Quality standards and applied risk management in sterile supply of medical devices and pharmaceutical products

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Topics

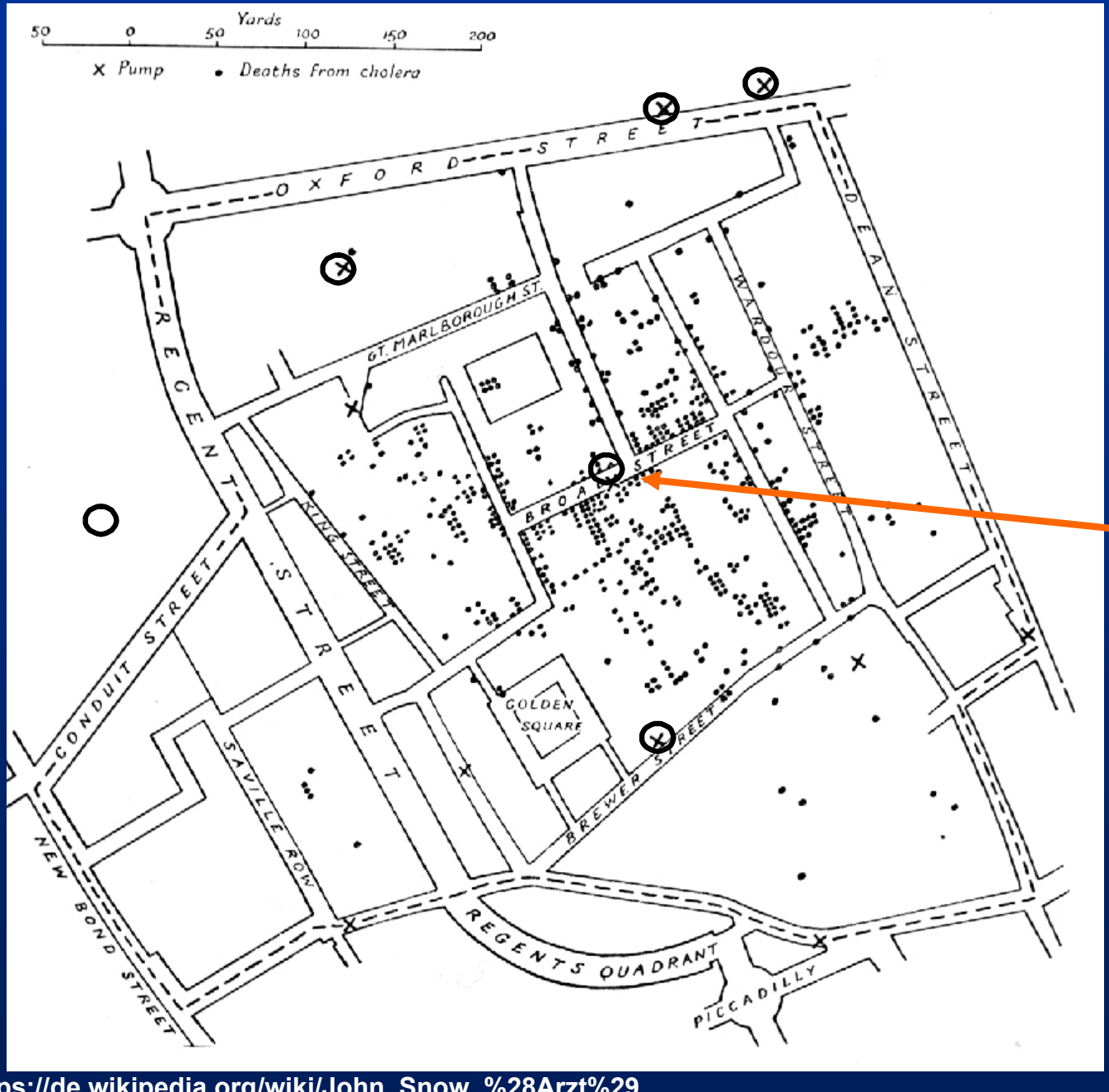
1. Example of establishing a quality standard in drinking water hygiene – a brief look back into history

2. Risk management by validation of maintenance of sterility of terminally sterilized products: compatibility of airborne microbial filtration efficiency of sterile barrier systems with airborne microbial challenge

3. Consequences of the validated shelf life calculation for the transport and storage of sterile products

4. Risk of infection when using sterilized products contaminated with a low count of environmental microbes

Example of establishing a quality standard in drinking water hygiene – a brief look back into history

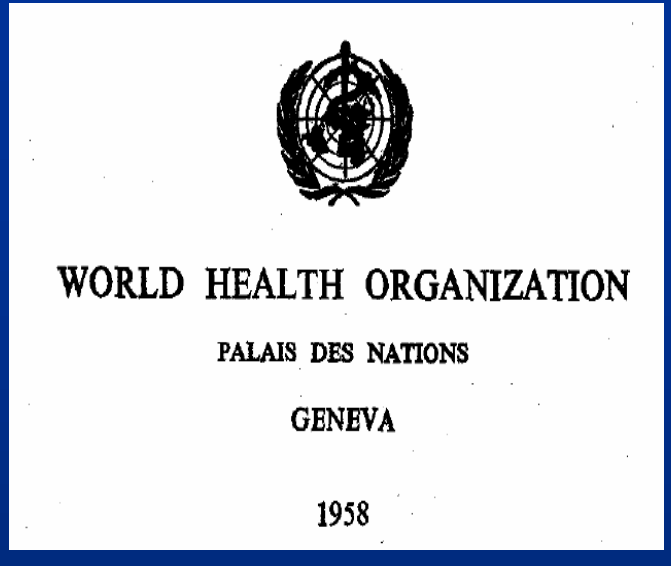


Snow's map of the 1854 London Cholera outbreak

Water pump Broad Street of London

https://de.wikipedia.org/wiki/John_Snow_%28Arzt%29

INTERNATIONAL STANDARDS FOR DRINKING-WATER



„Thus, the use of normal excremental bacteria as indicators of faecal pollution introduces a margin of safety.”

