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Costs of validation of sterilization methods: Gamma radiation versus ethylene oxide

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ABSTRACT

A cost evaluation was made of the validation of two of the most commonly applied sterilization processes: gamma irradiation and ethylene oxide sterilization. This was done following the requirements in the appropriate European Standards.
Validation was defined as a procedure establishing both the effectiveness and the reproducibility of a process. For gamma sterilization the validation is process oriented, while for ethylene oxide it is more product dependent. This is possible because gamma radiation has a high penetration degree and therefore reproducibility is not a critical factor. For ethylene oxide it is much more difficult to prove that all internal and external surfaces have effectively been exposed to the sterilizing conditions; product design, product packaging and loading pattern need to be considered.
As a consequence of the above mentioned conclusions validation of gamma sterilization is much cheaper than validation of ethylene oxide sterilization.
Especially the overkill method (25 kGy) is not expensive, presuming that the manufacturer is working according to EN 46002 and historical data show consistent effectiveness of the 25 kGy sterilization dose. The main reason for these low costs is the fact that under the above mentioned conditions no additional bioburden testing is required.
Depending on the validation method used, the costs for validating a gamma sterilization process are between Fl. 150,= and Fl. 16000,=. For ethylene oxide the costs are between Fl. 29000,= and Fl. 37000,=.

SUMMARY

The interpretation of the European Standards for validation of sterilization processes by manufacturers of medical devices in practice is not done in a uniform way. In order to determine whether cost aspects of the validation procedure might play a significant role in management decisions regarding the steps that must be taken for the validation of a sterilization process, a cost evaluation was made for two of the most commonly applied processes: gamma irradiation and ethylene oxide sterilization. This was done following the requirements in the appropriate European Standards.

An important starting point was the definition of validation as a procedure which establishes two important process parameters: effectiveness and reproducibility. For gamma sterilization the validation is process oriented, while for ethylene oxide it is more product dependent. This is possible because gamma radiation has a high penetration degree and therefore reproducibility is not a critical factor. For ethylene oxide it is much more difficult to prove that all internal and external surfaces have effectively been exposed to the sterilizing conditions; product design, product packaging and loading pattern need to be considered.

As a consequence of the above mentioned conclusions validation of gamma sterilization proves to be much cheaper than validation of ethylene oxide sterilization.

Especially the overkill method (25 kGy) was demonstrated not to be expensive, presuming that the manufacturer is working according to EN 46002 and historical data show consistent effectiveness of the 25 kGy sterilization dose. The main reason for these low costs is the fact that under the above mentioned conditions no additional bioburden testing is required.

Depending on the validation method used, the costs for validating a gamma sterilization process are between Fl. 150,= (25 kGy) and Fl. 16000,= (AAMI b2 method). At prices between these two figures alternative methods are possible, resulting in lower sterilization doses. For ethylene oxide sterilization the costs are between Fl. 29000,= (half-cycle method or fraction-negative method) and Fl. 37000,= (survivor curve construction).

SAMENVATTING

De interpretatie van de Europese normen voor validatie van sterilisatieprocessen door fabrikanten van medische hulpmiddelen gebeurt in de praktijk niet op uniforme wijze. Om te bepalen of de kostenaspecten van de validatie-procedure een significante rol zouden kunnen spelen bij beleidsbeslissingen aangaande de verschillende stappen die ondernomen moeten worden voor de validatie van een sterilisatieproces, is een kostenevaluatie gemaakt voor twee van de meest toegepaste processen: gammabestraling en ethyleenoxide-sterilisatie. Hierbij is gebruik gemaakt van de eisen in de hierop van toepassing zijnde Europese normen.

Een belangrijk uitgangspunt was de definitie van validatie als een procedure om twee belangrijke parameters vast te stellen: effectiviteit en reproduceerbaarheid. Voor gammasterilisatie is de validatie voornamelijk proces-georiënteerd, terwijl er bij ethyleenoxide-sterilisatie meer sprake is van productafhankelijkheid. Dit is mogelijk doordat gammastraling een hoge penetratiegraad heeft en daarom reproduceerbaarheid geen kritieke factor is. Voor ethyleenoxide is het veel moeilijker te bewijzen dat alle interne en externe oppervlakken effectief worden blootgesteld aan de sterilisatiecondities; produktontwerp, produktverpakking en ladingspatroon zijn hier belangrijke parameters.

