PANEL ON GAMMA AND ELECTRON IRRADIATION
MICROBIOLOGY WORKING GROUP

Overview of Selected Aspects of

ISO 11137-2:2006

Sterilization of health care products – Radiation –

Part 2: Establishing the sterilization dose

MARCH 2012

Important: This document has been prepared by the Microbiology Working Group to clarify selected aspects of ISO11137- Part 2. This document has no legal standing and it is essential that it is used in conjunction with the standard.

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1. **Purpose**

ISO 11137-2 is a standard that covers dose establishment requirements relating to radiation sterilization processing. The Microbiology Working Group of the Panel on Gamma and Electron Irradiation has summarised selected areas from ISO 11137-2 for clarification. The information below is the result of an analysis by the Microbiology Working Group based on their direct experiences of implementing the standard.

The amount of information in ISO11137-2 is significant for anyone new to radiation sterilization processing. Whilst not written exclusively for the inexperienced, this overview has been compiled to assist those new to the field. Some insight into the rationale of dose establishment methods in the standard has therefore been included in this overview. There is an extensive bibliography at the end of ISO 11137-2 should more detail be required.

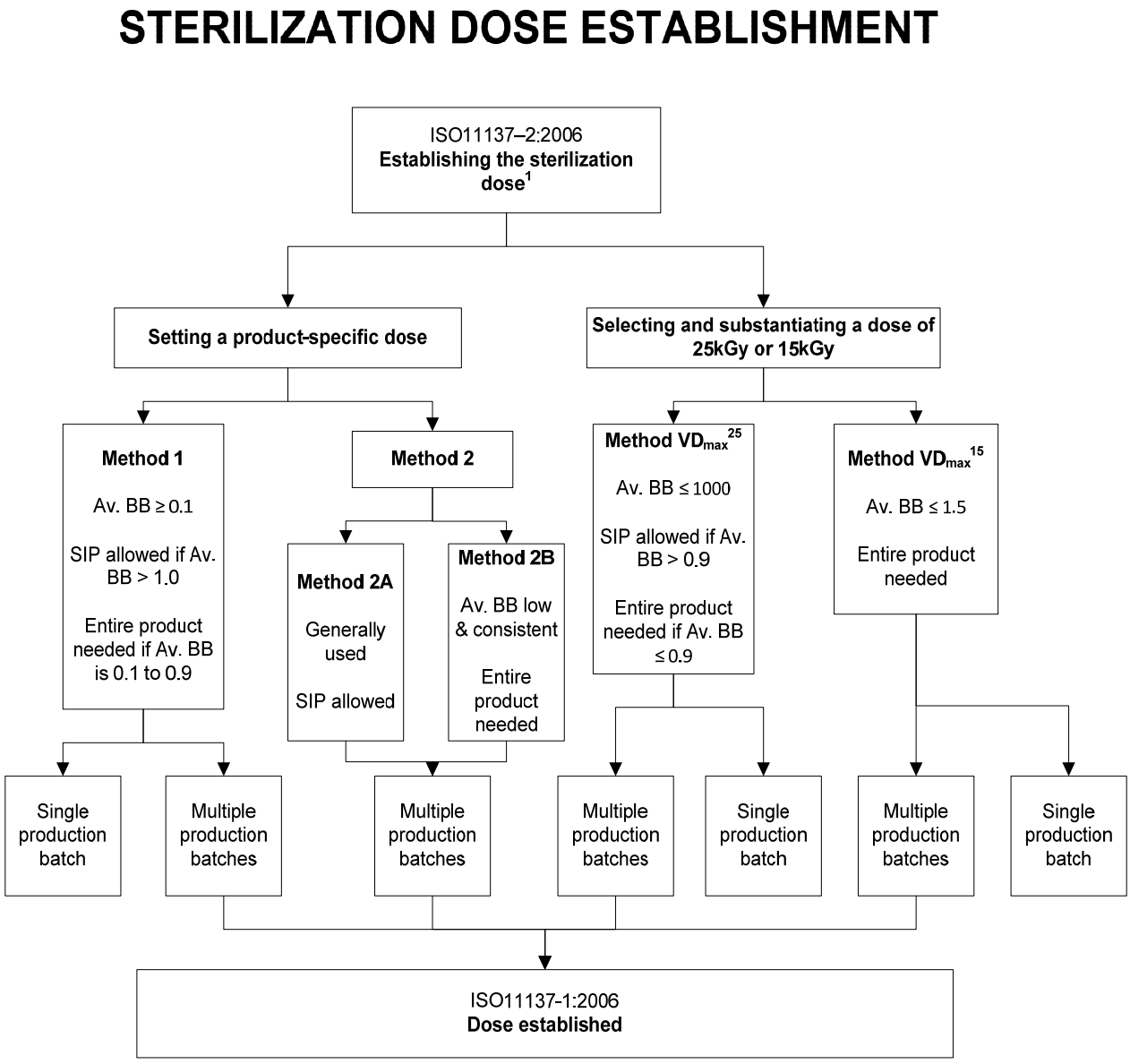
2. **Summary of Dose Establishment Methods**

