सत्यमेव जयते

**Agricultural Radiation Processing Facility**
**Raja Ramanna Centre for Advanced Technology**
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**Government of India**
**Indore - 452013**

राष्ट्र की सेवा में परमाणु
राराप्रौ के
RRCAT
ATOMS IN THE SERVICE OF THE NATION

# Guideline for Dose Establishment and Dose Audit

| | Department | Name & Designation | Signature and Date |
|---|---|---|---|
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## Preface

The document "*Guidelines for Dose Establishment and Dose Audit*" is intended to provide a structured and harmonized approach for establishing, validating, and routinely verifying the radiation sterilization dose. The guideline is aligned with the principles of internationally accepted standards such as IS/ISO 11137 and related regulatory expectations

This guideline is intended to assist primary manufacturers in dose establishment and dose audit in accordance with prevailing regulatory requirements. In the event of any changes, amendments, or obsolescence in these regulatory requirements, it shall be the responsibility of the primary manufacturer to ensure appropriate compliance.

## 1. Purpose

The purpose of this SOP is to define the procedure to:

a) Establish the *minimum sterilization dose (MSD) using $VD_{max}$ method* ensuring a SAL (Sterility Assurance Level) of $10^{-6}$ in accordance with IS/ISO 11137 and ISO 13004.

b) Establish *maximum acceptable dose (MAD)* ensuring that the product meet its specified functional requirements throughout the defined lifetime of the product.

c) Perform *periodic Sterilization Dose Audits (SDA)* to confirm the appropriateness of an established sterilization dose in accordance with IS/ISO 11137 and ISO 13004.

## 2. Scope

This guideline is applicable to the products to be irradiated at ARPF, RRCAT, Indore, manufactured by primary manufacturer.

## 3. Responsibility

### 3.1. Primary manufacturer of product

i. Provide the information of product family including determining the representative product.
ii. Controlling the manufacturing process(es), including meeting the specifications for the products submitted to irradiator operator, i.e. product density, orientation, dimensions.
iii. To provide the requisite quantities of the product samples for irradiation.
iv. Bio-burden analysis & sterility testing of the product through a NABL or equivalent certified laboratory and share report to ARPF-RRCAT.
v. Selection of verification dose from Tables specific method $VD_{Max}^{SD}$ IS/ISO 11137-2/ ISO 13004 for required SAL & inform to ARPF-RRCAT.
vi. Post irradiation testing for maximum acceptable dose establishment.
vii. Revision of specifications if any, shall be shared to ARPF, RRCAT, immediately.
viii. Change control of the product to include a review of product related variables that affect processing categories.
ix. Product safety, integrity, sterility.
x. To prepare the final report and submit to ARPF, RRCAT.
xi. Periodic dose audit.

### 3.2. ARPF-RRCAT

i. Facility qualification in compliance with IS/ISO 11137
   - Installation Qualification,
   - Operation Qualification and
ii. Calibration and traceability of dosimetry system
iii. Controlling the irradiation process to deliver specified dose
iv. Delivery of specified verification dose & various doses for MAD study within the specified tolerance limit.
v. Issuance of certificate of irradiation.
vi. To facilitate sterilization dose audit experiments.

vii. Developing processing category

*Note: An Irradiation Agreement defining the role and responsibility of ARPF, RRCAT and primary device manufacturer shall be in place before starting commercial sterilization.*

## 4. Procedure for selection of representative product or product family

**4.1.** The dose establishment exercise is being conducted for the representative product or product family packed in polybag. The representative product to be sterilized, including the packaging materials, shall be specified. This product family includes the following components:

- ***[List the name of product and their model no.]***

Validation of addition product need to be done separately unless equivalence can be demonstrated for the components.