Als gevolg van het bovenstaande blijkt de validatie van gammasterilisatie aanzienlijk goedkoper te zijn dan de validatie van ethyleenoxide-sterilisatie.

Vooral voor de overkill methode (25 kGy) werd aangetoond dat de kosten niet hoog zijn, aangenomen dat de fabrikant volgens EN 46002 werkt en dat historische gegevens consistente effectiviteit van de 25 kGy sterilisatiedosis bewijzen. De belangrijkste reden voor deze lage kosten is het feit dat onder de bovengenoemde voorwaarden geen extra bioburden-onderzoek vereist is.

Afhankelijk van de gebruikte validatiemethode liggen de kosten voor de validatie van een gammasterilisatieproces tussen Fl. 150,= (25 kGy) en Fl. 16000,= (AAMI b2 methode). Hiernaast zijn nog alternatieve methoden mogelijk, waarvan de kosten tussen deze bedragen in liggen. Hiermee kunnen lagere sterilisatiedoses mogelijk worden gemaakt. Voor ethyleenoxide-sterilisatie liggen de kosten tussen de Fl. 29000,= (half-cycle methode of fraction-negative methode) en Fl. 37000,= (survivor curve constructie).

1. INTRODUCTION

Sterilization of medical devices in Europe is regulated through EU legislation.[1] This legislation contains so-called essential requirements in which the procedures for compliance are specified. The system applied is constructed by the principles of legislation, standardization and certification.

As sterilization is considered to be an important safety issue, the essential requirements demand validation and monitoring of sterilization quality. Standards have been developed within the EU frame of regulation i order to assist manufacturers to comply with the essential requirements.[2-6] These standards are developed in the technical committees TC 102 and 204 of the European standardization body CEN (Comité Européen de Normalisation).

The requirements in these European Standards are concerned with items like facilities, personnel, process design, product compatibility, production process, equipment, calibration and maintenance. Emphasis is put on validation, process control and monitoring of the sterilization processes.

It must be understood, however, that the texts of the standards for the different processes are not identical. Consequently, the interpretation by those who have to apply and control the standards in practice is not uniform. The result that is currently observed is the existence of different, often certificated, processes from which it cannot be consistently determined that equivalent quality is obtained.

Some of these processes are not sufficiently validated. This can be illustrated by the fact that in 1995 the RIVM has reported several operation packs from renowned manufacturers that were not sterile and/or unsafe. Since specific products were involved, the reports on these cases are confidential. Because the validation of a sterilization process is expensive, manufacturers try to limit the steps that must be taken and may therefore interpret the standards in a way that yields the least costly validation protocol. In order to determine whether this type of considerations really plays a significant role in management decisions regarding the validation of sterilization processes, a cost evaluation was made. Since ethylene oxide and gamma radiation are the two most commonly applied methods for the sterilization of industrially manufactured medical devices, a comparison was made between these two.

Preliminary results of this investigation were presented by Dorpema at Nordion's 5th Gamma Processing Seminar in September 1995.[7]

2. STRATEGY

In order to be able to make an evaluation of the costs of adequately validating an ethylene oxide and a gamma radiation sterilization process, the respective European Standards, EN 550[2] and EN 552[3], were closely studied. The requirements in the standards were split up into several steps and for each step an estimate was made of the associated costs.
The costs are dependent on the process selected, the sterilizer and the load. Validation in this perspective can be defined as a procedure that establishes the effectiveness and the reproducibility of a process. In processes with low or restricted penetration such as ethylene oxide sterilization, the reproducibility is of extreme importance. Product design, Product packaging and load orientation are parameters which have a substantial influence. This fact should constantly be kept in mind when comparing the ethylene oxide process with gamma irradiation. The latter, namely, is a process with high penetration and consequently reproducibility is much easier accomplished.
In cases where costs are directly related to the dimensions of the sterilizer and the load, certain dimensions are assumed for ease of survey of the numerical example.

