

## **Rationale behind the principal changes to and inclusion of new elements in the requirements of EN ISO 11137**

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## Introduction

The preparation of standards for the validation and routine control of sterilization of medical devices by irradiation, EN 552 (1994) and ISO 11137 (1995), started in 1989. EN 552 is a harmonised European Standard and gives a presumption of conformity to the European Medical Devices Directives; ISO 11137 has been adopted as an American National Standard and is recognised by the United States Food and Drug Administration. The standards are technically equivalent and entirely compatible, but they are editorially different, adding complexity for manufacturers and radiation processors who need to comply with both the European and United States requirements. Under the normal practice of the respective Standards Organizations, standards are reviewed after five years and it was agreed in 1999 that a joint revision should be prepared under the leadership of the International Standards Organization (ISO). This process is now concluded and a revised standard has been published.

The review and revision of the radiation sterilization standard was undertaken in parallel with those of the standards for development, validation and routine control of the sterilization methods employing ethylene oxide and moist heat. It was decided at the beginning of the revision process that the structure of the standards for the three methods of sterilization should be the same, based on that of ISO 14937 (2000), *General requirements for characterizing a sterilizing agent and the development, validation and routine control of a sterilization process*. In addition, it was agreed that the same definitions should apply in the three process standards.

As review and revision progressed, it became obvious that management of the application of the standard would best be satisfied if its content was divided. Accordingly, three parts have prepared, under the title EN ISO 11137: 2006, *Sterilization of health care products – Radiation*, as follows:

*Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices,*

*Part 2: Establishing the sterilization dose,*

*Part 3: Guidance on dosimetric aspects.*

The purpose of the present paper is to document the rationale behind the principal changes that have been incorporated into the requirements specified in the revised standard. A record of this type will, it is anticipated, assist users of standard to understand why changes were made, as well as comprising an *aide memoire* for others, who in the future could be faced with further revision activities. As far as the authors are aware, no 'official' record of this kind was prepared at or after the 10 or so meetings of Working Group 2 (WG) that were held to undertake the revision process. It has to be said that the content of the

paper is constituted from recollections of two members of the WG who were delegates to the group on behalf of the British Standards Institution and, as such, is not necessarily at one with the views of all members of the WG.

Note: The numerals and headings associated with the various main sections of the paper correspond to those comprising ISO 11137-1 (2006). However, the content of the sections is drawn, where appropriate, from requirements stipulated in both ISO 11137-1 and -2 (2006).

## 1 Scope

In the scopes of the European and International standards there were differences in applicability; EN 552 (1994) was applicable to radiation using gamma sources or accelerated electrons, whereas ISO 11137 (1995) was additionally applicable to machine-generated X-rays. Furthermore, EN 552 (1994) stipulated a maximum energy level of 10MeV for electrons applied in sterilization, but ISO 11137 (ISO 1995) had no maximum energy level for either electron beam sterilization or for electrons used to generate X-rays for sterilization. In the revision process, these differences needed to be addressed.

With the increasing application of X-rays on a commercial scale since the publication of EN 552 in 1994, agreement to include X-rays within the scope of the revised standard was readily reached. Not so with the issue of energy levels that was discussed at length, the discussion resulting in the specification of an additional requirement for processes using energy levels above a specified level for each of electrons used directly and electrons used to generate X-rays (see **Sterilizing agent characterization** below for details).

On a separate issue, a note in the scope of the standard points out that regulation for medical devices in some jurisdictions and for supply of products to some markets might require the application of a quality management system throughout the design, manufacture and distribution of medical devices and that third party assessment of the quality management system accompany this requirement. For example, compliance with ISO 13485 (2003) is a regulatory requirement in Canada; in Europe, compliance with the European adoption of ISO 13485 (2003) gives a presumption of conformance with the requirements for a quality management system; and in the USA, compliance with the Quality System regulation and FDA assessment might be necessary. It is worth pointing out that while the elements required by ISO 11137-1 (2006) are by reference to ISO 13485 (2003), the elements required are also consistent with the requirements of the US Quality System Regulation (FDA1996). The rationale behind this approach was (i) to retain compatibility with the regulatory requirements in different jurisdictions, (ii) to avoid imposing quality systems requirements over and above those needed effectively to develop, validate and control radiation sterilization, and (iii) to reflect the level imposed by regulations in different countries or regions.

## 2 Normative references

The Normative Reference section stipulates those standards that, either in whole or in part, are indispensable to the application of ISO 11137-1, -2 (2006). The inclusion of such references obviates the need to repeat sections of text dealt with adequately in other standards and, when undated references are cited, keeps the standard up-to-date with the latest revision of the normative reference. It should be noted that inclusion of a standard as a Normative Reference does not indicate automatically that the whole of the referenced standard applies; the application of the Normative Reference is only to the extent stipulated in the text of ISO 11137-1, -2 (2006).

