TOOLKIT DANIEL PRINCE 76

Biological Product Inspection Issues and Regulatory Update

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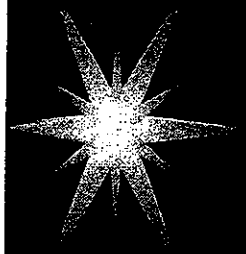
4th Annual Biological Production Forum

April 2005



Looking for Inspectional trends?...It will Depend...!

Factors that influence the issues found:

PLI/PAI vs routine GMP inspection

Experience and history of firms

Going from R&D to license/market approval

Older facilities

Contract manufacturing - seems to cut across all experience levels

One recent look at inspections found....*

For field routine GMP inspections, failure to follow procedures was most common citation.

For field PAIs, laboratory issues were most often cited.

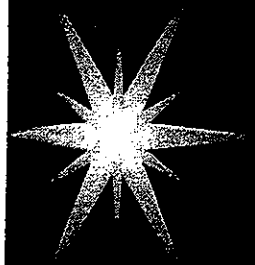
* the Gold Sheet, May 2004

CBER Reviews and Inspections

Pre-license/pre-approval inspections are an integral part of application/supplement review process prior to approval

Pre-approval inspections are conducted by CBER (review committee)

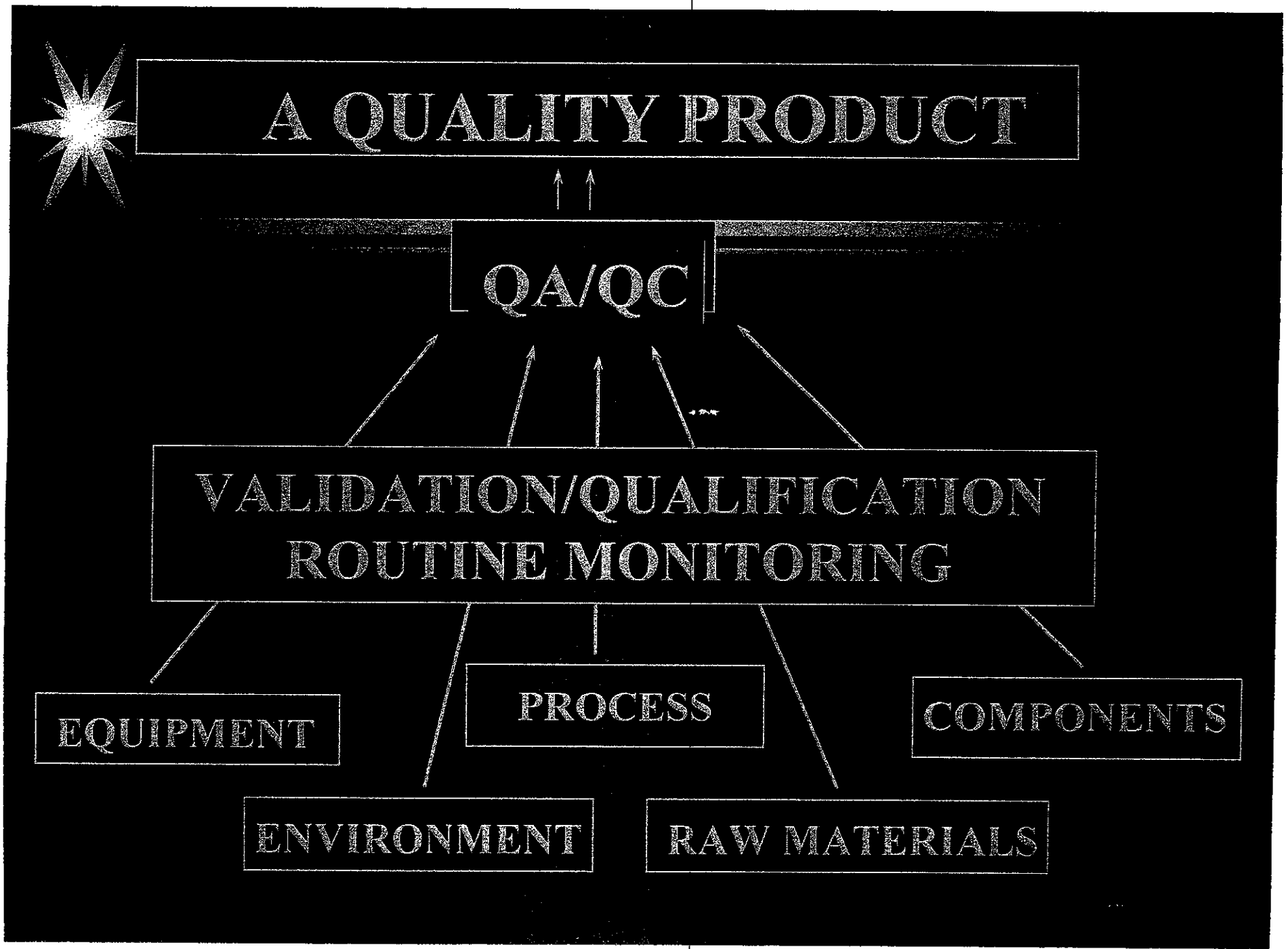
CBER reviewers provide recommendation for approval of application/supplement

