
**Sterilization of health care products —
Radiation sterilization — Selection of
sterilization dose for a single production
batch**

*Stérilisation des produits médicaux — Stérilisation par irradiation —
Sélection d'une dose stérilisante pour un lot unique de fabrication*



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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.

The main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

- type 1, when the required support cannot be obtained for the publication of an International Standard, despite repeated efforts;
- type 2, when the subject is still under technical development or where for any reason there is the future but not immediate possibility of an agreement on an International Standard;
- type 3, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example).

Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until data they provide are considered to be no longer valid or useful.

ISO/TR 15844, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This document is being issued in the type 2 Technical Report series of publications (according to subclause G.3.2.2 of part 1 of the ISO/IEC Directives, 1992) as a "prospective standard for provisional application" in the field of radiation sterilization because there is an urgent need for guidance on how procedures in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard." It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this type 2 Technical Report will be carried out not later than three years after its publication with the options of: extension for another three years; conversion into an International Standard; or withdrawal.

Introduction

This Technical Report is intended to be used in conjunction with ISO 11137, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*. One of the activities encompassed within this Technical Report is the selection of the sterilization dose to be applied to health care products. ISO 11137 specifies that one of two approaches is to be used to select the sterilization dose; either i) the selection of a product-specific sterilization dose, or ii) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

An informative annex to ISO 11137:1995 (annex B) describes two methods for 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 [4], [5] and [6]. Subsequently, standardized methods were developed [2], [3] and [7] which formed the basis of the dose selection procedures put forward in the AAMI recommended practice for sterilization by gamma irradiation, *Guideline for gamma radiation sterilization* (AAMI, 1984 [1]).

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 various microbial species, assumes that each species has its own unique 'D₁₀' value. 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 D₁₀ 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, are used to establish the sterilization dose. This is not always practicable. Manufacturers of health care products 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, selection and maintenance of a validated sterilization dose is as important as for large production batches. The method described in ISO/TR 13409 [8] provides guidance on how to carry out substantiation subject to the following limitations:

- a) products with an average bioburden of less than 1 000 colony-forming units (cfu), and
- b) products manufactured in small quantities (less than 1 000 product units).

The method described in this report provides guidance on how to select a sterilization dose for a single production batch of health care products. The method is based upon Method 1, described in ISO 11137:1995, B.3.4.1.1 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, ten product units from three batches are selected and 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 of one in 100 probability of a non-sterile product unit. A sample of 100 product units or portions thereof (SIP) is then exposed to the verification dose and each product unit is tested individually for sterility. If there are no more than two positive tests out of the 100 tests, the sterilization dose is selected for the desired SAL from the response of microorganisms having the standard distribution of resistances at the estimated level of bioburden.

With the present method, only one production batch is manufactured and therefore the estimate of the average bioburden is made on that batch. The verification experiment and selection of the sterilization dose remain consistent with Method 1 in ISO 11137.

It was decided to publish the present method as a Technical Report (type 2) 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 document so that this experience can be taken into account when ISO 11137 is next revised.

Manufacturers of health care products who intend to use the protocols contained in this Technical Report are reminded that the requirements contained in ISO 11137 for all users of radiation sterilization equally apply to the manufacture and control of a single production batch for which the selection of a sterilization dose 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 requirements for proper control of the quality of raw materials, for the manufacturing environment, and for the establishment of the basic properties of the packaging material are all essential.

