Terminal Sterilization or Bioburden Reduction Processes Using Ionizing Radiation

Betty Howard

Sr. Radiation Sterilization Manager, STERIS AST

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Topics for Today

- Types of radiation processes
- Key Considerations in use of Radiation Pros and Cons
- Over view of each process modality (Gamma, Electron Beam, X Ray)
- Similarities and differences in modalities
- Consideration specific to Pharmaceutical Industries

Advantages of Radiation processes vs other Sterilization methods

- No added heat or moisture to process
- Only one variable to optimize: dose
- Short processing times
- Well tolerated by most materials used in healthcare
- Deep penetration into cases of product
- No vacuum applied in processing
- No residuals created that need to be removed or reduced
- No specialized packaging needed
- Can process frozen, dry or liquid products
- History (continuous use on industrial levels since early 1950’s)
- Availability worldwide
- Validation of dose ranges, fast, within a few months with small amounts of product tested in most cases

Advantages

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- Robust, effective, great deal of history as a successful sterilization method.
- Can be used with wide density ranges of products
- Ability to determine dose required is
  - Well established
  - Has published standards with international recognition (ANSI/AAMI/ ISO documents provide guidance).

Potential Cons or Areas of Concern

- Material modification is possible so must be evaluated.
- Areas of concern include:

A few well known materials are not recommended or have concerns:

- PTFE (teflons) unless used as a lubricant
- Natural unstablized polypropylene; stable formats are available
- Acetals (ex. Delrin)
- Unbuffered liquids where final pH is critical
- Active proteins especially in solution
- Discoloration possible

- In some cases there are fixes, resin formulations, color corrected resins, freezing or lyophilizing to limit changes in liquids, antioxidants, free radical scavengers.

Radiation vs. Irradiation
What is it?

- *Radiation* – energy transmitted by waves or a stream or particles (like gamma waves, X ray, alpha particles, electrons, heat)…

- Generic Term

- *Irradiation* – the process of exposing a material to ionizing radiation.

- Very Specific, refers to energy capable of changing atoms and molecules by creating charged units called ions

energy ***process***

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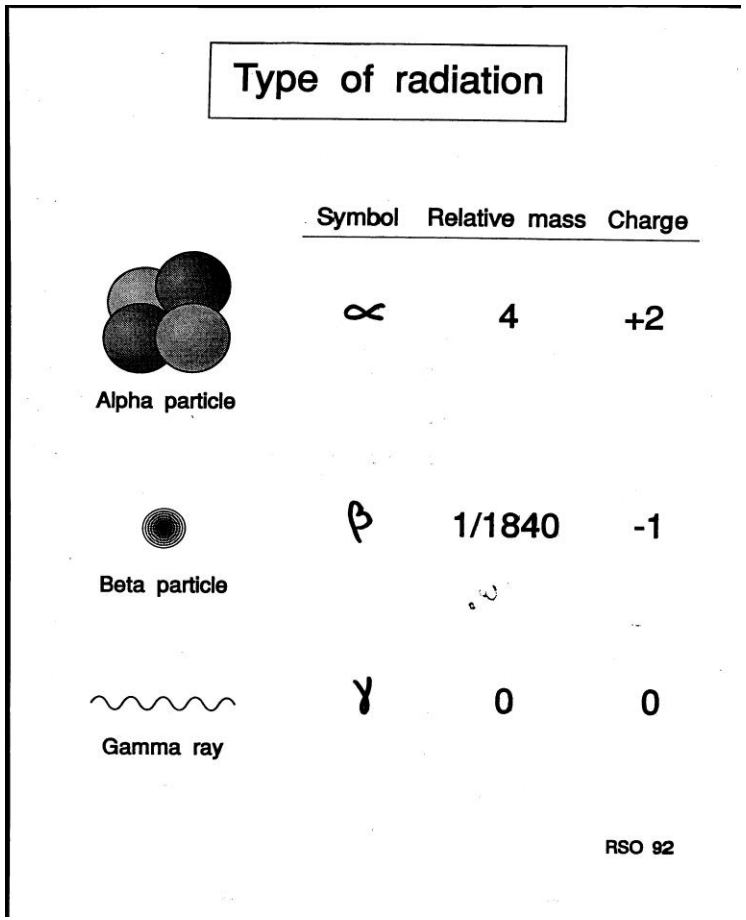
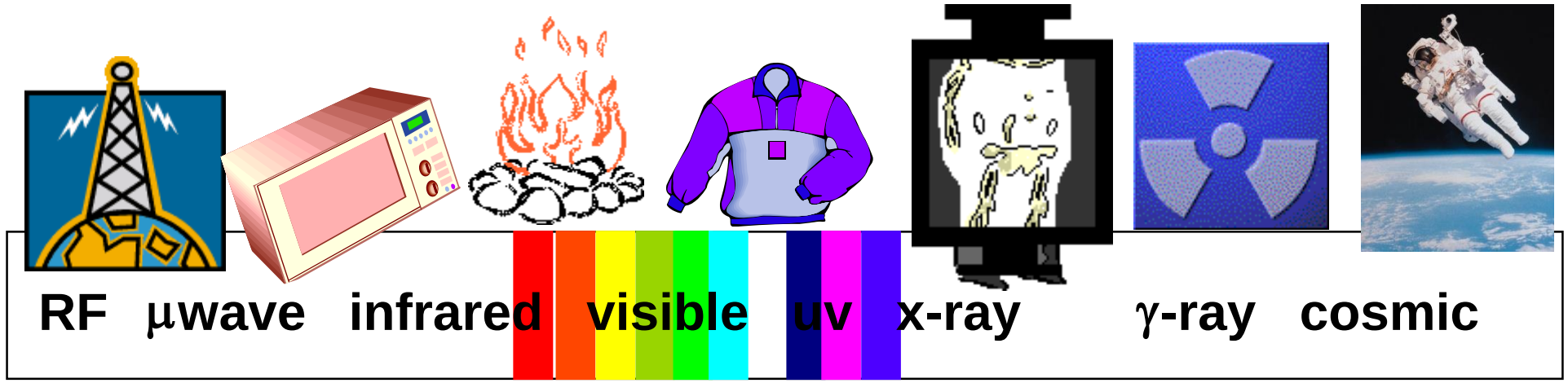
Types of Ionizing Radiation



- Alpha, beta, gamma, and x-ray were all discovered between 1895 and 1900
- Alpha and beta are “particulate” or have mass
- Gamma and X Ray are photons ; no mass, no charge.

Electromagnetic Spectrum



Non-ionizing

Longer wavelength

Low Energy

Ionizing radiation

Shorter wavelength

High Energy

α

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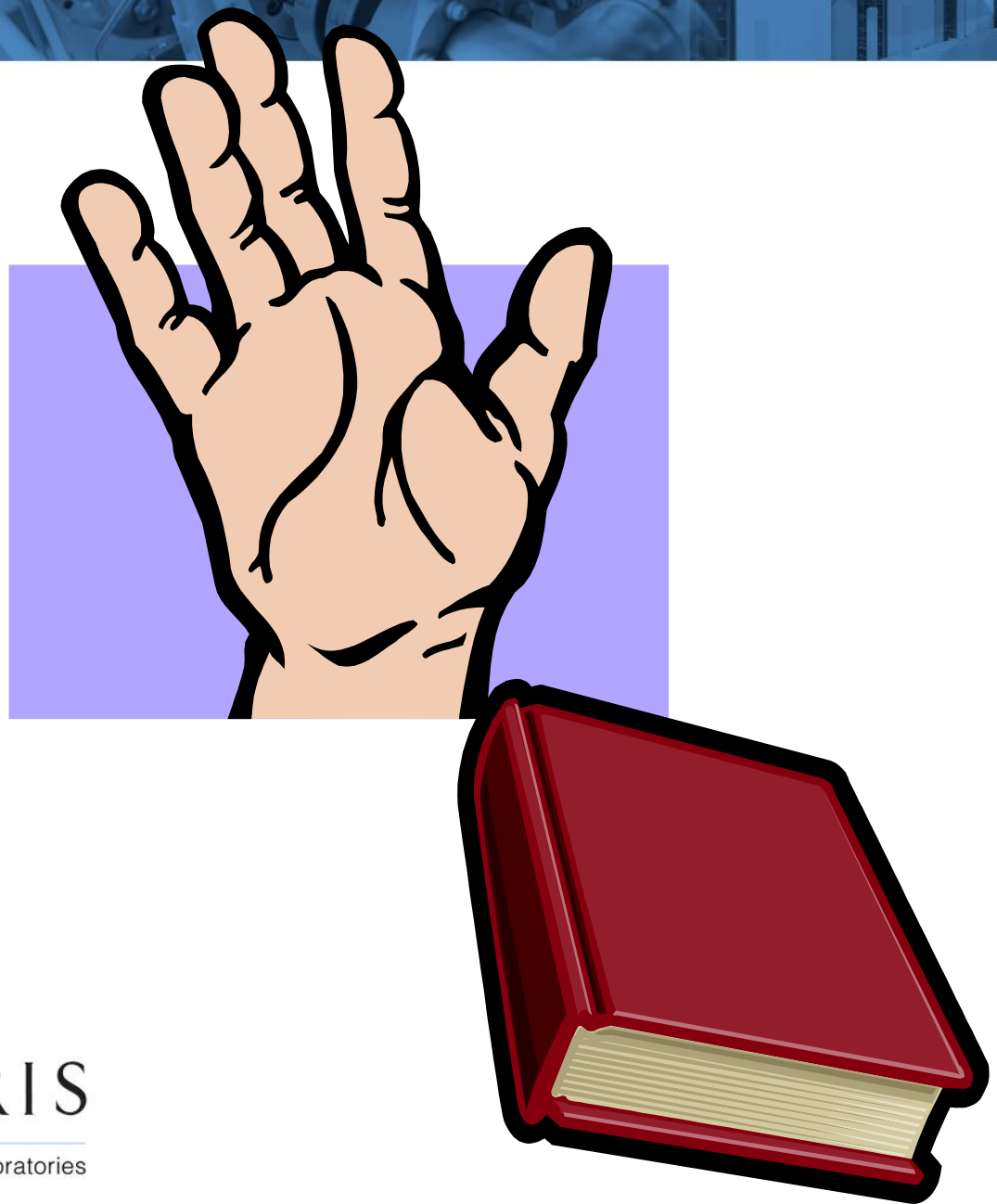
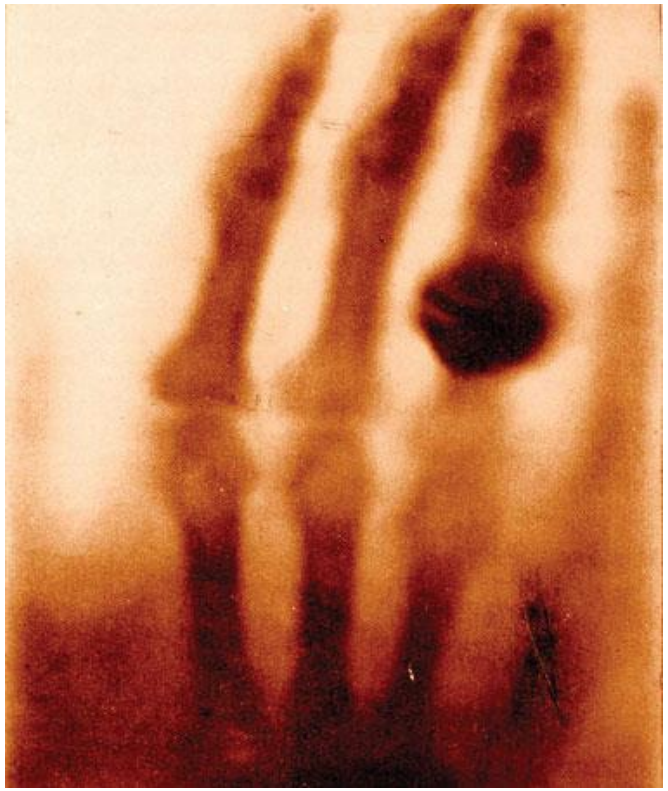