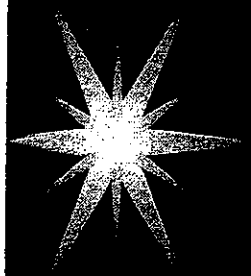


More experienced firms have issues with...

Following existing systems, such as failure investigations, completion of deviations, taking appropriate corrective actions

Verifying that process changes, either single or cumulative, have not had adverse effects on product quality


A QUALITY PRODUCT
QA/QC
VALIDATION/QUALIFICATION
ROUTINE MONITORING
EQUIPMENT
PROCESS
COMPONENTS
ENVIRONMENT
RAW MATERIALS



Issues to Consider for Facilities and Operation

Are support systems (HVAC, WFI) adequate?

Is the design adequate for expansion, facility changes, retrofitting?

Proper segregation of process steps?

Multi-product/multi-host issues addressed?

Contract manufacturing(adequate control?)

Quality systems in place?

General Issues to Consider for Facilities

Older facilities

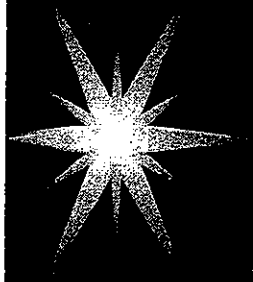
- Suitable for the new product/process?
- Retrofits and system capabilities

New facility

Designed for R&D but not GMP

Adequate control through procedures and personnel

Occasional pilot batches vs continuous production



Problem areas: Facility Issues

Improper qualification of facilities

Equipment qualification/suitability issues

Contamination in equipment that is difficult to eradicate

Introduction of new products - cleaning validation and product changeover issues

Facility - Water Monitoring

Is the water system appropriately monitored for system performance? (sampling sites, sampling frequency)

FDA 483 example "Sampling of <water system> does not reflect actual use in production. For example, prior to sampling, there is a 3 minute flush and production does not include a flush prior to use."

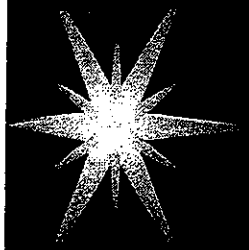
Facility Issues - Support Systems and Equipment

Are the clean steam and compressed gas systems appropriately monitored?

Equipment qualified for intended use?

Product contact surfaces appropriately addressed? (cleaning, sterilization, changeover, storage)

Performance testing performed? (filter



Facility issues - Personnel

Personnel gowning practices appropriate? (includes segregation of steps)

Personnel adequately trained?

Supervisors experienced with the process?

Quality approach to operations?

Personnel-related 483 item

"Operators qualified to work in the aseptic processing suite had skin exposed <face> under laminar airflow in the Class A area while performing aseptic operations <6 different items were noted>"

Process Issues: Bioburden FDA 483 Example

"The ultrafiltration step after cell culture harvest is not validated with respect to bioburden control." During validation, lot XXX was OOS for bioburden at the UF/DF step."

Bioburden in the UF/DF pre-filtration pools were implicated as the cause of OOS XXX levels in several lots.

GIBRALTAR LABORATORIES, INC.

AAMI Method 1 Dose Calculation
ANSI/AAMI/ISO 11137:1994 & ANSI/AAMI/ISO 11137:1994/A1:2002

1. Review the bioburden results. Check that three lots were done and that the total and average of each lot is correct. Check that the Efficiency Recovery Factor has been applied.
2. Take the three lot averages and determine if one of the three lots is two or greater than the overall average. If there is one lots that is two or more times greater this is the lot to use for the dose calculation (see example A). If all are about the same you must add the three lots up and take average of the three.

