Sterile supply of medical devices and pharmaceutical products

Quality standards and applied risk management*)

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ABSTRACT

Microbiological quality standards of terminally sterilized medical devices have to protect the patient's safety. The sterility assurance level of 1:1,000,000 must be maintained when sterilized products wrapped with flexible porous packaging material are supplied. The proposed data based risk management enables manufacturers and hospital staff to calculate the compatibility of a given airborne microbial filtration efficiency of the packaging material with the airborne microbial challenge during the storage period. The use of this method results in an approximate confirmation of the sterility assurance level (SAL) for sterile supply and clearly minimizes the risk of hospital acquired infections. This procedure makes it possible to meet requirements of the International Standard ISO 11607-1.

ZUSAMMENFASSUNG

Qualitätsstandards und angewandtes Risikomanagement in der Sterilgutversorgung

Die mikrobiologischen Qualitätsstandards für in der Endverpackung zu sterilisierende Medizinprodukte dienen dem Schutz der Patientensicherheit. Der Sterilitätssicherheitswert von 1:1 000 000 muss auch bei der Bereitstellung sterilisierter und durch luftdurchlässige flexible Verpackungen geschützter Produkte aufrechterhalten werden. Mit dem vorgestellten datengestützten Verfahren zum Risikomanagement können Hersteller wie auch das Fachpersonal in der Patientenversorgung die Kompatibilität des Verpackungsmaterials mit der Beanspruchung durch luftgetragene Keime während des Transports und der Lagerung abschätzen. Diese Methode erlaubt näherungsweise eine Bestätigung des Sterilitätssicherheitswerts zum Zeitpunkt der Sterilgutentnahme aus der Verpackung und reduziert nachvollziehbar das Risiko für Krankenhausinfektionen. Erst mit diesem Verfahren wird es möglich, die Anforderungen des Internationalen Standards ISO 11607-1 zu erfüllen.

KEY WORDS

- Sterile barrier system
- Applied risk management
- Validation
- Sterility assurance level

Pharm. Ind. 78, No. 11, 1644–1648 (2016)

*)Presented in part at the 1st European Lab Technology Forum, November 5–6, 2015, Göttingen, Germany, and the 16th World Sterilization Congress & Annual conference of AFS, October 7–10, 2015, Lille, France.

1. Introduction

Risk analysis and hazard identification are methods of toxicology and hospital hygiene to clarify the relationship between the type and frequency of diseases and the underlying causes and mechanisms. Knowledge of these mechanisms allows the determination of proper quality standards and risk management. The respect of established quality standards in terms of exposure to microbiological pathogens or toxicological compounds minimizes the probability of additional harmful effects.

The relevant criteria for the evaluation of both, toxic compounds and microbiological pathogens are similar in some points, but clearly differ in others. The dose of a compound is an important factor in toxicology: "sola dosis facit venenum" ("the dose makes the poison") – an adage credited by Paracelsus (around 1535). Correspondingly, the number of infective microbes which enter the human body is relevant for the onset of an infection. Unlike chemicals compounds, single bacteria or fungi can multiply at room temperature in liquids such as injection or infusion solutions, blood and blood products to a concentration which is thereafter infective even if the organism has only a low pathogenic potential. Furthermore, the health status of staff in the workplace area is generally assumed to be healthy. However, the susceptibility for infections within the human population increases significantly if people are impaired by illness or treated by means of hospitalization or outpatient care (surgery, immunosuppressive treatment). For these reasons, a clear risk assessment cannot be carried out for exposure to potentially microbial contaminated products when medical devices or pharmaceuticals are used for parenteral treatments of patients. These circumstances and the quest for the highest possible level of safety led to the

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requirement of sterility for products and devices which penetrate human skin or enter human tissue. Sterility is defined as the probability of a nonsterile product being equal to or less than 1:1,000,000 (International Standard EN 556-1:2001). This quality standard is referred to as the sterility assurance level (SAL). For the process of sterilization, a probability function can be derived from the basis of an inactivation curve for test organisms. Therefore, a product's initial sterility can be ensured at the level of the SAL for different sterilization methods established in the past.

