

Gamma Sterilization of Medical Devices

FDA MEDICAL DEVICE ADVISORY MEETING

NOVEMBER 6, 2019

Typical gamma sterilization applications

Healthcare products including (but not limited to):

- Syringes, vacutainers
- Bandages, gauze
- Implantable devices (e.g., stents, orthopedic)
- Surgical gloves, drapes, gowns
- Human tissue products
- Pharmaceuticals
- Tubing sets, IV products



Other sterile products including

- Labware
- Single use bioreactors

Components used in medical devices

- Raw materials used in manufacturing
- UHMWPE for implants



Overview of Gamma Sterilization Process

A gamma irradiator consists of

- a source of radiation inside a shielded room,
- conveyance to bring the product into and out of the shield in order to expose it to the radiation, and
- a control and safety system.



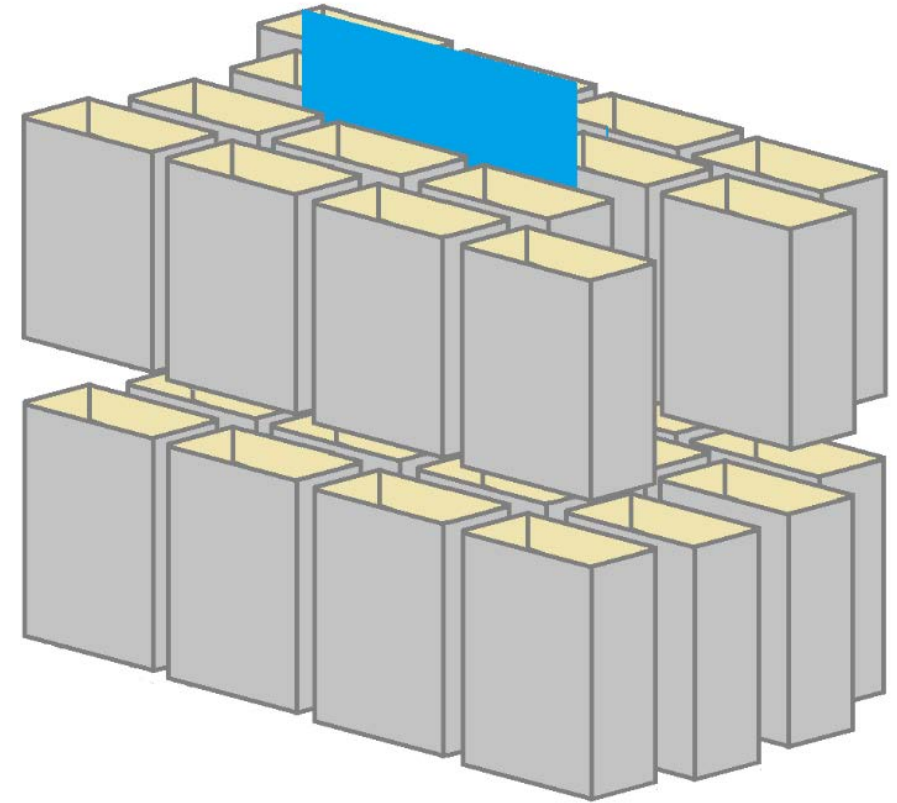
Gamma process continued

Products in their final shipping packages are loaded into totes or carriers which circulate around the gamma source in order to expose both sides to the source of radiation.

The process is validated to ensure:

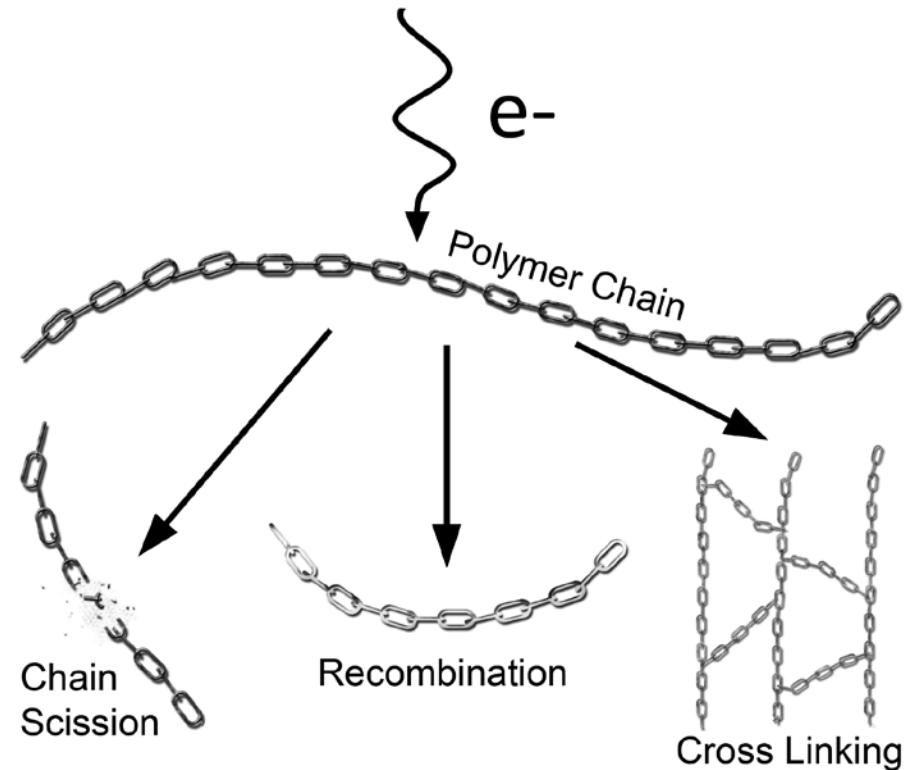
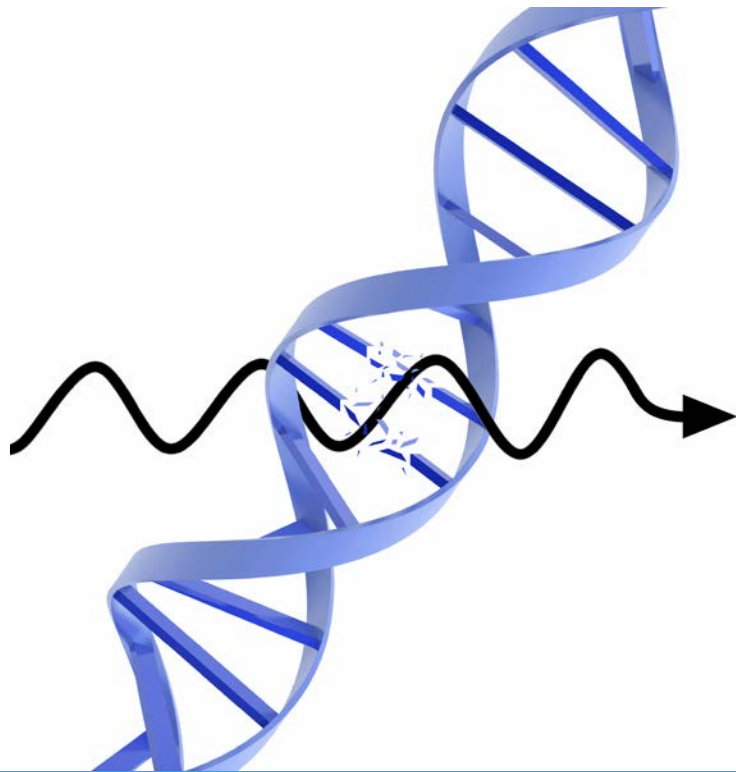
- 1) a minimum sterilization dose is achieved to meet the desired Sterility Assurance Level (SAL); and
- 2) a maximum allowable dose is not exceeded to maintain product functionality.

The delivery of the process is a function of source activity, product density, and the dwell timer setting is adjusted to achieve the validated process parameters.