e-

e-

β particle - electron

X-ray

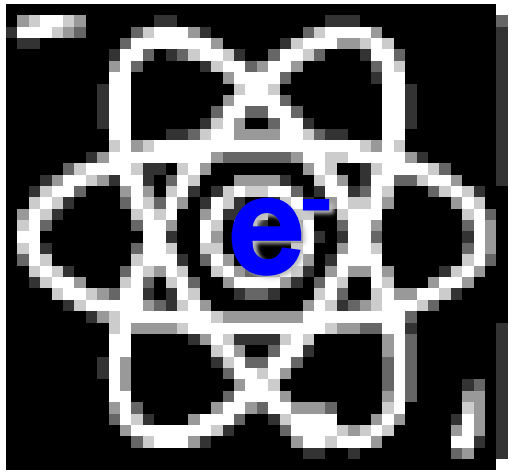


- A form of electromagnetic radiation produced mainly by artificial means rather than by radioactive substances
- Penetration similar to gamma

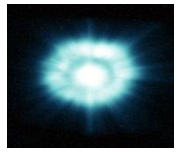
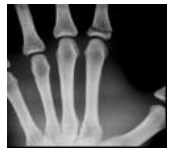
Ionizing Radiation

- Ionization - Atomic interactions resulting in the loss or gain of electrons
- Ionizing radiation – particles or photons that have sufficient energy to cause ionization

Ionizing Radiation
Ionizing Radiation
Ionizing Radiation
Ionizing Radiation
Ionizing Radiation
Ionizing Radiation



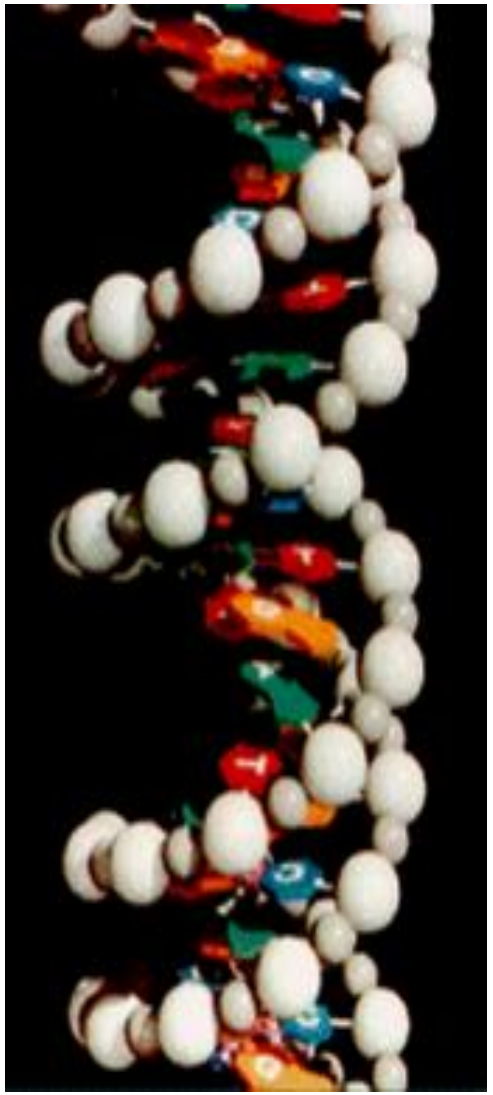
Nature of Ionizing Radiation

- Gamma 
- X-Rays 
- Accelerated electrons 

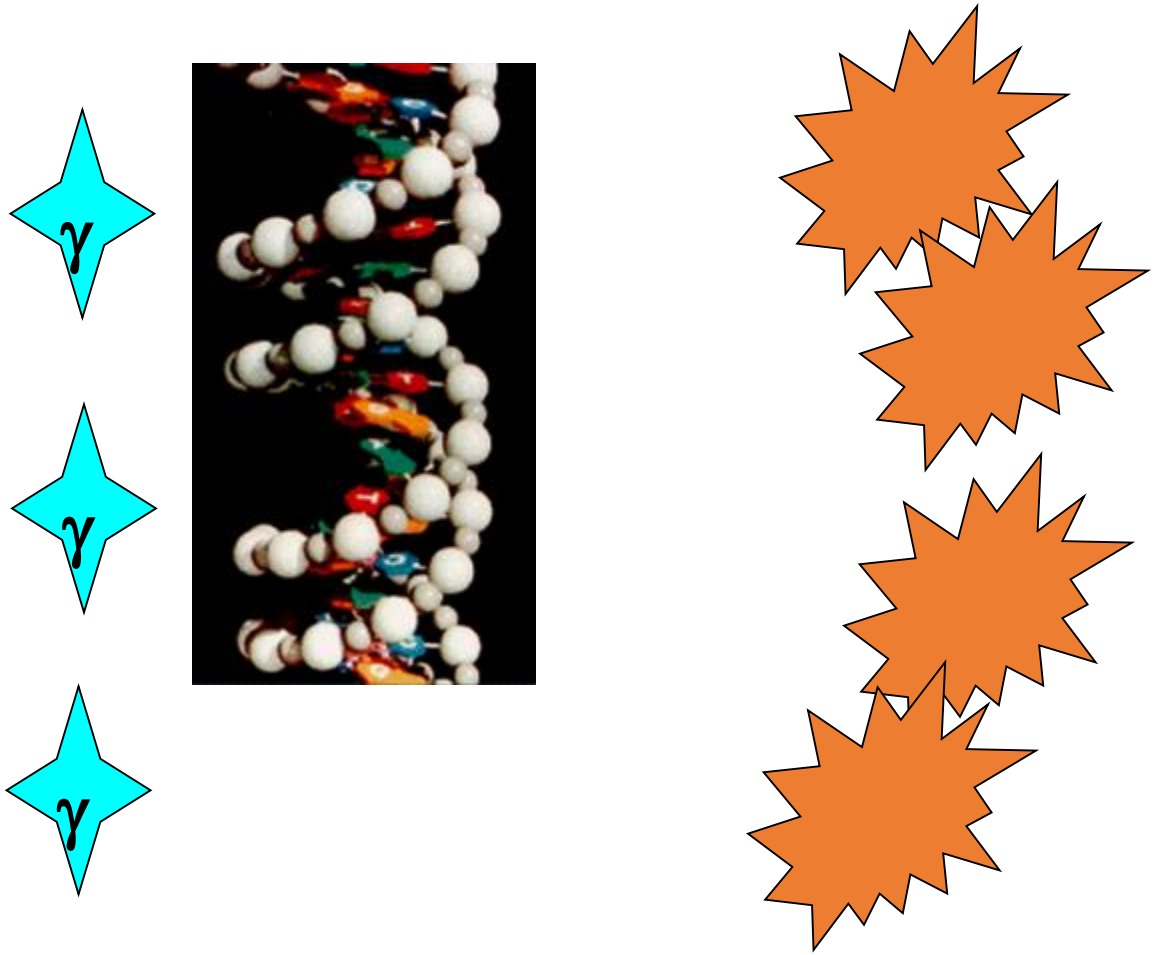
Ionizing radiation

Lethality and Irradiation: How and Why Does it Kill?

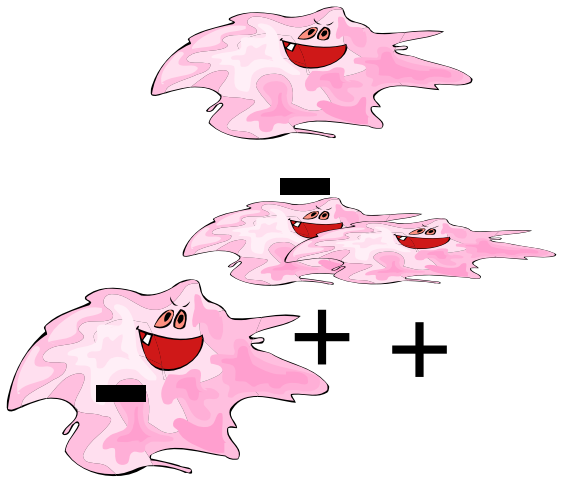
- Complex systems have many points of disruption that can lead to catastrophic damage or lethality.
- Ex. DNA is a large molecule and fairly easily disrupted.
- Ionizing Radiation can break DNA's chemical bonds and render it non-viable or incapable of reproduction (sterile).



How Does it Kill? Direct



How Does it Kill? Indirect



Where do we start?

- Healthcare products start with the needs for patients
  - A need is determined
  - RD to figure out a way to solve the need
  - Design a device/product for purpose
    - How it will be made?
    - What it will be made of?
    - What is required for its use?

