RESEARCH

Medical Device SALs And Surgical Site Infections: A Mathematical Model

Sopheak W. Srun, Brian J. Nissen, Trabue D. Bryans, and Maxime Bonjean

About the Authors

Sopheak W. Srun, MPH, SM(NRCM), is a sterilization specialist at Quality Tech Services in Bloomington, MN. E-mail: ssrun@qtspackage.com

Brian J. Nissen, BS, CQE, CQA, is a project engineer at Quality Tech Services in Bloomington, MN. E-mail: bnissen@qtspackage.com

Trabue D. Bryans, BS, M(ASCP), is president and principal consultant of BryKor LLC, and technical expert for WuXi AppTec, Inc., in Marietta, GA. E-mail: trabue@brykor.com

Maxime Bonjean, MB, PhD, is is a research scholar at the University of California, San Diego, and at the Salk Institute for Biological Studies. E-mail: bonjean@salk.edu

Abstract

It is commonly accepted that terminally sterilized healthcare products are rarely the source of a hospital-acquired infection (HAI). The vast majority of HAIs arise from human-borne contamination from the workforce, the clinical environment, less-than-aseptic handling techniques, and the patients themselves. Nonetheless, the requirement for a maximal sterility assurance level (SAL) of a terminally sterilized product has remained at 10^{-6}, which is the probability of one in one million that a single viable microorganism will be on a product after sterilization. This paper presents a probabilistic model that predicts choosing an SAL greater than 10^{-6} (e.g. 10^{-5} or 10^{-4}, and in some examples even 10^{-3} or 10^{-2}) does not have a statistically significant impact on the incidence of surgical site infections (SSIs). The use of a greater SAL might allow new, potentially life-saving products that cannot withstand sterilization to achieve a 10^{-6} SAL to be terminally sterilized instead of being aseptically manufactured.

1. Introduction

Used for the first time with medical devices in 1984 by the National Center for Devices and Radiological Health,[1] "sterility assurance level" (SAL) is now a term formally defined as the probability of a single viable microorganism occurring on an item after being subjected to the sterilization process.[2] SAL is the target for a sterilization process and is normally intended to imply the outcome of microbial inactivation through a sterilization process using heat, chemicals, radiation, or a combination of these agents. Although the concept has evolved with time, the term and its definition continue to cause confusion in the industry.[3]

Used to describe the predicted outcome of applying a lethal agent in the sterilization process, SAL generally takes a value less than 1 and is, for convenience, expressed as the negative logarithm to base 10, i.e. 10^{-x}. Typically, SAL takes the value of 10^{-6} or 10^{-3} in industrial applications. When applying this quantitative value to assurance of sterility, a 10^{-6} SAL is a lower value than 10^{-3}, but provides in theory a greater assurance of sterility (Figure 1).[4]

The idea of a 10^{-6} SAL initially originated in the food canning industry, the goal of which was to virtually eliminate the possibility of a canned product containing *Clostridium*, a spore-forming organism that is resistant to the high heat process in canning.[5] That same concept was also promoted by the aerospace industry, where NASA concluded that it wanted to reduce the probability of introducing a contaminant from one world into another to no greater than one in one million.[6] Though both of these applications of sterility assurance had very specific purposes, neither of these applications was designed with the healthcare industry in mind. Yet the idea that an SAL should be 10^{-6} was seized upon and promoted throughout the healthcare industry, without a justification for the appropriateness of that number.

To this day, terminally sterilized blood-contacting medical devices throughout the medical

device industry are nearly universally sterilized to achieve an SAL of 10^{-6}, with rare exceptions in special cases granted by regulatory agencies for greater SALs. In addition, non-blood contacting medical devices used in operating room and sterile environments, such as equipment drapes, shoe covers, and electrodes are commonly terminally sterilized[7] to achieve a 10^{-3} SAL.

Because it has been recognized that many drugs and biologics would not withstand sterilization to achieve a 10^{-6} SAL, a majority of drug products and parenterals—which are directly introduced into a patient's body or bloodstream and therefore constitute a significant septic risk—are produced aseptically, rather than being terminally sterilized. Most biologics, such as cell therapies and vaccines, are also manufactured aseptically, and these are also used by direct injection into a patient.

