Advancing the Science of Gamma Irradiation

Continuous improvement in radiation sterilization

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Why are we here today?

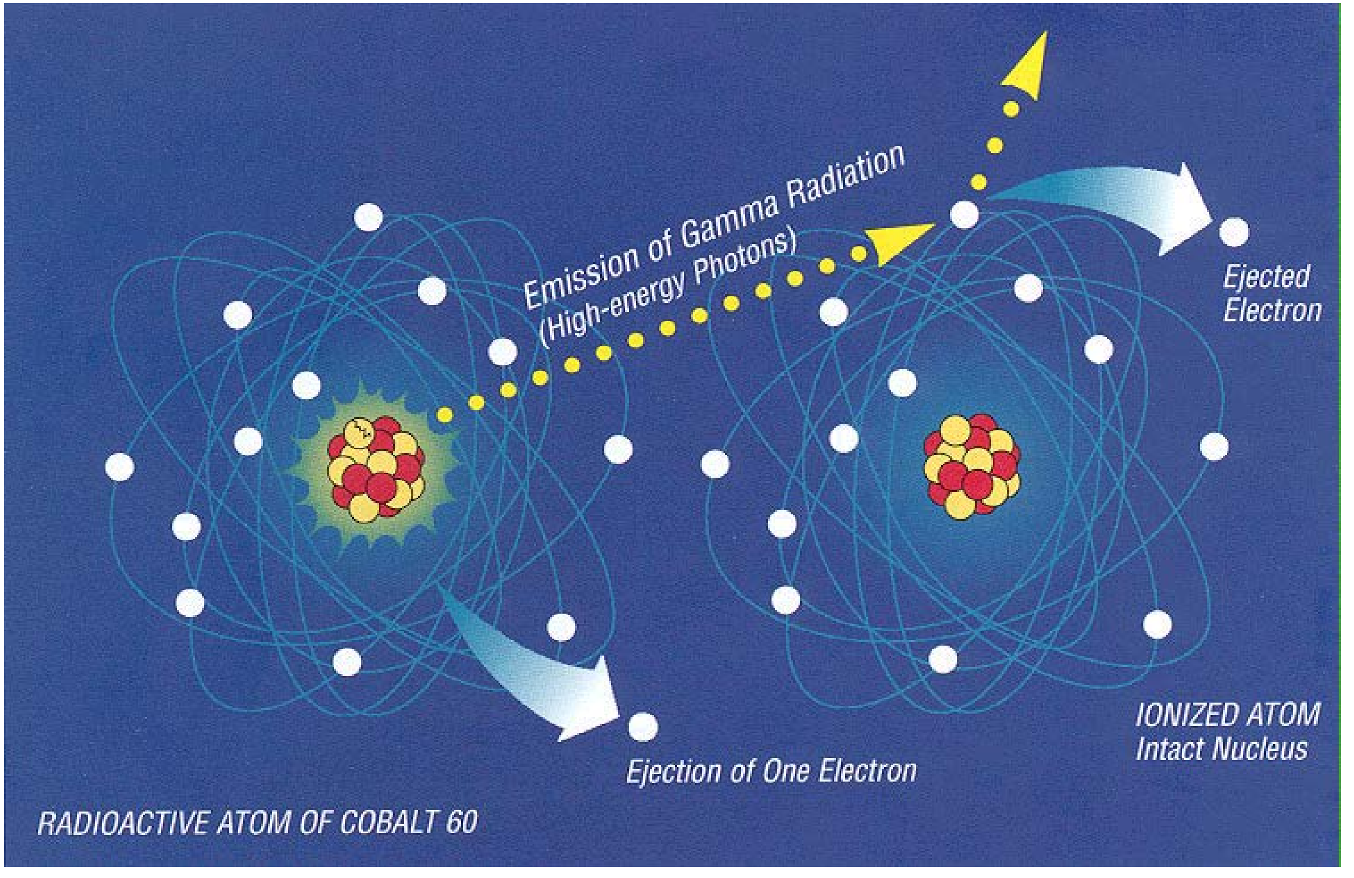
Overview

- Radiation sterilization technology
- Irradiations of sensitive and combination products
- Sterilization of pharmaceuticals