Since many products are implanted, injected or used on open wounds must consider in design that they will be sterilized as part of requirements for its use.

Will product tolerate and be effective if it is sterilized?

All of the decisions made even in early stages can impact ability to process and ease of sterilization.

How is it made?

- Sources of materials
- Location of Manufacture
- Manufacturing environment
- Manufacturing processes (cutting, assembly, cleaning, purification , packaging , all contact points)

- Any thing that a product touches or is exposed to can add Bioburden (microbial contamination)

What is Bioburden and why do we care

- Bioburden is the amount and types of viable organism that end up on your product as part of manufacturing.
- Everything up until the sterile barrier/ package is sealed count.
- Bioburden is measured in quantity (cfus; colony forming units) but quantity alone does not tell you how it will respond to a sterilization process. The types of organisms matter too.
- Bioburden is the most common variable used to set a minimum sterilization doses so it must be controlled and be in control over time.

Dose setting Methods

- Most commonly applied methods are in published standards used worldwide
  - ANSI/ AAMI/ ISO or other national requirements
    - American National Standard
    - Association for the Advancement of Medical Instrumentation
    - International Standards Organization

Irradiation References

- ANSI/AAMI/ISO 11137-1, 2 and 3 Dose setting methods/dose tables and requirements
- ANSI/AAMI/ISO 11737-1 Microbiology methods for testing bioburden
- ANSI/AAMI/ISO 11737-2 Microbiology Methods for testing sterility
- AAMI/ISO TIR 13004 Additional dose setting methods and tables
- AAMI TIR 17 Materials Compatibility to sterilization processes
- AAMI TIR 29 Process characterization and control in radiation processes
- AAMI TIR 35 Product adoption and alternate sampling plans in testing
- AAMI TIR 37 Guidance on human tissue processing
- AAMI TIR 40 Modified Method 2

All and more available in pdf form from aami.org

Testing for dose setting

- Method development for Bioburden measurements (Recovery Efficiency assure most accurate cfu count)
- Bioburden using validated methods
- Suitability of Sterility test method (Bacteriostasis/ Fungistasis)
- Sterility
- Determination of maximum allowable dose (worst case dose that will be used)
- These tests allow you to accurately measure and monitor your production process, assure it is process control and set a dose range that will be used in terminal sterilization of the product.

Dose setting methods

- Using the tests in previous slides , the standards define sample numbers and tests for a series of methods:
- VD max methods , validates a selected minimum dose based on bioburden type and resistance
- Method 1 validates a minimum dose based on bioburden types and resistance
- Method 2 sets a dose based on radiation resistance

- In the interest of time today we cannot go through the details of each listed method. But all can be used to set a dose range for a sterile product and achieve the Sterility Assurance Level SAL) required for a product.

Brief look at types of Radiation Processes

- Options :

- Gamma
- Electron Beam
- X Ray

Gamma, E-beam & X Ray Processing

- <u>Similarities</u>
- Processing
  - Load product, pass through irradiation zone & unload
- Ionization (dose = dose)
- Mode of interactions with biological molecules
- Regulatory /Guidance
  - CFR's, GMP's and ANSI/AAMI/ISO documents
- Qualification / validation of product and process
  - Material and microbial effects
  - Process Control: AAMI TIR 29
  - Dose Setting: AAMI/ISO 11137, AAMI/ISO TIR13004,
  - TIR 35, TIR 37, TIR 40.

Gamma , E-beam and X Ray Processing

Differences

- Physics: Gamma vs. E-beam/ X Ray
  - How ionizing radiation is generated
- Facility design
  - E-beam/ X Ray requires different shielding
  - Product Conveyance systems are different
- Penetration E beam vs X Ray and gamma
- Dose rate
  - kGy/sec (E-beam) vs. kGy/hr (Gamma)
- Dosimetry (how dose is monitored)

Gamma Processing Variables

Dose is related to time More time in the irradiator more dose.

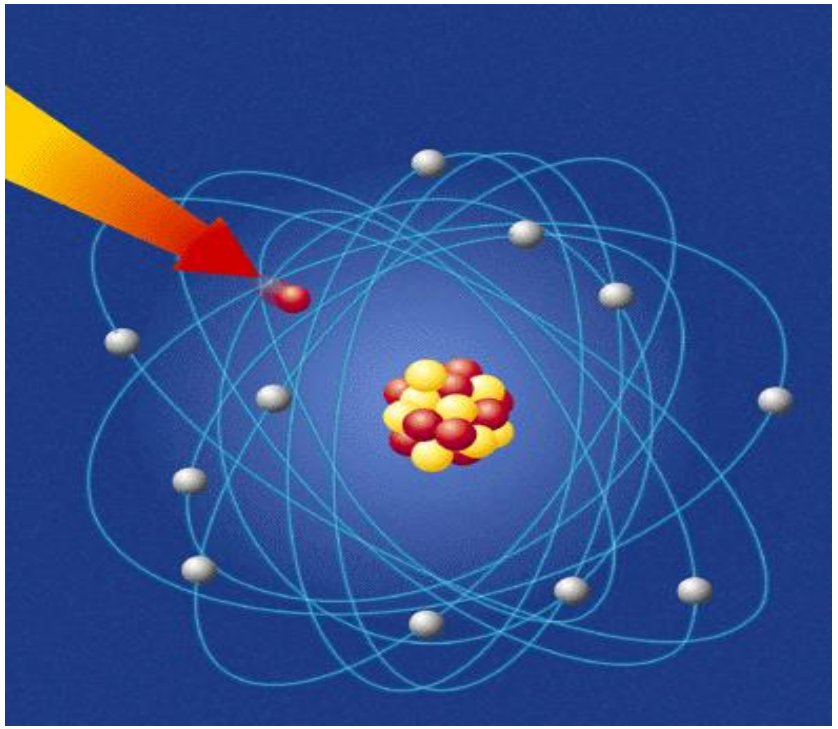
What can be modified at the product level (not at the equipment level)

- Dose requested
- Environment at the product level (Oxygen availability, temperature)

What is a Gamma Irradiator?

- **Irradiator**: Assembly/instrument that allows the safe and reliable delivery of irradiation. Includes conveyors to get product into and out of irradiator, source rack containing Cobalt 60, and all shielding and safety, and mechanical devices needed to operate it.

Gamma Irradiation Source Material: Cobalt 60



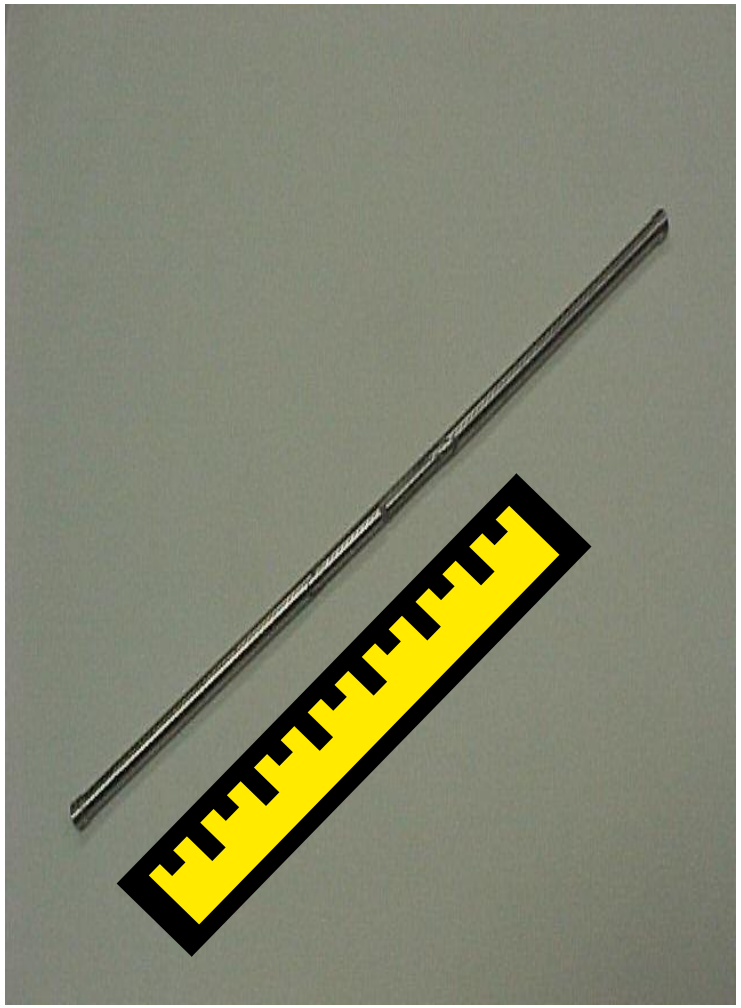
Will My Product become Radioactive?

- Gamma Photon energy averages 1.25 MeV (one photon at 1.17 and one at 1.33 Mev) well below energy needed to activate a material to create radioactive materials. Can't make something radioactive.
- Accelerated Electrons (Electron Beam) are used at energy levels in sterilization below levels with ability to potentially activate metals. 10 MeV or less.
- X-Ray is used at energy levels also not expected to activate metals 7.5 MeV or less .

Components of a Gamma Irradiator

- **Cobalt 60** (to provide photons)
- **Pencils** (to hold Cobalt 60)
- **Source Rack** (to hold pencils and allow safe controlled movement and storage of Cobalt 60)
- **Carriers or Totes** (hold product cartons so they can be transported into irradiator system, through the energy field and back out of the irradiator)
- **Conveyance System** (allows for controlled movement of carriers)
- **Containment** (safe storage of source when not in use).

