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## ABSTRACT

### Background

The sterility assurance level (SAL) was first developed by the food canning industry. In order to demonstrate sterility, since it is impossible to sample all canned items after moist heat sterilization. A safety factor was established incorporating the kinetics of inactivating bacterial spores that would give an equivalent of a 12-log spore reduction. In the 1960's the Swedish public health authority required a stated SAL of 10<sup>-6</sup> (probability of 1 viable organism per 1,000,000 products) for medical devices labeled "sterile". Currently SALs are used to measure sterilization process efficacy and apply to terminally-sterilized medical products.

### Objectives

The intent is to determine what are acceptable SALs for new/emerging health care products such as combination products (medical device with a pharmaceutical and/or biologic component), devices with materials that cannot withstand traditional terminal sterilization processes, and products that are cell-and tissue- based.

### Methods

The U.S. Food and Drug's Medical Device Reporting Program (MedWatch) was examined to determine if there is an increase in infections associated with products that are labeled "sterile" and do not have an SAL of 10<sup>-6</sup>, such as combination products, medical devices with sterilization-sensitive materials, and products that are cell- and tissue-based.

### Results

Combination products and cell-and tissue-based medical devices are relatively new on the market, so there are few reports of infections associated with these devices having an SAL of 10<sup>-6</sup> or other SAL (e.g., 10<sup>-3</sup>). In addition, there is no evidence at this time that shows conclusively that devices with an SAL of 10<sup>-3</sup>, for example, are more likely to be linked to nosocomial infections than devices with an SAL of 10<sup>-6</sup>. Data indicates that the majority of nosocomial infections arise in the clinical environment due to post-sterilization handling, the environment itself, and in-use handling practices that are not aseptic.

### Conclusions

As health care products continue to expand to include devices with new materials that cannot withstand traditional terminal sterilization, combination products that include pharmaceuticals and/or biologics, and cell- and tissue-based products, new sterilization methods for these products may need to incorporate a variety of SALs if these items are to be terminally sterilized, labeled "sterile", and still function as intended for use.

## OBJECTIVE

The intent of this study was to research data regarding healthcare-related infections associated with the use of traditional sterilized medical products. This research was evaluated to determine if a link exists between incidence of infection and various product SALs. An understanding of this link is necessary to determine what SALs are acceptable for new /emerging health care products. These emerging products include those with materials that cannot withstand traditional terminal sterilization processes and their associated SALs, such as combination products (medical device with a pharmaceutical and/or biologic component), cell-and tissue-based products, and devices that include sterilization-sensitive materials.

## BACKGROUND

The classical definition of sterility is an absolute condition, namely: the state of being free from all living microorganisms. By this definition an item is either sterile or it is not. The effectiveness of a sterilization process, on the other hand, cannot be so categorically defined. This is because a microbial population when exposed to a sterilization process typically follows an exponential pattern of inactivation and as a result there is always a finite probability of a microorganism surviving, regardless of the extent of processing applied. Because of this, sterility must be measured as a probability of one surviving microorganism in a population (i.e one contaminated item), which is termed a Sterility Assurance Level (SAL) and is expressed as a negative exponent such as 10<sup>-3</sup> or 10<sup>-6</sup>. For example, an SAL of 10<sup>-3</sup> indicates a probability of 1 in 1000 and 10<sup>-6</sup> a probability of 1 in 1,000,000 and so on.

The SAL of 10<sup>-6</sup> originated in the food canning industry. SAL's were also used during NASA's development of dry heat sterilization processes for the Viking planetary space probe, where the probability of landing a microorganism on Mars would be 10<sup>-4</sup> or less. Swedish public health authorities subsequently adopted the concept, and required that pre-packaged single-use medical products be subject to terminal sterilization processes that achieve a minimum SAL of 10<sup>-6</sup> in order to be labeled sterile. At the same time, pharmaceutical products manufactured by aseptic processing with an SAL of 10<sup>-3</sup> – 10<sup>-4</sup> were used in hospitals under the same conditions as those products requiring an SAL of 10<sup>-6</sup>. The SAL of 10<sup>-6</sup> was subsequently adopted by the USFDA and many other countries for terminally-sterilized single-use medical products.