Radiation Sterilization Technology

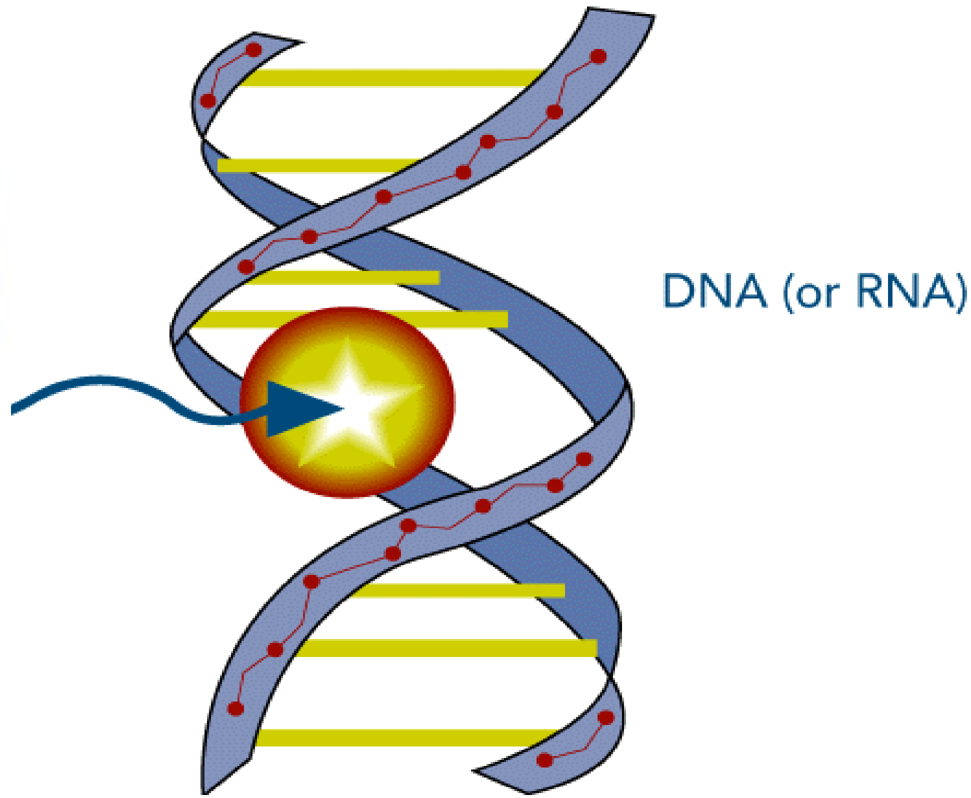
Overview

Ionizing Radiation

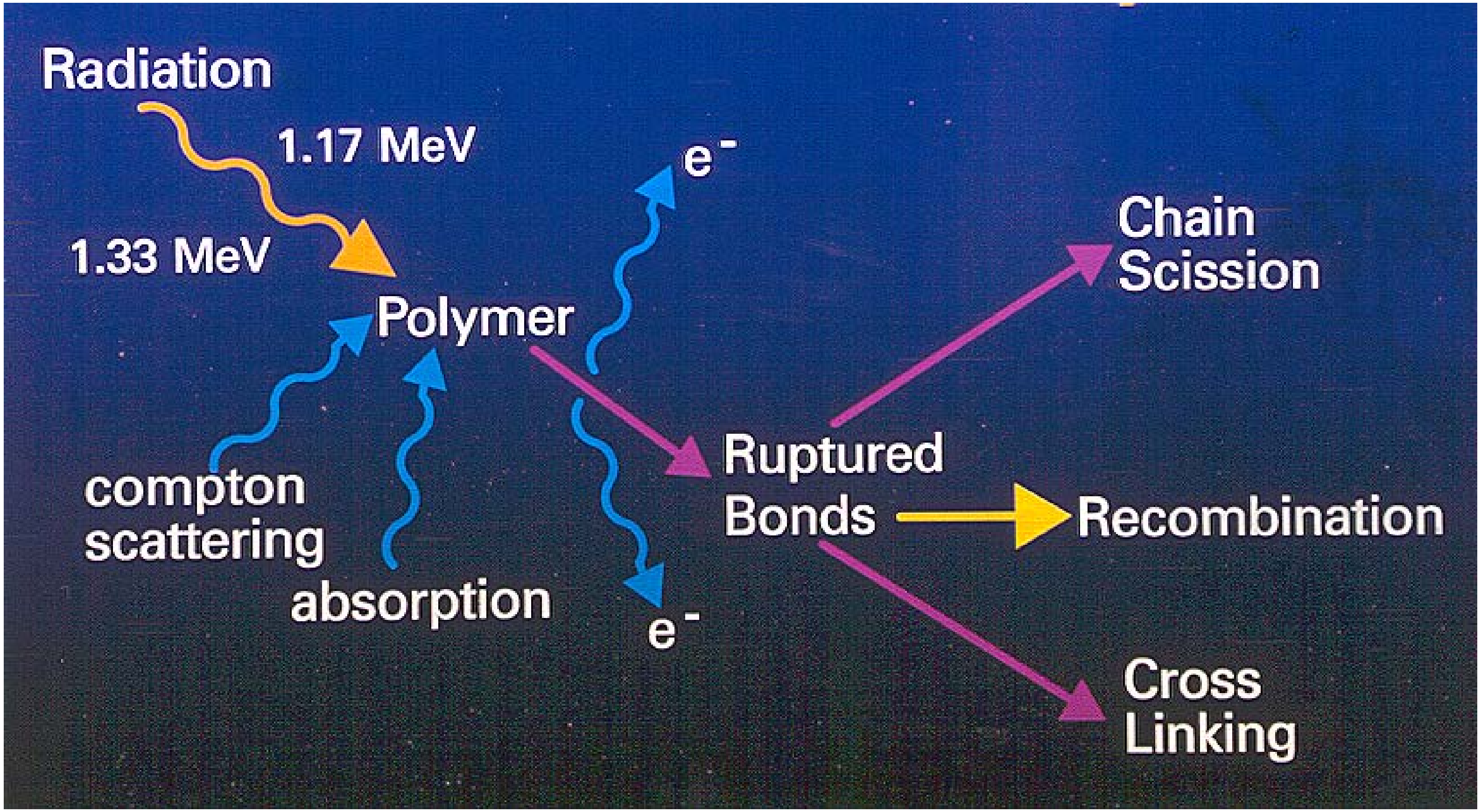


How Does Radiation Sterilization Work?