The standards for ethylene oxide sterilization and gamma irradiation both identify 3 methods of validation, which are tabled in comparison below. As far as possible for two very different processes, it can be stated that methods A, B and C of gamma sterilization are roughly comparable to methods A, B and C of ethylene oxide sterilization (ETO), if the scope and accuracy of the respective methods are considered.

Table 1 : Methods of validation

Method	Gamma	ETO
A	Overkill approach (25 kGy)	Half-cycle method
B	AAMI method b2	Survivor curve method
C	Alternative methods	Fraction negative method

3. GAMMA STERILIZATION

Three basic approaches can be employed to develop a sterilization process for radiation processing: Overkill (25 kGy), AAMI-methods (bioburden-based or Species-Specific, bioburden-based)[8] and an alternative method like EDSS (European Dose Setting System)[9]. The combination of a high dose rate and a high penetration degree which characterizes gamma irradiation is an important feature in validation, because it practically guarantees reproducible results. Therefore, reproducibility of the process is hardly a parameter and one can concentrate on the effectiveness of the process. This means that the sterilization dose setting is far less dependent on the type of medical device. Dose setting margins can thus be relatively broad. The advantages connected to this property become obvious, when validation costs of especially the overkill method are analyzed.

For gamma irradiation, the validation of the sterilization process includes the establishment of the irradiation suitability or compatibility of the product materials, determination of sterilization dose, establishment of product loading pattern and completion of dose mapping in the sterilization container (including identification of the minimum and maximum dose zones), establishment of timer setting, and demonstration of the delivery of the required sterilization dose.

3.1. Overkill method

Based on years of extensive experience a standard sterilization dose of 25 kGy has proved to be effective. This approach has traditionally been used when the product withstands radiation doses in excess of 25 kGy (i.e. no adverse effects). Irradiation time and loading parameters are adjusted to assure that the product receives a minimum dose of 25 kGy and that the maximum tolerated dose is not exceeded.

According to EN 552[3], paragraph 4.2.2, in this case "the primary manufacturer shall have evidence to show compliance with EN 556[5]", i.e. "the theoretical probability of there being a viable micro-organism present on the device shall be equal to or less than one in 1 x 10^{-6}". To obtain the necessary evidence, "the primary manufacturer shall have access to competent microbiological laboratory services". The same requirements in different words can be found in ISO 11137[8], paragraph 6.2.2. This means bioburden determination is required. However, when manufacturing according to EN 46002[10,11] this already is a demand.

In NOTE 1 on p. 6 of EN 556 it says "achievement of sterility is predicted from the bioburden level on the products, the resistance of the micro-organisms comprising that bioburden and the extent of treatment imposed during sterilization". For

this prediction it is allowed to make use of historical data. This means additional testing is not necessary for products that are manufactured according to EN 46002 and have consistently been found to be effectively sterilized with a dose of 25 kGy in the past.

This means only the physical qualification, which is much less expensive than the microbiological qualification, needs to be done. Physical qualification costs on average are about fl. 150,= (estimated by a sterilization company).

Total	fl.	150

3.2. AAMI methods

The bioburden-based approach is the basis of the AAMI methods. In this approach, the process is validated to demonstrate that the product's bioburden is similar in nature to that assumed for the AAMI calculations. In Annex A of EN 552[3], Method B1, B2 in ANSI/AAMI ST 31-1990 are recommended. These should be replaced by Method 1 and 2 in Appendix B of ISO 11137[8]. Dose auditing should be carried out not less than once every three months, unless otherwise justified. For validated estimates of the bioburden of medical devices reference is made to EN 1174-1[12].
The Species-Specific Bioburden approach relates the radiation dose delivered to the most resistant organism in the bioburden population found in the manufacturing area. This population should be significantly skewed in the direction of radiation sensitive organisms, especially when dealing with aseptic processing areas. This should result in a much lower radiation dose required to achieve sterility.