The Normative References cited cover calibration and quality management system elements (see later section), methods of sterilization dose establishment, and microbiological methods for determination of bioburden and for conducting tests of sterility in establishing the sterilization dose.

## 3 Definitions

Changes made to the definitions used in the previous standards were chiefly made for clarification purposes or to align definitions across all the standards for development, validation and routine control of sterilization of the different sterilization methods. Newly introduced definitions were approved by ISO TC 198, the parent committee overseeing the development of all the ISO sterilization standards.

The most significant change for those familiar with ISO 11137 (1995) is the discontinuation of the use of the term 'product unit'. This term is not used in other sterilization standards, and it was agreed to use the term 'product' as a singular and a collective noun. Where there was a need to refer to the handling of individual articles, the term 'product item' has been employed in the revised standard.

## 4 Quality management system elements

In order to demonstrate that the radiation sterilization process is being developed, validated and routinely controlled in reproducible manner, it is necessary to have certain parts of a quality management system in operation (i) at the manufacturer, if manufacture and radiation sterilization of medical devices are undertaken in house, or (ii) at both the primary manufacturer and the irradiator operator, if there are two separate organizations involved. It is not required by the standard to have a complete quality management system nor is it required that the stipulated elements be subject to third party assessment (see the rationale for this approach described under **Scope**).

In EN 552 (1994) and ISO 11137 (1995), requirements for quality assurance activities were spread throughout the documents. In contrast, the quality management system elements that are required by ISO 11137-1 (2006) have been brought together into a single clause of the standard. Normative reference is made to ISO 13485 (2003) to provide detail in regard to adequate documentation and records, defined responsibilities, trained and competent personnel, identification and traceability of product throughout the sterilization process, calibration, correction, and corrective action. Particularly, in regard to calibration, the standard requires that dose measurement is traceable to appropriate national or International standards, reflecting the vital part played by reliable and consistent dose measurement in the development, validation and routine control of radiation sterilization.

The need for measurements to be traceable to national or international standards has long been understood as a requirement in a quality management system and both EN 552 and the original ISO 11137 had this as an implicit requirement. However, uncertainty is not mentioned explicitly in EN 552 (1994) and, in ISO 11137 (1995), there is a requirement for 'proper dosimetric measurement procedures, with appropriate statistical controls' in the normative element, the need for a statement of uncertainty being stated in informative Annex C. Measurement uncertainty is coupled with traceability and there is a general requirement in metrology that no measurement result is valid without a statement about the uncertainty. Process limits in radiation sterilization that are based on the measurement of dose therefore have to take account of the uncertainty of the measurement. The publication of two significant documents in this respect (Panel on Gamma and Electron Irradiation, 2002; 2006), which provide the necessary information for use of measurement uncertainties, enabled the WG to include a more explicit requirement incorporating dose measurement for a knowledge of uncertainty of dose measurement [subclause 4.3.4 of ISO 11137 (2006)] and for this uncertainty to be taken into account in defining the requirements for designating a sterilization process as conforming [subclause 11.2 of ISO 11137 (2006)].

## **5 Sterilizing agent characterization**

The potential for induced radioactivity in products irradiated with high energy electrons or photons is widely recognized (Meissner *et al.*, 2000; Gregoire *et al.*, 2003 a). From a processing perspective, several advantages arise as energy levels increase; penetration improves and, for X-rays, power conversion efficiency improves and angular dispersion decreases (Gregoire *et al.*, 2003 b). For the irradiation of foods for human use, a limit of 10 MeV had been established for electrons and initially 5 MeV for X-rays (FDA, 1986), the latter being subsequently raised to 7.5 MeV (FDA, 2004).

It was the widely agreed choice of 10 MeV as the upper energy limit for electron irradiation of food that led to a similar choice for irradiation of medical devices

stipulated in EN 552. The passage of time showed this choice to be generally acceptable and so the value of 10 MeV was included in ISO 11137-1 (2006).

Gregoire *et al.* (2003 b) have described theoretical and practical findings on radioactivity induced in materials used in the fabrication of medical devices irradiated with X-rays at an energy level of 7.5 MeV. Their work was given detailed consideration by the Working Group. The studies showed that care is needed in the choice of materials for conveyor totes irradiated with X-rays produced from high energy electrons. They also showed that induced activities in many medical device materials irradiated with 7.5 MeV X-rays at absorbed doses exceeding 25 kGy are negligible with respect to personnel safety and public health.