Medical packaging material for non-liquid sterile items in hospitals or for commercially terminally sterilized medical devices is normally porous or has porous components to ensure sterilant access. Consequently, specific test results are required to evaluate the barrier efficiency of the packaging material to retain airborne microbes, if air flow into the package occurs during transport and storage. The International Standard ISO 11607-1, subclause 5.1.3, points out the relevant factors of the packaging material and of the environment which can limit the maintenance of sterility: *"the conditions under which the [...] preformed sterile barrier system are handled shall be established, controlled and recorded, if applicable, in order to ensure that [...] the conditions are compatible with the use for which the material and/or sterile barrier system is designed; [...]. As a minimum, the following shall be considered: a) temperature range, b) pressure range, c) humidity change, d) maximum rate of change of the above, [...], g) bioburden, [...]."* Contrary to the process of sterilization, in which a validation procedure ensures the initial sterility of medical devices at the level of the SAL, no adequate procedures have been established for the post-sterilization period, where the barrier performance of porous packaging material should maintain the product's continued sterility. Sterility tests which are used to assess the continued sterility of sterilized items have methodological and statistical limitations. Firstly, the majority of the available tests are destructive, i. e. the examined products cannot be used thereafter. Secondly, the level of 1:1,000,000 for sterility cannot be proven because testing of the statistically required large sample size is impossible and cannot be performed free from laboratory error.

When using packaging with a porous component, air flow into the packaging during transport and storage challenges the gas-permeable components and requires sufficient filtration efficiency for the removal of airborne microbes. Some factors which affect the maintenance of sterility include the following: concentration of airborne microbes in the storage area in relation to their particle size, air pressure differences between the inside of the packages and the outer environment caused by weather-influenced atmospheric pressure changes, by transport to different heights above sea level (within buildings, by plane or road), and by temperature variations. It has to be emphasized that the average pore diameter of porous packaging material is limited according to International Standards. For example, the pore diameter of paper for paper bags or pouches shall be lower than or equal to 35 µm (EN 868-3 2009; 4.2.13). It has to be mentioned that in a long-term study in hospital wards, the fraction of airborne microbial concentration with a particle size < 3.0 µm (bacteria and fungi) was shown to be within the range of 17.3–44.4 % [1]. The mechanisms of the particle-capture efficiency cannot be addressed here in detail, but it should be emphasized that microbes and other small particles with a size between 0.5 and 10 µm are not typically captured by a sieve-like function. These particles have to be captured by the fibrous structure of the packaging material. This filtration mechanism is referred to as impaction and interception.

According to ISO 11607-1 (subclause 5.2), the term "impermeability" in relation to the microbial barrier properties should only be used for packaging material which has been tested according to the "Test method for resistance of impermeable materials to the passage of air" (Annex C of ISO 11607-1). "Impermeability" should not be used to characterize the barrier of porous packaging material such as paper or nonwoven materials for airborne microbes or particles. For this reason, the use of the term "microbial impermeability" in relation to porous packaging material by the German Society for Sterile Supply (DGSV e. V.) is misleading and hinders efforts of the hospital staff to demonstrate the compatibility of porous packaging material with the airborne microbial challenge caused by the environmental conditions (ISO 11607-1, subclause 5.2.3) [2].

Different methods for testing the barrier properties were developed in the past. For example, the Standard ASTM 1608, first published in 1995, describes a "Test Method for Microbial Ranking of Porous Packaging Materials". This method uses a bacterial aerosol of *Bacillus subtilis* spores and a flow rate of 2.8 L/min which provides a minimum challenge of 10^6 microbes per sample, measuring 50 mm in diameter.

