Revised Dose Tolerances in EN ISO 11137-2:2012

PANEL ON GAMMA & ELECTRON IRRADIATION

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Introduction

The revision of EN ISO 11137-2 “Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose” published in 2012 contains a number of changes to the required dose tolerances and the actions to taken if the tolerances are not met. This guidance note outlines the changes with respect to the 2007 version of the standard and reproduces the relevant clauses from the 2012 standard.

This document is intended only to highlight the dose tolerance aspects and does not cover other significant changes in the EN ISO 11137-2:2012 standard. A further document containing details of the rationale for the dose tolerances is being prepared.

Method 1

Change from 2007 – The requirements have been reworded but there are no technical changes.

7.2.5.2 Irradiate these product items at the verification dose.

The highest dose to product items shall not exceed the verification dose by more than 10 %.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of the verification dose.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds the verification dose by more than 10 %, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of the verification dose, the verification dose experiment may be repeated. If this mean dose is less than 90 % of the verification dose and, on performance of tests of sterility, acceptable results are observed (see 7.2.6.1), the verification dose experiment need not be repeated.

Method 2A – Incremental dose

Change from 2007 – The requirements have been reworded and a change made to make a repeat in the event of under-dosing mandatory.

8.2.3.1.1 For each of three production batches, irradiate 20 product items at each of a series of at least nine doses, starting at 2 kGy and increasing in nominal increments of 2 kGy.

For a given incremental dose, the highest dose to product items shall not exceed the nominal incremental dose by more than 10 % or 1,0 kGy, whichever is greater.

For a given incremental dose, the arithmetic mean of the highest and lowest doses to product items shall not be less than 90 % of the nominal incremental dose or the nominal incremental dose minus 1,0 kGy, whichever is the lesser.

Determine the dose delivered at each of the incremental doses (see 5.5).

If, for a given incremental dose, the highest dose to product items exceeds the nominal incremental dose by more than 10 % or 1,0 kGy, whichever is greater, irradiation of 20 further product items at the particular incremental dose shall be carried out.

If, for a given incremental dose, the arithmetic mean of the highest and lowest doses to product items is less than 90 % of the nominal incremental dose or the nominal incremental dose minus 1,0 kGy, whichever is the lesser, irradiation of 20 further product items at the particular incremental dose shall be carried out.

Method 2A – Verification dose

Change from 2007 – There has been a major revision to the requirements. Actions to be taken in event of over- or under-dosing are now dependent on the value of CD*.

8.2.4.1 Irradiate 100 product items from the CD batch at a dose of D*.*

The highest dose to product items should not exceed D by more than 10 % or 1,0 kGy, whichever is greater.*

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of D or less than D* minus 1,0 kGy, whichever dose is the lesser.*

Determine the dose delivered (see 5.5). Designate the highest dose delivered as DD.*

NOTE Actions in regard to the upper and lower dose limits are dependent on the value taken by CD (see 8.2.4.2).*

8.2.4.2 Subject each irradiated product item individually to a test of sterility (see 5.4.1) and record the number of positive tests of sterility. Designate this value as CD.*

NOTE 1 CD is used to determine FNP (see 8.2.5) and DS (see 8.2.6).*

If CD is equal to zero and DD* exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, the verification dose experiment shall be repeated.*

If CD is 1 to 15 inclusive and DD* exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, the verification dose experiment need not be repeated.*

NOTE 2 A repeat verification dose experiment may, however, be carried out to obtain a value of DD lower than that found originally which, in turn, would give low FNP and DS values.*

NOTE 3 CD values of 1 to 15 inclusive, together with DD*, provide an estimate of the dose that achieves a 10^{-2} SAL.*

An acceptance of DD that exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, is permitted as the resulting values of FNP and DS will give conservative values of D** and the sterilization dose.*

If CD is greater than 15 and the arithmetic mean of DD*, and the lowest dose to product items is less than 90 % of D* or less than D* minus 1,0 kGy, whichever dose is the lesser, the verification dose experiment may be repeated. If this mean is not less than 90 % of D* or not less than D* minus 1,0 kGy, whichever dose is the lesser, the cause for the occurrence of more than 15 positive tests of sterility should be investigated, corrective action implemented and D* redetermined.*

Method 2B – Incremental dose

Change from 2007 – The requirements have been reworded and a change made to make a repeat in the event of under-dosing mandatory. A new tolerance has been introduced in the case of the 1 kGy incremental dose.