Example A: Lot 1 Average = 142
Lot 2 Average = 170
Lot 3 Average = 650
Overall Average = 321
Lot 3 Average is 2X greater than 321 therefore we use 650 for the dose calculation. **Note: The client must use samples from this lot for the 10^{-2} sterility verification.**

Example A: Lot 1 Average = 142
Lot 2 Average = 170
Lot 3 Average = 130
Overall Average = 147
All lots are close in count – no lot is two or more time greater. We use the overall average of 147.

3. Go to table B.1, in ANSI/AAMI/ISO 11137:1994 & ANSI/AAMI/ISO 11137:1994/A1:2002 Sterilization of health care products-Requirements for validation and routine control-Radiation sterilization, 3ed. Find the average bioburden in the left hand column. If there is not the exact number you pick the larger one above it. Read across to the 10^{-2} column and this is the dose for the verification sterility testing.

Example A: 10^{-2} = 10.4 kGy
10^{-6} = 24.2 kGy

Example B: 10^{-2} = 8.5 kGy
10^{-6} = 21.9 kGy

GIBRALTAR LABORATORIES, INC.

Quiz on AAMI Method 1 Dose Calculation ANSI/AAMI/ISO 11137:1994 & ANSI/AAMI/ISO 11137:1994/A1:2002.

1. The samples submitted for bioburden testing must be sterile or non sterile? (circle correct answer)
2. How many lots are to be submitted by the sponsor for testing? ____lot(s)
3. How many units per lot? _____
4. What is SIP? _____
5. How many megarads (mR) = 10 kiloGray (kGY)_____
6. The following are the bioburden results of the three lots. Calculate the sterilization dose. SIP = 1

   Lot 1 = 350
   Lot 2 = 433
   Lot 3 = 167

   10^{-2} Dose = _____
   10^{-6} Dose = _____

7. The following are the bioburden results of the three lots. Calculate the sterilization dose. SIP = 1

   Lot 1 = 627
   Lot 2 = 3,123
   Lot 3 = 466

   10^{-2} Dose = _____
   10^{-6} Dose = _____

8. The following are the bioburden results of the three lots. Calculate the sterilization dose. SIP = 0.1

   Lot 1 = 0.1
   Lot 2 = 0.3
   Lot 3 = 0.1

   10^{-2} Dose = _____
   10^{-6} Dose = _____

9. For verification 100 units are tested. How many must be sterile in order for the validation to be successful? _____
10. To determinate the continued validity of a dose the above audit strategy should be performed how often?
11. Regarding AAMI 13409, the production size is 750. How many units are required for Bioburden? ____ and how many units for verification dose?_____
12. Bioburden population is 10 cfu. Calculate verification Dose 10^{-2}= _____. What is the sterilization dose 10^{-6} = _____
13. What would the Verification Dose be if the bioburden was 10 cfu according to AAMI Method I. 10^{-2} = _____ and what would be 10^{-6} SAL = _____

Compare the three batch averages to the overall average bioburden. Determine whether any one of the batch averages is two or more times greater than the overall average bioburden.

Table B.1—Radiation dose (kGy) required to achieve a given SAL for different bioburdens having standard distribution of resistances

(Tabulated values are used in Stages 3, 4, and 5 of Method 1 of dose setting)