The dose establishment methods are summarised in the table below:

Abbreviations

BB = Bioburden

SIP = Sample Item Portion



[1] When this standard is employed, the methods described in ISO11137-2 become normative and have to be followed exactly as described in the standard.

3. Differences Between Dose Establishment Methods in ISO 11137-2

3.1 Comparison Tables

The main features of the dose establishment methods are shown in Tables 1 and 2. The most similar methods are tabulated together to ease comparison.

Advantages and disadvantages are shown in Table 3 to assist in selection of the most appropriate dose establishment method.

Abbreviations: SDR = Microbial population having a standard distribution of resistances.
FNP = First number positive (see ISO11137-2 for definition).

Table 1: Main Features of Method 1 and Method VD_{max}

	Method 1 for product with an average bioburden ≥ 1.0 for multiple production batches	**Method 1 for product with an average bioburden ≥ 1.0 for a single production batch**	**Method 1 for product with an average bioburden in the range of 0.1 to 0.9 for multiple or single production batches**	**Method VD_{max}^{25} for multiple production batches**	**Method VD_{max}^{25} for a single production batch**	**Method VD_{max}^{15} for multiple production batches**	**Method VD_{max}^{15} for a single production batch**
Clause/Page in ISO 11137	7.2/11	7.3/16	7.4/18	9.2/26	9.3/29	9.4/30	9.5/33
Verification that microbial radiation resistance is ≤ the SDR.	√	√	√				
Verification that maximal microbial radiation resistance is ≤ the SDR				√	√	√	√
Bioburden is based on average bioburden of all 3 batches of 10 product items.	√		√ (if multiple)	√		√	
Bioburden is based on average bioburden of a single batch of 10 product items		√	√ (if single)		√		√
Use of a bioburden correction factor is optional	√	√					
Use of a bioburden correction factor is mandatory			√	√	√	√	√
Average bioburden must be between 1 and 1,000,000 (although very high values are discouraged from a GMP perspective)	√	√					
Average bioburden must be between 0.1 and 0.9			√				
Average bioburden must be ≤ 1,000				√	√		
Average bioburden must be ≤ 1.5						√	√
Uses SAL of 10^{-2} for verification dose from Table 5 in 11137-2	√	√					
Uses SAL of 10^{-2} for verification dose from Table 6 in 11137-2			√				
Uses SAL of 10^{-1} for the VDmax dose from Table 9 in 11137-2				√	√		
Uses SAL of 10^{-1} for the VDmax dose from Table 10 in 11137-2						√	√
Sample can be the entire	√	√		√	√		