8.3.3.1.1 For each of the three production batches, irradiate 20 product items at each of a series of at least eight doses, starting at 1 kGy and increasing in nominal increments of 1 kGy.

For an incremental dose of 1 kGy, the highest dose to product items shall not exceed 1,2 kGy and, for other incremental doses, this dose shall not exceed the nominal incremental dose by more than 10 % or 0,5 kGy, whichever is greater.

For an incremental dose of 1 kGy, the arithmetic mean of the highest and lowest doses to product items shall not be less than 0,8 kGy and, for other incremental doses, the mean dose shall not be less than 90 % of the nominal incremental dose or the nominal incremental dose minus 0,5 kGy, whichever is the lesser.

Determine the dose delivered at each of the incremental doses (see 5.5).

If, for an incremental dose of 1 kGy, the highest dose to product items exceeds 1,2 kGy and, for other incremental doses, this dose exceeds the nominal incremental dose by more than 10 % or 0,5 kGy, whichever is greater, irradiation of 20 further product items at the particular incremental dose shall be carried out.

If, for an incremental dose of 1 kGy, the arithmetic mean of the highest and lowest doses to product items is less than 0,8 kGy and, for other incremental doses, this mean dose is less than 90 % of the nominal incremental dose or the nominal incremental dose minus 0,5 kGy, whichever is the lesser, irradiation of 20 further product items at the particular incremental dose shall be carried out.

Method 2B – Verification dose

Change from 2007 – There has been a major revision to the requirements. Actions to be taken in event of over- or under-dosing are now dependent on the value of CD*.

8.3.4.1 Irradiate 100 product items from the CD batch at a dose of D*.*

The highest dose to product items should not exceed D by more than 10 % or 1,0 kGy, whichever is greater.*

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of D or less than D* minus 1,0 kGy, whichever dose is the lesser.*

Determine the dose delivered (see 5.5). Designate the highest dose delivered as DD.*

NOTE Actions in regard to the upper and lower dose limits are dependent on the value taken by CD (see 8.3.4.2).*

8.3.4.2 Subject each irradiated product item individually to a test of sterility (see 5.4.1) and record the number of positive tests of sterility. Designate this value as CD.*

NOTE 1 CD is used to determine FNP (see 8.3.5) and DS (see 8.3.6).*

If CD is equal to zero and DD* exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, the verification dose experiment shall be repeated.*

If CD is 1 to 15 inclusive and DD* exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, the verification dose experiment need not be repeated.*

NOTE 2 A repeat verification dose experiment may, however, be carried out to obtain a value of DD lower than that found originally which, in turn, would give low FNP and DS values.*

NOTE 3 CD values of 1 to 15 inclusive, together with DD*, provide an estimate of the dose that achieves a 10^{-2} SAL.*

An acceptance of DD that exceeds D* by more than 10 % or 1,0 kGy, whichever is greater, is permitted as the resulting values of FNP and DS will give conservative values of D** and the sterilization dose.*

If CD is greater than 1 and the arithmetic mean of DD*, and the lowest dose to product items is less than 90 % of D*, or less than D* minus 1,0 kGy, whichever dose is the lesser, the verification dose experiment may be repeated. If this mean is not less than 90 % of D* or not less than D* minus 1,0 kGy, whichever dose is the lesser, the cause for the occurrence of more than 15 positive tests of sterility should be investigated, corrective action implemented and D* re-determined.*

VD_{max}^{25} – Verification dose

Change from 2007 – The requirements have been reworded but there are no technical changes.

