White Paper

Development of a Spreadsheet for Automated Calculation of Method VD_{max} Verification Dose, SIP Dose Reduction Factor, and Dose Augmentation Values

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Introduction

Method VD_{max} has been used for a number of years to substantiate minimum sterilization doses at a sterility assurance level (SAL) of 10^{-6} (1,2,3); the method can be readily extended to other SAL values (4). During discussion of developing an AAMI TIR for Method VD_{max} for an SAL of 10^{-3}, the notion was raised to use equations to identify VD_{max} values rather than a set of tables relating bioburden level to the three tabulated VD_{max} values: the VD_{max} verification dose, the SIP dose reduction actor, and the dose augmentation value.

In support of this notion, the details of using an equation-based approach were investigated.

Steps Required for an Equation-Based Approach

To calculate VD_{max} verification dose, SIP dose reduction factor, and dose augmentation values, the following steps are required:

1. Generate and publish a table of dose values for Population C shown to two decimal places for bioburden values from 0.1 to 10^6 for SAL values of 10^{-1}, 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6}; addition of SAL values $10^{-3.5}$, $10^{-4.5}$, and $10^{-5.5}$ would be desirable.

2. Choice of the sterilization dose to be substantiated.

3. Choice of the attained SAL at the chosen sterilization dose.

4. Verification that the average bioburden is acceptable for the chosen sterilization dose and SAL values.

5. Calculation the $\log_{10}$ of the bioburden.

6. Calculation of D_{lin} taking into account the sterilization dose and SAL values.

7. Calculation of TD_{10} taking into account the sterilization dose and SAL values.

8. Choice of D_{lin} or TD_{10}, as appropriate, to make subsequent calculations.

9. Calculation of the VD_{max} verification dose.

10. Calculation of the VD_{max} SIP dose reduction factor.

11. Calculation of the VD_{max} dose augmentation value.

The six calculations and other actions required for an equation-based approach clearly raises the possibility of making an error particularly if a manual entry calculator is used. Introduction of erroneous values can also occur in recording calculated values onto other paper- or computer-based systems. Another problematic aspect of an equation-based methodology is the lack of any comparison values that would be present with a table-based process as a "sanity check" on the correctness of the calculated values.

Use of an Excel Spreadsheet to Automate Calculation of VD_{max} Values

To reduce the risk of making an incorrect calculation, the use of an Excel spreadsheet to automate some of the calculations was investigated.

1. To start this process, the ISO 11137-2 Method 1 Table was recalculated for bioburden levels from 0.1 to 10^6 at SAL values of 10^{-1}, 10^{-2}, 10^{-3}, $10^{-3.5}$, 10^{-4}, $10^{-4.5}$, $10^{-5,}$ $10^{-5.5}$, and 10^{-6}. The bioburden values used in the table recalculation were the same as those in previously published VD_{max} tables. The rationale for this complete recalculation of this table was to identify the $10^{-3.5}$, $10^{-4.5}$, and $10^{-5.5}$ doses for the tabulated bioburden values and to ensure that all dose values were identified using a specified Excel function.

   In the early development of the VD_{max} methodology (ca. 1999), a "Master Dose Calculation Spreadsheet" was developed that gave, for an input value of a given bioburden, a set dose values for SAL values of 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6}. SAL values were shown to two decimal point resolution, e.g., 1.00×10^{-6}; such SAL values were visually identified and transcribed to yield a "Master Data Table". For the Master Data Table, dose values were recorded at two decimal point resolution.

   An example of the output of the Master Dose Calculation Spreadsheet is shown in the table below for a bioburden of 1000 for Population C:

Dose (kGy)	SAL
24.88	9.89×10^{-7}
24.87	9.95×10^{-7}
24.86	1.00×10^{-6}
24.85	1.01×10^{-6}
24.84	1.01×10^{-6}
24.83	1.02×10^{-6}

   Due to the dose increment of 0.01 kGy and the two decimal point resolution, it was common to find the same SAL value for two tabulated dose values. In the case where this occurred at SAL values of 1.00×10^{-X}, the higher of the two dose values was transcribed onto the Master Data Table.

   To mistake-proof and automate the process of development of Master Data Tables, it was decided to use the Excel LOOKUP function to identify doses for given bioburden and SAL values. Because Excel retains 15 significant figures, the calculation of SAL values essentially never results in a $1.00000000000000 \times 10^{-X}$ outcome. If the LOOKUP function cannot find an exact match, it chooses the largest value in the look-up range that is *less than or equal to* the specified value. In the table above, 9.95×10^{-7} would be chosen and the function would report a corresponding dose of 24.87 kGy for an SAL of 10^{-6}. The LOOKUP function is ideal for this task yielding a radiation dose that is conservative being very slightly higher (< 0.01 kGy) than required to attain the specified SAL.