The following figures represent a breakdown of the costs involved in AAMI method b2 (as obtained by contacting several manufacturers):

1) Bioburden (30 samples * fl. 50,=)	fl.	1500
2) Sterilization doses (100 * sterility à fl. 34 ; 4*/year)	fl.	13600
3) Dosimetry	fl.	400
4) Calibration	fl.	100
5) Validation	fl.	150
Total	fl.	15750

3.3. Alternative methods

Annex A of EN 552[3] also specifies that there may be methods and procedures other than those described in the annex, which are also capable of achieving the requirements of EN 552. The RIVM is currently developing such a method. The method proposed will be less exhaustive and expensive than those described in ISO 11137[8].

It is based on the IMO-concept[13] and focuses on sterility tests. An improved version was presented as EDSS at the last IMRP conference in Istanbul (September 1994).[14] Other presentations at that conference demonstrated concern on the applicability and costs of AAMI b2.[14]

EDSS is roughly characterized as an ongoing validation of the overkill method. Subsequently the costs are in the range between those of the overkill method and those of the AAMI b2 method, respectively fl. 150 and 16.000. The first stage in the development of the method will be the substantiation of a sterilization dose of 25 kGy. For more information on the method see Appendix 1.

4. ETHYLENE OXIDE STERILIZATION

A breakdown of the costs for validation of an ETO sterilization process in compliance with EN 550[2] was obtained by the following analysis.

4.1. Performance qualification - physical

4.1.1. Preconditioning

Performance qualification should be performed with the preconditioning area in both fully loaded and typical partially loaded states. The number of sensors used should provide a complete profile of the sterilization load. This number of sensors will depend upon the design of the preconditioning area, the commissioning data, and the sterilization process specification. From practical experience, the following numbers of sensors have been found to provide adequate profiles:

a) five temperature probes and two humidity sensors for sterilization loads of nominal volume not more than 2,5 m^3;

b) for volumes of product in excess of 2,5 m^3, two additional temperature probes and one additional humidity sensor within each nominal 2,5 m^3 of product;

c) for larger preconditioning areas holding more than 50 m^3 of nominal volume of product, probes need not be located in each nominal 2,5 m^3 of product but the profile should include sufficient locations to demonstrate the attainment of the required conditions throughout each sterilization load.

* As an example a product volume of 5 m^3 is assumed. In that case seven temperature probes and three humidity sensors are needed.

* Further assumption will be made that the probes and sensors will be used only for 20 processes.

Calculation 1

7 probes x fl. 8.000/20	fl. 2.800
3 sensor x fl. 1.500/20	fl. 225

Total:	fl. 3.025

4.1.2. Conditioning

Practical experience has indicated that an adequate profile can be obtained using the following number of temperature probes:

a) for chambers with usable sterilizer chamber volume of 5 m^3 and less, at

least 10 evenly distributed;

b) for chambers with usable sterilizer chamber volume larger than 5 m^3, at least one additional position should be measured for each additional 1 m^3 of chamber volume.

* Again the same example of a usable sterilizer chamber volume of 5 m^3 will be used.

Calculation 2

10 probes x fl. 8000/20	fl.	4.000

So, in conclusion, the costs of **Performance qualification - physical** are:

Calculation 1	fl.	3.025
Calculation 2	fl.	4.000
Total	fl.	7.025

4.1.3. Sterilization

The costs are expressed as the ethylene oxide exposure costs per load.

Net Usable Chambers	Approximate Number of Pallets	Charge per Load Below 500 mg/l EtO	Above 500 mg/l EtO
5 m^3	5	fl. 2.200	fl. 2.737

Total (per cycle)	fl.	2.200
For load orientation two extra cycles are required	fl.	4.400

4.2. Performance qualification - microbiological

4.2.1. General

Biological indicators should be placed in the part of the product which is the most difficult to sterilize. The number of biological indicators used for microbiological performance qualification should demonstrate microbial inactivation throughout the sterilization load. From practical experience the following number of biological indicators has been found to provide an adequate profile of the sterilization load;

a) for usable sterilizer chamber volumes of less than 5 m^3, at least 20

Paper Spore Strip, per strip	fl.	6
Liquid Spore Suspension, per unit	fl.	9

b) for usable sterilizer chamber volumes between 5 m^3 and 10 m^3, the number of biological indicators should be increased by two for every additional 1 m^3.

c) for usable sterilizer chamber volumes greater than 10 m^3 the number of biological indicators should be increased again by two for every additional 2 m^3.