2. Material and Methods

A whole package microbial challenge test is designed as an exposure chamber method using a nebulizer and a *Micrococcus luteus* suspension for the airborne microbial exposure [3, 4]. Using a vacuum pump, the atmospheric pressure within the exposure chamber can be periodically reduced by 0–100 hPa, which leads to an air flow through the permeable component of the exposed test packages. A microbial aerosol of *Micrococcus luteus* with a mean particle size of about 3 µm is generated by a nebulizer. A glass impinger air sampler is used to determine the airborne bacterial concentration in the chamber. The test packages are loaded with non-covered nutrient agar plates or dishes before sterilization, cultivated after exposure to monitor the bacteria count (Patent-No. US 8,053,210 B2; EP 1 485 135 B1) and registered as colony forming units (CFU). The periodic air pressure changes and the humidity inside the chamber are continuously registered. The microbial challenge of the

package can be determined by calculation of the total air volume passing the porous component and by the consideration of the average airborne microbial concentration in the chamber. The use of an airborne microbial concentration of 1,000,000 CFU/m³ and about 20 periodic air pressure changes of between 20 and 70 hPa are sufficient to demonstrate filtration efficiency between 90 and 99.999 % for package volumes of 0.1 L and above. For the calculation of the filtration efficiency of the packaging against the airborne microbial challenge, the number of bacteria in the volume of air entering the exposed packaging and the number of bacteria which passed the packaging barrier and are registered as CFU have to be considered. The filtration efficiency is calculated according to the following equation:

$$\text{Filtration efficiency (\%)} = \left[1 - \frac{N_1}{N_0}\right] \times 100$$

where:

N_0 = calculated mean number of bacteria present in the total air volume passing through the packages.

N_1 = number of the bacteria registered as CFU on the plates within the test packages.

The following test example of flexible packaging material may be presented. Four types of flexible sterilization pouches (15 x 18 cm) manufactured by different producers were exposed to determine their filtration efficiency with the whole package microbial challenge test. A sample size of 30 packages per group was used. 50 periodic air pressure changes of 75 hPa were applied. Two types of paper/film pouches with a volume of about 0.2 L were used, denoted by A and B, pouches of 60 gsm non-woven/film material denoted by C were another type, and finally non-woven/film pouches made of high-density polyethylene (HDPE), denoted by D were used.

3. Results

The filtration efficiencies were 98.4 for (A), 98.8 (B), 85.6 (C) and more than 99.7 % in the case of D, where no bacterial growth was observed (Fig. 1). The differences between C and A, B or D were significant. In order to enhance the barrier function, double wrapping was used. After double wrapping, the same types of pouches were tested using the same test runs and compared with the single wrapping method.

As expected the removal of airborne microbes increased clearly. The double packaging of types A and B led to no bacterial growth. In the case of C a mean microbial count of 0.19 CFU per pouch was observed. The examination of the HDPE pouches resulted again in exclusively sterile items.

Comparable test results of microbial barrier properties of porous flexible packaging material were published by Sinclair et al in 2002 [5]. Using the ASTM 1608 test, they measured the filtration efficiency of 16 commercial porous packaging materials against airborne microbial spores. In most cases, the maximum spore penetration was between 1 to 10 % or above 10 %.

The risk management and calculation of the compatibility of the tested porous packaging material with the storage conditions of the post-sterilization period, i. e. the airborne microbial challenge, should be based on a quantitative procedure. The relevant performance parameter is the airborne microbial retention capacity or filtration efficiency of the packaging material. The relevant factors to be considered are the level and relevant sizes of airborne particles bearing microorganisms and the flow rate of air through the layers of packaging material in the period of storage and transport. The following set data is used to give an example:

- package volume (V_1): 0.1 L,
- the filtration efficiency of the single wrapping material may be 98.8 % (pouch B, Fig. 1),
- room temperature (T_1) : 293 K, 20 °C respectively,
- estimated airborne microbial load in the storage area of particles sized < 3 µm: 20 CFU/m³.

