Process Flow



X-ray Sterilizer

- Use X-rays to sterilize with substantially greater penetrating power than electron beam.
- No change in dose over time.
- Pallets (multiple pallets are possible) are brought into the chamber intermittently.
- Heat input to materials can be substantial given the speed of the process.

Typical X-ray Sterilizer Layout



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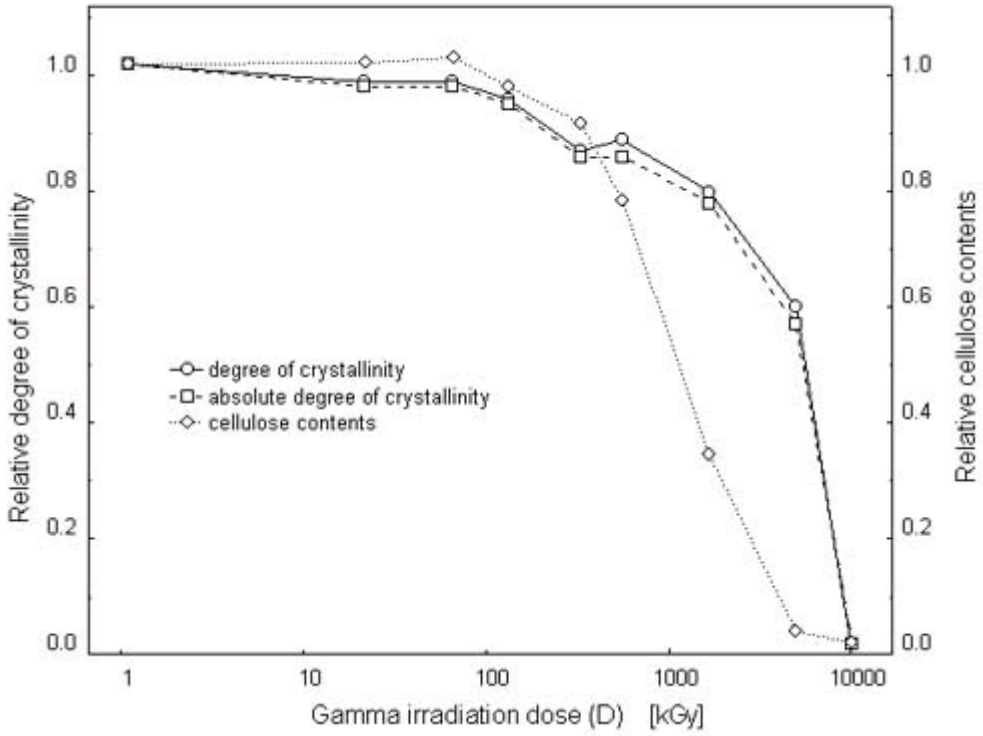
Material Effect vs. Dose



Establishing the Dose

- Initial work in the 1950's indicated that a dose of 2.5 Mrad (25 kGy) would safely render materials sterile.
- Later studies showed that a 4.5 Mrad (45 kGy) dose was required.
- With control over the bioburden, the level can be reduced.
  - Europe requires a 3.2 Mrad (32 kGy) dose??
  - The US is more flexible in its approach and has no required minimum dose

Radiation Sterilization Dose Setting

- ANSI/AAMI/ISO 11137-2 -2006
  - Method 1 - dose is based on product bioburden
  - Method 2 - dose is based upon radiation response of the bioburden
  - VD_{max} Method – substantiation of 15 and 25 kGy dose
- AAMI TIR33:2005
  - VD_{max} Method – application expanded to substantiation of 15 - 35 kGy dose (to be changed in next revision ISO 11137)

Sterilization Method Choices

Sterilization Methods		1	2	3
Bioburden	<1,000 CFU	X	X	X
	>1,000 CFU	X	X	
Radiation Tolerance	<25 kGy	X	X	
	>25 kGy	X	X	X
Lot Size	<500 items			X
	>500 items	X	X	
Production Frequency	Routine	X	X	
	Infrequent			X
Bioburden Resistance	Resistant		X	
	Non-Resistant	X		X

Validation Method & Sample Size

Validation Method	Samples Required	
	Initial Validation	Dose Audit
Method 1	136	110
Method 2	643	110
Method 3	66-306	20-100

Dose Confirmation

- Dosimeters which rely on color change are almost universally used to confirm dose delivery. Their response has been correlated to microbial destruction.
- As radiation sterilization is the simplest method to control, BI use is less common.
- Dosimeters measure lethality directly.