Radioactive Material: Cobalt 60 Encapsulated



Radioactive Material:
Cobalt 60 Encapsulated

Source Racks

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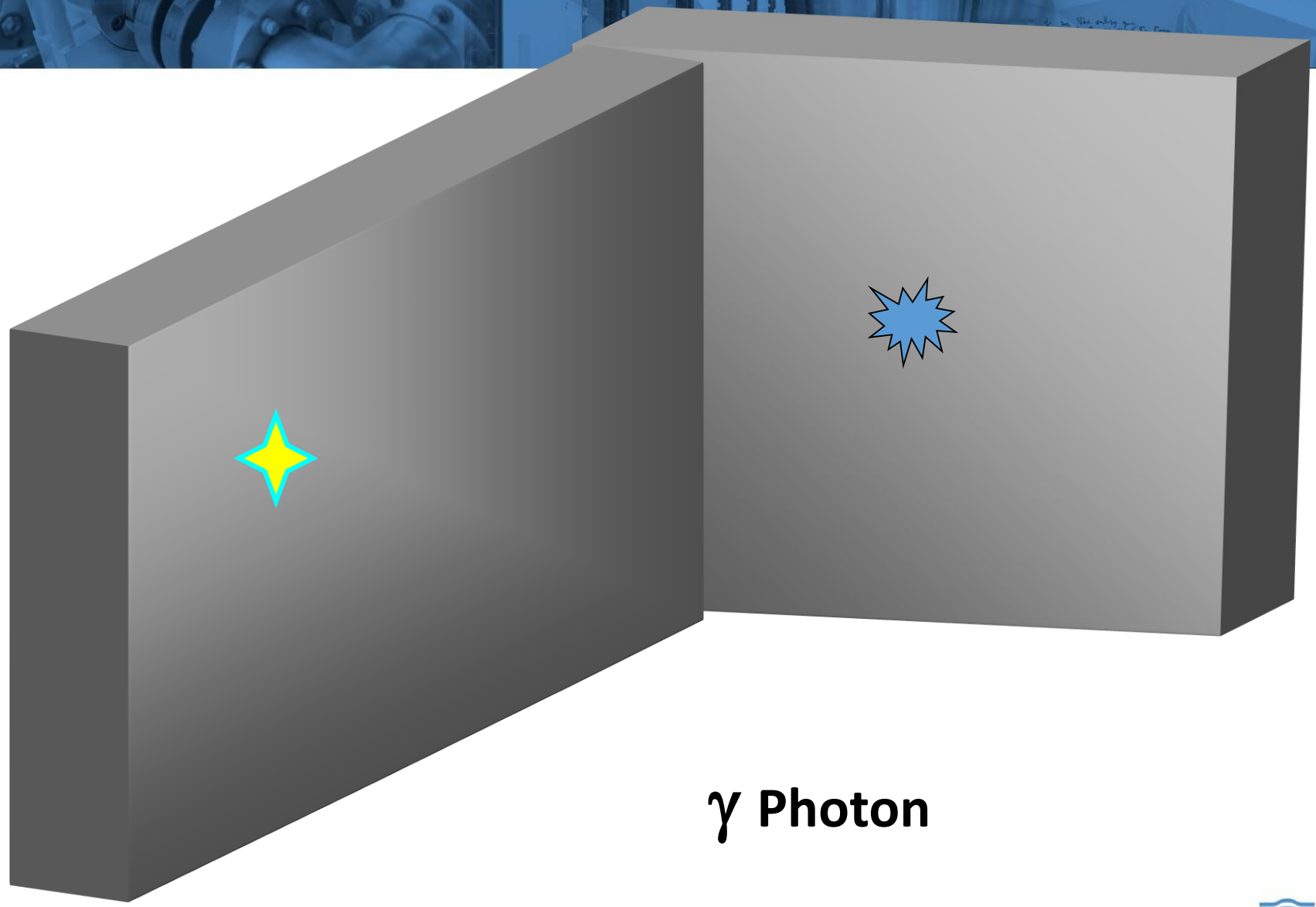
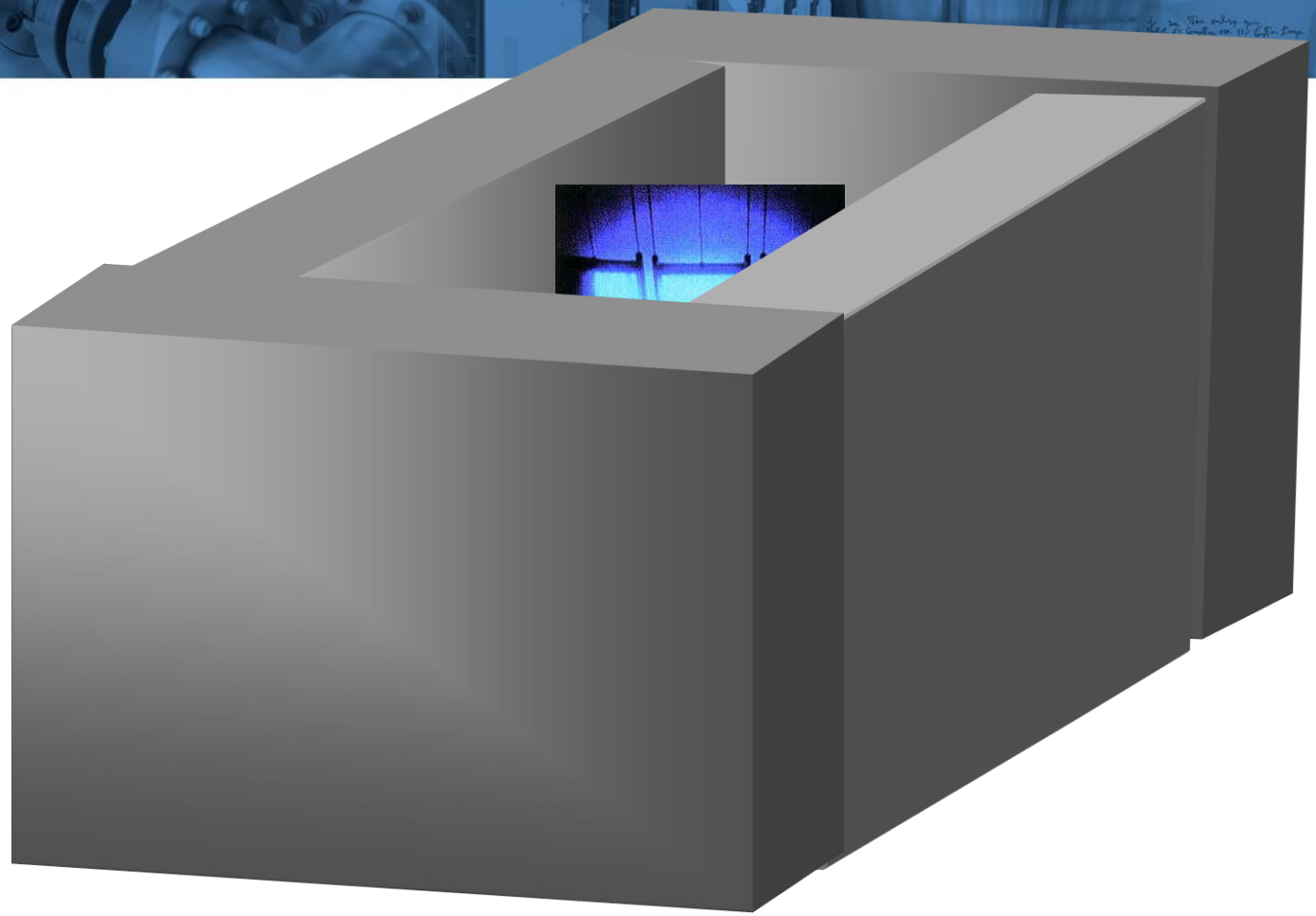