The flow of ambient air into the package ΔV_p which follows the atmospheric air pressure changes can be calculated according to p x V = const (law of Boyle and Mariotte). The flow ΔV_t as a result of temperature changes can be calculated according to

$$\Delta V_t = V_1 \times \frac{\Delta t}{T_1}$$

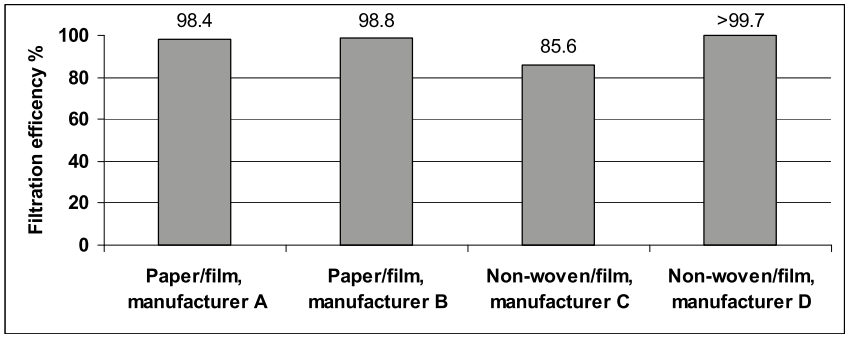

Figure 1: Filtration efficiency of 4 types of pouches sized 15 x 18 cm. Using the whole package microbial challenge test, the pouches were exposed to a microbial aerosol of Micrococcus luteus (Source: all figures made by the author).

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The microbial challenge (N_0) of the package per event is obtained according to

$N_0 = \Delta V_{t+p} \times 20/1000$ CFU/m^3

The following example considers 2 exposure scenarios for the calculation of the maintenance of sterility according to the event related concept. One event reflects a temperature variation (Δt) of 2 °C and a weather dependent atmospheric air pressure change of 15 hPa. The event, e.g. both effects, occurs once per week in scenario A and 7 times per week in scenario B respectively. It should be remarked that the assumptions according to scenario A seem to be rather underestimated in relation to realistic conditions. The compatibility was determined for single and double wrapping (Table 1).

The compatibility of the number (n) of events with the packaging filtration efficiency in order to meet the maintenance of sterility at the sterility assurance level (SAL) of 10^{-6} is calculated according to

$$N_o \times \frac{100 - Filtration\ efficiency\ (\%)}{100} \times n \leq 10{-}6$$

The result is: n is equal to 1.95 for the number of events which are compatible with maintenance of sterility when single wrapping is used. This corresponds to a maximum shelf life of about 2 weeks in scenario A and of 2 days in scenario B. Double wrapping leads to n = 162 for the number of events. This corresponds to a shelf life of 3.1 years (scenario A) and to 0.4 years for scenario B where temperature and air pressure change daily, a more realistic precondition.

The results demonstrate that usual paper pouches can maintain sterility at the SAL only for a few days in a relatively clean environment.

In a first approximation, the used risk management procedure confirms the proof of maintenance of sterility for a sterile barrier system which is exposed to specified environmental storage conditions. This data based method corresponds to the requirements which are outlined in the International Standard ISO 11607-1.

4. Discussion

The risk management of maintenance of sterility during the post-sterilization period is obviously relevant in view of the fact that millions of sterilized products, wrapped with air permeable porous packaging material, are manufactured and used worldwide daily. They are transported by car, plane and ship and exposed to different altitudes, temperatures, air pressures and airborne microbial concentrations. The loss of sterility of single items or of small parts of the produced lot can induce sporadic occurrences of severe hospital acquired infections, if single bacteria are able to multiply to an infective dose outside or inside the human body.