Radiation sterilization principles

Radiation as a sterilant works by breaking down DNA molecules but the same process can also alter the polymers that make up most single use medical devices



Sterilization dose determination

Radiation sterilization dose determinations are based on the radiation resistance of the natural product bioburden – 3 methods are used for this determination:

- Method 1 and VD_{max} methods assume a standard distribution of resistances based on a presumed population of microorganisms
- Method 2 determines the resistance of the population specific to the product

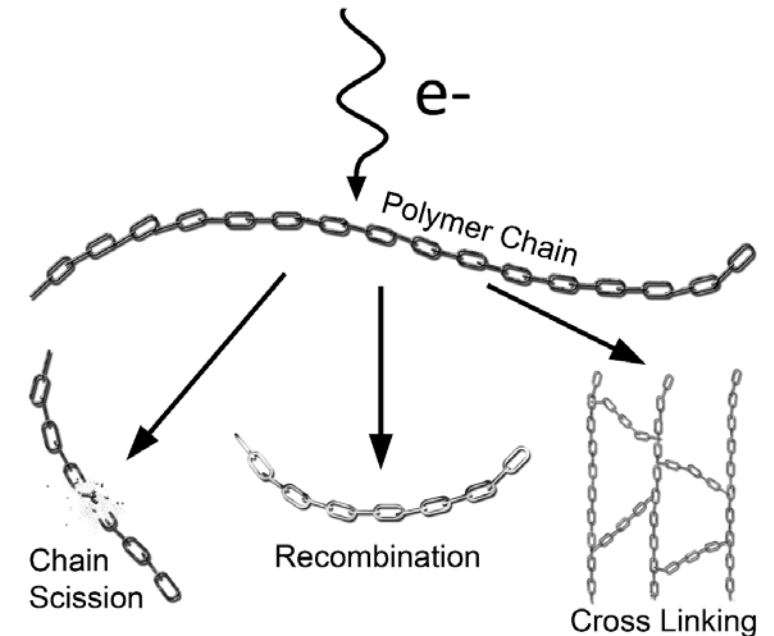
The minimum sterilization dose for a given method may be determined per product (Method 1 or 2), or a chosen sterilization dose may be substantiated (VD_{max} , e.g., 25 kGy).

The method chosen is typically based upon the product requirements, manufacturing controls and radiation process selected.

Maximum Allowed Dose – Material compatibility

Typical mechanisms for radiation interactions with po

Mechanism	Effect
Recombination	Properties are maintained
Chain-Scission	Polymer is degraded
Cross-Linking	Polymer is strengthened



Different polymers are naturally more or less radiation resistant (AAMI TIR 17)

Mechanism may be influenced by oxygen-based reactions, radioprotectants (including antioxidants), and temperature

Plastics comparison

Example polymers	Max dose range	Example polymers	Max dose range
Polyesters Phenolics	>10,000 kGy	Polyacrylics (e.g., PMMA) PVC, PVDC Elastomers	100 kGy
Polystyrene Polysulfone Polyurethane Polyimides	10,000 kGy	Polypropylene (radiation stabilized)	50 kGy
Epoxies Polycarbonate Polyethylene ABS, PET, PETG	1000 kGy	PTFE Polyacetals Polypropylene, natural Polymethylpentene Butyl	Poor

Radiation as an alternative to EO

Challenge with certain materials and components, e.g., PTFE, electronics

For some medical devices challenges may be overcome:

- Different choice of materials, e.g., selection of more radiation resistant materials
- Testing components to failure for maximum dose determination
- Use of radioprotectants where available, e.g., radiation stabilized polypropylene
- Lower radiation doses for sensitive materials, e.g., less than 25 kGy, alternative dose determination methods
- Modified radiation processes, e.g., product presentation to improve dose uniformity, lower temperature and/or humidity conditions, dose rate
- For kits, ensure all components are radiation compatible, e.g., remove non-radiation resistant components
- Cosmetic vs functional requirements, e.g., discoloration or odor