In the mid 1970's, in North America, as a result of work conducted by AAMI Working Group TC 198 (Sterilization of medical devices), the practice of using a standard sterilizing dose of 2.5 Mrad was replaced by the introduction of more rational sterilization dose setting methods based upon a product's natural bioburden numbers and their resistance to radiation compared to a model population.

However these rational dose setting methods, which later gained international acceptance still required establishing sterilization cycles that achieved an SAL of 10<sup>-6</sup> in order for medical devices to be labeled sterile. In 1979 the USFDA supported the use of a 10<sup>-3</sup> SAL for some sterile medical devices depending upon their end use (e.g. topically applied medical devices).

While SAL is a reflection of the efficacy of the overall process, to date no relationship has been established between a specific SAL and the safety of the treated product for its intended use in the clinical environment. Thus we operate in a regulatory environment where depending upon the type of product, its method of sterilization, and/or its end use, it can be labeled sterile having been subjected to sterilizing processes that achieve SALs ranging from 10<sup>-3</sup> to 10<sup>-6</sup>. This issue was discussed in a paper published in 1992, which was subsequently reprinted by the U.S. Department of Health and Human Services Centers for Disease Control. The paper stated that "it is likely that an SAL of 10<sup>-3</sup> may provide an adequate assurance against infection for all medical devices, though further research is needed to support this contention". In 2003 AAMI published the ST67 standard which allowed an SAL of 10<sup>-3</sup>, 10<sup>-4</sup>, or 10<sup>-5</sup> in cases where a product could not withstand a 10<sup>-6</sup> terminal sterilization process. However this standard included numerous restrictions to using an SAL other than 10<sup>-6</sup>. The revision of ST67 will address these restrictions.



## METHODS

A search was conducted on the Medical and User Facility Device Experience (MAUDE) database covering records from January 2009 through March 2009, using the search item "infections". The total number of reports searched was over 52,000 for the three month period and the word "infection" appeared in less than 100 reports:

- January 1, 2009-Feb. 1, 2009: There were a total of 14,679 reports with 38 having the word "infection" in it
- February 1, 2009 - March 1, 2009. There were a total of 19211 reports (18432 manufacturers reports) with 42 out of 70,964 text records searched having the word "infection" in it
- March 1, 2009-April 1, 2009. There were a total of 20,063 reports (19,115 manufacturers reports) with 26 out of 72,866 text records searched having the word "Infection" in it.

## RESULTS

Of the reports with the word "infection", most patients who had infections already had a history of MRSA and Staphylococcus infections. However, there are reported cases of infections that may or may not be associated to the sterility of the device. Those are:

1. Prosthesis, hip, hemi-, femoral, metal/polymer, cemented or un-cemented. There were 6 infections in a row using the 5 knees and 1 hip. No information was provided as to the infection/organism type. It is assumed the SAL is 10<sup>-6</sup> for these implants.
2. Dressing, wound and burn, interactive. Dermagraft applied to a patient who developed significant infection within a week of application. It is assumed the SAL is 10<sup>-6</sup> for these dressings.
3. Mesh, surgical, polymeric. Patient underwent a hernia repair procedure with a placement of a Composix Kugel mesh patch. Within weeks afterwards, the patient had chronic infections resulting from a non-healing wound with significant pain. It is assumed the SAL is 10<sup>-6</sup> for this implanted device.
4. Set, administration, intravascular. Many bloodstream infections associated with use of luer activated valve for IV access. Education on how to use the positive activated connectors led to drop in bloodstream infections. It is assumed the SAL is 10<sup>-6</sup> for these IV sets.
5. Implant, cochlear: patient developed infection at site of implant. It is assumed the SAL is 10<sup>-6</sup> for this implant.
6. Pump, infusion, implanted, programmable. Patient developed infection since implant. It is assumed the SAL is 10<sup>-6</sup> for this implanted pump.
7. Coronary drug-eluting stent. Patient developed "blood poisoning" by the infections. The physician states that it is unknown the relationship of the device to the event (infection). It is assumed the SAL is 10<sup>-6</sup> for this implant.
8. Stimulator, electrical, implanted, for Parkinsonian tremor. Patient developed infection and device was removed due to infection at the lead track. Literature search done by a group to look at 10-year period of complications of deep brain stimulation: a longitudinal single surgeon, single institution study: 191 patients received 330 electrode implants. There were 59 complications in 53 of the 191 patients. Patient 2 of 12 experienced a major wound related problem. Major wound related problems required hardware removal problems included infections. It is assumed the SAL is 10<sup>-6</sup> for this implant.
9. Stimulator, autonomic nerve, implanted for epilepsy. One patient had battery site infection. No other information reported. It is assumed the SAL is 10<sup>-6</sup> for this implant.