The Working Group found this work reassuring. However, the standard does not prescribe the choice of tote materials and, while the work covered a range of materials used in fabricating medical devices, it did not encompass all possible materials. Thus, the WG, recognising it is the responsibility of the manufacturer to demonstrate the appropriateness and safety of a medical device, decided to include in ISO 11137-1 (2006) a requirement for the performance of an assessment of the potential for induced radioactivity in medical devices irradiated with electrons of energy exceeding 10 MeV and in those irradiated with X-rays generated using electrons of energy exceeding 5 MeV. In taking this decision, the WG chose to err on the side of safety.

## **6 Process and equipment characterization**

This clause of the standard describes in detail those aspects of the irradiator and the ancillary systems that are required to be documented in the equipment specification(s). While there have been some editorial adjustments to the text for consistency between the different types of radiation, there are no major changes in this clause other than inclusion of a new section dealing with X-ray irradiators.

## **7 Product definition**

### *Control of product for sterilization*

Such control was addressed in EN 552 (1994) through requiring in Clause 4 that manufacture of medical devices be conducted under conditions that ensure bioburden is consistently low. No comparable requirement was stated in ISO 11137 (1995). Product definition is a crucial element of the general format laid down for the normative parts of the revised sterilization standards and definition in terms of microbiological status of product is a key element in the provision of the requisite assurance of sterility. Hence, the WG was obliged to develop appropriately worded requirements concerning the condition of product presented for sterilization. Consensus on specific requirements was not reached because of the wide range of medical devices that are sterilized by irradiation

and so the WG had to resort to two requirements of a more general nature. The intention behind these requirements and means by which they might be implemented are outlined in the guidance section of the revised standard (ISO 11137-1, Annex A, 2006).

### *Product families*

The term 'product family' was a part of ISO TS 15843 (2000), much of which has been incorporated into the revised ISO 11137-1, -2 (2006). Its origins reside primarily with large manufacturers of medical devices. The latter often manufacture product of a given kind in a variety of forms under a given set of production conditions. Such product can possess bioburden comprising similar numbers and types of microorganism, so that if establishment of the sterilization dose were performed, the outcome would be a common sterilization dose. Devices of this kind constitute a product family that can be represented by an appropriate family member. Selection of a medical device of one form to represent all devices that make up the family reduces the resource that is required to establish and maintain the sterilization dose. However, the disadvantage associated with using a product family is that the ability to detect changes in the microbiological status of all family members might be reduced. Furthermore, an event such as a failure of a sterilization dose audit requires action to be taken in regard to all family members, not only the device used to represent the family. The requirements for creating and maintaining a valid product family are stipulated in ISO 11137-2 (2006). It is worth noting that the product family concept has also been applied in instances where appropriately grouped product is manufactured with minor variations in small batches.

### *Processing categories*

Processing category is a term newly introduced into ISO 11137-1 (2006) but the concept has been widely used in radiation processing for a good number of years. It is of paramount importance in the efficient operation of irradiators. Inclusion in the revised standard of requirements relative to such categories is a natural outcome of this general use.

A processing category is a group of medical devices that can be processed together through the irradiator. Processing categories are generally made up of medical devices that require processing at the same dose range (sterilization dose and maximum acceptable dose) and have similar characteristics in absorbing radiation (composition, loading pattern and bulk density). Guidance on the inclusion of product in processing categories is given in ISO 11137-1 (2006), Annex A.

## **8 Process definition**

### *Establishing the maximum acceptable dose*

The term 'maximum acceptable dose' was included in ISO 11137 (1995) but without definition and without any further elaboration other than the dose was required to be established. The WG recognized that the manufacturer of a medical device is responsible for the safety and quality of that device when placed on the market and throughout its defined lifetime. The evaluation of radiation effects on the device properties is a crucial element in discharging this responsibility in relation to devices sterilized by irradiation, an activity that leads directly to the definition of the maximum acceptable dose. The WG unanimously saw the need for a similar requirement on evaluation in the revised version of ISO 11137, as well as for providing the technical requirements for the performance of evaluation of radiation effects.

The WG considered the content the publication of AAMI TIR 17 (1997) on evaluating radiation effects and decided that, rather than incorporate this material in whole or in part within the guidance annex to ISO 11137-1 (2006), it would be appropriate to reference the AAMI publication. This would avoid possible future revision of ISO 11137-1 (2006) should the AAMI TIR be modified in the light of technical developments.

### *Establishing the sterilization dose*

This clause of Part 1 stipulates the options available for sterilization dose establishment. It effectively covers the content of the clauses titled **Choice of sterilizing dose** and **Sterilization dose selection** of the previous standards, EN 552 (1994) and ISO 11137 (1995) respectively, as well as calling up new methods for substantiating each of a sterilization dose of 25 or 15 kGy. The thinking behind the inclusion of new elements in this area of the revised standard was as follows.