* As an example: chamber volume of 5 m^3 , 20 spore strips;

Paper Spore Strip (fl.6 x 20)	fl.	120

The prices below were obtained from producers who have applied one of three methods A, B or C. It was not possible to get a detailed breakdown of the costs.

4.2.2. Method A. Survivor curve construction

Survivor curve, 5 points:		
5 cycles * fl. 2.200 + fl. 1.000 of other tests	fl.	12.000

4.2.3. Method B. Fraction-negative method

D-Value, 7 points survivor:		
7 cycles * fl. 2.200 + fl. 5.000	fl.	20.400

4.2.4. Method C. Half-cycle method

For processes and products that differ little from processes and products validated earlier, experienced operators need only 4 cycles.

Half-cycle:		
4 cycles * fl. 3.000	fl.	12.000

4.2.5. Bioburden Testing

It is not possible to determine the exact bioburden and therefore, in practice, a

viable count is determined using a defined technique. Validation exercises are erformed to relate this viable count to a bioburden estimate on a material or product by application of a correction factor.

The costs of bioburden testing are:

30 samples * fl. 50	fl. 1.500

Note: One manufacturer claimed to be able to do complete bioburden testing for fl. 150.

4.2.6. Certification of validation

Medical Device Validation Reporting	fl. 3.800

4.2.7. Performance qualification - microbiological: summary of costs

Three different totals depending which method is applied (A, B, or C).

4.2.1.	fl. 120
4.2.2.	fl. 12.000
4.2.5.	fl. 1.500
4.2.6.	fl. 3.800
Total of initial validation (A)	fl. 17.420

4.1	fl. 120
4.3	fl. 20.400
4.5	fl. 1.500
4.6	fl. 3.800
Total of initial validation (B)	fl. 25.820

4.1	fl. 120
4.4	fl. 12.000
4.5	fl. 1.500
4.6	fl. 3.800
Total of initial validation (C)	fl. 17.420

4.3. Revalidation

The revalidation report includes recommissioning and requalification. For the salary fl. 100 per hour was taken; this is based on information of 6 companies which calculated respectively: 75, 80, 100, 100, 125, 160 (fl./hour).

Recommissioning including report (± 80 hours * fl. 100)	fl.	8.000
Requalification (± 38 hours * fl. 100)	fl.	3.800
Total	fl.	11.800

4.4. Process control and monitoring

An operating specification documenting the procedures for routine operation of the sterilization process should be prepared.

4.4.1. Preconditioning

The reference position for monitoring temperature and relative humidity during preconditioning should be that at which it is most difficult to achieve the desired conditions. Data for this routine monitoring should be reviewed for acceptability before the product is released for sterilization.

4.4.2. Conditioning

Continuous monitoring and recording of humidity during conditioning can also be used to provide additional data on this phase of the sterilization cycle.
20 processes as an example:

Recorder (fl. 8000/20)	fl.	400
Sensor (fl. 1500/20)	fl.	75
Total	fl.	475

4.4.3. Sterilization

The number of biological indicators for routine use should be adequate to map the full sterilization load. A common qualification practice for routine microbiological monitoring is to use the following numbers of biological indicators:

1) for usable sterilizer chamber volumes of less than 5 m^3, at least 10;
2) for usable sterilizer chamber volumes between 5m^3 and 10 m^3, the number

of biological indicators should be increased by one for every additional 1 m^3.

Again the example of a chamber volume of 5 m^3 is used:

Paper Spore Strips (10 * fl. 6/strip)	fl.	60

Total monitoring cost:

4.4.2	fl.	475
4.4.3	fl.	60
Total (per process)	fl.	535

4.5. Concluding overview of ETO validation costs

Validation is depending on the method used.