Radiation vs EO sterilization process

Consideration	Ethylene Oxide	Radiation
Sterilization “dose” determination	Overkill or bioburden methods	Bioburden methods ✓
Temperature	Typical 37-63 °C	Typical ambient to +20 °C ✓
Pressure/ RH	Controlled during process	Not applicable ✓
Residuals	Need to be evaluated	Not applicable ✓
Packaging	Gas permeable, may be sterilized in final shippers	Changes to packaging likely not required ✓
Sterilization time	1-7 days	<24 hours ✓

Regulation of Gamma Sterilization

ISO 11137-1 is the Standard for Radiation Sterilization of Medical Devices

- Established sterilization method with decades of safe effective use
- Gamma is the “default” radiation sterilization method, accounting for >80% of radiation sterilization in the United States, standards and guidance also cover e-beam and x-ray

Additional controls are required specific to Gamma Sterilization

- 10 CFR 37 – Requires physical protection of radioactive sources
- Licenses for Gamma Irradiators regulated at State level and through USNRC
- Concerns about radiological security have lead to Alternative Technologies Working Group through the Department of Homeland Security
- U.S. Department of Energy National Nuclear Security Administration incentives to use alternatives to isotope sources

Gamma Capacity Constraints

Factors affecting gamma capacity:

Infrastructure

- Is there extra processing capacity in existing sites? (~47 sites in the US, 11/36 in-house/contract)
- Is there license room to add more isotope vs building more irradiators?

Cobalt-60 availability

- Cobalt-60 activity is reduced by ~1% per month, this means that a certain amount of isotope annually is required to compensate for decay
- Global supply tightening* announced, supply is not meeting decay, therefore no potential for growth in short term
- Producing new cobalt-60 supply is a long and expensive process

*Report – The business and science of radiation processing in 2019 – IMRP 2019 Strasbourg, available through iia (International Irradiation Association)

Can gamma capacity replace EO?

Some amount of capacity can be realized through significant changes over time.

Short term:

- Free up capacity by moving gamma products that are not medical devices to other radiation technologies, e.g. labware, spices, other products for decontamination (months)

Longer term:

- Revalidate medical devices for lower minimum doses (months to years)
- Revalidate medical devices for alternative radiation technologies (years to decades)
- Find new sources of cobalt-60 (decades)

Other radiation sterilization options

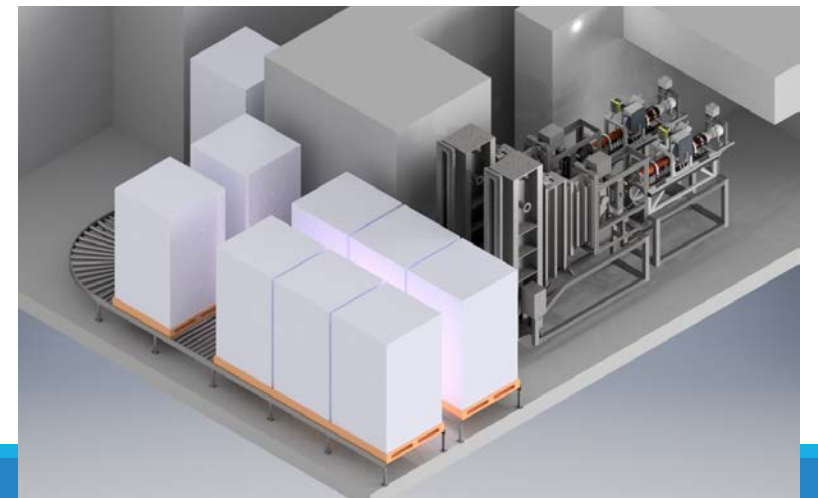
Electron beam

- Machine source
- Less penetrating
- Higher dose rate
- Infrastructure available



X-ray

- Uses electron beam to generate x-rays
- Less efficient than e-beam, requires high power input
- Penetration equal or better than gamma
- Infrastructure being built in North America



Thank you

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