**4.2.** Justification shall be provided by the customer for selection of representative product (also known as Master product item) in below table:

| **Product Family Information** | | | | | |
|---|---|---|---|---|---|
| **Assessment sheet for selection of representative product for irradiation qualification** | | | | | |
| **S. No.** | **Criteria to be considered** | **[Name of product]** | **[Name of product]** | **[Name of product]** | **Justification/ Remarks** |
| 1. | Nature and source of Raw materials | Same/ Different | Same/ Different | Same/ Different | |
| 2. | Number of microorganisms comprising the bioburden | More/ Less number of microorganisms | More/ Less number of microorganisms | More/ Less number of microorganisms | |
| 3. | Types of microorganisms comprising the bioburden | Same/ Different | Same/ Different | Same/ Different | |
| 4. | Environment in which microorganisms occur | Same/ Different | Same/ Different | Same/ Different | |
| 5. | Size of the Product | Same/ Different | Same/ Different | Same/ Different | |
| 6. | No. of components | Same/ Different | Same/ Different | Same/ Different | |
| 7. | Complexity of the Product | Same/ Different | Same/ Different | Same/ Different | |
| 8. | Degree of Automation during manufacturing | Same/ Different | Same/ Different | Same/ Different | |
| 9. | Manufacturing environment | Same/ Different | Same/ Different | Same/ Different | |
| **Conclusion:** Based on the above criteria's *[Name of product]* ***(Name of selection criteria)*** is considered as representative product of product family of *[Name of product]*. | | | | | |

## 5. Procedure for applying Method $D_{min.}^{SD}$

### 5.1. Determination of average bio-burden (Stage I)

5.1.1. If the production is in multiple batches then minimum 10 product item from each of three independent product batches shall be taken or if the production is in single batch then minimum 10 product item from that single product batch shall be taken and use entire product for testing (Sample Item Portion (SIP)-1).

5.1.2. Bio-burden analysis shall be carried out as per IS/ISO 11737-1 or equivalent through a NABL or equivalent certified laboratory and share report to ARPF-RRCAT. Bioburden must be consistent and within expected manufacturing limits.

### 5.2. Selection of $VD_{max}^{SD}$ dose (maximum verification dose for a particular sterilization dose-SD) and performing the verification dose experiment (Stage-II)

5.2.1. Based on the bioburden report, customer select the $VD_{max}^{SD}$ dose either from Table-9/ Table-10 of IS/ISO 11137-2 or from Table-3, Table-4 and clause-8 of ISO 13004 and inform to ARPF-RRCAT.

| Average CFU/sample | Verification Dose ($VD_{max}^{SD}$ dose) | Sterilization Dose for SAL 6 |
|---|---|---|
| XXX | XX kGy | XX kGy |

5.2.2. Irradiation of 10 product items at verification dose.

5.2.3. The highest dose determined after dosimetry shall not exceed the $VD_{max}^{SD}$ by more than 10%.

| $VD_{max}^{SD}$ dose | Highest dose permitted (10% of $VD_{max}^{SD}$ dose) | Highest dose imparted | Complying/ Non complying |
|---|---|---|---|
| XX kGy | XX kGy | XX kGy | |

5.2.4. The arithmetic mean of the highest and lowest doses should not be less than 90% of the calculated $VD_{max}^{SD}$.

| $VD_{max}^{SD}$ dose | Minimum delivered Dose | Maximum delivered Dose | Mean Delivered Dose | 90% of $VD_{max}^{SD}$ dose | Complying/ Non complying |
|---|---|---|---|---|---|
| XX kGy | XX kGy | XX kGy | XX kGy | XX kGy | |

### 5.3. Sterility testing (Stage- III)

5.3.1. Double packed minimum 10 product items from one of the batches on which bioburden test carried out OR from another batch manufactured under conditions that are representative of normal production.

5.3.2. Sterility testing shall be performed on individual product item and record of number of positive tests of sterility (sterility failures) shall be recorded.

5.3.3. The sterility test shall be performed as per IS/ISO 11737-2 or equivalent through a NABL or equivalent certified laboratory and share report to ARPF-RRCAT.

### 5.4. Interpretation (Stage-IV)

| No. of Sterility failures (positive test of sterility) | Course of action |
|---|---|
| 0 to 1 | Verification dose is accepted and selected $D_{min.}^{SD}$ dose is substantiated. |
| 2 or more | Refer the IS/ISO 11137-2 or ISO 13004 standard |

## 6. Procedure for establishment of $D_{max,\ acc}$ (maximum acceptable dose-MAD)

### 6.1. Irradiation of product items (Stage-I)

6.1.1. 5 packets (each packet contains at least 10 product items) shall be sent by customer.