	Method 1 for product with an average bioburden ≥ 1.0 for multiple production batches	**Method 1 for product with an average bioburden ≥ 1.0 for a single production batch**	**Method 1 for product with an average bioburden in the range of 0.1 to 0.9 for multiple or single production batches**	**Method VD_{max}^{25} for multiple production batches**	**Method VD_{max}^{25} for a single production batch**	**Method VD_{max}^{15} for multiple production batches**	**Method VD_{max}^{15} for a single production batch**
product or less				(if bioburden is > 0.9)	(if bioburden is > 0.9)		
Sample must be the entire product			√	√ (if bioburden is ≤ 0.9)	√ (if bioburden is ≤ 0.9)	√	√
If applicable, bioburden is the SIP average for obtaining the verification dose from the SDR Table	√	√					
Bioburden is corrected, if necessary, to correspond to the whole product for obtaining the VDmax dose from the VDmax Table				√	√		
100 product items from a single production batch are used for verification dosing and test of sterility	√	√	√				
10 product items from a single production batch are used for verification dosing and test of sterility				√	√	√	√
If necessary, an additional 10 product items from a single production batch are used for confirmatory verification dosing and test of sterility				√	√	√	√
Verification is acceptable with up to 2 positive tests of sterility	√	√	√				
Verification/substantiation is acceptable with up to 1 positive test of sterility				√	√	√	√
A confirmatory verification dose is necessary if there are 2 positive tests of sterility				√	√	√	√
Confirmatory verification/substantiation is acceptable if there are 0 positive tests of sterility				√	√	√	√
Bioburden is corrected, if necessary, to correspond to the entire product for obtaining sterilization dose from the SDR Table used to obtain the verification dose	√	√					

Table 2: Main Features of Method 2

Method 2 – For Multiple Production Batches		
	Method 2A	**Method 2B**
Clause/Page in ISO 11137	8.2/19	8.3/22
Direct measurement of microbial radiation resistance rather than verification against a SDR	√	√
This method is appropriate for consistent and very low bioburdens		√
Requires a large number of product items from each of three independent production batches (required number indicated per batch)	√ (280)	√ (260)
Sample need not be the entire product	√	
Sample must be entire product		√
Incorporates an incremental dosing stage using 20 product items/dose (minimum number of dose increments indicated)	√ (9)	√ (8)
Increments start at 2 kGy and increasing in nominal increments of 2 kGy	√	
Increments start at 1 kGy and increasing in nominal increments of 1 kGy		√
Positive tests of sterility must not exceed 14 at any incremental dose		√
FNP must not exceed 5.5 kGy		√
Verification dose is calculated based on results from incremental dosing	√	
Verification dose is calculated based on results from incremental dosing but using different equations to those used in Method 2A		√
100 product items from a single production batch are used for verification dosing and test of sterility	√	√
Sterilization dose is calculated based on results from incremental dosing and verification dosing	√	
Sterilization dose is calculated based on results from incremental dosing and verification dosing but using different equations to those used in Method 2A		√

Table 3: Advantages/Disadvantages of the Dose Establishment Methods

	Method 1	Method 2	VD_{max}
Small no. of samples (50 per batch max)			ADVAN
Moderate no. of samples (130 per batch)	ADVAN		
Large no. of samples (840 per batch)		DISADVAN	
Very resource/cost effective			ADVAN
Moderately resource/cost effective	ADVAN		
High level of resource/cost		DISADVAN	
Provides a product specific dose	ADVAN	ADVAN	
Covers a wide numerical range of microorganisms	ADVAN	ADVAN (Method 2a only)	
No upper or lower microbial limit on product		ADVAN (Method 2a only)	
Particularly useful for very low bioburden		ADVAN (Method 2b only)	
Limited to no more than 1,000 microrgs/product for 25 kGy substantiation and 1.5 microrgs/product for 15 kGy substantiation			DISADVAN (15 kgy substantiation only)
Dose establishment potentially effective over a wide range of doses depending on the natural bioburden	ADVAN	ADVAN	
Some conservatism in resistance values	ADVAN		ADVAN
Less conservatism than Method 1 or Method VD_{max} and therefore a greater chance of subsequent dose audit failure		DISADVAN	
Sterilization dose is likely to be lower than that established by Method 1 or VD_{max}		ADVAN	
Lower risk of test failure at the time of dose establishment due to an unsuccessful outcome from the verification dose experiment being very unlikely		ADVAN	
Nearly 30 years of proven success in using the method	ADVAN	ADVAN	
Approximately 10 years of proven success in using the method			ADVAN
Difficult to implement for low product bioburden if bioburden test method sensitivity is limiting (see 'Closing Remarks' in section 4	DISADVAN		DISADVAN

3.2 Conclusion:

The first choice would normally be VD_{max} unless specific circumstances dictated otherwise. Two examples of specific circumstances are too high a bioburden or the need for a product specific dose.