- Radiation Biological Interaction



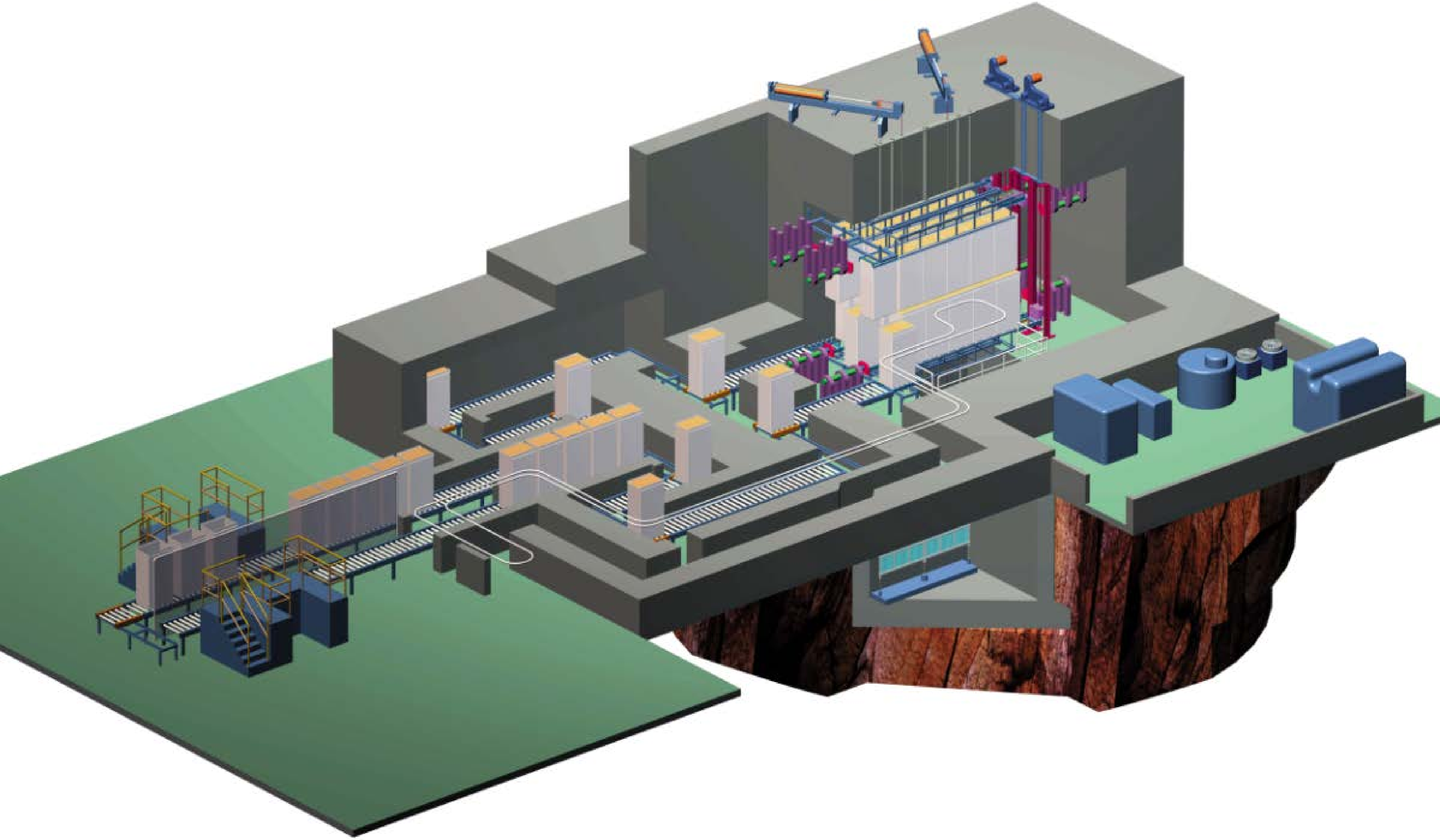
Radiation Effect on Materials



Radiation Dose

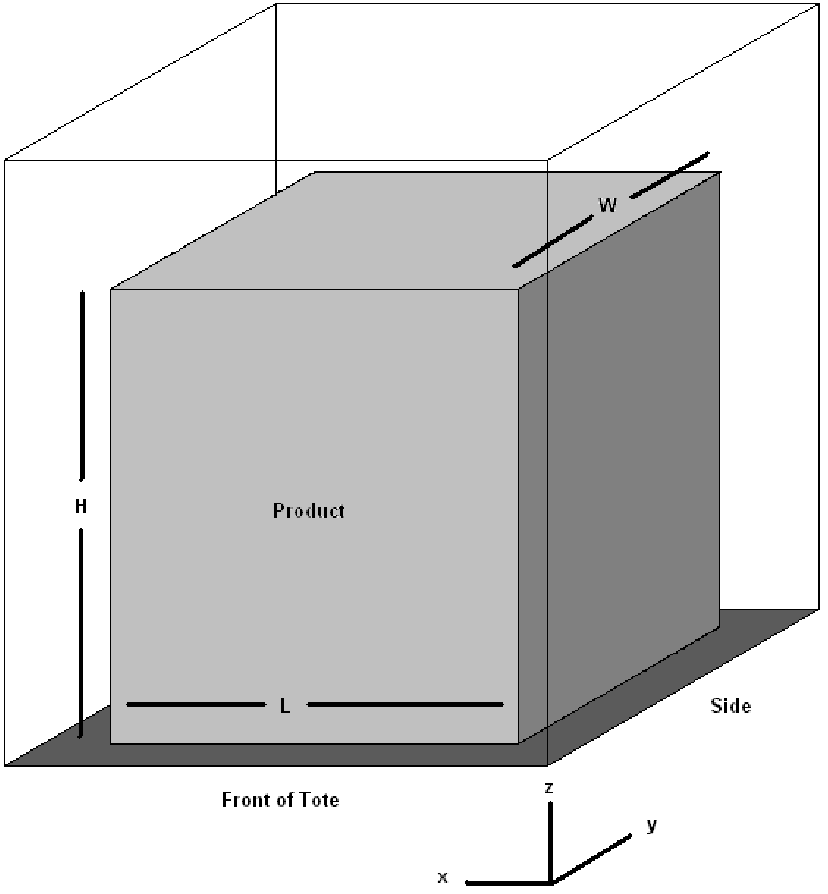
- "Dose" refers to the amount of energy transferred to the product by the radiation
  - 1 kGy = 1 kJ/kg
- Required minimum dose for sterility is the amount of energy transfer required to reduce the microbiological population by a SAL of 10^{-6}
- Maximum dose is established by evaluating material properties and stability of sample