Average	Sterility Assurance Level					Average	Sterility Assurance Level				
bioburden	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	bioburden	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
0.063	1.0	2.6	4.8	7.4	10.4	28.00	6.4	9.3	12.4	15.8	19.3
0.075	1.1	2.7	5.0	7.6	10.6	30.48	6.5	9.4	12.6	15.9	19.4
0.088	1.2	2.8	5.1	7.8	10.8	33.16	6.6	9.5	12.7	16.0	19.5
0.10	1.3	3.0	5.3	8.0	11.0	36.06	6.7	9.7	12.8	16.1	19.6
0.12	14	3.1	5.5	8.2	11.3	39.20	6.8	9.8	12.9	16.2	19.8
0.14	1.5	3.3	5.7	8.4	11.5	42.60	6.9	9.9	13.0	16.4	19.9
0.17	1.6	3.5	5.9	8.6	11.7	46.28	7.0	10.0	13.2	16.5	20.0
0.19	1.7	3.6	6.0	8.8	11.9	50.25	7.1	10.1	13.3	16.6	20.2
0.22	1.8	3.7	6.2	9.0	12.1	54.55	7.2	10.2	13.4	16.8	20.3
0.26	1.9	3.9	6.4	9.2	12.3	59.20	7.3	10.3	13.5	16.9	20.4
0.29	2.0	4.0	6.5	9.4	12.5	64.22	7.4	10.4	13.6	17.0	20.5
0.34	2.1	4.1	6.7	9.6	12.7	69.65	7.5	10.5	13.7	17.1	20.7
0.39	2.2	4.3	6.8	9.8	12.9	75.51	7.6	10.6	13.9	17.3	20.8
0.44	2.3	4.4	7.0	9.9	13.1	81.83	7.7	10.7	14.0	17.4	20.9
0.50	2.4	4.5	7.1	10.1	13.3	88.67	7.8	10.9	14.1	17.5	21.0
0.57	2.5	4.7	7.3	10.3	13.5	96.04	7.9	11.0	14.2	17.6	21.2
0.65	2.6	4.8	7.5	10.4	13.6	104.0	8.0	11.1	14.3	17.7	21.3
0.73	2.7	4.9	7.6	10.6	13.8	112.6	8.1	11.2	14.4	17.9	21.4
0.83	2.8	5.1	7.8	10.8	14.0	121.9	8.2	11.3	14.5	18.0	21.5
0.93	2.9	5.2	8.0	10.9	14.2	131.9	8.3	11.4	14.7	18.1	21.7
1.05	3.0	5.3	8.1	11.1	14.3	142.6	8.4	11.5	14.8	18.2	21.8
1.17	3.1	5.4	8.2	11.2	14.5	154.3	8.5	11.6	14.9	18.3	21.9
1.32	3.2	5.6	8.3	11.4	14.7	166.8	8.6	11.7	15.0	18.5	22.0
1.47	3.3	5.7	8.5	11.5	14.8	180.3	8.7	11.8	15.1	18.6	22.2
1.64	3.4	5.8	8.6	11.7	15.0	194.8	8.8	11.9	15.2	18.7	22.3
1.83	3.5	6.0	8.8	11.9	15.1	210.5	8.9	12.0	15.3	18.8	22.4
2.04	3.6	6.1	8.9	12.0	15.3	227.4	9.0	12.2	15.5	18.9	22.5
2.27	3.7	6.2	9.0	12.2	15.5	245.6	9.1	12.3	15.6	19.0	22.7
2.51	3.8	6.3	9.2	12.3	15.6	265.2	9.2	12.4	15.7	19.2	22.8
2.79	3.9	6.4	9.3	12.4	15.8	286.3	9.3	12.5	15.8	19.3	22.9
3.09	4.0	6.6	9.4	12.6	15.9	309.0	9.4	12.6	15.9	19.4	23.0
3.42	4.1	6.7	9.6	12.7	16.1	333.4	9.5	12.7	16.0	19.5	23.1
3.77	4.2	6.8	9.7	12.9	16.2	359.7	9.6	12.8	16.1	19.6	23.3
4.17	4.3	6.9	9.9	13.0	16.4	388.0	9.7	12.9	16.2	19.8	23.4
4.60	4.4	7.0	10.0	13.1	16.5	418.4	9.8	13.0	16.4	19.9	23.5
5.06	4.5	7.1	10.1	13.3	16.6	451.1	9.9	13.1	16.5	20.0	23.6
5.57	4.6	7.3	10.2	13.4	16.8	486.3	10.0	13.2	16.6	20.1	23.7
6.13	4.7	7.4	10.4	13.6	16.9	524.2	10.1	13.3	16.7	20.2	23.9
6.74	4.8	7.5	10.5	13.7	17.1	564.9	10.2	13.4	16.8	20.3	24.0
7.40	4.9	7.6	10.6	13.8	17.2	606.6	10.3	13.5	16.9	20.5	24.1
8.12	5.0	7.7	10.7	14.0	17.4	655.6	10.4	13.7	17.0	20.6	24.2
8.91	5.1	7.9	10.9	14.1	17.5	706.2	10.5	13.8	17.1	20.7	24.3
9.76	5.2	8.0	11.0	14.2	17.6	760.5	10.6	13.9	17.3	20.8	24.5
10.69	5.3	8.1	11.1	14.4	17.8	818.8	10.7	14.0	17.4	20.9	24.6
11.70	5.4	8.2	11.2	14.5	17.9	881.4	10.8	14.1	17.5	21.0	24.7
12.80	5.5	8.3	11.4	14.6	18.1	948.7	10.9	14.2	17.6	21.1	24.8
13.99	5.6	8.4	11.5	14.7	18.2	1,021	11.0	14.3	17.7	21.3	24.9
15.28	5.7	8.5	11.6	14.9	18.3	1,099	11.1	14.4	17.8	21.4	25.1
16.69	5.8	8.6	11.7	15.0	18.5	1,182	11.2	14.5	17.9	21.5	25.2
18.21	5.9	8.8	11.8	15.1	18.6	1,271	11.3	14.6	18.0	21.6	25.3