#### Methods 1 and 2

At the outset of revision, the WG agreed that, unless there were soundly-based reasons, the procedures for dose setting Methods 1 and 2, as described in Annex B of ISO 11137 (1995), should remain unchanged technically in the revised version. Method 2 was effectively unchanged but, for Method 1, it was felt that changes could be made, with advantage, to the table that lists the doses to achieve values of SAL for a range of average bioburdens having the standard distribution of resistances (SDR). For average bioburdens  $\geq 1,0$  (Table 5 of EN ISO 11137-2, 2006), the tabulated levels of average bioburden have been amended to whole numbers and the progressive increases in bioburden have been so arranged to allow generally corresponding rounded increases in dose at an SAL of  $10^{-2}$  (the verification SAL) of 0.1 kGy. The belief was that these changes gave the table a more rational structure and made it easier for users to

comprehend. A second change to the table was more contentious – it was concerned with the setting of the lower limit of average bioburden for Method 1.

In ISO 11137 (1995), the lower limit of the average bioburden given in the Method 1 table (Table B.1) is 0.063; this limit was set by a verification dose at an SAL of  $10^{-2}$  of 1 kGy, a dose considered the lowest deliverable in a consistent and accurate manner. Early in the revision process, the Working Group decided a more rational approach to the choice of the lower limit of average bioburden should be taken.

Following consideration of computer simulations of Method 1 (Aoshuang and Tallentire, 1999) which showed that, for levels of bioburden around 1.0 and below, the method is not always discriminating and becomes inappropriate, members of WG generally agreed that the lower limit of average bioburden should be set at 1,0. The obvious question then became “how is a sterilization dose to be established for product with levels of bioburden < 1,0?”

Consideration of what constitutes an acceptable level of conservativeness on treatment of low bioburden product with radiation led to a U.K. proposal that, for product having a bioburden of 1.0 and below, treatment with a pre-selected dose of 14.2 kGy without performance of a verification dose experiment was a possible way forward (Tallentire, 2004). The U.S. delegation could not support this proposal as it was aware that its regulatory body would not generally accept the selection of a sterilization dose without an acceptable outcome from a verification experiment. Moreover, it was pointed out that failure of Method 1 to discriminate between microbial populations at levels of bioburden below 1,0 that could or could not provide a sterilization dose had a low and acceptable associated risk and, consequently, proposed that the lower limit in the Method 1 table should be lowered to 0,1. Such an action, if approved, would accommodate certain device manufacturers who had in the past set, and were still setting, sterilization doses using Method 1 for product with average bioburden within the range 0,1 to 1,0. The U.S. proposal was approved by the WG. However, the WG felt that, for this particular domain of average bioburden for which uncertainty around the outcomes from applying Method 1 existed, conditions should be imposed to ensure accuracy of bioburden determinations. It therefore required (i) such determinations be performed on entire product items, (ii) the application of a correction factor in the determination of bioburden, and (iii) the provision in ISO 11137-2 (2006) of a separate Method 1 table (Table 6) covering product having an average bioburden in the range 0,1 to 0,9 inclusive. The latter requirement was aimed at drawing attention to the conditions associated with such product and to avoid them being considered as candidates for sterilization dose setting using general Method 1.

Method VD<sub>max</sub><sup>25</sup>

Both EN 552 (1994) and ISO 11137 (1995), in addition to allowing a product-specific sterilization dose to be chosen using an approved dose setting method, permitted the selection of a sterilization dose of 25 kGy. However, to employ this fixed dose, the European standard required that the primary manufacturer had “evidence to show compliance with EN 556” – the ‘sterility standard’, currently EN 556-1 (2001) - and the International standard required “substantiation of the appropriateness of this dose”.

In its guidance section, EN 552 (1994) suggested a clearly defined approach to provision of evidence of compliance, namely, the performance of a Method 1 or Method 2 dose setting exercise resulting in a derived sterilization dose of less than 25 kGy. Contrasting with this formal and resource-demanding course of action, it also gave some non-specific guidance on alternative types of evidence that might be used to support the effectiveness of a 25 kGy sterilization dose. The intention behind this latter action was to allow primary manufacturers, who had traditionally treated product at this fixed dose in accordance with national regulatory practices, the opportunity to provide Notified Bodies with historical data for compliance purposes. ISO 11137 (1995), on the other hand, did not describe a method specific for or give guidance on substantiation of a sterilization dose of 25 kGy - this had to change.

ANSI/AAMI ST32-1991 (1991) included a “dose determination method” - Method 3 – developed specifically for verification of a 25 kGy sterilization dose. The method was an adaptation of Method 1 and was for use with a single production lot or small batch sizes produced infrequently. It was used for substantiation purposes in countries outside Europe where 25 kGy was employed as the sterilization dose and eventually was recognised as an ISO method by publication in ISO TR 13409:1996 (1996). However, the method was shown to possess a design fault which resulted in it being unable to discriminate between product that can and cannot be sterilized by exposure to 25 kGy (Tallentire, 1998; Aoshuang and Tallentire, 1999) and consequently ISO TR 13409 (1996) was not included in the portfolio of EN standards. The need clearly existed for a method for substantiation of 25 kGy that was scientifically sound and universally acceptable.