Aseptically manufactured drug and biologic products are produced in a manner as to prevent the introduction of microorganisms into the product, versus being exposed to a terminal process after manufacture that will eliminate (sterilize) microorganisms. Aseptic processing is considered to assure sterility based on controlling and monitoring all potential sources of contamination during processing, rather than assuring sterility based on controlling and monitoring the presterilization bioburden and the variables in the sterilization process. As such, the assurance of sterility of aseptic processes is expressed in terms of the probability of a non-sterile unit (PNSU) rather than the probability of a surviving microorganism, or SAL.

Because of the increased difficulty and risks (and therefore increased expenses in time and costs) in assuring sterility based on microbial control versus assuring sterility based on microbial inactivation, and because of the associated PNSU limitations, it is logical that terminal sterilization would be preferred over aseptic manufacturing whenever possible. Yet because of the persistent idea that a maximum SAL of 10^{-6} is the only acceptable definition of "sterile" for terminally sterilized medical devices, many products are not being terminally sterilized because of their sensitivity to conditions necessary to achieve the rigorous 10^{-6} SAL target. It has been established[8,9] that the PNSU of products manufactured by aseptic processes is 1 in 1,000 (10^{-3}), or 1 in 10,000 at best (10^{-4}). Thus, a drug or biologic product manufactured by aseptic processes with a probability of a nonsterile unit of 1 in 1,000 (a PNSU of 10^{-3}) is considered acceptable, yet a drug or biologic product that is terminally sterilized to achieve a probability of a surviving microorganism of 1 in 1,000 (an SAL of 10^{-3}) would in most cases not be considered acceptable.

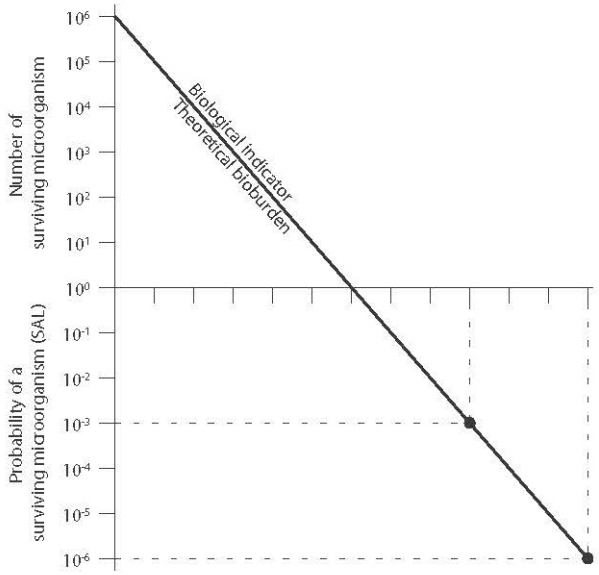

Figure 1. Semilog plot of theoretical microbial inactivation and the probability of a surviving microorganism (SAL). The straight-line relationship reflects the assumption that a homogeneous population of microorganisms subjected to a sterilizing agent decreases exponentially with time at a uniform rate.[4]

Despite these discrepancies, there has been tremendous resistance among regulatory agencies to adopt SALs other than 10^{-6}, largely due to the unknown impact that SALs other than 10^{-6} would have on the incidence of HAIs. Using a probabilistic model to analyze published data on SSIs, which account for 17% of HAIs among hospitalized patients,[10] we demonstrate the absence of a statistically significant impact on SSIs with the use of an alternate SAL of 10^{-5} or 10^{-4}, and in some examples even 10^{-3} or 10^{-2}.

Keywords

Sterility assurance level (SAL), medical device, hospital-acquired infections (HAI), surgical site infections (SSI), terminally sterilized, probabilistic model

2. Experimental Procedures

2.1 Probability Concepts

The mathematics used to create the probabilistic model for predicting the impact of choosing an alternate SAL are based on the statistics used to calculate the probability of occurrence of a specific set of events. Specifically, the

model uses the basic properties for the union of events and the intersection of independent events. We refer the reader unfamiliar with these notions to the Appendix.