19.87	6.0	8.9	'12.0	15.3	18.7	1,387	11.4	14.7	18.2	21.8	25.4
21.66	6.1	9.0	12.1	15.4	18.8	1,470	11.5	14.8	18.3	21.9	25.5
23.61	6.2	9.1	12.2	15.5	19.0	1,581	11.6	14.9	18.4	22.0	25.7
25.72	6.3	9.2	12.3	15.6	19.1	1,699	11.7	15.0	18.5	22.1	25.8
1,827	11.8	15.1	18.6	22.2	25.9	75,463	17.2	20.8	24.5	28.2	32.0
1,963	11.9	15.2	18.7	22.3	26.0	80,629	17.3	20.9	24.6	28.3	32.1
2,109	12.0	15.3	18.8	22.4	26.1	86,142	17.4	21.0	24.7	28.4	32.3
2,266	12.1	15.5	18.9	22.6	26.2	92,025	17.5	21.1	24.8	28.5	32.4
2,435	12.2	15.6	19.0	22.7	26.4	98,302	17.6	21.2	24.9	28.6	32.5
2,615	12.3	15.7	19.1	22.8	26.5	105,000	17.7	21.3	25.0	28.8	32.6
2,808	12.4	15.8	19.3	22.9	26.6	112,140	17.8	21.4	25.1	28.9	32.7
3,016	12.5	15.9	19.4	23.0	26.7	119,760	17.9	21.5	25.2	29.0	32.8
3,238	12.6	16.0	19.5	23.1	26.8	127,890	18.0	21.6	25.3	29.1	32.9
3,476	12.7	16.1	19.6	23.2	26.9	136,560	18.1	21.7	25.4	29.2	33.0
3,731	12.8	16.2	19.7	23.3	27.1	145,810	18.2	21.8	25.5	29.3	33.1
4,004	12.9	16.3	19.8	23.4	27.2	155,670	18.3	21.9	25.6	29.4	33.3
4,297	13.0	16.4	19.9	23.6	27.3	166, 190	18.4	22.0	25.7	29.5	33.4
4,611	13.1	16.5	20.0	23.7	27.4	177,410	18.5	22.1	25.8	29.6	33.5
4,946	13.2	16.6	20.1	23.8	27.5	189,360	18.6	22.2	25.9	29.7	33.6
5,306	13.3	16.7	20.2	23.9	27.6	202,110	18.7	22.3	26.1	29.8	33.7
5,691	13.4	16.8	20.4	24.0	27.7	215,710	18.8	22.5	26.2	29.9	33.8
6,104	13.5	16.9	20.5	24.1	27.9	230,200	18.9	22.6	26.3	30.1	33.9
6,545	13.6	17.0	20.6	24.2	28.0	245,650	19.0	22.7	26.4	30.2	34.0
7,018	13.7	17.1	20.7	24.3	28.1	262,110	19.1	22.8	26.5	30.3	34.1
7,524	13.8	17.2	20.8	24.5	28.2	279,660	19.2	22.9	26.6	30.4	34.2
8,065	13.9	17.4	20.9	24.6	28.3	298,370	19.3	23.0	26.7	30.5	34.3
8,645	14.0	17.5	21.0	24.7	28.4	318,310	19.4	23.1	26.8	30.6	34.5
9,265	14.1	17.6	21.1	24.8	28.6	339,560	19.5	23.2	26.9	30.7	34.6
9,928	14.2	17.7	21.2	24.9	28.7	362,200	19.6	23.3	27.0	30.8	34.7
10,638	14.3	17.8	21.3	25.1	28.8	386,320	19.7	23.4	27.1	30.9	34.8
11,397	14.4	17.9	21.4	25.2	28.9	412,030	19.8	23.5	27.2	31.0	34.9
12,209	14.5	18.0	21.6	25.3	29.0	439,420	19.9	23.6	27.3	31.1	35.0
13,078	14.6	18.1	21.7	25.4	29.1	468,600	20.0	23.7	27.4	31.2	35.1
14,006	14.7	18.2	21.8	25.5	29.2	499,690	20.1	23.8	27.5	31.3	35.2
15,000	14.8	18.3	21.9	25.6	29.3	532,810	20.2	23.9	27.6	31.5	35.3
16,062	14.9	18.4	22.0	25.7	29.5	568,080	20.3	24.0	27.7	31.6	35.4.
17,197	15.0	18.5	22.1	25.8	29.6	605,660	20.4	24.1	27.8	31.7	35.5
18,411	15.1	18.6	22.2	25.9	29.7	645,680	20.5	24.2	28.0	31.8	35.7
19,709	15.2	18.7	22.3	26.0	29.8	688,310	20.6	24.3	28.1	31.9	35.8
21,096	15.3	18.8	22.4	26.1	29.9	733,710	20.7	24.4	28.2	32.0	35.9
22,578	15.4	18.9	22.5	26.2	30.0	782,060	20.8	24.5	28.3	32.1	36.0
24,162	15.5	19.0	22.6	26.3	30.1	833,540	20.9	24.6	28.4	32.2	36.1
25,885	15.6	19.1	22.7	26.4	30.3	888,370	21.0	24.7	28.5	32.3	36.2
27,664	15.7	19.2	22.8	26.6	30.4	946,746	21.1	24.8	28.6	32.4	36.3
29,596	15.8	19.3	23.0	26.7	30.5	1,008,900	21.2	24.9	28.7	32.5	36.4
31,661	15.9	19.4	23.1	26.8	30.6						
33,867	16.0	19.5	23.2	26.9	30.7						
36,222	16.1	19.7	23.3	27.0	30.8						
39,739	16.2	19.8	23.4	27.1	31.0						
41,426	16.3	19.9	23.5	27.2	31.1						
44,296	16.4	20.0	23.6	27.3	31.2						
47,360	16.5	20.1	23.7	27.4	31.3						
50,632	16.6	20.2	23.8	27.6	31.4						
54,126	16.7	20.3	23.9	27.7	31.5						
57,855	16.8	20.4	24.0	27.8	31.6						
61,836	16.9	20.5	24.1	27.9	31.7						
66,086	17.0	20.6	24.2	28.0	31.8						
70,622	17.1	20.7	24.3	28.1	31.9						