Validation Requirements - 1

- Irradiation equipment I/OQ - initial
- Irradiator dose mapping - periodic
  - w/o load – similar to empty chamber
  - with mock load – to determine dose ratio (maximum/minimum dose) which should be minimized
- Definition of loading pattern with objective of minimizing the dose ratio,

Validation Requirements - 2

- Product Dose Mapping
  - Map load with dosimeters
  - Dose ratio will vary with load density and may differ substantially from mock load
  - Average load density may not be accurate when very dense materials are processed
- Results of fractional dose studies during development support the lethality delivered in full dose studies

Process Control

- Dosimeters are used for confirmation that minimum and maximum dose requirements are met.
- Lots are released based upon satisfactory dosimetry results. **No microbiological testing is necessary!!!**
- Unusual variations in either the maximum dose, minimum dose, or the dose ratio indicate that some change has occurred which should be investigated.

Other Requirements

- Tight change control on materials to preclude subtle changes which could impact key product attributes
- Ongoing bioburden monitoring program to ensure continued acceptability of process.
- Periodic audits of contract sterilization providers required.

Radiation Sterilization Standards

Document	EU	ISO	USA
Estimation of population	EN 1174	11737-1: 1995	AAMI TIR No. 8: 1991
Microbiological sterility		11737-2: 1996	AAMI TIR No. 8: 1991
Validation sterilization methods 1 and 2	EN 552: 1994	11137: 1994	EAAMI ST 31: 1990 ST 32: 1991
Validation sterilization small lots & single batch			AAMI/ISO TIR 13409: 1996 15844: 1998

VD_{max} Method

- Bioburden method validation
- Bioburden determination (10 units, from 3 batches)
- Identification of verification dose
- Verification dose experiment
  - Irradiate 10 units at the verification dose
  - Bacteriostasis and fungistasis test
  - Sterility test of 10 units using SCDM incubating at 28-32ºC for 14 days
- Interpretation
  - ≤1 non-sterile – validation passes and can release product at selected kGy
  - 2 non-sterile – confirmatory test required
  - ≥2 non-sterile – validation failed

Biological Indicators Unnecessary

- The original BI for radiation, *B. pumilus*, is contraindicated in current standard:
  - Its resistance is not representative of bioburden organisms (many less resistant, some more).
  - Its resistance is inadequate to confirm a 25 kGy dose (the most common dose) in use.
  - Dosimeters are simpler to use, and give near immediate results.
- Any possible substitute microorganism would have the same limitations.
- Dose setting based upon the actual resistance of real world bioburden is safer and more accurate.

Dose Audits

- Periodic confirmation that the numbers / types of organisms in the bioburden are consistent with the established sterilization dose.

- Dose audits are performed initially on a quarterly basis, with defined rules for change to semi-annual and then annual audits.

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- Tight change control on materials to preclude subtle changes which could impact key product attributes
- Ongoing bioburden monitoring program to ensure continued acceptability of manufacturing process.
- Periodic audits of contract sterilization providers required.

Possible Post A/P Radiation Treatments

- Develop methods that utilize microbial resistance models more aligned with potential contaminants in aseptically-produced products.
  - Populations “A” and “B”
- Combined approach: A/P then low dose radiation
  - “A/P” to a PNSU of 10^{-3}
  - Irradiate at 5.4 kGy (provides an additional 3 SLR)
- Adopt notion of a “Aseptic Processing Equivalent Dose”
  - Irradiate product to an SAL of 10^{-4} - outcome equivalent microbiologically to A/P
  - Get to “make it sterile” versus trying to “keep it sterile”.
  - Control endotoxin & particle by process means.