2. After the new Master Data Table was generated that included Sal values of $10^{-3.5}$, $10^{-4.5}$, and $10^{-5.5}$, it was locked and checked for correctness by inspection and by plotting the bioburden

versus dose values for SAL values of 10^{-1}, 10^{-2}, 10^{-3}, $10^{-3.5}$, 10^{-4}, $10^{-4.5}$, $10^{-5,}$ $10^{-5.5}$, and 10^{-6}. The results are shown in Figure 1 (plots for $10^{-3.5}$, $10^{-4.5}$, $10^{-5.5}$ not labeled).

As can be seen, smooth plots were obtained with no indication of aberrant values. This technique was used in previous Method VD_{max} development work; aberrant values ~0.05 kGy from "being on the line" can be detected.

3. Using the values from the new Master Data Table, the development of an Excel spreadsheet to perform the required calculations was investigated. Constructing formulas in separate unrelated cells to calculate log_{10} of the bioburden, D_{lin}, TD_{10}, and the three VD_{max} values was straightforward but clearly did not take advantage of cell reference calculation ability of Excel. It was decided, therefore, to attempt to fully automate the calculation of the three VD_{max} values for a given bioburden, minimum sterilization dose to be substantiated, and SAL value. The desired spreadsheet would have these input values (bioburden, minimum sterilization dose, SAL) and would yield the VD_{max} verification dose, the SIP dose reduction factor, and the dose augmentation value.

   The development of the desired spreadsheet was successful; a screen shot is shown in Figure 2. Using the Master Data Table described above and the inputs provided by the user (bioburden, minimum sterilization dose, SAL), the spreadsheet performs the appropriate calculations and the desired outputs are obtained (VD_{max} verification dose, the SIP dose reduction factor, dose augmentation value).

   All cells in the spreadsheet except for the ones for the three input values (shaded in green in Figure 1) are locked and password protected so the functions/equations cannot be intentionally or inadvertently changed. In the unlikely event that the file could somehow be corrupted and still appear to function correctly, at test case is provided to exercise the spreadsheet before use.

4. To initially qualify the spreadsheet, 35 challenges were performed over a range of bioburden and minimum sterilization dose values. The results of the spreadsheet calculations were compared to the values given in published VD_{max} tables and custom VD_{max} tables generated for custom product-specific applications. The results are shown in Tables 1, 2, and 3.

   A total of 101 comparisons of pairs of values were made with two disagreements found; these are highlighted in red on the tables. In one case there was a 0.1 kGy disagreement in a dose augmentation value and in the second a 0.01 disagreement in a SIP dose reduction factor.

   The root cause of both disagreements was investigated and found not to be a fault of the spreadsheet calculations but rather related to the originally used visual inspection method of determining the dose that yields a given SAL versus use of the Excel LOOKUP function as described in detail above. For the disagreement in the dose augmentation value (3.6 vs. 3.7 kGy) the root cause was a difference of 0.01 kGy in the 10^{-1} dose used in the spreadsheet calculation. For the disagreement in the SIP dose reduction value (2.84 vs. 2.83), the root cause was a 0.01 difference in the 10^{-1} and 10^{-6} doses used in the spreadsheet calculation. Slight changes in the 10^{-1} and/or 10^{-6} doses can affect the results of the intermediate D_{lin} and TD_{10} calculations and therefore the subsequent calculations of the one or more of the three VD_{max} values.

The results of the challenge studies clearly demonstrate that the spreadsheet yields correct output VD_{max} values compared to previously published tabulated values. The challenges shown in Tables 1, 2, and 3 were performed using a SAL input value of 10^{-6}; initial challenges at other SAL values have given 100% agreement between tabulated and spreadsheet-derived values.

5. Since the possibility of an input error always exists, even though only three entries are required, error messages have been built into the spreadsheet.

   a. A SIP dose reduction factor will not be returned if the entered bioburden is <1.

   b. An error message will be returned if the bioburden is <1 or >10^6.

   c. If a SAL value is entered that is not allowed, an error message will be returned.

   d. If the entered minimum sterilization dose to be substantiated is too low for the entered bioburden and SAL values, an error message will be returned.