4.5.1 Using Method A

Physical qualification			
- General			fl. 7.025
- Load orientation			fl. 4.400
Microbiological qualification			
- Initial validation			fl. 17.420
- Revalidation (excluded)	fl.	11.800	
- Control and monitoring (excluded)	fl.	535	
Total Validation cost (using A)			fl. 28.845

4.5.2. Using method B

Physical qualification			
- General			fl. 7.025
- Load orientation			fl. 4.400
Microbiological qualification			
- Initial validation			fl. 25.820
- Revalidation (excluded)	fl.	11.800	
-Control and monitoring (excluded)	fl.	535	
Total Validation cost (using B)			fl. 37.245

4.5.3. Using method C

Physical qualification			
- General			fl. 7.025
- Load orientation			fl. 4.400
Microbiological qualification			
- Initial validation			fl. 17.420
- Revalidation (excluded)	fl.	11.800	
- Control and monitoring (excluded)	fl.	535	
Total validation cost (using C)			fl. 28.845

5. DISCUSSION AND CONCLUSIONS

Comparing the standards for validation of sterilization using gamma irradiation, respectively ethylene oxide, an important conclusion can be drawn: The validation of gamma sterilization is process oriented, while the validation of ethylene oxide sterilization is a more product dependent process. This can be explained by looking at the characteristics that are inherent to sterilization method.

Due to the high penetration degree of gamma radiation, the reproducibility of gamma sterilization is not an issue. As validation was defined as a procedure establishing both the effectiveness and the reproducibility of a process, the validation of gamma sterilization is less technically demanding. For ethylene oxide it is much more difficult to prove that all internal and external surfaces have effectively been exposed to the sterilizing conditions; product design, product packaging and loading pattern need to be considered. Consequently the costs are considerably lower.

Additional bioburden testing for the overkill method (25 kGy) is superfluous if manufacturers operate in a controlled microbiological environment as required when working in compliance with EN 46002 and the 25 kGy dose can be substantiated by historical data.

Validation of sterilization by gamma irradiation is much cheaper than validation of ethylene oxide sterilization, as is demonstrated in Table 2.

The costs for validation vary depending on the method used. Especially for gamma sterilization there is a large difference in the costs of the overkill method compared to the costs using the AAMI or an alternative method. The latter two possibilities, however, may result in a lower sterilization dose. Since for gamma sterilization, in contrast to ethylene oxide sterilization, the costs are proportional to the applied sterilization dose, these methods may be well worth investigating.

Table 2 : Costs of validation

	Gamma		Ethylene Oxide	
	Method	Costs	Method	Costs
A	Overkill	150	Half-Cycle	29.000
B	AAMI	16.000	Survivor curve	37.000
C	Alternative	< 16.000	Fraction negative	29.000

6. REFERENCES

1 Council Directive **93/42/EEC** of 14 June 1993 concerning Medical Devices. *Official Journal of the European Communities* **No L 169**, 12.7.93.

2 Sterilization of medical devices - Validation and routine control of ethylene oxide sterilization (1994), **EN 550**.

3 Sterilization of medical devices - Validation and routine control of sterilization by irradiation (1994), **EN 552**.

4 Sterilization of medical devices - Validation and routine control of sterilization by moist heat (1994), **EN 554**.

5 Sterilization of medical devices - Requirements fot medical devices to be labelled "STERILE" (1994), **EN 556**.

6 Sterilization - Steam sterilizers - Large sterilizers (1995), **prEN 285**.

7 Nordion's 5th Gamma Processing Seminar - Proceedings, Ottawa, September 26-29 1995.

8 Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization (1995), **ISO 11137**.

9 The EDSS-method is currently being developed at the RIVM, see Appendix 1.

10 Quality systems - Medical devices - Particular requirements for the application of EN 29002 (1993), **EN 46002**.

11 Quality systems - Model for quality assurance in production and installation (1987), **EN 29002**. (N.B.: inmiddels vervangen door EN ISO 9002: 1994.)

12 Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 1: Requirements, **EN 1174-1**.

13 Dorpema, J.W.; Asten, J.A.A.M. van; (1983) "A new approach to sterilization conditions - The IMO concept, Part II" *Third Gamma Processing Seminar*, GPS 323.

14 9th International Meeting on Radiation Processing - Conference Abstracts, Istanbul, September 11-16 1994.

APPENDIX 1: EDSS hand-out at Nordion's 5th Gamma Processing Seminar (September 1995).

EDSS - Description of the method

The proposed European Dose Setting System (EDSS) is based on the following basic principles:

1 The dose setting system must be reliable and validated.
2 The number of samples per batch must be limited to a realistic level, i.e. a practicable number even in small laboratory settings.
3 The system must use all data available to an optimum.