γ Photon



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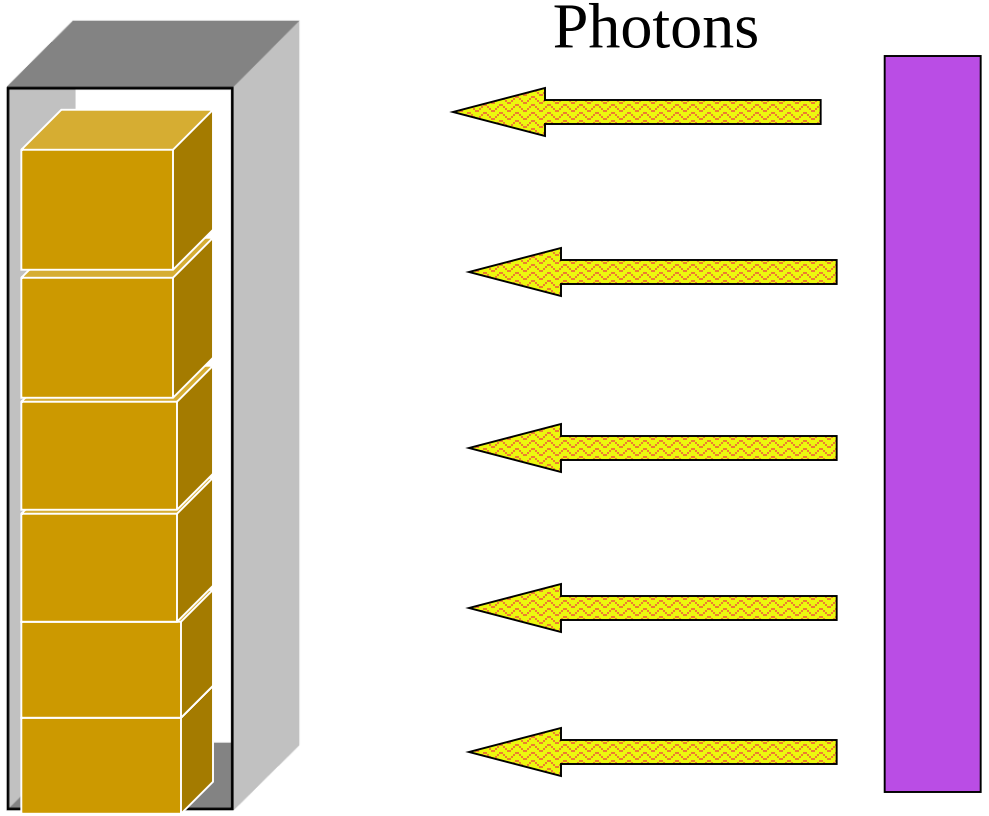
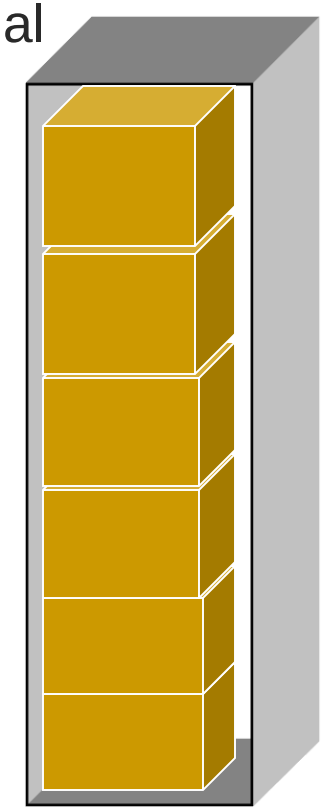
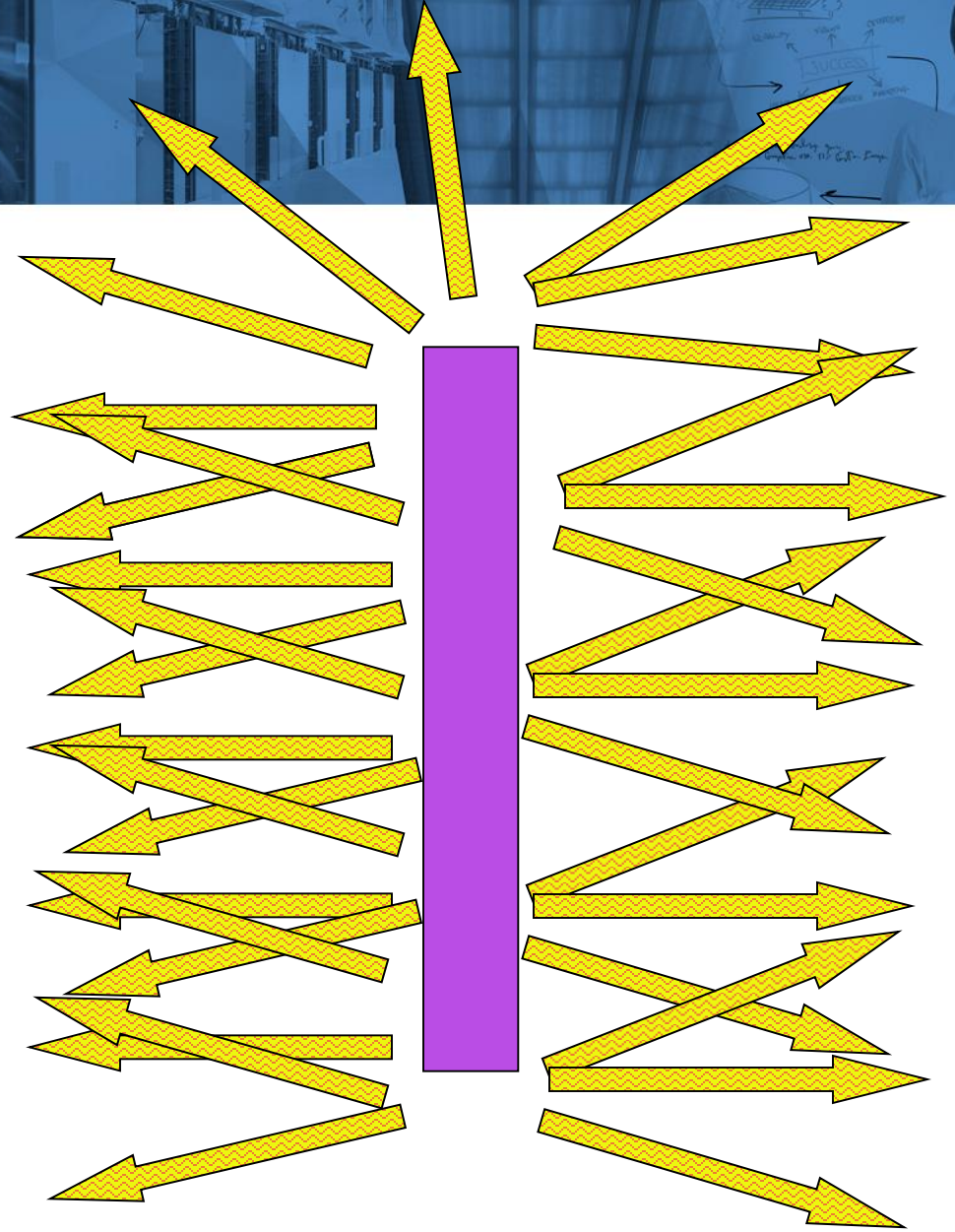
Running Product: Each configuration of Cobalt 60 will result in a specific energy interaction with a given product



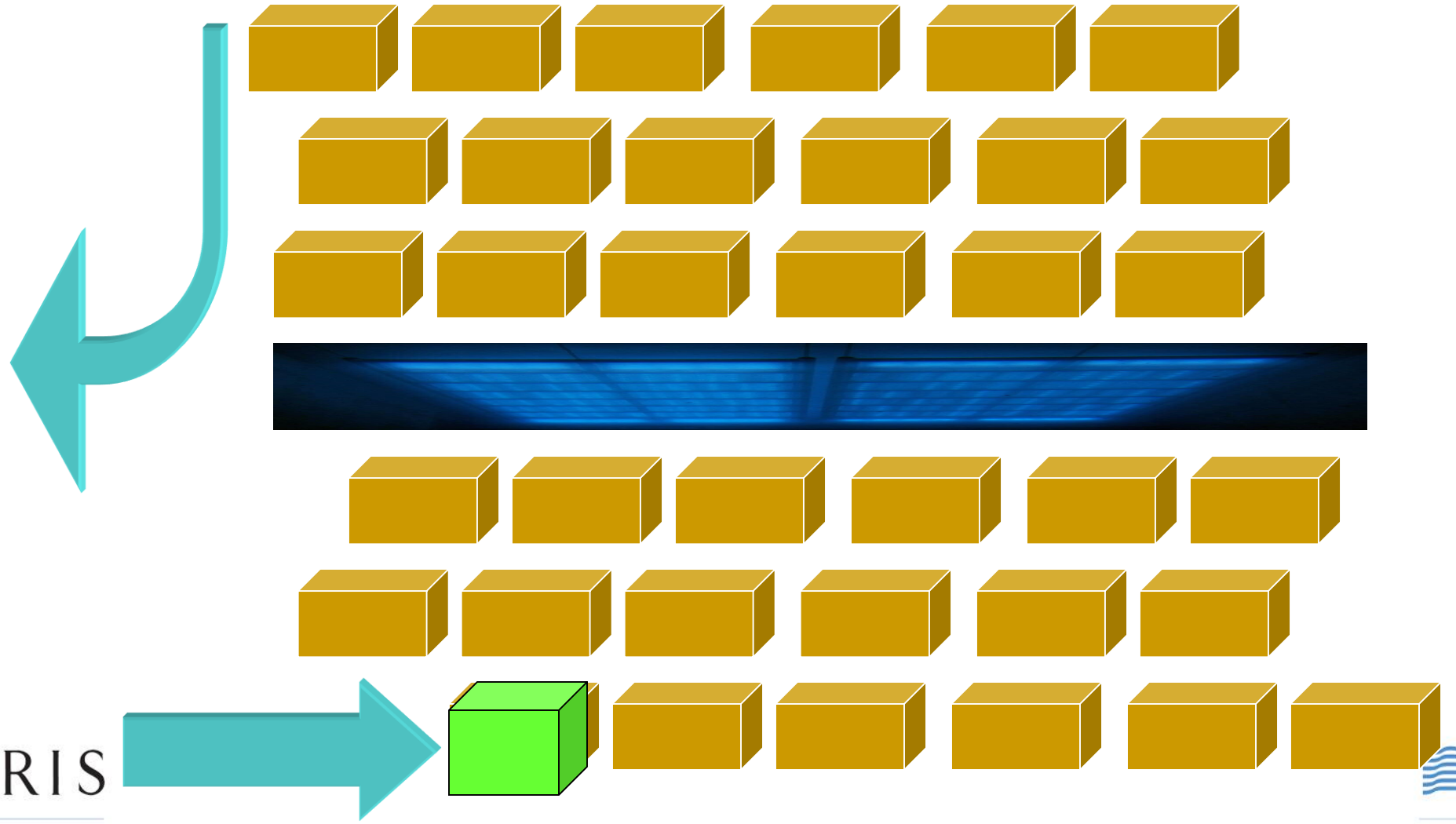
Isotropic energy:

photons are multi-directional



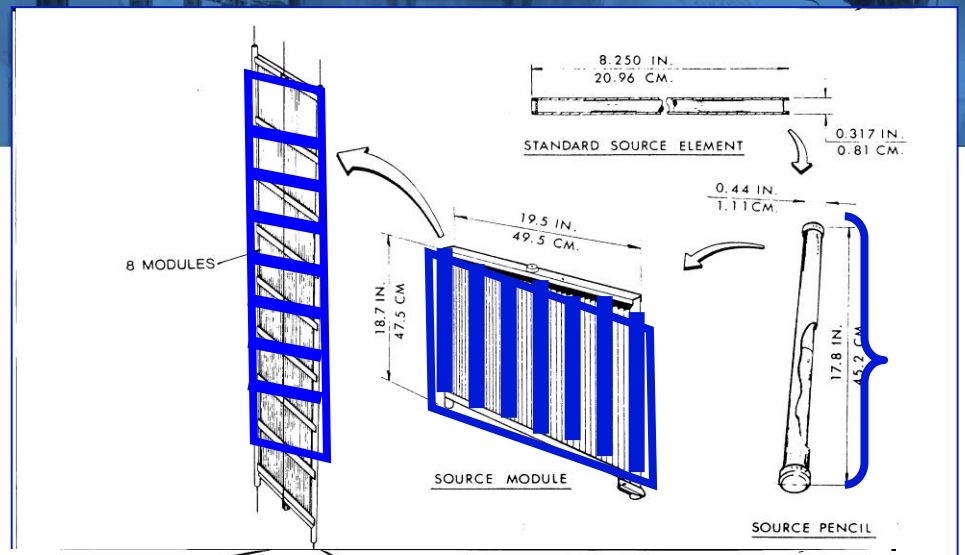


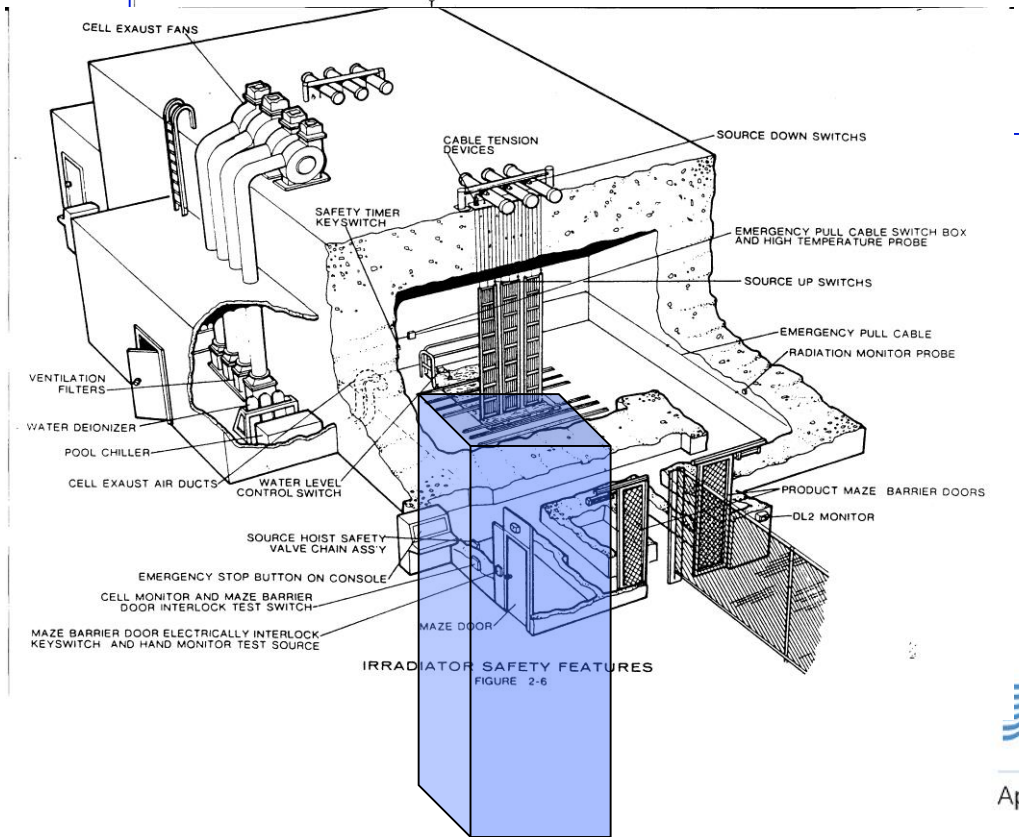
This is an overhead view of positions that may exist in a carrier's path around a source



Gamma Irradiator

Gamma irradiation requires a radioactive source, Cobalt 60 in a double encapsulated stainless steel rods, which emit photons of energy that penetrate product

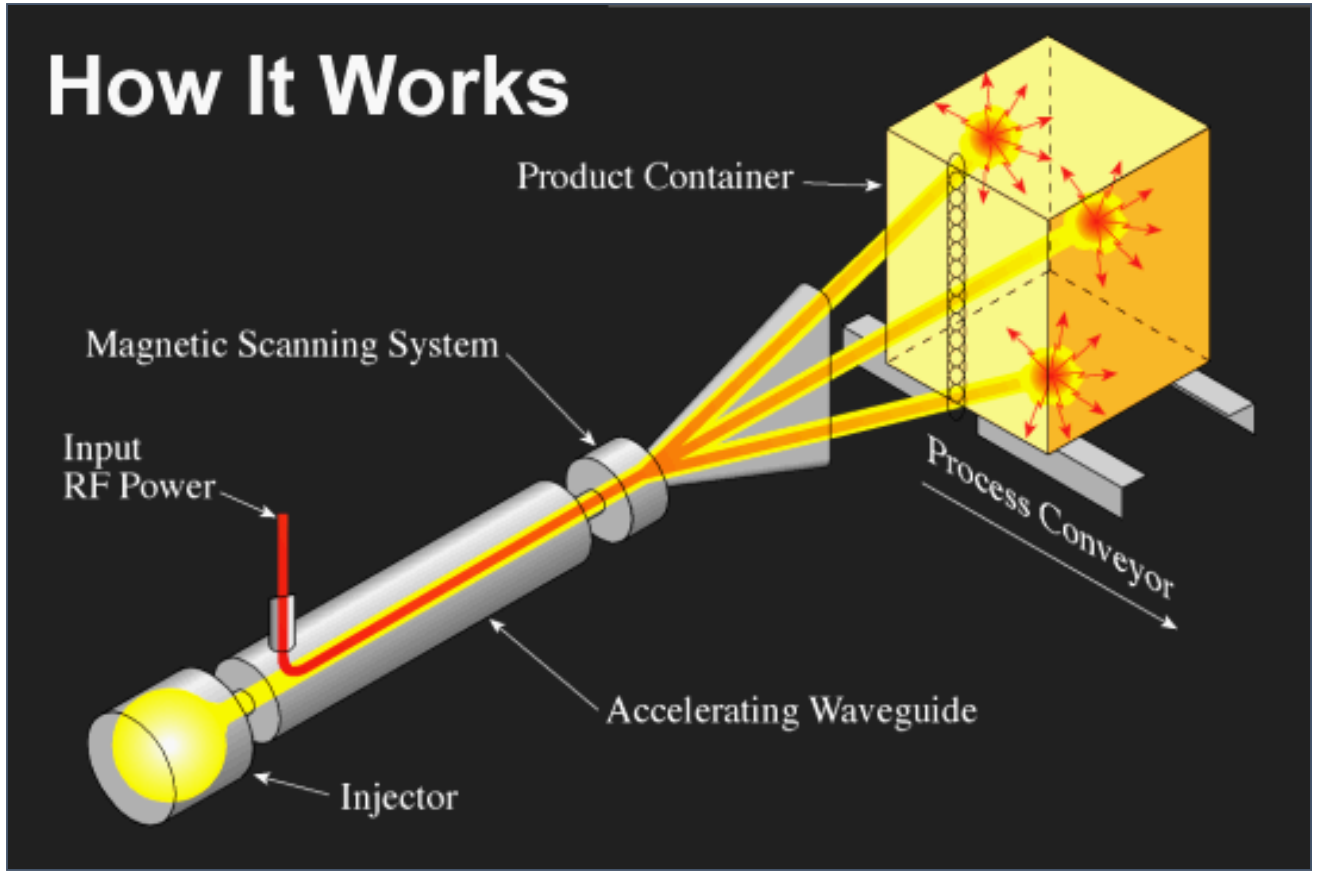




Electron Beam And X Ray

- Formats
- How X Ray is related to E Beam

The E-Beam Process



The E-beam Process

- **Energy source is electricity;**
- Using high voltage and magnets, **the electrons from the electricity source are sped up to just under the speed of light** via an accelerator.
- The resulting energy, ranging from 3 to 10 MeV and coupled with 1 – 50 kW of power, has **sufficient strength to penetrate** a wide range of materials;
- The electrons are **scanned** in a sweeping motion, creating a curtain of electrons;
- Product is **conveyed through the scan curtain at a tightly controlled speed**

Processing Variables

1. **Product Design and Orientation within Shipper Case**
   Established and controlled by Customer
2. **Carrier/Conveyor Loading Pattern**
   Defined by dose mapping
   Illustrated on Customer Specification Document
3. **Beam Scan Width**
   Defined by dose mapping
   Noted on Customer Specification Document
4. **Processing Speed**
   Calculated and verified from dose mapping

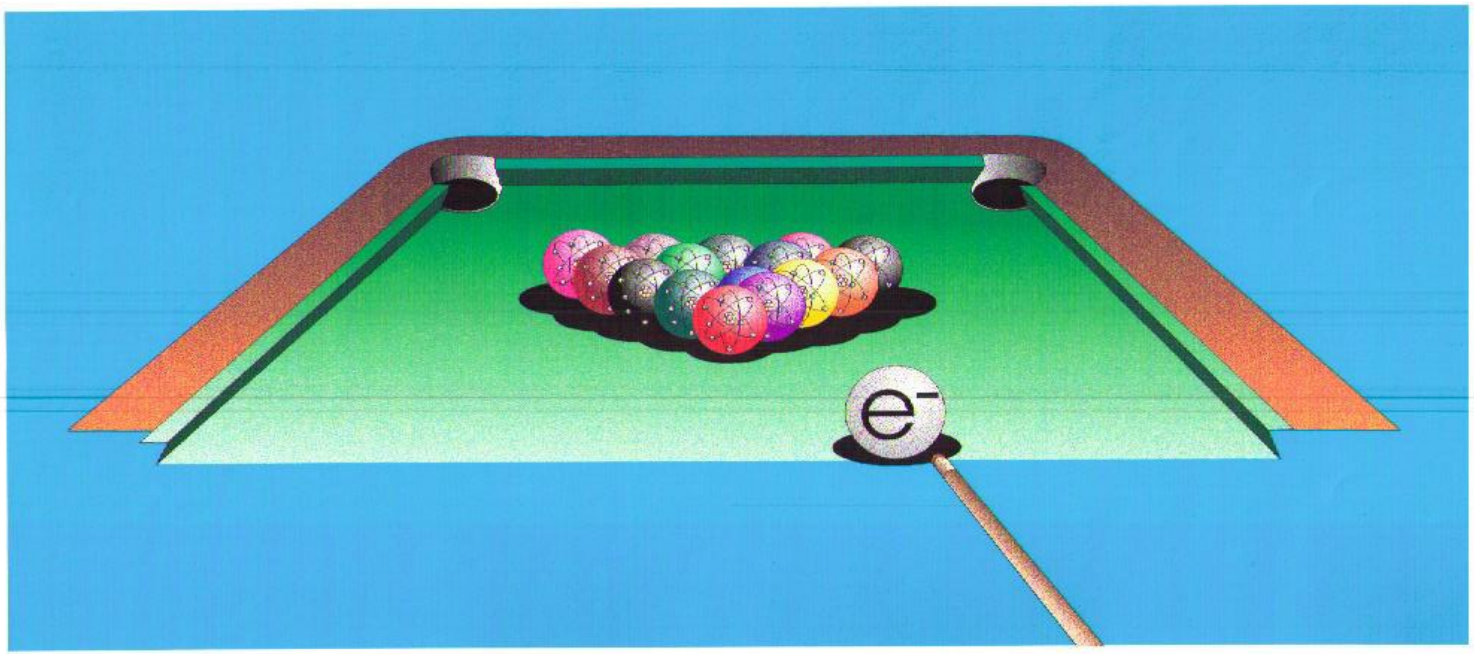
Important Terms: E Beam

Power

- Measured in kW (kilowatts)
- Measure of the number of accelerated electrons produced per unit time
- Determines processing capacity (throughput)