2.2 Mathematical Model

The probability of developing a hospital-acquired infection (HAI) can be broken down into two independent events, classified by the source of the microorganisms that would lead to infection. Let the probability of infection from a terminally sterilized medical device be the first independent event, and the probability of infection from a source other than the medical device be the second independent event.

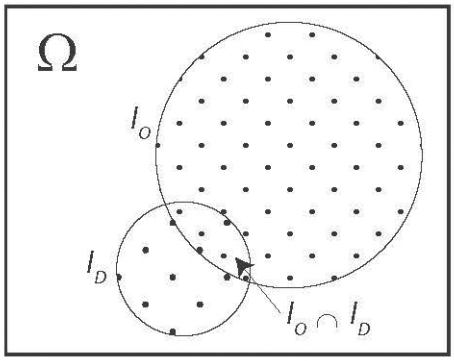

Figure 2. Venn diagram depicting the probability of infection based on the union of two independent events, infection from a device, I_D, and infection from any other source, I_O, in a given sample space, Ω.

Based on this nomenclature, the outcome of developing an HAI results from the occurrence of one or both of these events. This can be illustrated in the Venn diagram shown in Figure 2, where an infection results if one or both events occur. Mathematically, this can be expressed in Eq. (1), where $P(I_D \cup I_O)$ is the overall probability of an HAI, $P(I_D)$ is the probability of infection resulting from a terminally sterilized medical device, and $P(I_O)$ is the probability of infection resulting from a source other than the medical device.

$$P(I_D \cup I_O)=P(I_D)+P(I_O)-[P(I_D)\times P(I_O)] \quad (1)$$

$P(I_D \cup I_O)$ can be calculated based on HAI data, which is collected by hospitals and reported to the Centers for Disease Control and Prevention (CDC). In addition, the probability of infection resulting from a medical device can be approximated based on the device SAL. Thus, the remaining unknown value can be calculated by algebraically solving Eq. (1) for $P(I_O)$. This results in Eq. (2):

$$P(I_O) = \frac{P(I_D \cup I_O)-P(I_D)}{1-P(I_D)} \quad (2)$$

To make a basis for comparison, we can assume that $P(I_O)$ is a constant. $P(I_O)$ and $P(I_D)$ are independent events, so changing $P(I_D)$ would have no impact on $P(I_O)$. The impact of choosing an alternate SAL on the incidence of HAIs can then be predicted by adjusting $P(I_D)$ accordingly.

2.3 Simulations

Numerical calculations for the results presented were performed using Excel 2007 (Microsoft Inc., WA). Hypothesis testing of proportions was performed using Minitab v.14 (Minitab Inc., PA).

For hypothesis testing of proportions, the test was carried out by comparing the hypothesized proportion (P_1) to the original proportion from CDC data (P_0). The null hypothesis tested was H_0: $P_0 \geq P_1$, with the alternative hypothesis of H_1: $P_0 < P_1$. The normal approximation of the binomial distribution was used for hypothesis testing. A resulting *p*-value of less than 0.05 indicates 95% or better confidence in the alternative hypothesis (H_1), at which level the null hypothesis (H_0) can be rejected.

3. Results

3.1 Simulations of the Model

Using 2006 to 2008 data on HAIs obtained from a CDC report in the *American Journal of Infection Control,* [11] we performed a statistical analysis to evaluate the impact of an SAL on the cited overall likelihood of infection. Because terminally sterilized medical devices were not necessarily used on all patients who developed an HAI, this analysis focuses on SSI data, in which it can be assumed that at least one terminally sterilized medical device was used per procedure. The CDC report shows the overall SSI rate based on different operative procedures and different risk categories. Using these data, analyses were performed to assess the impact on the overall incidence of SSIs when selecting SALs other than 10^{-6}.