A mathematical model has been developed that uses the results of sterility testing on products that have been irradiated with several different sub-lethal doses. Based on these results the system defines a theoretical worst-case bioburden, which is used to calculate the required sterilization dose.

The model is based on the IMO concept for sterilization by gamma irradiation, as presented by J.W. Dorpema and J.A.A.M. van Asten at the 1983 AECL seminar[1]. The basic idea behind this concept is that, if bioburden data are not, or only partially available, the data of an Imaginary Micro-Organism (IMO) can be used to substitute. This is visualized by calculating "ability profiles". These are representations of the maximum bioburden - characterized by the number of micro-organisms (N_0) and their resistance (D_{10}) - that can be sterilized using a certain dose. They can be calculated using the following formula:

$$\text{dose} = D_{10} * (\log(N_0) + 6)$$

With the assumption that an upper limit of ten thousand micro-organisms is considered as rather high, the imaginary bioburden could be cut off at this level. This is shown in Figure 1 (ability profile of 25 kGy and cut-off at N_0 = 10.000).
Depending on the amount of available information on the bioburden, certain performance states are defined in which this imaginary bioburden is reduced gradually.

In practice, using EDSS would mean starting with e.g. three sets of 20 samples. Each of these sets will be irradiated with a different sub-lethal dose and then be submitted to sterility testing. The results (x/20 positive) are then translated by the model to a worst-case bioburden. These three different bioburdens are combined, resulting in a more accurate bioburden estimate. The ability profile that covers just this bioburden is selected and yields the first minimum sterilization dose (see Figure 2).

If the objective was the validation of a certain dose (e.g. 25 kGy), and the first sterilization dose is less than this dose, the procedure is now finished.
If the objective was to determine the minimum sterilization dose, the procedure is repeated with three new sets of 20 samples, irradiated with three new sub-lethal doses. This yields three new estimated bioburdens. The newly determined bioburden is compared with the existing data, and if no discrepancy is found, the data are combined. A more accurate estimate of the worst-case bioburden is calculated, so a smaller safety margin is allowed and a smaller dose can be guaranteed as the sterilization dose.
If so desired, the procedure can be repeated again and again, until the objective is reached. Ultimately, the actual minimal sterilization dose for a certain product is found.

Reference

1 Dorpema, J.W.; Asten, J.A.A.M. van; (1983) "A new approach to sterilization conditions - The IMO concept, Part II" *Third Gamma Processing Seminar*, GPS 323.

Figure 1

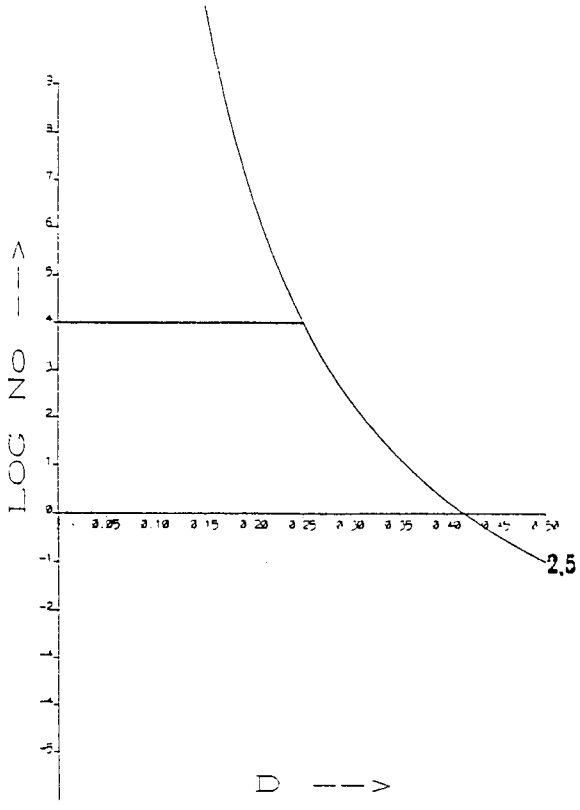

Figure 2