When considering the infection risk caused by the use of sterilized medical products with questionable maintenance of sterility, the focus has to be on those cases where probably very few bacteria which rarely cause an infection have contaminated a formerly sterile product and can thereafter multiply, mostly unimpaired, to an amount which is infectious, even in the case of low pathogenicity. Staes et al reviewed outbreaks of hospital acquired infections associated with contaminated drugs produced by compounding pharmacies and found 5 outbreaks caused by organisms that were atypical for hospital acquired infections such as the 2012 fungal meningitis outbreak [6]. A report of this fungal meningitis outbreak demonstrated a strong association between the age of the vials and the infection rate [7]. The authors explained this increase with the microbial growth during storage followed by a higher fungal burden. A case control study showed that the administration of propofol was significantly associated with postoperative infections when storage conditions of the filled syringes allowed microbial growth, e.g., when syringes are prepared once daily for use throughout the day [8].

Generally it is difficult, almost impossible in the everyday hospital practice to trace back a single hospital acquired infection to a sporadic loss of sterility of a regular wrapped and terminally sterilized medical device as root cause, because the microbiological status of the unopened device can no longer be examined and the loss occurs isolated in time and location. The probability to detect infections caused by recontaminated items increases with increasing recontamination rate and when a cluster of case-patients indicates an abnormal transmission route of organisms. Gunaratne et al for example, reported an outbreak of *Aspergillus fumigatus meningitis* in 2 hospitals in Sri Lanka with 5 affected women following spinal anaesthesia for caesarean section [9]. 43 of 679 unused syringes showed *A. fumigatus*

Table 1

Risk management of the maintenance of the sterility of pouches (15 x 18 cm) by calculation of the compatibility of the filtration efficiency with the airborne microbial challenge during the storage period.

wrapping method	number of events (n)	1 event per week (scenario A)	7 events per week (scenario B)
		shelf life	shelf life
single wrapping	1.95	2 weeks	2 days
double wrapping	162	3.1 years	0.4 years

in culture. The contamination was explained by inadequate storage conditions for donations which were given worldwide after the tsunami from health care facilities.

In summary, even a few bacterial cells can be the starting point of microbial growth and the origin of a hospital acquired infection even if the inoculated strain has low pathogenicity. The prevention through risk management of the compatibility of the sterile barrier system with the environmental airborne microbial challenge is the only method to avoid these sporadic and sometimes serious healthcare associated infections.

Data of the filtration efficiency against airborne microbes is a necessary and immediately comprehensible condition for risk management of porous packaging material, but it is normally not shown in the instruction sheets for packaging material. The barrier efficiency against airborne microbes frequently may not even be known. The reason is that different methods to determine the barrier properties are listed in ISO 11607-1 to demonstrate compliance with this standard. However, tests with airborne microbes or airborne particles are not prescribed explicitly as mandatory. When tests with airborne microbial challenge are not performed or this data is not given, a data based risk management and shelf life calculations are impossible.

5. Conclusion

The maintenance of the sterility of terminally sterilized items during the post-sterilization period requires a sufficient microbial barrier property of the packaging material. It is difficult, almost impossible to trace back sporadic device-associated infections to a loss of sterility of a single medical device as root cause. It is evident and necessary to comprehensibly ensure the compatibility of the barrier properties, i.e. the filtration efficiency, of the porous packaging components with the environmental challenge by airborne microbes. A quantitative data-based procedure is recommended for a risk management in order to assess the compatibility of the sterile barrier system with the environmental airborne microbial challenge. The recommended validation procedure confirms in a first approximation the proof of maintenance of sterility for the exposure of a sterile barrier system to specified environmental storage conditions. It corresponds to the requirements which are outlined in clauses of ISO 11607-1.

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Chefredaktion: Claudius Arndt. Sekretariat: Gudrun Below. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 75 25 94 00, Fax: +49 (0) 75 25 94 01 80. e-mail: redaktion@ecv.de. http://www.ecv.de. Herstellung: Reemers Publishing Services GmbH / Holzmann Druck GmbH & Co. KG.