
**Sterilization of health care products —
Radiation sterilization — Substantiation of
25 kGy as a sterilization dose for small or
infrequent production batches**

*Stérilisation des produits de santé — Stérilisation par irradiation —
Justification d'une dose de stérilisation de 25 kGy pour des lots de
fabrication de faible volume ou intermittents*



Reference number
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

- an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;
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An ISO/PAS or ISO/TS is reviewed after three years with a view to deciding whether it should be confirmed for a further three years, revised to become an International Standard, or withdrawn. In the case of a confirmed ISO/PAS or ISO/TS, it is reviewed again after six years at which time it has to be either transformed into an International Standard or withdrawn.

Attention is drawn to the possibility that some of the elements of ISO/TS 13409 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TS 13409 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

Introduction

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*, specifies the requirements for assuring that the activities associated with the process of radiation sterilization are performed properly. One of the activities encompassed within that International Standard is the selection of the dose of radiation to be applied to health care products to render them sterile (the sterilization dose). ISO 11137:1995 specifies that one of two approaches be used to select the sterilization dose ; either

- a) the selection of a product specific sterilization dose, or
- b) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

Annex B to ISO 11137:1995 describes two methods of selecting a sterilization dose. These methods are designated Method 1 and Method 2. The basis for these methods owes much to the ideas first propounded by Tallentire [8], [9], [10]. Subsequently, standardized methods were developed [4], [5], [11] which formed the basis of the dose substantiation procedures put forward in the Association for the Advancement of Medical Instrumentation *Guideline for gamma radiation sterilization* (AAMI, 1984).

These methods of selection of sterilization dose use data derived from the inactivation of the microbial population in its natural state, and are based on a probability model for the inactivation of microbial populations. The probability model, as applied to bioburden made up of a mixture of microbial species, assumes that each species has its own unique D_{10} values. In the model, the probability that a particular item will be sterile after exposure to a given dose of radiation is defined in terms of the initial number of organisms on the item prior to irradiation, and their D_{10} values.

The application of Methods 1 and 2 as described in annex B of ISO 11137:1995 requires that a relatively large number of product items, drawn from a number of separate production batches, be used to establish the sterilization dose. This is not always practicable. Health care manufacturers regularly produce new products and they are also, on occasion, required to manufacture a single batch of a product for a special order, field trial or clinical investigation. In addition, batches of many health care products are small and might be produced infrequently (that is, less than once every three months). For products manufactured in all these situations, determination and maintenance of a validated sterilization dose is as important as for large production batches. The method described in this Technical Specification provides guidance on how to allow substantiation of 25 kGy as an appropriate sterilization dose within the limitations stipulated in the method.

The present method is based on Method 1, described in ISO 11137:1995, B.3.4.1 to B.3.4.1.3. Method 1 depends upon experimental verification that the response to radiation of bioburden is greater than that of a microbial population having a standard distribution of resistances. In practice, an estimate is made of the average bioburden prior to irradiation. For this bioburden, the dose that gives an SAL of 10^{-2} for the standard distribution of resistances is obtained. This dose is designated the verification dose, and it represents the dose that will reduce a microbial population with a standard distribution of resistances to a level that gives on average a 1 in 100 probability of a non-sterile product unit. A sample of 100 product units or portion thereof (SIP) is then exposed to the verification dose and each product unit is tested individually for sterility. If there are not more than two positive tests out of the 100 tests, the sterilization dose is selected for any desired SAL at the estimated level of bioburden.

With the present method, if the verification dose experiment is passed, the product is sterilized using a sterilization dose of 25 kGy on the assumption that microorganisms having a standard distribution of resistances represent a more severe challenge to the sterilizing dose than organisms occurring on products.

It was decided to publish the present method as a Technical Specification because, unlike Methods 1 and 2 which had been used extensively since 1984, there was little practical experience in the application of this method. Users of this method are urged to submit any comments on the application and content of this Technical Specification so that this experience can be taken into account during the current revision of ISO 11137.

Manufacturers of health care products who intend to use the protocols contained in this Technical Specification are reminded that the requirements contained in ISO 11137:1995 for all users of radiation sterilization apply equally to the manufacture and control of products for which a sterilization dose of 25 kGy is to be substantiated by this method. In particular, there is a requirement that products be manufactured in circumstances such that the bioburden is controlled. Compliance with the requirement, and for the establishment of the basic properties of the packaging material are all essential.