Energy

- Measured in MeV (million electron volts)
- Measure of the amount of kinetic energy of the accelerated electron
- Determines the penetration capability of the electron



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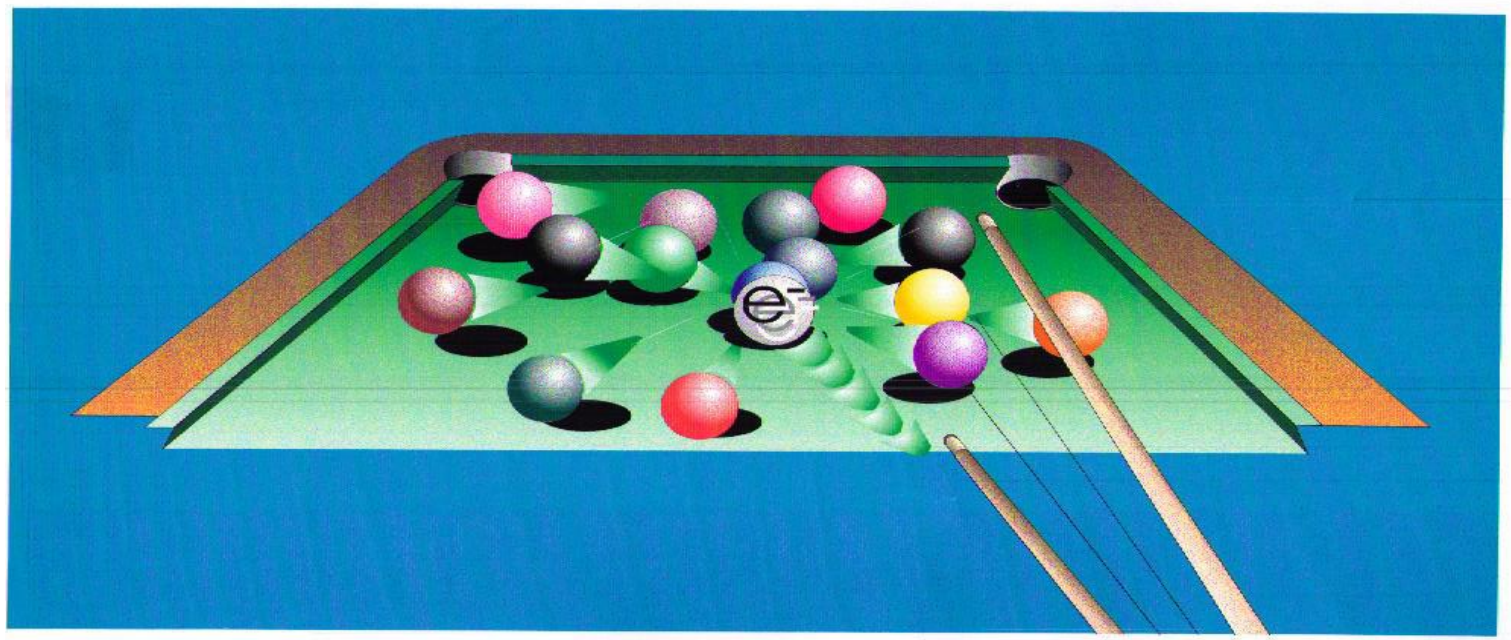

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Carrier Based E-Beam System – Overhead Conveyor

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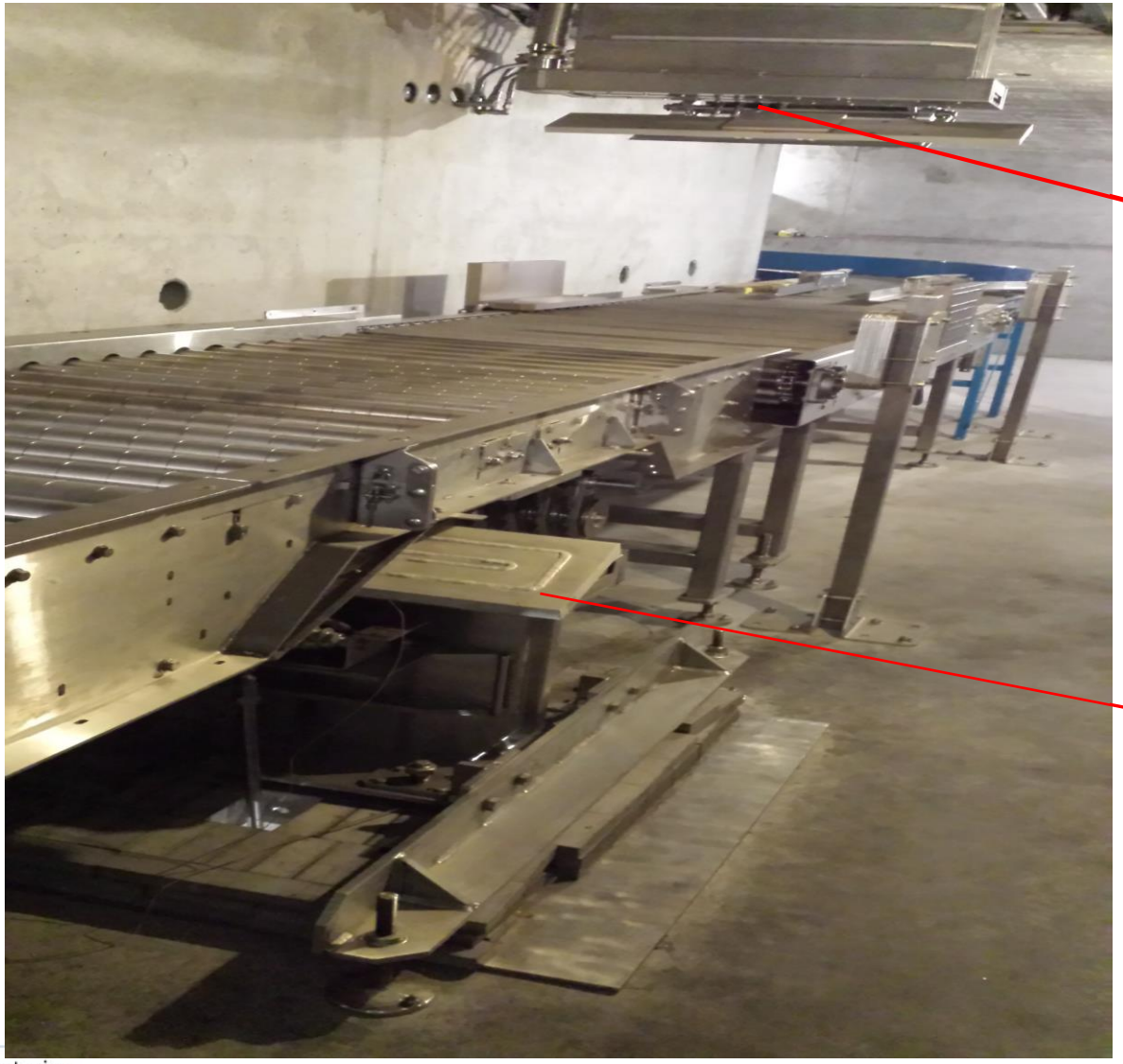
Newest System Design --

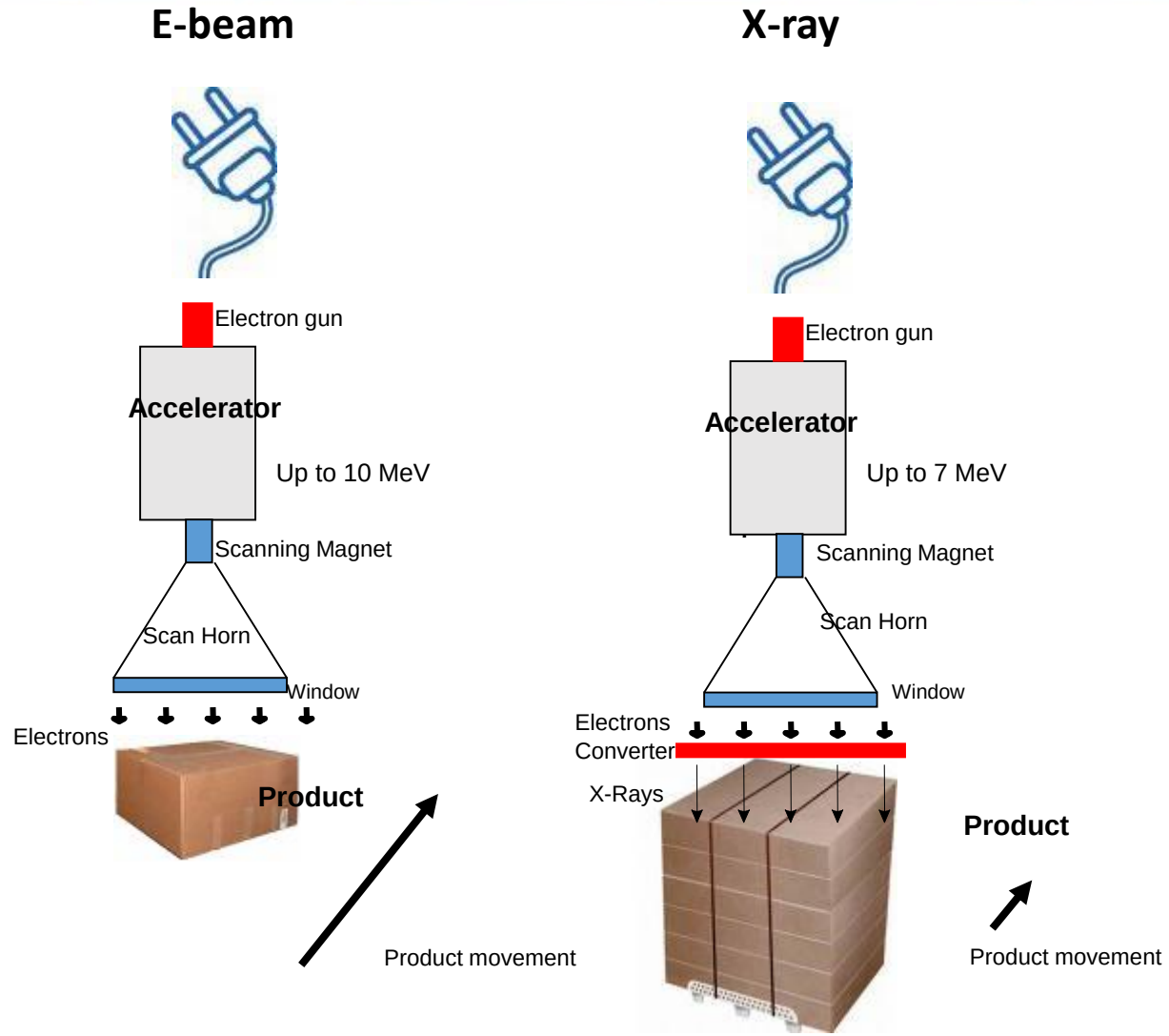
OPPOSING DUAL VERTICAL BEAMS



Upper Beam scans across conveyor and down

Lower Beam scans across conveyor and up

E-Beam vs. X-Ray – it's all in the Plate!