9.2.5.2 Irradiate these product items at VD_{max}^{25} obtained from Table 9 or derived using Equation (10), whichever is appropriate.

The highest dose to product items shall not exceed VD_{max}^{25} by more than 10 %.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{25}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{25} by more than 10 %, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{25}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{25} and, on performance of tests of sterility, acceptable results are observed (see 9.2.6.1), the verification dose experiment need not be repeated.

VD_{max}^{15} – Verification dose

Change from 2007 – The requirements have been reworded but there are no technical changes.

9.4.5.2 Irradiate these product items at VD_{max}^{15} obtained from Table 10.

The highest dose to product items shall not exceed VD_{max}^{15} by more than 10 % or 0,1 kGy, whichever is greater.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{15}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VDmax15 by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{15}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{15} and, on performance of tests of sterility, acceptable results are observed (see 9.4.6.1), the verification dose experiment need not be repeated.

Sterilization dose audit – Dose established using Method 1, 2A or 2B

Change from 2007 – The requirements have been reworded. The required tolerances in the case of a sterilization dose set by Methods 2A and 2B have been made more explicit.

*10.2.4.1 Irradiate 100 product items at the verification dose or D** found in the most recent dose setting exercise or, if applicable, at the adjusted dose (see 10.2.6.4) obtained from the most recent sterilization dose audit that resulted in augmentation of the sterilization dose. When applicable, use the adjusted dose until the sterilization dose has been re-established.*

On auditing a sterilization dose set by Method 1, the highest dose to product items shall not exceed the verification dose by more than 10 %. On auditing a sterilization dose set by

*Method 2A or 2B, the highest dose to product items shall not exceed D** by more than 10 % or 1,0 kGy, whichever is greater.*

*On auditing a sterilization dose set by Method 1, the arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of the verification dose. On auditing a sterilization dose set by Method 2A or 2B, this mean dose should not be less than 90% of D** or less than D** minus 1,0 kGy, whichever dose is the lesser.*

Determine the dose delivered (see 5.5).

*If, on auditing a sterilization dose set by Method 1, the highest dose to product items exceeds the verification dose by more than 10 % or, on auditing a sterilization dose set by Method 2A or 2B, the highest dose to product items exceeds D** by more than 10 % or 1,0 kGy, whichever is greater, the verification dose experiment shall be repeated.*

*If, on auditing a sterilization dose set by Method 1, the arithmetic mean of the highest and lowest doses to product items is less than 90 % of the verification dose or, on auditing a sterilization dose set by Method 2A or 2B, this mean dose is less than 90 % of D** or less than D** minus 1,0 kGy, whichever dose is lesser, the verification dose experiment may be repeated. If the conditions pertaining to a repeat of the verification dose experiment apply and, on performance of tests of sterility, acceptable results are observed (see 10.2.5.1), the verification dose experiment need not be repeated.*

Sterilization dose audit – Dose established using VD_{max}^{25} or VD_{max}^{15}

Change from 2007 – The requirements have been reworded but there are no technical changes.

10.3.4.1 Irradiate 10 product items at VD_{max}^{25} or VD_{max}^{15} obtained from the original substantiation exercise, whichever is applicable.

The highest dose to product items shall not exceed VD_{max}^{25} by more than 10 % or VD_{max}^{15} by more than 10 % or 0,1 kGy, whichever is greater.

The arithmetic mean of the highest and lowest doses to product items should be less than 90 % of VD_{max}^{25} or VD_{max}^{15}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{25} by more than 10 % or VD_{max}^{15} by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{25} or VD_{max}^{15}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{25} or VD_{max}^{15} and, on performance of tests of sterility, acceptable results are observed (see 10.3.5.1), the verification dose experiment need not be repeated.