For simplicity, the following worst-case assumptions were used. First, it was assumed that all products used in the surgical procedures were at exactly a 10^{-6} SAL. This is a worst-case assumption because terminally sterilized products possess a range of SALs usually within several orders of magnitude beyond the required SAL, such as 10^{-6} to 10^{-9}, with 10^{-6} being the least rigorous SAL in the range. Table 1 demonstrates several typical examples of the potentially achieved SAL ranges for a given lot of product sterilized by gamma radiation where a minimum dose of 25 kGy was substantiated based on Method VD_{max} to provide an SAL of 10^{-6}. Second, it was also assumed that the likelihood of one viable organism surviving sterilization will always translate into a patient infection. In reality,

Average Device Bioburden	*D* Value Based on Validation Data[a]	Specified Dose Range	Actual Dose Delivered to Product	Achieved SAL Range[b]
50 CFU	3.25 kGy	25 to 40 kGy	27 to 37 kGy	$10^{-6.6}$ to $10^{-9.7}$
100 CFU	3.13 kGy	25 to 40 kGy	27 to 37 kGy	$10^{-6.6}$ to $10^{-9.8}$
250 CFU	2.98 kGy	25 to 40 kGy	27 to 37 kGy	$10^{-6.7}$ to $10^{-10.0}$
500 CFU	2.87 kGy	25 to 40 kGy	27 to 37 kGy	$10^{-6.7}$ to $10^{-10.2}$
1000 CFU	2.78 kGy	25 to 40 kGy	27 to 37 kGy	$10^{-6.7}$ to $10^{-10.3}$

[a] $D \text{ value} = \dfrac{\text{terminal sterilization dose}}{\log_{10}(\text{average bioburden}) - \log_{10}(\text{validated SAL})}$

[b] $\text{Actual SAL} = 10^{\left[\log_{10}(\text{average bioburden}) - \frac{\text{actual sterilization dose}}{D \text{ value}}\right]}$

Table 1. Examples of potentially achieved actual SALs for medical devices sterilized by gamma radiation where a minimum dose of 25 kGy was substantiated based on Method VD_{max} to provide an SAL of 10^{-6}.

this is not the case since many factors come into play as to whether an organism that survived sterilization could produce an infection. Some of these factors include whether 1) the organism is still viable at the time of use, 2) the titer/level of the organism is sufficient to cause infection, 3) the surviving organism is located on the portion of the product that has patient contact, and 4) whether the organism is pathogenic.

Taking into account these worst-case assumptions and using the SSI rates from the CDC report, the statistical probabilities were calculated as follows. The CDC reports that there were 16,301 SSIs out of a total of 843,786 surgical procedures as reported by hospitals and ambulatory surgical centers participating in the National Healthcare Safety Network (NHSN) from January 2006 through December 2008. This data can be used to calculate the overall probability of an SSI as shown in Eq. (3).

$$P(I_D \cup I_O) = \frac{16{,}301 \text{ surgical site infections}}{843{,}786 \text{ surgical procedures}} = 0.019319 \quad (3)$$

According to this data, the probability of an SSI is about 1.9% (*i.e.* 1 in 51.76) regardless of the source of the infection.

Based on the regulatory requirement for a maximal 10^{-6} SAL, the probability $P(I_D)$ of infection resulting from a single medical device can be approximated as shown below. By definition, the upper-bound value of this probability is the device's SAL, as shown by Eq. (4). The equality in Eq. (4) is obtained for a worst-case situation that assumes that all devices possess the least rigorous SAL and that any viable organism surviving sterilization will always translate into a patient infection.

$$P(I_D) \le \frac{1 \text{ viable microorganism on a single device}}{1{,}000{,}000 \text{ medical devices}} = 0.000001 \quad (4)$$

Substituting Eqs. (3) and (4) into Eq. (2), the probability of infection from any source other than the medical device can then be calculated as shown in Eq. (5):

$$P(I_O) = \frac{0.019319 - 0.000001}{1 - 0.000001} = 0.019318 \quad (5)$$

By keeping the probability $P(I_O)$ constant as calculated above, $P(I_D)$ can be adjusted based on various alternate SALs to calculate what the overall probability of an SSI would be. Each resulting $P(I_D \cup I_O)$ can be multiplied by the number of surgical procedures to determine the new number of SSIs. Table 2 demonstrates the impact of choosing various SALs based on these calculations. The likelihood of an SSI

$P(I_D)$ (Maximum Device SAL)	Incidence of SSIs	Number of SSIs[a]	*p*-value
10^{-6}	1 in 51.763	16,301	Not Applicable
10^{-5}	1 in 51.739	16,309	0.476
10^{-4}	1 in 51.504	16,383	0.259
10^{-3}	1 in 49.264	17,128	0.000
10^{-2}	1 in 34.335	24,575	0.000
10^{-1}	1 in 8.519	99,049	0.000

[a] *Out of a total of 843,786 surgical procedures*

Table 2. Impact of SALs on the incidence of surgical site infections.