   An example screenshot of input results, that generate an "Input Error" message in the spreadsheet, is shown in Figure 3. In this example, a 24-kGy minimum dose is too low for a bioburden of 1000 and an SAL of 10^{-6}.

Conclusions and Way Forward

The use of the VD_{max} Calculation Worksheet offers both convenience and greatly minimizes the possibility of errors when calculating Method VD_{max} values for use in sterilization dose substantiation exercises. Its use will also ensure reproducible output values for all users for a given set of input values. The use of variety of “home brewed” approaches to performing these calculations would work against obtaining correct and reproducible output values.

Prior to distribution for routine use, possibly as an AAMI TIR, several activities are planned:

- Exercise of the spreadsheet by a small cadre of experienced radiation sterilization professionals to look for issues/improvements.

- The execution of a formal spreadsheet validation.

- Discussions with experienced radiation sterilization professionals on limits that should be built into the spreadsheet. One limit might involve the range of allowable input sterilization doses; doses <15 kGy are currently not codified in Method VD_{max} standards documents for an SAL of 10^{-6}.

References

1. Kowalski, J.B., Tallentire, A., 1999. Substantiation of 25 kGy as a sterilization dose: a rational approach to establishing verification dose. Radiat. Phys. Chem. **54**, 55-64.

2. Kowalski, J. B., Aoshuang, Y., Tallentire, A., 2000. Radiation sterilization – evaluation of a new approach for substantiation of 25 kGy. Radiat. Phys. Chem. **58**, 77-86.

3. Kowalski, J.B., Tallentire, A., 2003. Aspects of putting into practice VD_{max}. Radiat. Phys. Chem. **67**, 137-141.

4. Kowalski, J.B. 2012. New applications of the VD_{max} approach to substantiation of preselected sterilization doses. Radiat. Phys. Chem. **81**, 1232-1235.

Figure 1. Dose required for a range of bioburden values to attain the indicated SAL.