NOTE The presence in table B. 1 of high bioburden levels is not intended to imply that such levels are the norm.

5 Method of substantiation of 25 kGy

5.1 Rationale

This Method is an adaptation of Method 1 described in ISO 11137.

Method 1 depends upon experimental verification that the response to radiation of the product bioburden is greater than that of a microbial population having a standard distribution of resistances; this is achieved by performance of a verification dose experiment employing 100 product units, or portions thereof, and a requirement to meet the defined acceptance criteria that demonstrate an SAL of 10^{-2}.

The present method is intended for products manufactured in batches of less than 1,000 product units; consequently, the total number of product units taken for bioburden determination is less than the minimum required with Method 1 and the number taken for the verification dose experiment is less than the 100 required when using Method 1.

As fewer product units are tested in the verification dose experiment, an SAL of 10^{-2} cannot be the basis of acceptance, but rather a higher SAL value has to be employed. This higher SAL value is derived from the reciprocal of the number of product units tested in the verification dose experiment. Inevitably, the use of a higher SAL value means that the ability of the method to detect bioburden with a higher resistance to radiation than that corresponding to the standard distribution of resistances is diminished. Consequently, an upper limit of SAL of 10^{-1}, corresponding to a minimum of 10 product units for the verification dose experiment, is imposed for the present method of dose substantiation.