How does Gamma work?

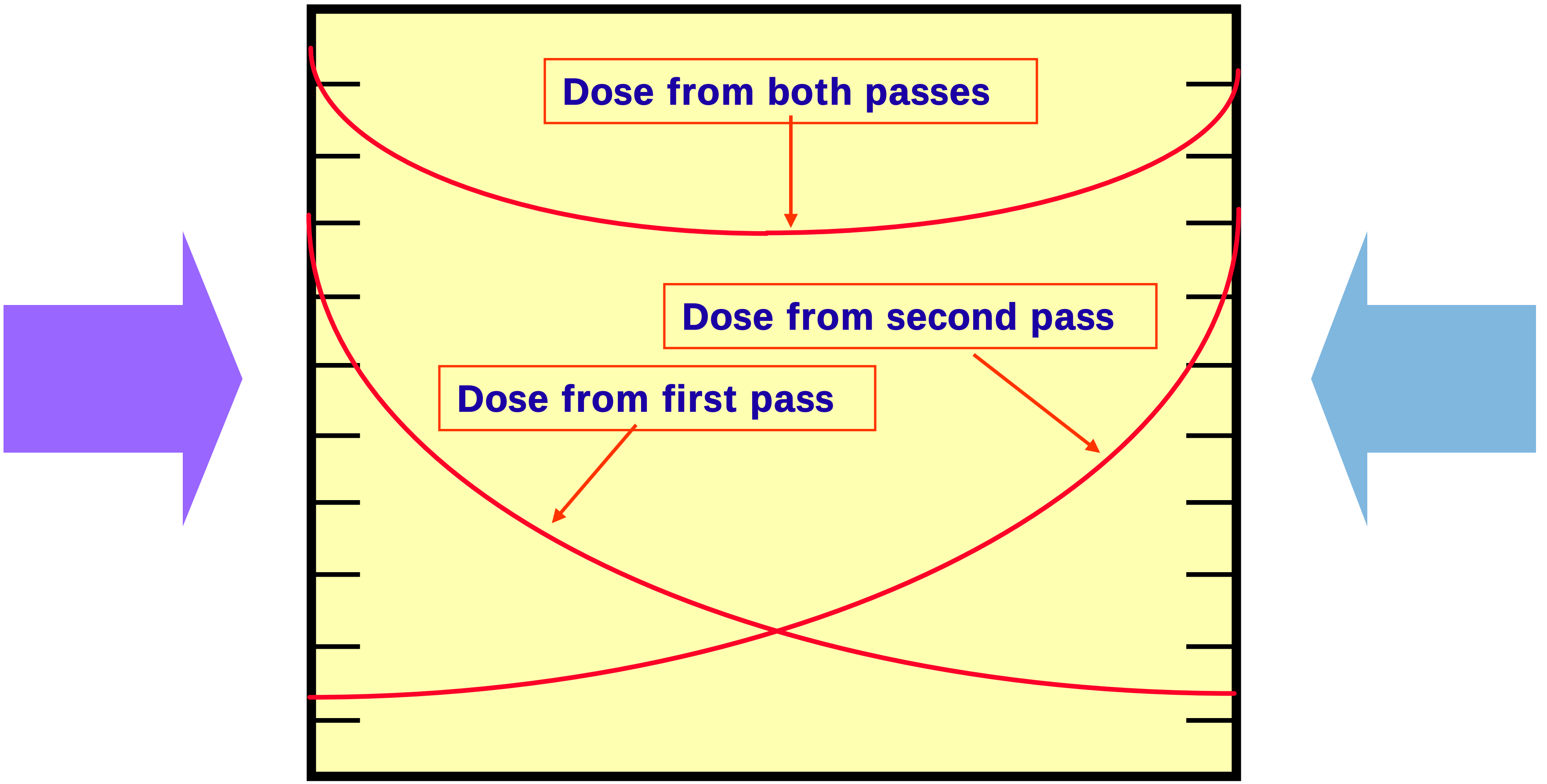


Dose Distribution

- Distribution of dose through the product stack
- Dose ratio (DUR) depends on stack size, density and irradiator design