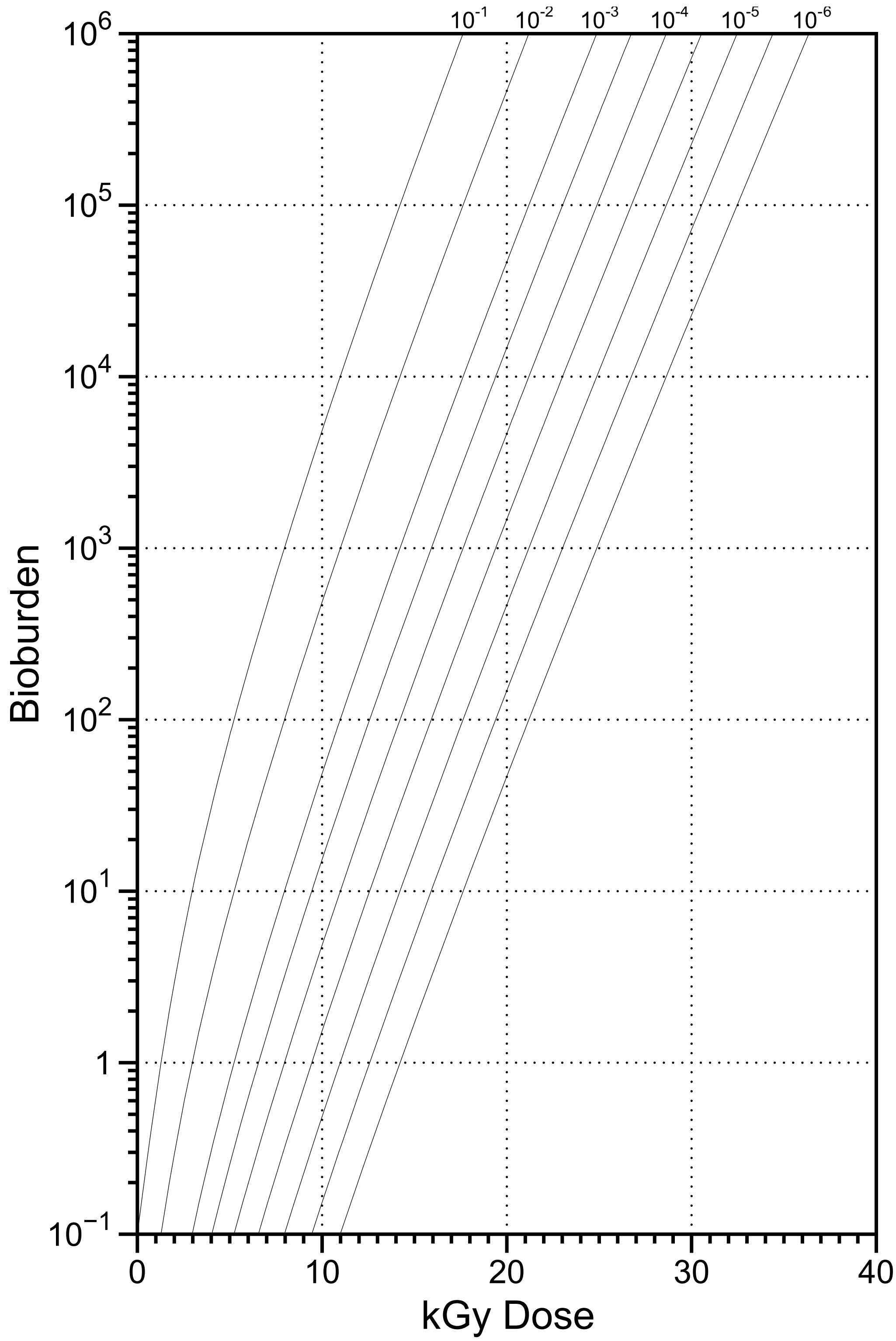

Figure 2. Screen shot of Method VD_{max} Calculation Worksheet.

Spreadsheet for Calculation of VD_{max} Values for a Given Bioburden, Sterility Assurance Level, and Minimum Dose to Be Substantiated

			Input Values
Average Bioburden	1000		1000
Sterility Assurance Level	-6	Acceptable values are: -6, -5.5, -5, -4.5, -4, -3.5, -3	-6
Minimum Sterilization Dose (kGy)	25	Dose to be substantiated with Method VD_{max}^{SD}	25
			Run this test case by inputting the values above into the spreadsheet to the left to verify that the correct output values shown below are obtained.
			Correct Output Values
VD_{max} Verification Dose (kGy)	***8.1***		8.1
SIP Dose Reduction Factor	***2.02***		2.02
Dose Augmentation Value (kGy)	***3.4***	*© 2016 John B. Kowalski, Ph.D. & SteriPro Consulting*	3.4

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Input Error*: Chosen minimum sterilization dose to be substantiated is too low for the entered bioburden and/or SAL values or an unacceptable SAL value has been entered.*

Table 1. Challenge testing results for a range of sterilization doses and bioburden values.

Sterilization Dose (kGy)	Bioburden	Source of Values	Verification Dose (kGy)	Agreement	SIP Dose Reduction Factor	Agreement	Dose Augmentation Value (kGy)	Agreement
15	0.15	Table	0.5	Agree	NA	NA	2.9	Agree
		Spreadsheet	0.5		NA		2.9	
	1.5	Table	1.7	Agree	NA	NA	2.7	Agree
		Spreadsheet	1.7		NA		2.7	
17.5	1	Table	2.9	Agree	2.92	Agree	2.9	Agree
		Spreadsheet	2.9		2.92		2.9	
	9	Table	2.9	Agree	1.49	Agree	2.9	Agree
		Spreadsheet	2.9		1.49		2.9	
20	1	Table	3.3	Agree	3.33	Agree	3.3	Agree
		Spreadsheet	3.3		3.33		3.3	
	45	Table	4.4	Agree	1.67	Agree	3.1	Agree
		Spreadsheet	4.4		1.67		3.1	
22.5	1	Table	3.6	Agree	3.75	Agree	3.8	Agree
		Spreadsheet	3.6		3.75		3.8	
	220	Table	6.2	Agree	1.85	Agree	3.3	Agree
		Spreadsheet	6.2		1.85		3.3	
27.5	1	Table	4.6	Agree	4.58	Agree	4.6	Agree
		Spreadsheet	4.6		4.58		4.6	
	5,000	Table	10.1	Agree	2.14	Agree	3.5	Agree
		Spreadsheet	10.1		2.14		3.5	
30	1	Table	5.0	Agree	5.00	Agree	5.0	Agree
		Spreadsheet	5.0		5.00		5.0	
	22,000	Table	12.1	Agree	2.27	Agree	3.6	Agree
		Spreadsheet	12.1		2.27		3.6	
32.5	1	Table	5.4	Agree	5.42	Agree	5.4	Agree
		Spreadsheet	5.4		5.42		5.4	
	100,000	Table	14.3	Agree	2.38	Agree	3.6	Not Agree
		Spreadsheet	14.3		2.38		3.7	
35	1	Table	5.8	Agree	5.83	Agree	5.8	Agree
		Spreadsheet	5.8		5.83		5.8	
	440,000	Table	16.4	Agree	2.47	Agree	3.7	Agree
		Spreadsheet	16.4		2.47		3.7	

Table 2. Challenge testing results for a 25 kGy sterilization dose over a range of bioburden values.