$P(I_D)$ (Maximum Device SAL)	$P(I_D)$ (Achieved Device SAL)	Incidence of SSIs	Number of SSIs[a]	*p*-value
10^{-6}	10^{-8}	1 in 51.763	16,301	N/A
10^{-5}	10^{-7}	1 in 51.762	16,301	0.499
10^{-4}	10^{-6}	1 in 51.760	16,302	0.497
10^{-3}	10^{-5}	1 in 51.736	16,309	0.474
10^{-2}	10^{-4}	1 in 51.501	16,384	0.257
10^{-1}	10^{-3}	1 in 49.262	17,129	0.000

[a]*Out of a total of 843,786 surgical procedures*

Table 3. Impact of SALs on the incidence of surgical site infections, with calculations based on potentially achieved SALs instead of maximum SALs.

$P(I_D)$ (Maximum Device SAL)	Incidence of SSIs (Risk Index 0 & 1)	Number of SSIs[a] (Risk Index 0 & 1)	*p*-value	Incidence of SSIs (Risk Index 2 & 3)	Number of SSIs[b] (Risk Index 2 & 3)	*p*-value
10^{-6}	1 in 39.890	2,325	N/A	1 in 23.369	1,297	N/A
10^{-5}	1 in 39.890	2,325	0.493	1 in 23.369	1,297	0.497
10^{-4}	1 in 39.737	2,334	0.426	1 in 23.315	1,300	0.468
10^{-3}	1 in 38.404	2,415	0.031	1 in 22.858	1,326	0.208
10^{-2}	1 in 28.723	3,229	0.000	1 in 19.099	1,587	0.000
10^{-1}	1 in 8.159	11,367	0.000	1 in 7.220	4,198	0.000

[a]*Out of a total of 92,745 surgical procedures*

[b]*Out of a total of 30,310 surgical procedures*

Table 4. Impact of SALs on the incidence of surgical site infections for the procedure "coronary bypass with chest and donor incision," with data stratified based on risk index category.

changes only slightly, from a likelihood of 1 in 51.76 for a 10^{-6} SAL, to a likelihood of 1 in 51.74 for a 10^{-5} SAL, and to a likelihood of 1 in 51.50 for a 10^{-4} SAL. These worst-case calculations demonstrate that using an alternate SAL of 10^{-5} or 10^{-4} would not have a statistically significant impact on the incidence of SSIs (*p*-value not less than 0.05).

To calculate the potential implications of choosing different SALs based on the achieved SAL, an average potentially achieved SAL that was one hundred fold less than the maximal SAL requirement as calculated per Table 1 was assumed in Table 3. These calculations predict that requiring a maximal SAL of 10^{-3} or possibly even 10^{-2} would not have a statistically significant impact on the incidence of SSIs (*p*-value not less than 0.05).

3.2 Application to Higher Risk Populations

One of the main issues that has barred regulatory acceptance of different SALs is the assumption that choosing such SALs could adversely impact the patients who have a higher risk of developing an HAI. The same mathematical model can be used to predict the impact of choosing a greater SAL on the incidence of HAIs in higher risk populations. The CDC data on SSIs includes information on risk index categories, which are determined based on risk factors for SSIs[14] such as duration of procedure in minutes (above the 75th percentile of the duration of surgery for the given procedure); contaminated [Class 3] or dirty/infected [Class 4] wound class; and American Society of Anesthesiology (ASA) classification of 3 (a patient with severe systemic disease), 4 (a patient with severe systemic disease that is a constant threat to life), or 5 (a moribund patient who is not expected to survive without the operation).[15] The patient's SSI risk index category is calculated by counting the number of these factors present at the time of the operation.[14]

In one selected example, the rate of SSIs following a coronary bypass procedure was approximately 2.5% in patients with a risk index of 0 or 1 (2,325 SSIs out of 92,745 total procedures), compared to a rate of approximately 4.3% in patients with a risk index of 2 or 3 (1,297 SSIs out of 30,310 procedures). The impact of choosing different SALs for these patients is shown in Table 4. As with the example reported in Table 2, these calculations demonstrate worst-case figures with the assumption that all devices possess the least rigorous SAL, and that a single viable microorganism on a medical device will always result in an SSI, regardless of the infective dose, the patient's immune status, or any other factors that would impact the variable $P(I_D)$.