Dose Distribution



Achieving Sterility

- Minimum dose for sterility
  - Verification testing
  - Sterility Assurance Level (SAL)
  - Microbiological Controls

- Maximum dose for functionality
  - Radiation resistance of materials
  - Product testing to determine or establish maximum dose

Sterilization Standards

AAMI
Advancing Safety in Medical Technology

ASTM
INTERNATIONAL
Standards Worldwide

ISO

ANSI
American National Standards Institute

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Irradiation of Sensitive and Combination Products

Gamma Sterilization

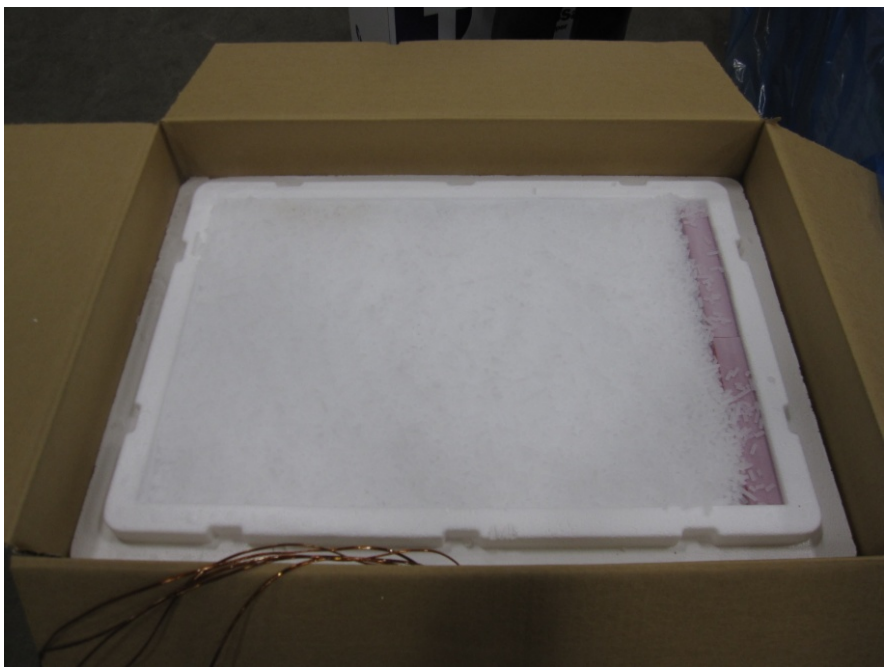
- Standard Method
  – High volume
  – Low value
  – Wide acceptable dose window
  – High minimum dose to guarantee SAL 10^{-6}
- Modified Methods
  – Re-evaluate the minimum dose requirements
  – Environmental conditions during irradiation

CASE 1 – Human Tissues and Biologics

- Chronology of Tissue Irradiation
  - – Past
    - Initial studies in 1950s and 1960s
    - Standard processing techniques
    - Outcome – Poor mechanical results
  - – Present
    - Re-evaluate the minimum dose requirements
    - Environmental conditions during irradiation
    - Pre/post treatment and radioprotectants

Human Tissues and Biologics

- Low temperature irradiations used to minimize mechanical degradation
- Dry ice irradiations to Low temp chamber



CASE 2 – Bone Grafts

- Objective
  - Investigate gamma irradiation effect on demineralized bone matrix and polymeric materials for the reconstruction of bone
- Irradiation conditions
  - Room temperature irradiations
  - Doses 8-15 kGy
  - Precise dosing and tight dose uniformity ratio

Results of Bone Grafts

- Results
  - Samples have osteoinductive potentials

	12 kGy	After 12 kGy Score	Original Score
Animal 3 L	APS-014226-09	3	4
Animal 4 L	APS-014226-09	3	4
Animal 5 R	TPS-013234-08	2	2
Animal 6 R	TPS-013234-08	2	2