Sterilization Dose (kGy)	Bioburden	Source of Values	Verification Dose (kGy)	Agreement	SIP Dose Reduction Factor	Agreement	Dose Augmentation Value (kGy)	Agreement
25 kGy	1	Table	4.2	Agree	4.17	Agree	3.5	Agree
		Spreadsheet	4.2		4.17		3.5	
	21	Table	8.0	Agree	3.40	Agree	3.4	Agree
		Spreadsheet	8.0		3.40		3.4	
	40	Table	8.6	Agree	3.29	Agree	3.3	Agree
		Spreadsheet	8.6		3.29		3.3	
	82	Table	9.1	Agree	3.11	Agree	3.2	Agree
		Spreadsheet	9.1		3.11		3.2	
	160	Table	8.8	Agree	2.76	Agree	3.2	Agree
		Spreadsheet	8.8		2.76		3.2	
	322	Table	8.5	Agree	2.43	Agree	3.3	Agree
		Spreadsheet	8.5		2.43		3.3	
	650	Table	8.3	Agree	2.16	Agree	3.4	Agree
		Spreadsheet	8.3		2.16		3.4	
	1,000	Table	8.1	Agree	2.02	Agree	3.4	Agree
		Spreadsheet	8.1		2.02		3.4	

Table 3. Challenge testing results for values taken from custom VD_{max} tables.

Sterilization Dose (kGy)	Bioburden	Source of Values	Verification Dose (kGy)	Agreement	SIP Dose Reduction Factor	Agreement	Dose Augmentation Value (kGy)	Agreement
15.9	2.0	Table	2.4	Agree	1.84	Agree	2.7	Agree
		Spreadsheet	2.4		1.84		2.7	
16.1	2.5	Table	2.4	Agree	1.74	Agree	2.7	Agree
		Spreadsheet	2.4		1.74		2.7	
17	0.5	Table	2.1	Agree	NA	NA	3.0	Agree
		Spreadsheet	2.1		NA		3.0	
18	11	Table	2.9	Agree	1.49	Agree	2.9	Agree
		Spreadsheet	2.9		1.49		2.9	
19	5	Table	4.8	Agree	2.84	Not Agree	2.8	Agree
		Spreadsheet	4.8		2.83		2.8	
21	45	Table	5.4	Agree	2.05	Agree	3.1	Agree
		Spreadsheet	5.4		2.05		3.1	
22	3.5	Table	5.2	Agree	3.36	Agree	3.4	Agree
		Spreadsheet	5.2		3.36		3.4	
23	170	Table	6.8	Agree	2.10	Agree	3.2	Agree
		Spreadsheet	6.8		2.10		3.2	
24	19	Table	7.5	Agree	3.30	Agree	3.3	Agree
		Spreadsheet	7.5		3.30		3.3	
26	400	Table	9.4	Agree	2.62	Agree	3.3	Agree
		Spreadsheet	9.4		2.62		3.3	
36.3	15,000	Table	18.5	Agree	3.57	Agree	3.6	Agree
		Spreadsheet	18.5		3.57		3.6	

Figure 3. Screen shot of a Method VD_{max} Calculation Worksheet showing an input error message (24 kGy dose is too low for an SAL of 10^{-6} and a bioburden of 1000).

Spreadsheet for Calculation of VD_{max} Values for a Given Bioburden, Sterility Assurance Level, and Minimum Dose to Be Substantiated

			Input Values
Average Bioburden	1000		1000
Sterility Assurance Level	-6	Acceptable values are: -6, -5.5, -5, -4.5, -4, -3.5, -3	-6
Minimum Sterilization Dose (kGy)	24	Dose to be substantiated with Method VD_{max}^{SD}	25

Run this test case by inputting the values above into the spreadsheet to the left to verify that the correct output values shown below are obtained.

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		Correct Output Values
VD_{max} Verification Dose (kGy)	***Input Error***	8.1
SIP Dose Reduction Factor	***Input Error***	2.02
Dose Augmentation Value (kGy)	***Input Error***	3.4

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Input Error *: Chosen minimum sterilization dose to be substantiated is too low for the entered bioburden and/or SAL values or an unacceptable SAL value has been entered.*