The basis of a properly designed approach to substantiation of 25 kGy was proposed by Kowalski and Tallentire (1999). In association with colleagues, the approach was evaluated theoretically (Kowalski, Aoshang and Tallentire, 2000) and practically (Kowalski *et al.*, 2002) and shown to be valid. The underlying principles were embodied in an experimental protocol, Method VD<sub>max</sub>, published as an AAMI Technical Information Report (AAMI TIR27, 2001). Thereafter, the method was written into ISO 11137-2 (2006), where, described in detail, it was deemed appropriate for substantiation of a selected sterilization dose of 25 kGy for product of bioburden  $\leq 1000$ . For this purpose, the method was designated Method VD<sub>max</sub><sup>25</sup>.

## Method $VD_{max}^{15}$

Around the time that the debate on the use of Method 1 to set a sterilization dose for low bioburden product was taking place in the WG, it became apparent that Method  $VD_{max}$ , first developed for substantiation of a selected 25 kGy sterilization dose, could be further developed to allow substantiation of pre-selected sterilization doses ranging from 15 to 35 kGy (Kowalski *et al.*, 2002). Each such dose has associated with it a characteristic maximal average bioburden which cannot be exceeded, the maximum being one element in the provision of a level of conservativeness within Method  $VD_{max}$  at least equal to that built into the SDR and hence Method 1. For example, to maintain this level with Method  $VD_{max}^{25}$ , the upper limit of average bioburden of product to which the method can be applied is 1000 (the bioburden having the SDR that achieves an SAL of  $10^{-6}$  at 25 kGy. For a dose of 15 kGy, the upper limit of average bioburden is 1.5 (a level of bioburden having the SDR that achieves an SAL of  $10^{-6}$  at 15 kGy), thus making Method  $VD_{max}^{15}$  an appropriate method for substantiation of a selected sterilization dose of 15 kGy for product of average bioburden  $\leq 1.5$ . With the recent publication on evaluations in support of Method  $VD_{max}^{15}$  (Kowalski *et al.*, 2006), the inclusion of this method in ISO 11137-2 (2006) received the support of all participating countries represented on the WG. Selection and substantiation of 15 kGy clearly provided an alternative to the use of Method 1 for dose establishment over a range of average bioburden about which concern was expressed. Furthermore, it met, in part, the proposal aired by the U.K. delegation that product having bioburden at the low end of the range be sterilized by application of a pre-selected sterilization dose.

### *Nature of product item for establishing and verifying the sterilization dose*

There has always been a concern in regard to the product item to be taken in establishing and verifying the sterilization dose. This concern was addressed initially in ISO TS 15843 (2000) in the form of a table defining four general types of product; (i) an individual device in its packaging system, (ii) a set of components in a packaging system, (iii) a number of identical devices in their packaging system, and (iv) a kit of procedure-related devices. The table gave the product item to be selected for the performance of bioburden determination and the verification and/or incremental dose experiment. The corresponding rationale for this choice was also given and is generally based on the use of the item in clinical practice. This table has been carried forward with minor modification and clarification into ISO 11137-2 (2006).

### *Transference of maximum acceptable, verification or sterilization dose between radiation sources*

Interestingly, no requirements were specified for transference of doses between different radiation facilities in either the normative or informative sections of EN

552 (1994); this omission was probably an inadvertent error. The omission was partly rectified with the publication of Amendment EN 552 (1994)/A2 (2000) which required that the type of radiation to be used for routine processing is that used in establishing the sterilization dose. ISO 11137 (1995) also did not specify requirements for the types of radiation employed for dose establishment and subsequent processing. However, it stipulated the following under clause **6.2.3 Transfer of sterilization dose**, (i) for transfer of a sterilization dose between an electron beam or X-ray facility and any other facility, data shall be available to show that microbial inactivation is not affected by differences between the two facilities in source characteristics, particularly radiation energy and rate at which dose is delivered, or by differences in dose distribution through the product, and (ii) for transfer between two gamma radiation facilities, data shall be available to show that microbial inactivation is not affected by differences between the two gamma radiation facilities in dose distribution through the product. There were no similar actions stipulated in regard to such transfers of the maximum acceptable and verification doses – these omissions were addressed in developing ISO 11137-1 (2006).

#### Transference of maximum acceptable dose

As a consequence of the need to establish the maximum acceptable dose, the issue of transference of this dose from one radiation source to another was raised. The WG recognized that such transfer might occur between experimental and production irradiation facilities and therefore required that an assessment be made of the effect of differences in the radiation conditions on the validity of the maximum acceptable dose.