## DISCUSSION

Current efforts to advance medical science are focused on regenerative therapeutics, targeted drug delivery involving biologically active molecules, cellular therapies, microelectronics and nanotechnologies; here the synergies of converging technologies and converging processes will be further realized. However these new products present new challenges to sterilization processing. Because many of these new products cannot withstand current SAL 10<sup>-6</sup> sterilization processes, aseptic processing is often used, which typically achieves an SAL of 10<sup>-3</sup> at best (1 in one thousand chance of contamination). It is time to reevaluate the approach that has been taken to establishing terminal sterilization processes for these products.

Based upon a survey of the healthcare industry there is wide-scale support to develop an approach to the selection of SALs that would result in the establishment of sterilizing processes that would render products safe for their intended use rather than to achieve a mandated SAL of 10<sup>-6</sup>. The results showed that:

- 134 (99.4%) of 144 companies responding to the survey indicated support for this endeavor.
- 118 (80%) of the 147 responding indicated that their current radiation sterilization requirements would benefit from the wider dose range resulting from the establishment of lower minimum doses
- 101 (69%) of 147 respondents have products that cannot currently be radiation sterilized because of unacceptable physical material degradation at the sterilizing doses required in order to achieve an SAL of 10<sup>-6</sup>
- 101 (69%) of 147 respondents have products that cannot currently be radiation sterilized because of unacceptable physical material degradation at the sterilizing doses required in order to achieve an SAL of 10<sup>-6</sup>

It is estimated that 1 out of 10 causes of death in the USA result from hospital-acquired infections (HAI's)(2008 Cynthia Bascetta US GAO Director Healthcare 55 page report to Henry Waxman). When considering the association of a medical product with patient infection there are a number of factors that must be considered that go beyond the SAL of the packaged medical product. Regardless of the SAL of packaged product, once the product is opened, its sterility is largely determined by the cleanliness of the environment and in-use handling practices. For example, a product with an SAL of 10<sup>-6</sup> (1 in one million chance of a contaminated product) does not maintain this level of sterility assurance when used in most healthcare settings where the chance of contamination is significantly higher.

For this study the results demonstrated no evidence that devices with an SAL of 10<sup>-6</sup> are likely to be associated with a lower incidence of HRIs than those with an SAL of 10<sup>-3</sup>. Because of this, terminal sterilization of these new/ emerging products is now feasible, since an SAL other than 10<sup>-6</sup> can be considered. The flow chart in AAMI ST67:2003 (as shown here) outlines criteria and an approach to selecting an SAL other than 10<sup>-6</sup>.



## CONCLUSIONS

As health care products continue to expand to include devices with new materials that cannot withstand traditional terminal sterilization, combination products that include pharmaceuticals and/or biologics, and cell- and tissue-based products, new sterilization methods for these products must accommodate a variety of SALs if these items are to be terminally sterilized, labeled "sterile", and still function as intended for use.

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