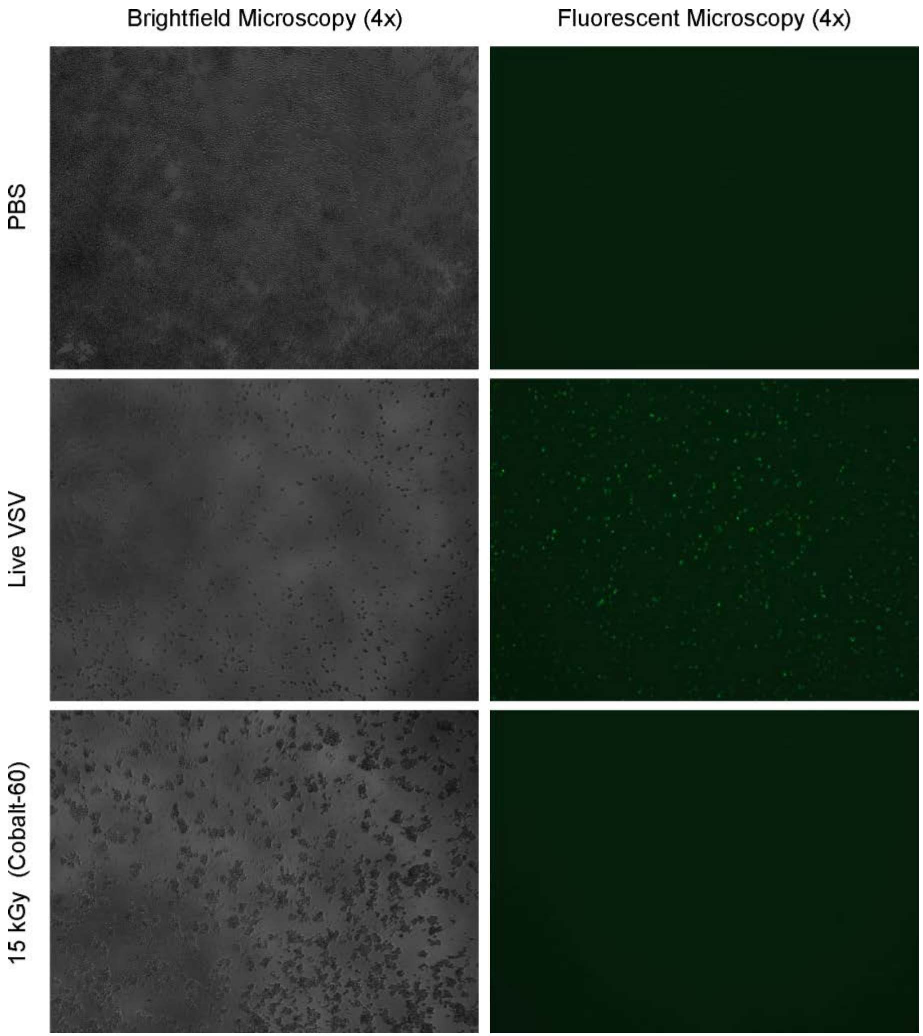
	15 kGy	After 15 kGy Score	Original Score
Animal 3 R	APS-014226-09	2	4
Animal 4 R	APS-014226-09	3	4
Animal 5 L	TPS-013234-08	3	2
Animal 6 L	TPS-013234-08	2	2

CASE 3 – Virus Inactivation

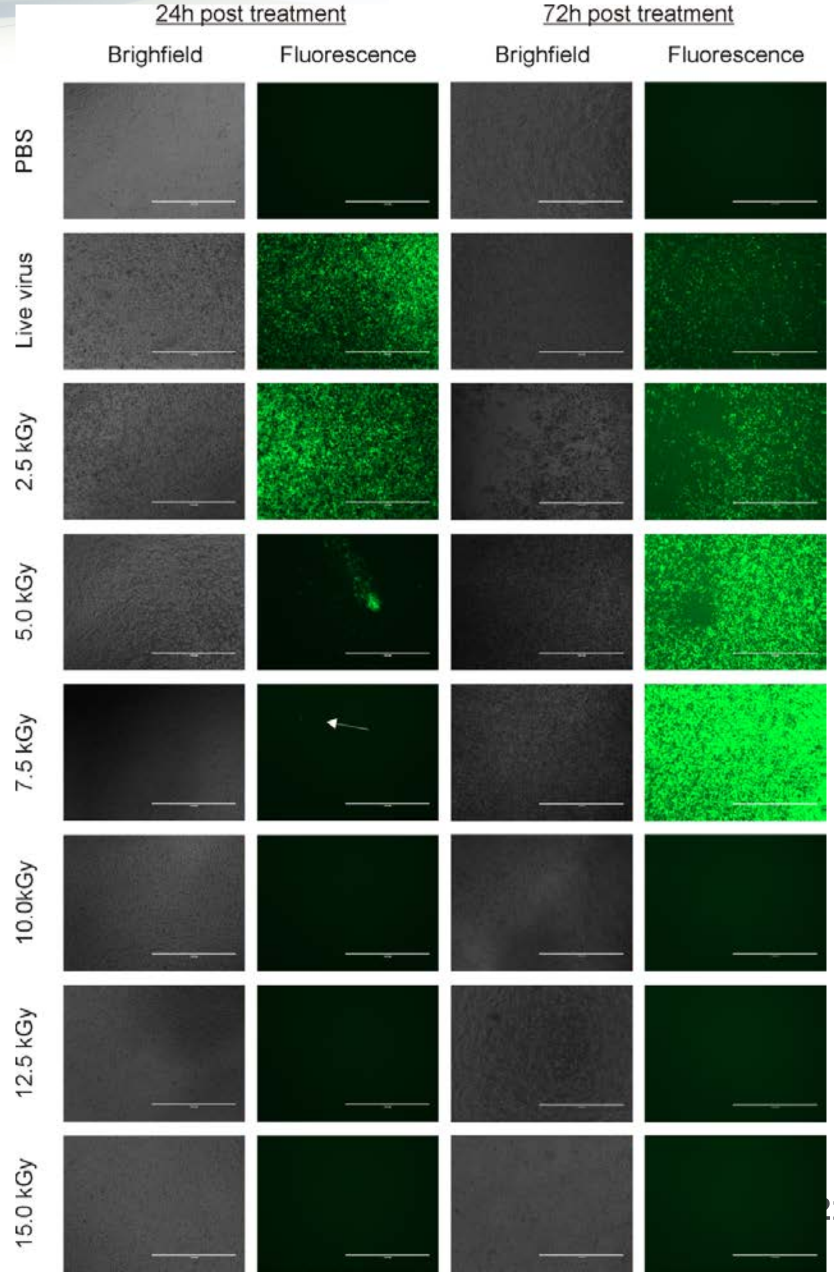
- Objective
  - To irradiate Rhabdovirus to generate a non-replicating particles that retained bioactivity (cytotoxic)
- Results
  - 4ºC study – particles did NOT maintain cytotoxic properties
  - Low temperature (-80ºC) generated a non-replicating bio-particles that retained bioactivity (cytotoxic)