The requirements, and associated guidance to assist in the implementation of these requirements, are unequivocal, rational and clearly stated.

#### Transference of verification dose or sterilization dose

Unlike the requirements specified in 6.2.3 of ISO 11137 (1995), those given in ISO 11137-1 (2006) relate solely to potential differences in microbial inactivation due to differences in intrinsic properties of the incident radiation. Measurement of dose distribution throughout product (dose mapping) exposed to any radiation source to be employed for sterilization purposes is a requirement stipulated elsewhere in ISO 11137-1 (1995) and the need for dose distribution to be known for the conduct of establishment of the sterilization dose is properly and fully recognised in ISO 11137-3 (2006). Thus, the impact on dose distribution of changing radiation source is not an issue in deciding whether or not transference of the sterilization dose or the verification dose can take place between sources. The crucial matter in regard to dose transfer requiring consideration by the WG was “does the manner in which dose is delivered to product using different sources influence the microbicidal effectiveness of the radiation?”

In considering available background information, the WG agreed to disregard early work describing comparisons of the microbicidal effectiveness of gamma and electron beam radiation sources. Reported findings are inconsistent, possibly consequent upon errors in dose measurements, the latter invariably lacking traceability to national standards. Given this and the production, in recent years, of little new comparative work on which to base a rationalised general position, the WG had no option but to include in the revised standard effectively the requirement specified in the earlier version, namely, transference of a verification dose or sterilization dose is not permitted unless data are available to demonstrate the differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness. How then might such a demonstration be sought? On this matter, the WG's thoughts were that a desire to transfer either of these doses from one radiation source to another would usually be preceded by the performance of a successful verification dose experiment using the original source. In such circumstances, it was agreed that an appropriate demonstration would be to perform a successful verification dose experiment using the other source.

Consideration by the WG of two sets of comparative data, for which all dose measurements were traceable to a national standards laboratory (UK National Physical Laboratory), led to the granting of further permissions to transfer doses between named, like sources operating under specified conditions.

One data set comprised findings from survival curve studies carried out on microorganisms (bacterial spores) suspended in water and irradiated with electrons delivered as pulses of various lengths (0.1 to 5.0  $\mu$ s), the manner of delivery of the integrated dose being such that the dose per pulse and the dose rate within the pulse could be varied independently as desired. Crucially, the studies showed that, for the microorganisms in water together with solutes or not, the dose delivered per pulse is a significant determinant of the rate of microbial inactivation (Tallentire and Barber, 1978; Barber and Tallentire, 1980; Tallentire, 1983). Since dose per pulse is likely to vary according to the operating conditions and set-up of the machines of the same type between which transfer of dose is being sought, the WG took a conservative position; it decided that, for product containing water, transfer of dose between one electron source and another such source or one X-ray source and another such source could take place without the provision of comparative data only if the two sources were functioning under identical operating conditions. On the other hand, for transfer between two gamma sources, no such restrictions were imposed as, historically, it has been found that differences in the rate of delivery of continuous gamma radiation are without effect on microbial inactivation, provided that microbial contaminants of the product are not replicating during irradiation (Ley, 1963). Authors' Note: If the radiation dose is delivered by the two gamma sources at widely different rates and the product has the ability to support microbial growth, caution should be exercised in transferring verification or sterilization dose without accompanying data to show that microbial inactivation is not affected by the difference in dose rate.

Contrasting with the findings from electron irradiation of 'wet' bacteria were those from similar experiments done on dried microorganisms. For bacterial spores dried onto the surfaces of different carrier materials (polyethylene, nylon, stainless steel), changing the dose delivered per pulse or the dose rate within the pulse over the same wide range as that employed in the 'wet' experiments in accumulating the integrated dose, was without a significant effect on the rate of spore inactivation. Table I summarises the unpublished findings considered by the WG. For product that does not contain liquid water, these results then form the basis of the rationale for allowing the transfer of dose between one electron source and another such source and one X-ray source and another without provision of comparative data. Also for such product, transfer of dose between gamma sources without data is well-established practice, founded on early data, and is seen as acceptable (Halls, 1992).

Regrettably, the wording of the guidance offered in A.8.4.2 of ISO 11137 (2006) is somewhat muddled and repetitive and so it is not easily related to the requirements listed in 8.4.2. An alternative, clearer version of A.8.4.2 might have read as follows:

A.8.4.2.1 There is a concern in transferring between types of radiation sources with widely differing dose rates that can provide different microbicidal effects. Demonstrating that the microbicidal effectiveness is not affected by the change in dose rate provides the necessary data for the transference to be permitted. A demonstration that microbicidal effectiveness is not affected by transference can be accomplished through the performance of a successful verification dose experiment (see ISO 11137-2) using the radiation source to which transfer is being considered.