6.1.2. Product packets will be irradiated at incremental higher doses (e.g., 1.25X, 1.5X, 1.8X, 2X of $D_{min}^{ster}$ or as per worst-case process dose)

Note: These dose points are typical, other dose points can also be suggested by customer.

### 6.2. Post irradiation testing for maximum acceptable dose establishment (Stage-II)

6.2.1. The irradiated packets will be evaluated by the customer for acceptability test.

6.2.2. Following tests may be done by customer-

- Functional biological safety & performance
- Biocompatability data
- Physical properties
- Stability data
- Packaging integrity
- Shelf-life simulation (accelerated aging, if applicable).

Note: This list is not exhaustive, customer can perform any kind of test which need to establish the product specific functional & safety performance throughout its defined life time, in conformance with applicable regulatory requirements.

### 6.3. Interpretation (Stage-III)

6.3.1. Product shall meet all predefined specifications & no unacceptable degradation observed.

6.3.2. Establish $D_{max}^{acc}$ as the highest dose meeting all criteria.

6.3.3. The customer will share the MAD (Maximum Acceptable Dose) test report with ARPF-RRCAT, for reference purpose.

## 7. Procedure for sterilization dose audit (SDA)

### 7.1. Frequency:

7.1.1. The Sterilization Dose Audits shall be performed as per IS/ISO 11137-1 (typically four times per year, with the interval not to exceed four months from the time period of the previous sampling).

### 7.2. Steps for conducting Sterilization Dose Audit

Following steps shall be carried out for conducting sterilization dose audit.

7.2.1. Minimum 20 product items shall be selected from a single batch.

7.2.2. Minimum 10 product items shall be used for determination of average bioburden as per IS/ISO 11737-1 or equivalent.

7.2.3. The verification dose ($VD_{max}^{SD}$) used in most recent successful substantiation of selected sterilization dose will be used for irradiation of product items.

7.2.4. 10 product items shall be irradiated at $VD_{max}^{SD}$ dose and the highest dose shall not exceed by 10 %, if exceed irradiation shall be repeated. The arithmetic mean of highest and lowest delivered dose should not be less than 90 % of $VD_{max}^{SD}$.

7.2.5. Each irradiated product item shall be individually tested for sterility.

### 7.3. Interpretation

| No. of Sterility failures (positive test of sterility) | Course of action |
|---|---|
| 0 to 1 | Acceptance of sterilization dose audit. |
| 2 or more | Refer the IS/ISO 11137-2 or ISO 13004 standard |

## 8. Records

**8.1.** The dose establishment report shall be comprised of following test reports

8.1.1. Bioburden test reports

8.1.2. Product irradiation certificates

8.1.3. Sterility test reports

8.1.4. Maximum Acceptable Dose (MAD) establishment report.

**8.2.** Dose audit reports

## 9. References


a) IS/ISO 11137-1: Sterilization of Health Care Products – Radiation – Part-1: Requirements for the development, validation and routine control of a sterilization process for medical devices.

b) IS/ISO 11137-2: Sterilization of Health Care Products – Radiation Part-2: Establishing the Sterilization Dose

c) IS/ISO 11137-3: Sterilization of Health Care Products – Radiation – Part-3: Guidance on Dosimetric Aspects of Development, Validation and Routine Control
d) ISO 13004: Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method $VD_{max}^{SD}$.
e) IS/ISO 11737-1: Sterilization of health care products — Microbiological methods, Part 1: Determination of a population of microorganisms on products
f) IS/ISO 11737-2: Sterilization of health care products — Microbiological methods, Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
g) Medical Devices Rules, 2017, Ministry of Health and Family Welfare, the Gazette of India, Extraordinary, Part II, section 3, sub-section (i), vide notification number G.S.R. 78(A), 31-01-2017.
h) Indian Pharmacopoeia (IP) – 2018, Ministry of Health & Family Welfare, Govt. of India, Eighth edition, 29-09-2017.

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