In lower risk patients (risk index of 0 or 1), these calculations demonstrate that an SAL of 10^{-5} or 10^{-4} would not have a statistically significant impact on the incidence of SSIs, and in higher-risk patients (risk index of 2 or 3), the same calculations demonstrate that an SAL of 10^{-5}, 10^{-4}, or even 10^{-3} would not have a statistically significant impact on the incidence of SSIs. Paradoxically, it was shown that choosing a greater SAL would have less of an increase in the incidence rate of SSIs in the higher-risk population compared to the lower-risk population. These findings can be explained by the fact that higher-risk populations would be much more likely to develop SSIs due to factors other than the sterility of the medical device,

which as a result lowers the proportion of the impact from the SAL on the overall probability of infection.

4. Discussion / Conclusion

Using a probabilistic model for predicting actual SSI rates, the data indicates that choosing SAL values of 10^{-5} or 10^{-4} (and in some cases even 10^{-3} or 10^{-2}) for terminal sterilization of a medical device would not have a significant impact on the overall incidence of SSIs. This same probabilistic model can be applied to data on other types of HAIs or to data from hospitals outside of the U.S. to determine the impact of SALs greater than 10^{-6} in other situations not presented in this paper. Given the large samples sizes used in this present analysis, this probabilistic model could generalize well to other data sets.

Since many of the IV drug products used in clinical practice achieve a 10^{-3} PNSU versus a 10^{-6} SAL, and with the shown incidence of HAIs at approximately 2% where the majority are due to causes related to clinical practices, increasing the SAL of a single medical device would likely not impact the safety of the device as far as it being the cause of an infection in clinical procedures. While the present study examines the risk of infection posed by a single medical device only, procedures often involve multiple medical devices. The probabilistic model and the methods used in this current paper could be expanded and applied to analyze the effect on HAIs in situations where multiple devices sterilized to a higher SAL may be used.

If other SALs were selected, as presented in this paper, some medical products could be terminally sterilized instead of being aseptically manufactured, as currently performed. This in turn would allow new/emerging products to be terminally sterilized using a process based on inactivation of microbiological contaminants after manufacturing versus a process based on preventing contamination during manufacturing.

The benefits of having these new/emerging products on the market terminally sterilized to achieve a maximal SAL other than 10^{-6} could far outweigh any perceived increase in the likelihood of infection, and would contribute towards efforts to reduce healthcare costs without any adverse impact to patient safety.

5. Acknowledgements

Maxime Bonjean acknowledges support from the National Institutes of Health, NIH-NIBIB (Grant 1R01EB009282-01), the Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, CA, USA, Division of Biological Sciences, UCSD, La Jolla, CA, USA, and the Leon Fredericq Fund, Belgium.

6. APPENDIX

6.1 Sample Space

A sample space consists of all possible outcomes for a given event. This space can be represented by a Venn diagram, which is a diagram showing all of the possible outcomes of one or more events. A simple Venn diagram for a single event is shown in Figure 3A. This diagram represents a single event, event A,