Method 2 may be the choice for products requiring a particularly low sterilization dose, for example some combination products.

In exceptional circumstances, none of the dose establishment methods may be appropriate, such that an alternative method to irradiation sterilization processing is the only option.

4. Further Clarification of Methods 2A and 2B

Relevant detail has been extracted from clause 8 of ISO 11137-2 to provide clarification of how the values determined are linked to one another. Reference is made to equations cited in clause 8.

Important: This document is not a substitute for ISO 11137-2 which should always be the first point of reference.

4.1 Method 2A

Relevant detail is shown in Table 4 below:

Table 4: Summary of Method 2a

Stage	**Value(s) Determined** (see ISO11137-2 for definitions)	**Additional Information**
1: Select SAL ……	Sterility Assurance Level	An SAL of equal to or less than 1 X 10^{-6} for terminally sterilized medical devices is necessary to comply with EN 556-1.
	↓	
2: Perform incremental dose experiment	**ffp**	Direct measurement of three values of first fraction positive dose is obtained from results of test of sterility from incremental dose experiment on 3 production batches. This is effectively determining the delivered dose at an early stage of microbial inactivation.
	↓	
	median ffp	The most relevant of the three ffp values.
	↓	
	A	Determined using Table 7 which is based on equation (1). The lower the number of positive tests of sterility, the higher this adjustment factor in equation (2).
	↓	
	FFP	More accurate value of first fraction positive dose calculated from equation (2) and representative of the 3 production batches.
	Also	
	d*	Determination of three values of delivered dose obtained from results of test of sterility from incremental dose experiment on 3 production batches. This is effectively determining the delivered dose where microbial inactivation approximates to an SAL of 10^{-2} (i.e. the verification dose).
	↓	
	D*	Based on d* from one of the 3 batches which has the most relevant dose. The chosen batch is hereafter named the CD* batch. This batch is best used for stage 3. D* provides a more accurate estimate of the verification dose based on information obtained from the incremental dose experiment.
	↓	
3: Perform verification dose experiment	**DD***	Direct measurement of delivered verification dose results. DD* is the most relevant (i.e. highest) delivered dose after targeting delivery of D*.
	Also	

Stage	Value(s) Determined (see ISO11137-2 for definitions)	Additional Information
	CD*	Direct measurement of number of positive tests of sterility from verification dose experiment.
	↓	
4: Consideration of results	**FNP**	Calculation of the first number positive dose to provide an even more accurate estimate of the verification dose based on information obtained from the verification dose experiment. Obtained from any necessary adjustment to DD* depending on the value of CD*.
	↓	
5: Establish sterilization dose	**DS**	Calculated using equation (3) or (4) and the FNP and FFP values. DS is an estimated D_{10} value is based on the slope of the following two plots of dose against surviving microorganisms: (1)FFP at the start of microbial inactivation and (2)FNP representing microbial inactivation equivalent to a SAL of 10^{-2}. Note that for the purpose of 11137-2, D_{10} value and D value are synonymous.
	Also	
	D**	Calculation using equation (5) to provide a final estimate of the verification dose based on information obtained from both the incremental dose experiment and the verification dose experiment.
	Sterilization dose	Calculation using equation (6) to provide an accurate estimation of the sterilization dose based on the final estimate of the verification dose and the estimated D_{10} value. The calculation involves extrapolation to SAL values below 10^{-2} in order to obtain the sterilization dose.

4.2 Method 2B

The table above is the same for Method 2B except that:

Equation 1 is replaced by equation 7
Equation 3 is replaced by equation 8
Equation 6 is replaced by equation 9

4.3 In Summary

The incremental dose experiment provides ffp (kGy) and factor A.

FFP (kGy) is then calculated using ffp and factor A.