Test sample sizes for the performance of bioburden determination and verification dose experiment are given in Table 1. These sample sizes are based on Tables I and II-A of ISO 2859-1 ISO, Inspection Level II, using the relationship between the production batch size and sample size. This relationship is approximated by a straight line on log-log scales (that is, plotting log of sample size versus log of geometric mean of the limits of each batch size interval) (Hald, 1981). This relationship is fit by the following equation:

$$\text{Sample Size} = 0.58 \times (\text{Production Batch Size})^{0.74} \qquad \text{Equation 1}$$

Table 1—Test sample sizes for performance of bioburden determination and verification dose experiment

Production batch size	Test sample size	
	Bioburden determination	Verification dose
831 - 999	10	90
702 - 830	10	80
578 - 701	10	70
462 - 577	10	60
352 - 461	10	50
251 - 351	10	40
160 - 250	10	30
80 - 159	10	20
20 - 79	10	10

ISO 2859-1, Inspection level II also takes account of the economics of withdrawing large numbers of product units from small production batches. However, a lower limit of 10 is imposed for the number of product units for the verification dose experiment. The rationale for this is that the distribution of the microorganisms on

product units, produced in small batches, may not allow representative product units to be withdrawn as a sample size less than 10.

In practice, a determination is made of the average bioburden and this determination is used to calculate the verification dose at the predetermined value of SAL.

For Method 1, the verification dose for a 10^{-2} SAL may be read from a table, with values derived from the inactivation of a microbial population having a standard distribution of resistances. For the present method, however, a variety of SAL values are employed in the verification dose experiment depending upon the production batch size. An alternative approach has been employed in which the non-linear relationship between verification dose in kGy at a given SAL and log average bioburden is approximated to a series of linear relationships corresponding to different ten-fold domains of average bioburden within the limits of 1 and 1,000. Each of these linear relationships is characterized by 2 constants, the intercept (I) and slope (S) given in Table 2; thus

$$\text{Verification dose at a given SAL} = I + (S \times \log(\text{Average SIP Bioburden})) \qquad \text{Equation 2}$$

Table 2—(I) and (S) values for calculation of verification dose for test sample size and bioburden level

Test sample size	Bioburden 1 to 10		Bioburden 11 to 100		Bioburden 101 to 1,000	
	I	S	I	S	I	S
10	1.25	1.65	0.67	2.23	-0.26	2.71
20	1.71	1.82	1.14	2.4	0.35	2.81
30	2.00	1.93	1.46	2.49	0.71	2.87
40	2.21	2.01	1.69	2.55	1.00	2.90
60	2.52	2.12	2.03	2.63	1.40	2.95
70	2.65	2.16	2.16	2.66	1.55	2.97
80	2.76	2.19	2.30	2.67	1.67	2.99
90	2.86	2.22	2.39	2.70	1.80	3.00

NOTE 15 In entering Table 2, the bioburden value should be that obtained for the SIP used in the verification dose experiment.

NOTE 16 The verification dose (kGy) may be rounded (using standard rounding procedures) to one place of decimals.

In practice, the requisite number of product units, or portions thereof, are exposed to the calculated verification dose and each product unit is individually subjected to a test of sterility. If the results of tests of sterility meet the requirements defined in the procedure, then a 25 kGy dose is used for sterilization.

5.2 Limitations of the method

NOTE 17 Although the basis of this Method is Method 1 of ISO 11137 , changes have been made to the procedures. The result of these changes is an increased probability of failing the verification dose experiment. The increased probability is principally seen with product of low bioburden in combination with small sample sizes. It is important to recognize that failure means that the use of a sterilization dose of 25 kGy cannot be substantiated using this Method. When substantiation of 25 kGy is not achieved with this Method, the primary manufacturer may choose to develop information on the radiation resistance of selected isolates recovered from product after exposure to a screening radiation dose, on the assumption that the isolates' responses to radiation are typical of that of resistant organisms occurring on product. In designing the experiments, due consideration should be given to the nature of the test pieces used and the relevance to the conditions under which the

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Answers:

1. None sterile
2. 3 lots
3. 10 units
4. It is the portion of the product that is tested
5. 1mR = 10 kGy
6. 10^{-2} = 9.5
   10^{-6} = 23
7. 10^{-2} = 12.6
   10^{-6} = 26.8
8. 10^{-2} = 3.1
   10^{-6} = 14.5 0.16/0.1 = 1.16
9. 98 units
10. quarterly
11. 10 (bioburden), 80 (sterility)
12. verification dose = I + (S x log(Average SIP Bioburden)
    = 1.25 + (1.65 x log 10)
    = 1.25 + (1.65 x 1)
    = 1.25 + 1.65
    = 2.90 kGy verification dose
    25 kGY sterilization dose
13. 10^{-2} = 5.3 kGy
    10^{-6} = 17.8 kGY