A.8.4.2.2 Experimental evidence indicates that, when irradiation occurs under 'dry' conditions, microbicidal effectiveness is independent of the operating conditions of the radiation sources, hence, the granting of this permission.

A.8.4.2.3 Available experimental evidence indicates that, when irradiation occurs in the presence of liquid water, microbicidal effectiveness can be affected by the operating characteristics of the radiation sources, hence, the restrictions on permission being granted.

## **9 Validation**

EN 552 (1994) recognized two elements of validation, installation qualification and performance qualification. ISO 11137 (1995), on the other hand, included product qualification in its section on Validation, and also identified two validation elements that it termed installation qualification and process qualification. These differences needed to be resolved in preparing ISO 11137 (2006). With the

establishment of the maximum acceptable dose and the sterilization dose being covered in the clause on **Process Definition**, the WG agreed that the validation section of ISO 11137 (2006) should focus on requirements for confirming that the irradiator has been provided in accordance with its specification, functions appropriately and can deliver the required process to product. In EN 552 (1994) and ISO 11137 (1995), the requirements for validation of the process were based on monitoring process parameters and dosimetric determinations to demonstrate that the specified process can be delivered within defined tolerances. The WG could see no reason to change this rational and well-accepted approach.

The format being applied to the revisions of standards for development, validation and routine control of sterilization of the different sterilization methods recognized validation as comprising three elements, installation qualification (IQ) and operational qualification (OQ) of the irradiator and performance qualification (PQ) specific for a defined product or family of products. These stages are followed by a formal review and approval of validation culminating in production of a formal process specification for sterilization of a particular product or family of products. The WG recognized the benefits of consistency of approach to validation across the different sterilization technologies and that implementation of IQ, OQ and PQ had become common practice in validation of a radiation sterilization process.

## **10 Routine monitoring and control**

The requirements for routine control and monitoring focus on the demonstration that the validated process has been delivered consistently through measurement of process parameters and dosimetric measurement. The requirements in ISO 11137 (1995) are in accord with those previously stated in both EN 552 (1994) and ISO 11137 (2006), with some editorial revision to ensure consistency throughout the revised standard and to provide clarification where the WG felt that this would be beneficial.

## **11 Process release from sterilization**

The requirements for product release from sterilization are unchanged from those stated in the earlier European and International versions of the standard. A systematic review of the records of routine monitoring of the process is required against documented acceptance criteria. Should the acceptance criteria not be met, action is required to decide the disposition of the affected batch and also to identify and correct the cause of the failure to meet the predefined criteria.

## **12 Maintaining process effectiveness**

In EN 552 (1994) and ISO 11137 (1995), regular performance of dose audits was the specified means by which the continued effectiveness of an established sterilization dose had to be demonstrated. Wide experience of executing such

audits had clearly indicated their value and the WG unanimously agreed to the retention of the technical aspects of auditing in the revised standard. The requirements regarding the frequency of performance of audits, however, differed between EN 552 (1994) and ISO 11137 (1995). EN 552 (1994) required sterilization dose audits to be conducted at 'a frequency established by the primary manufacturer', whereas ISO 11137 (1995) required dose audits to be conducted at three-month intervals. Moreover, ISO/TS15843 (2000) described a strategy to reduce the frequency of sterilization dose audits but the legitimacy of a Technical Specification overriding a requirement in an International Standard was has to be questioned. Furthermore, the requirements on the conduct of sterilization dose audits in both the European and International standards applied to a sterilization dose established by dose setting but not to a selected and substantiated sterilization dose of 25 kGy. The WG felt that this deficiency had to be addressed in the revision process, together with specifying requirements for the performance of sterilization dose audits on product manufactured infrequently.

The initial selection of a three-month interval, quarterly, between the conduct for sterilization dose audits was based on the perceived potential for seasonal variation in bioburden (Hansen *et al*, 1994). However, the WG noted that i) in practice, quarterly sterilization dose audits had not been universally applied, (Hansen and Whitby, 1994), ii) a system to control bioburden was required by ISO 11137-1 (2006) to prevent seasonal or other variations in bioburden, and iii) quarterly changes of season were not observed in all parts of the world. The WG concluded that it could not justify the universal application of a quarterly frequency for conduct of sterilization dose audits and it decided to incorporate an option of selecting initially either a three-month interval between sterilization dose audits or permitting the manufacturer to rationalize the selection of an alternative time interval based on consideration of predetermined criteria defined in the standard. These criteria related to the magnitude, composition and means of control of bioburden, the conservativeness in the method used to establish the sterilization dose, and the frequency at which the product is manufactured. Given a specified number of successful outcomes from the conduct of sterilization dose audits at the initial frequency, a mechanism to reduce this frequency is documented.