What does the rest of the facility look like?

- Signs
- Monitoring devices
- Plant layout

Protecting Against Radiation

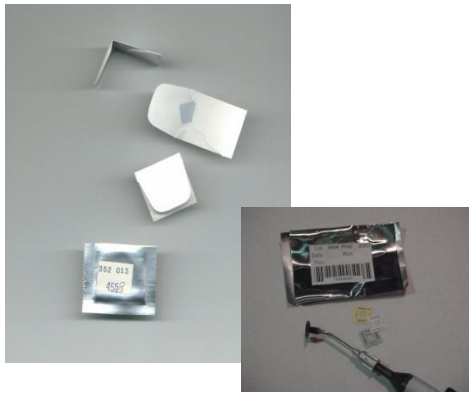
- **Signs are required to notify everyone of the presence of radiation**

Monitoring Radiation Exposure

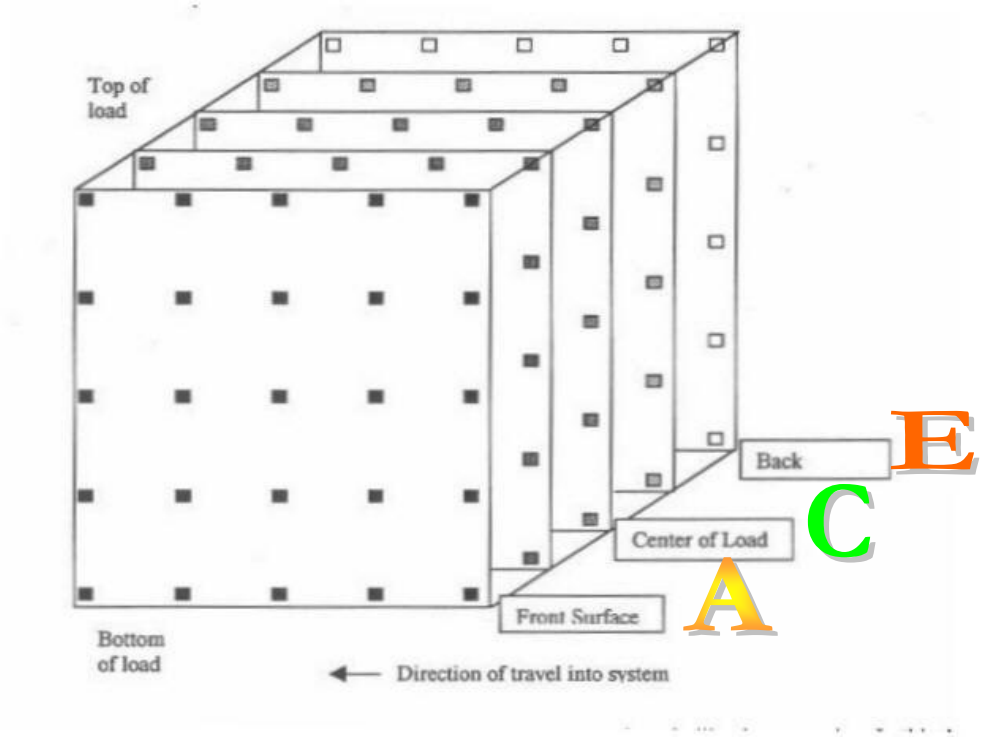
Dosimeter Examples

- Gamma/Xray
  - Most calibrated dosimeters are suitable

- Electron Beam
  - Use of thin film dosimetry (FWT, GEX)



Dose Mapping



Dose Mapping

- To release product on dosimetric results, must first understand where to put the monitoring dosimeters. The min and max doses are identified by placing dosimeters in a carrier in a three dimensional pattern throughout the carrier ; then irradiating them (repeated a minimum of three times).

The irradiated dosimeters can be analyzed resulting in a “dose profile” of the particular product

Dose Mapping

When do I dose map?

- New products
- Significant change in packaging or box configuration (changes to weight, orientation in box or size of process carton)
- Change of facility (where it will be processed)
- Change in Cobalt 60 configuration, change of modality (E beam Gamma or X-ray) or change in MeV of an accelerator

- Resources: ASTM standards, some guidance in ISO 11137-3, AAMI TIR 29

Specialized Product Considerations: Pharmaceutical Products

1. Trays, vials caps, etc for entry to a sterile suite
2. Liquids, Lotions, Gels, Suspensions
3. Active Compounds
   - Bulk API
   - Terminal product

Trays, Vials and Containers

- Materials that will be filled aseptically, need to go into the sterile suite sterile. Not making product sterile but keeping it sterile in the processing.

- Issues will be the same as any device and dose setting and materials test methods are the same.

- Goal is a container that can effectively act to contain and store the product plus maintain the sterility.

Liquids, Gels and Lotions

1. Viscosity changes
2. pH changes
3. Is an active ingredient present and is it's effectiveness changed.
   - If it changes can I live with it or adjust for it?
4. Can an additional component be added to protect the properties desired?
5. Can the properties be modified temporarily and solve or reduce problem? (freezing, lyophilization, dried and then reconstituted for use)

Liquids, Gels, Lotions (Continued)

6. Color
7. Scent
8. Texture
9. Maybe nothing at all
10. Need to evaluate

Active Compounds (APIs)

1. By their very nature Pharmaceutical compounds are very specific and often unique, in function, synthesis and components.

2. Each specific formulation should be checked as early as possible in development. Not just something similar to it.

3. CFR 21 part 310, Sec 310.502 a 11 Lists things what are considered to be new drugs. This includes specifically sterilization of new drugs by irradiation.

4. Tests of effectiveness/safety need to be on irradiated material.

5. Moisture content can matter

Formation And Interaction Of Radiolysis Products Of Water

$$H_2O \longrightarrow H_3O^+ + e^-$$

$$H_2O \longrightarrow H_2O^*$$

$$e^-_{aq} + H_2O \longrightarrow H + OH^-$$

$$H_2O^+ + H_2O \longrightarrow H_3O + OH$$

$$H_3O^+ + e^- \longrightarrow H_3O\bullet$$

$$H_3O\bullet \longrightarrow H_2 + \bullet OH$$

$$H_2O^* \longrightarrow H + \bullet OH$$

$$H\bullet + H\bullet \longrightarrow H_2$$

$$\bullet OH + \bullet OH \longrightarrow H_2O_2$$

$$H\bullet + \bullet OH \longrightarrow H_2O$$

$$e^-_{aq} + e^-_{aq} \longrightarrow H_2 + 2\,OH^-$$

$$e^-_{aq} + H\bullet \longrightarrow H_2 + OH^-$$

$$e^-_{aq} + \bullet OH \longrightarrow OH^-$$

$$e^-_{aq} + H_3^+O \longrightarrow H\bullet + H_2O$$

$$H\bullet + OH^- \longrightarrow e^-_{aq}$$

$$\bullet OH \longrightarrow O^- + H^+$$

$$H\bullet + O_2 \longrightarrow HO_2^\bullet$$

$$e^-_{aq} + O_2 \longrightarrow O_2^-$$

$$HO_2^\bullet \longrightarrow H\bullet + O_2^-$$

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Active Compounds (Continued)

5. Changes that can happen:
    a. Change in polymer length
    b. Conformational changes
    c. Creation of byproducts that are unacceptable or untested
    d. Change in efficacy, potency, color, etc.

6. Maybe nothing at all or minor. Changes may be minor but need to be investigated, documented, etc. Whatever is required by your regulating bodies
    a. Similar degradation profiles
    b. New degradation products
    c. What are acceptable limits

What Can You Do to Improve Results if Problems Happen?

Issue	Options	Notes
Viscosity Change	Add more of whatever makes the product thick or dilute if too thick	Manufacture at extreme to assure effects of irradiation process give end result needed.
pH Changes	Buffers	Appropriate buffer with capacity to handle radio lysis products; especially from water.
Color Change	Change carrier or filler materials; limit maximum allowable dose. Dose rate.	Limiting dose may mean better control of microbial population allowed. Faster dose rate can reduce time for oxidative damage.
Stability of active molecule	Free radical scavengers; antioxidants; freezing; lyophilization. Oxygen depletion.	Additives must be considered for biocompatibility; concentration must be worked out carefully. Freezing may impact stability if freeze thaw cycles are not acceptable. Lyophilization may be difficult or affect reconstitution. Purging Oxygen (vacuum, argon or nitrogen atmosphere) removes oxidation potential.
Potency	Buffers; solidifying by freezing or drying prior to irradiation process even if not needed for long term storage. Adjust initial compound mass to assure % active at end is where needed.	Freezing presents issue for transport and storage. Freezing may effect selection of containers provided. Cost and availability may limit ability to over fill an active compound.
Liquid stability	Freezing or drying	Freezing most common, to limit free radial damage by limiting active species mobility (forcing recombination to original compound)

Summary of today's discussion

- Irradiation Processes can be used for effective sterilization of products or material modifications
- Dose required is assured through dose setting activities (microbiological testing and physical testing of product).
- Dose delivery equipment vary with modality but all can deliver required doses to sterilize product.
- Dose is measured with calibrated devices called dosimeters
- Dose distribution throughout a load to assure minimum required dose is achieved to every unit in load and none get more than allowed maximum dose is confirmed by dose mapping.

- Contact Information:

- Betty Howard (Sr. Radiation Sterilization Manager) 847 367-5012 betty_howard@steris.com