The incremental dose experiment also provides D* (kGy) for use in the verification dose experiment.

The verification dose experiment provides DD* (kGy) and CD* positive tests of sterility.

FNP (kGy) is calculated using DD* and CD*.

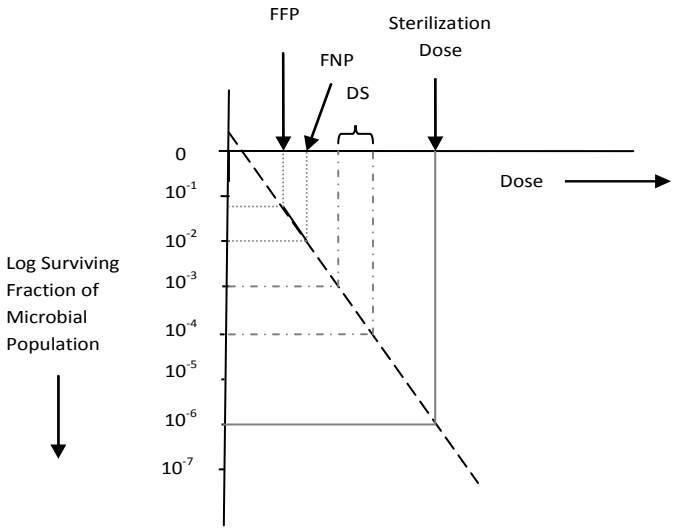
Then rate of kill factor DS (kGy) is calculated using FFP and FNP.

Then D** (kGy) is calculated using DD*, CD* and DS.

Then the sterilization dose (kGy) is calculated using D** and DS.

The relationship between FFP, FNP DS and sterilization dose is shown graphically below.

Fig. 1: Relationship Between FFP, FNP DS and Sterilization Dose



5 Closing Remarks

The most important point to note is that this overview is not a substitute for the standard. ISO 11137-2 should always be followed to ensure compliance. This overview document serves to indicate that application of dose establishment methods is not as complex as first appears from the standard.

There are two further important points to remember about implementing Method 1 or VD_{max} that are easily overlooked:

First, the methods are based on the principle that the verification dose experiment compares the frequency of occurrence of radiation resistant microorganisms, as they occur naturally on product, to the tables derived from the SDR. The tables can then only be used to extrapolate to a sterilization dose if the microbial population naturally occurring on the product is equal to or less than the SDR. If the naturally occurring microorganisms are more resistant than the SDR, these methods cannot be used to determine the sterilization dose. Evaluation of microorganisms, as they occur naturally, is essential due to D values changing under different environmental conditions. So, for example, if product had such a low microbial count that it was below the bioburden test method sensitivity, it would be incorrect to apply a challenge to this product with microorganisms grown in the laboratory in order to get a countable number. There is often a misconception that it is not critical that the verification dose is high because it would be fail safe in that the subsequent sterilization dose would also be higher than necessary. In this instance, extrapolation to the sterilization dose would be incorrect because it is not known if the microbial population naturally occurring on the product is equal to or less than the SDR.

Secondly, it is essential that the chosen verification dose is representative of the product. Too high a verification dose would give a false sense of security. An apparent successful verification dose experiment of 0, 1, or 2 positive tests of sterility with Method 1, for example, could in fact have been unsuccessful with 3 or more positive tests of sterility, if the true (lower) verification dose had been delivered. This is another instance where it is not known if the microbial population naturally

occurring on the product is equal to or less than the relevant table derived from the SDR due to the verification dose not being representative of the product. One instance of using too high a verification dose would be where a bioburden test is used which can only detect a bioburden of 10 and a value of 10 is assumed, even though the true bioburden could potentially have been 1 or less.

A detailed understanding of the complex theory behind the methodology in ISO11137-2 cannot always be given priority in a busy working environment. This overview should assist in the correct application of the standard without necessarily understanding all of the detail. In addition, the worked examples in clause 11 of ISO11137-2 are also very helpful in this respect. It is very important however that clause 7, 8 or 9 of the standard (whichever is relevant) is followed exactly and the worked examples then used to guide you through the method and check on correct implementation.

END