Results of Virus Inactivation

Second study at -80ºC



First study at 4ºC

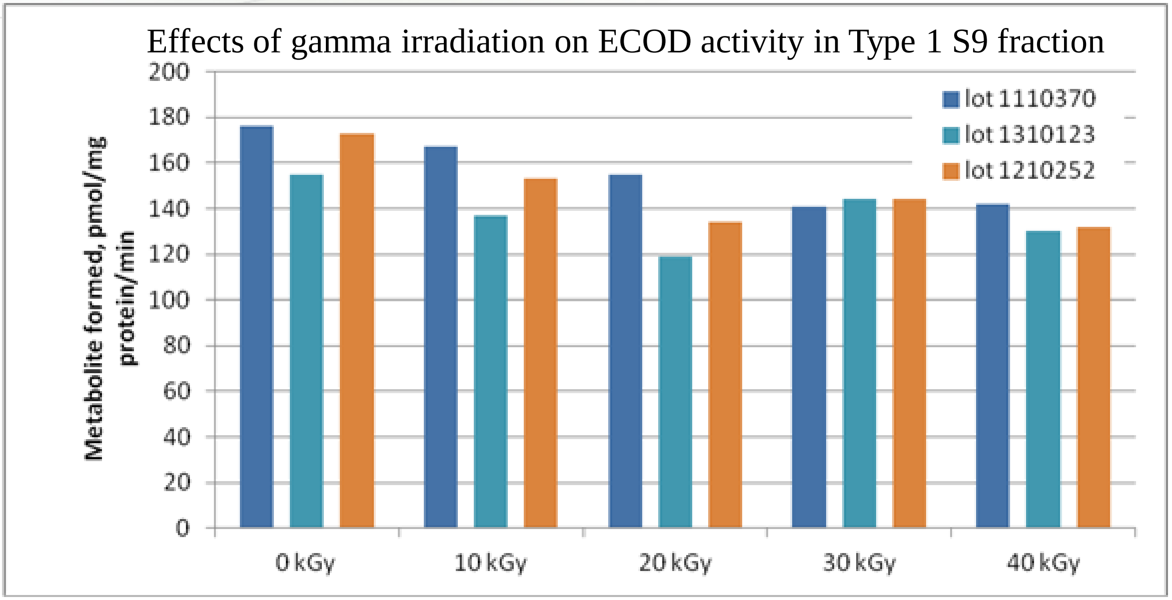


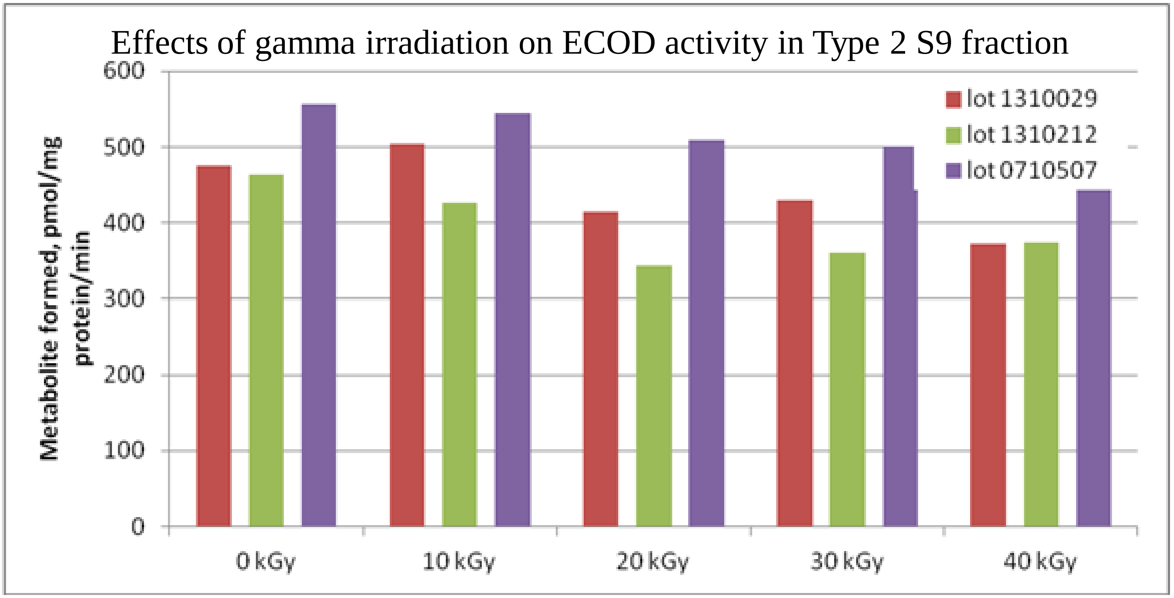
CASE 4 – Subcellular fractions of liver samples

- Objective
  - To find a dose that substantially reduces a microbial load and makes them a suitable pro-carcinogen activator
- Irradiation Conditions
  - Doses 10-40 kGy
  - Temperature -80ºC
- Tests
  - Sterility Test on of the subcellular fractions
  - Enzymatic activity – CYP marker activity on 7-ethoxy cumarine O-dealkylase (ECOD)

Results of Liver Samples

- Results
  - At 10 or 20 kGy elimination of microbial load was achieved with acceptable associated preservation of relevant enzymatic activity.