Whichever of these approaches is adopted, it was agreed that the minimum frequency for the conduct of a sterilization dose audit is one per year, in conjunction with bioburden determinations undertaken at a three-month interval for product of average bioburden > 1.5 and monthly for average bioburden ≤ 1.5. With the acceptance of the use of bioburden determinations as part of the strategy for assuring process effectiveness, it was agreed that a documented bioburden limit be required and that a sterilization dose audit be initiated if this limit is exceeded.

In addition, actions following the various outcomes from a sterilization dose audit, initially described in ISO 11137 (1995), Annex B, have been modified to ensure consistency. Also modification included formalisation, in a step-wise fashion, the rational approach on sterilization dose augmentation following audit failures elaborated by Herring (1999).

## **Comment**

The joint revision of EN 552 (1994) and ISO 11137 (1995) provided ISO TC 198 WG2 with the opportunity to update the revised standard in the light of progress and changes in the radiation processing and associated technologies. It also provided an opportunity to clarify some of the content and improve the understanding of the standard given 10 years experience of use of the original standards.

One perception that had arisen in some quarters with regard to the validation and routine control of radiation sterilization was that implementation of the requirements was more onerous than that for other sterilization methods. This was a concern to the WG. The perception was erroneous but probably arose from the inclusion in ISO 11137 (1995) of methods of dose setting in Annex B (informative), making the standard a bulkier document than the European Standards EN 550 (1994) for ethylene oxide, EN 552 (1994), EN 554 (1994) for moist heat sterilization, or the comparable ISO standards ISO 11134 (1994) and ISO 11135 (1994) for ethylene oxide and moist heat sterilization, respectively. This perception was reinforced by the relative length of ISO 11137 (1995) at 61 pages compared to 14 to 28 for the other International standards.

Apparently, some individuals considered the relatively sophisticated methods of dose setting that appeared in Annex B of ISO 11137 (1995) as obligatory when, in fact, this was not so. Annex B was informative and methods other than those given therein were available for selecting a sterilization dose. The requirements stipulated in the text describing a formal dose setting method only became obligatory once that method was being implemented. The inclusion of the dose setting methods, described in detail in Annex B, led to international acceptance of the appropriateness of the methods and the removal of a number of regulatory barriers that existed previously.

The agreement to employ a common template for all sterilization methods in the revision process has ensured that requirements for each sterilization method are presented in a similar format and style and that all critical areas are addressed for all sterilization methods. This has resulted in the number of requirements in standards for ethylene oxide, radiation and moist heat being very similar (140 in ISO FDIS 11135-1 (2006), 140-143 in ISO 11137-1 (2006) depending on whether gamma, electron beam or X-rays are to be employed, and 125 in ISO 17665-1 (2006)). In addition, the inclusion of the previous dose setting methods from Annex B of ISO 11137 (1995), together with methods of substantiation of the

sterilization doses of 15 and 25 kGy, in ISO 11137-2 (1996) further reduces regulatory barriers, as well as providing international recognition of the  $VD_{max}$  approach to dose substantiation.

The publication of ISO 11137 (2006) clearly shows the continuing development of irradiation as a method of sterilization. Developments in approaches to establishing the sterilization dose are undoubtedly contributing to taking sterilization technology forward.

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**Table I. Values of inactivation rate constants (k) for *Bacillus megaterium* spores dried onto different carriers and irradiated with 10 MeV electrons at a repetition rate of 50 pulses / s**

<b>Carrier</b>	<b>Orientation*</b>	<b>5 <math>\mu</math>s pulses 758 Gy / pulse</b>	<b>0.1 <math>\mu</math>s pulses 14 Gy / pulse</b>
Polyethylene (5 mm)	A $\rightarrow$ C	- 1.73 $\pm$ 0.03	- 1.75 $\pm$ 0.03
	C $\rightarrow$ A	- 1.51 $\pm$ 0.02	- 1.78 $\pm$ 0.02
Nylon (5 mm)	A $\rightarrow$ C	- 1.73 $\pm$ 0.03	- 1.75 $\pm$ 0.02
	C $\rightarrow$ A	- 1.42 $\pm$ 0.06	- 1.69 $\pm$ 0.01
Stainless steel (0.125 mm)	A $\rightarrow$ C	- 1.78 $\pm$ 0.04	- 2.08 $\pm$ 0.03
	C $\rightarrow$ A	- 1.78 $\pm$ 0.03	- 1.99 $\pm$ 0.03

\* For A  $\rightarrow$  C, the surface carrying the spores faced directly the incident electron beam

For C  $\rightarrow$  A, the surface carrying the spores faced away from the incident electron beam