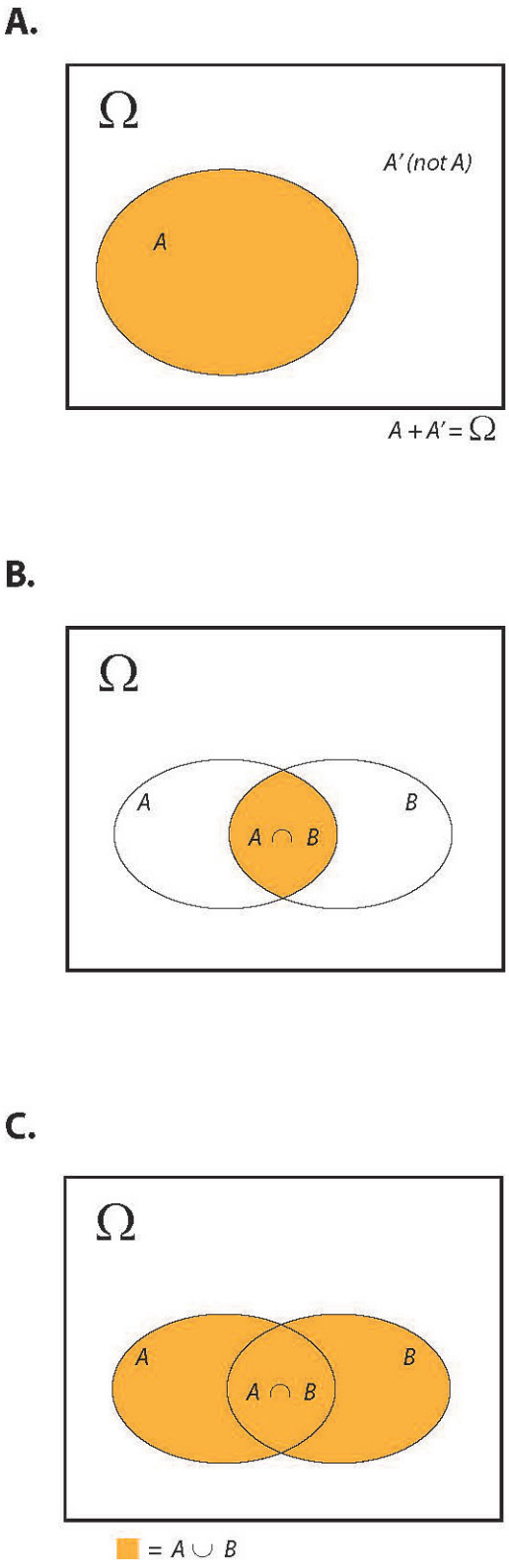

Figure 3. (A) Venn diagram depicting the outcome of event A. (B) Venn diagram depicting the intersection of events A and B. The highlighted area represents A ∩ B. (C) Venn diagram depicting the union of events A and B. The highlighted area represents A ∪ B.

where the outcome of event A "happening" is represented by the area inside the oval, with the alternative of event A being the remainder of the space. Because event A only has two outcomes, either it happens or it does not, the sample space represents all possible outcomes.

6.2 Independent Events

Events are said to be *independent* if the outcomes of the events being considered have no impact on one another. Said another way, two events (A and B) are considered to be independent if the probability of event B "happening" is the same regardless of whether or not event A "happens." Consider the following two examples:

Coin Tossing: Tossing a fair coin has a probability of producing a "heads" result 50% of the time.

$$P(\text{“Heads”})=0.5 \qquad (6)$$

If you were to toss the coin twice, the probability of a "heads" result on the second toss would not change based on the result of the first toss. In this case, the first toss and the second toss are considered to be independent events.

Dealing Cards: When dealing from a standard deck of 52 playing cards, there are 26 red cards and 26 black cards. On the first card dealt (without replacement), the probability of dealing a red card is:

$$P(\text{“Red”}) = \frac{\text{Count of red cards}}{\text{Count of red cards} + \text{Count of black cards}} \quad \frac{26}{26+26} = 0.5 \qquad (7)$$

If the first card is not replaced, and a second card is dealt from the same deck, the probability of dealing a red card has changed. This is because the count of the card types in the deck has changed. Based on the result of the first card dealt, the probability of dealing a red card on the second trial is:

First Card "Red"

$$P(\text{“Red”}) = \frac{25}{25+26} = 0.490$$

First Card "Black"

$$P(\text{“Red”}) = \frac{26}{26+25} = 0.510$$

In this example, the outcome of the second card dealt is directly affected by the result of the dealing of the first card. In this case, the two events cannot be considered to be independent.

6.3 Combinations of Events

The first type of event combination to be considered for the mathematical model used is an *intersection*, which is represented in probability functions with the symbol "∩". Two or more events are said to "intersect" if all of the events occur simultaneously. Figure 3B is a Venn diagram of two events, with the intersection of the two events highlighted.