Sterilization of Pharmaceuticals

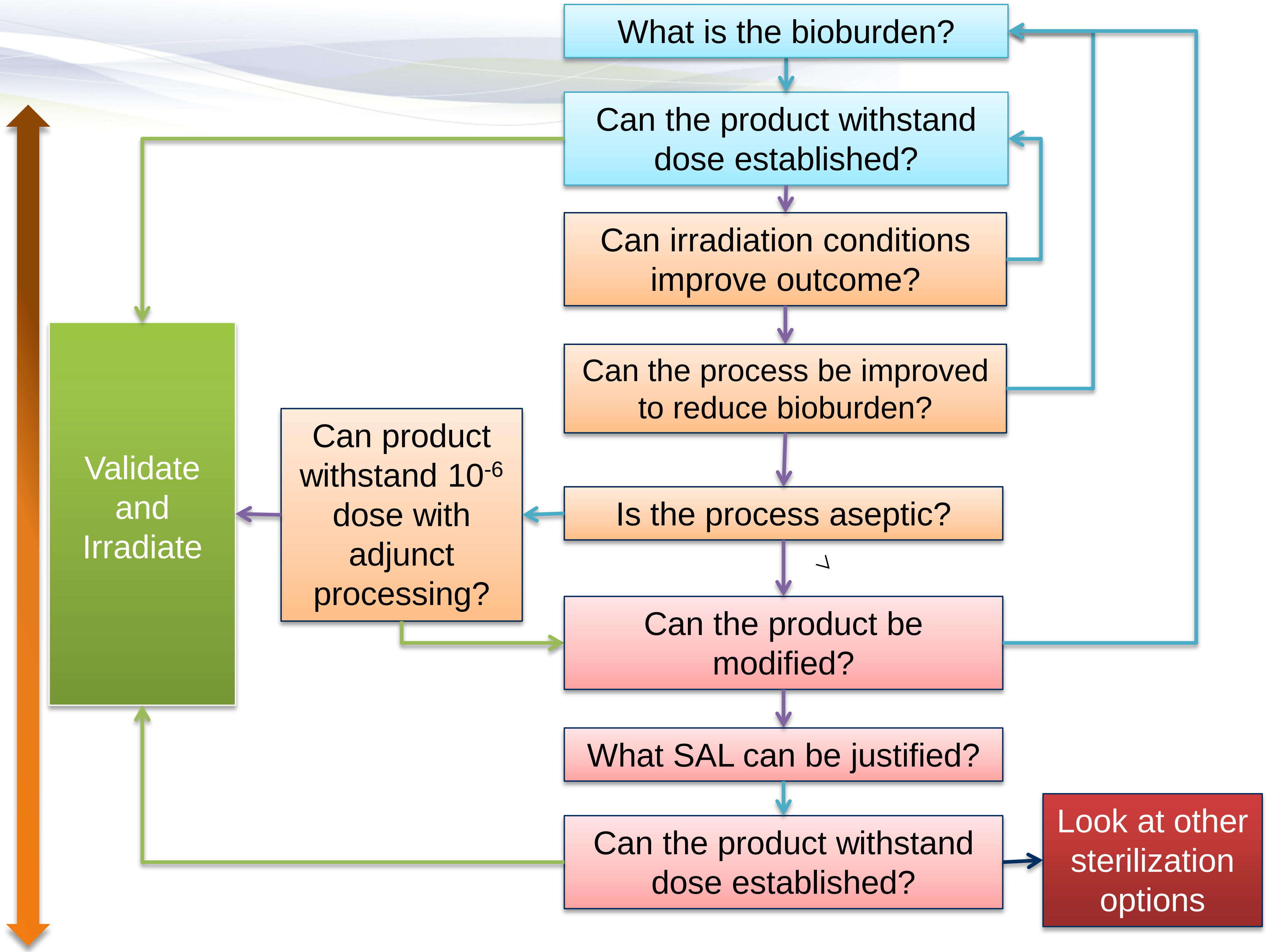
Review Paper

Gamma Sterilization Of Pharmaceuticals

- Review Paper - we looked at:
  - Class of pharmaceuticals
  - Different irradiation conditions
  - Characterization methods
  - Investigational outcomes

Gamma Sterilization Of Pharmaceuticals

Irradiation Conditions	Radiation Effect
Oxygen Deprivation	Oxygen – cause oxidations No Oxygen – reduces the chances of oxidation
Cold temperature Irradiation	Temperature range: -10° C to -100° C Less degradation
Solid/Liquid Samples	Solid samples – Relatively more radiation resistant. Liquid samples – Less radiation resistant
Precise Dose Delivery	Precise and uniform dose.


What is the bioburden?
Can the product withstand dose established?
Can irradiation conditions improve outcome?
Can the process be improved to reduce bioburden?
Is the process aseptic?
Can product withstand 10-6 dose with adjunct processing?
Validate and Irradiate
Can the product be modified?
What SAL can be justified?
Can the product withstand dose established?
Look at other sterilization options

Conclusion

- Pharmaceuticals need to be evaluated on a case by case basis
- The selection of the irradiation conditions may allow to terminally sterilize a product while maintaining its functional properties
- Effective radiation sterilization of combination products and pharmaceuticals are happening today
- Effective radiation sterilization techniques are available to provide a safe and effective drug/product

Questions?

Thank you!