Should the two events in Figure 3B be independent, meaning the outcome of event A has no impact on the outcome of event B, then the probability of the intersection can be expressed in Eq. (8).

$$P(A \cap B)=P(A)\times P(B) \qquad (8)$$

The second type of event combination to be considered is a *union*, which is represented in probability functions with the symbol "∪". A union of one or more events is the set of outcomes where at least one of the events being considered has occurred. Figure 3C is a Venn diagram highlighting the union of two events. The probability of the union of the two events in Figure 3C can be expressed with the formula in Eq. (9).

$$P(A \cup B)=P(A)+P(B)-P(A \cap B) \qquad (9)$$

Combining the formula for the union of two events with the formula for the intersection of two independent events produces the result in Eq. (10).

$$P(A \cup B)=P(A)+P(B)-[P(A)\times P(B)] \qquad (10)$$

This formula would remain true only for independent events—combinations considered where the result of event A has no influence on the result of event B. ■

References

1. **National Center for Devices and Radiological Health (NCDRH).** *Sterile Medical Devices: A Good Manufacturing Practices Workshop Manual*. 4th ed. Silver Spring, MD: U.S. Food and Drug Administration.
2. **ANSI/AAMI/ISO TIR11139:2006,** *Sterilization of health care products – Vocabulary*. Association for the Advancement of Medical Instrumentation; 2006. Arlington, VA.
3. **Mosley GA.** Sterility Assurance Level (SAL): The Term and Its Definition Continues to Cause Confusion in the Industry. *Pharmaceutical Microbiology Forum Newsletter*. 2008;14(5):2-15.
4. **Booth AF.** *Sterilization Validation & Routine Operation Handbook: Ethylene Oxide*. Lancaster, PA: Technomic Publishing Company, 2000.
5. **Morrissey RF, Bruch CW, Sharbaugh RJ, Favero MS, Jarvis WR, and Masefield J.** Sterility and Safety Assurance of Medical Devices. *Medical Device & Diagnostic Industry*. 1992;115:78-81.
6. **Pflug IJ.** Sterilization of Space Hardware. Environmental Biology and Medicine. 1971;1:63-81.
7. **ANSI/AAMI ST67:2011,** *Sterilization of health care products – Requirements and guidance for selecting a sterility assurance level (SAL) for products labeled "sterile."* Association for the Advancement of Medical Instrumentation. Arlington, VA.

8. **Akers JE, Agalloco JP, Carleton FJ, Korczynski MS.** A Review of Current Technology in Parenteral Manufacturing. *Journal of Parenteral Science and Technology*. 1988;42(2):53-6.

9. **Agalloco J, Akers J, Madsen R.** Aseptic Processing: A Review of Current Industry Practice. *Pharmaceutical Technology*. 2004;126:150.

10. **Klevens RM et al.** Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002. *Public Health Reports*. 2007;122:160-166.

11. **Edwards JR et al.** National Healthcare Safety Network (NHSN) Report: Data Summary for 2006 Through 2008, Issued December 2009. *American Journal of Infection Control*. 2009;37:783-805.

12. **ANSI/AAMI/ISO 11137-2:2006,** *Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose*. Association for the Advancement of Medical Instrumentation; 2006. Arlington, VA.

13. **Kowalski JB and Tallentire A.** Substantiation of 25 kGy as a Sterilization Dose: A Rational Approach to Establishing Verification Dose. *Radiation Physics and Chemistry*. 1999;5455-64.

14. **Centers for Disease Control and Prevention (CDC).** *NHSN Patient Safety Component Manual: Surgical Site Infection (SSI) Event*. Available at: www.cdc.gov/nhsn/TOC_PSCManual.html. Accessed Nov. 30, 2011.

15. **American Society of Anesthesiologists (ASA).** ASA Physical Status Classification System. Available at: www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx. Accessed Nov. 30, 2011.

16. **Hayter AJ.** *Probability and Statistics for Engineers and Scientists*. Boston, MA: PWS Publishing Company, 1996.

17. **Juran JM and Godfrey AB (Editors).** *Juran's Quality Handbook*. 5th ed. Singapore: McGraw Hill, 2000.