Risk management by validation of maintenance of sterility of terminally sterilized products: compatibility of the airborne microbial filtration efficiency of sterile barrier systems with the airborne microbial challenge

Sterile: state of being free from all living microorganisms (EN 556-1: 2001)

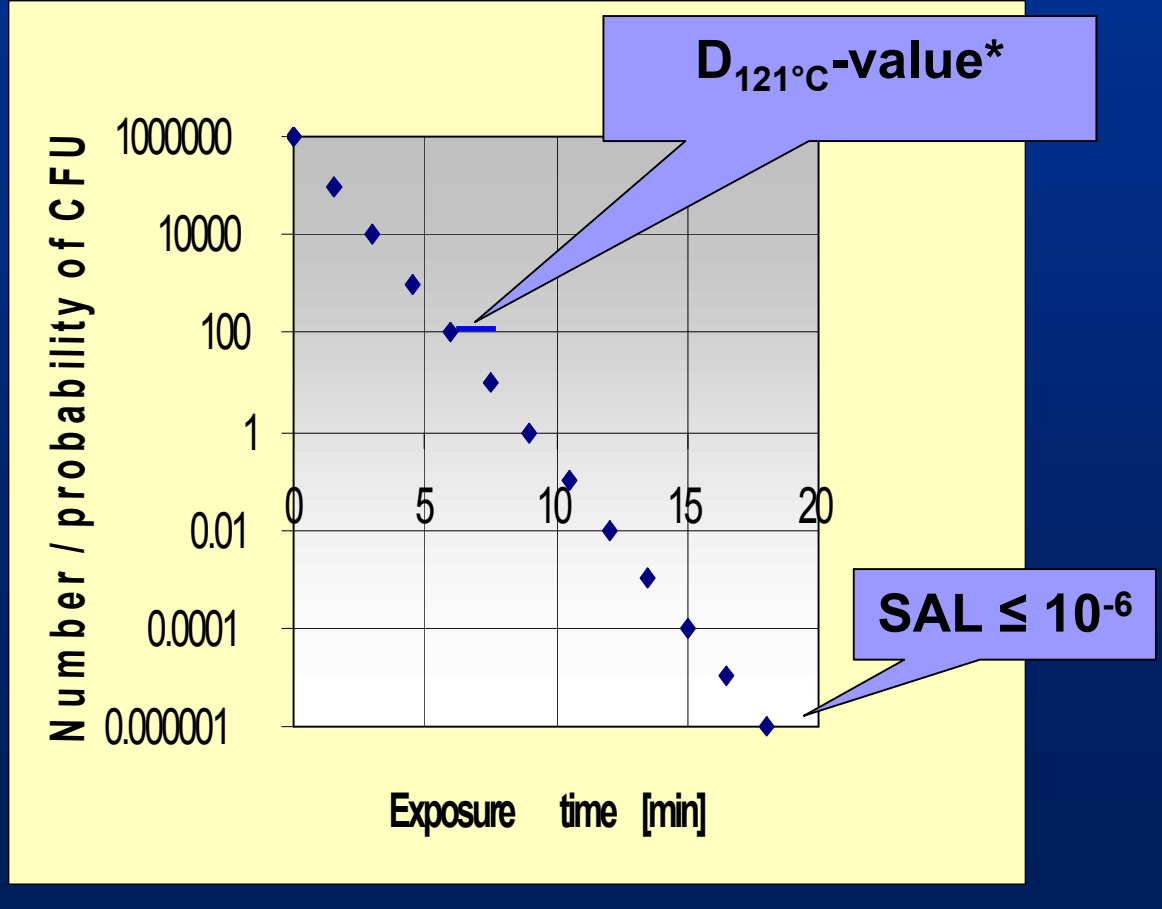
"For a terminally-sterilized medical device to be designated "sterile", the theoretical probability of there being a viable microorganism present on/in the device shall be equal to or less than $1x10^{-6}$."

= Sterility Assurance Level (SAL) of 10^{-6} *

*CDC: Guideline for disinfection and sterilization in healthcare facilities, 2008

Initial sterility provided by inactivation kinetic during steam sterilization process

CFU = colony forming units



***$D_{121°C}$-value= decimal reduction time for steam sterilization**

Food and Drug Administration, February 2008

Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products

conclusions that may be derived from the results. Because of the limitations of sterility tests described below, sterility tests are not recommended as a component of a stability program for confirming the continued sterility throughout a product's shelf life or dating period. Alternative methods may be more reliable in confirming the integrity of the container and closure system as a component of the stability protocol for sterile products.

ISO 11607-1

5.2.2

Demonstrating that the material is impermeable shall satisfy the microbial barrier requirement.

5.2.3

“Porous materials shall provide an adequate microbial barrier to microorganisms in order to provide integrity of the sterile barrier system and product safety.” *)

*ISO 11607-1, 2006, subclause 5.2.2

ISO 11607-1

"the conditions under which the … preformed sterile barrier system are handled shall be established, controlled and recorded…to ensure that the conditions are compatible with the use for which the material and/or sterile barrier system is designed … .": *)

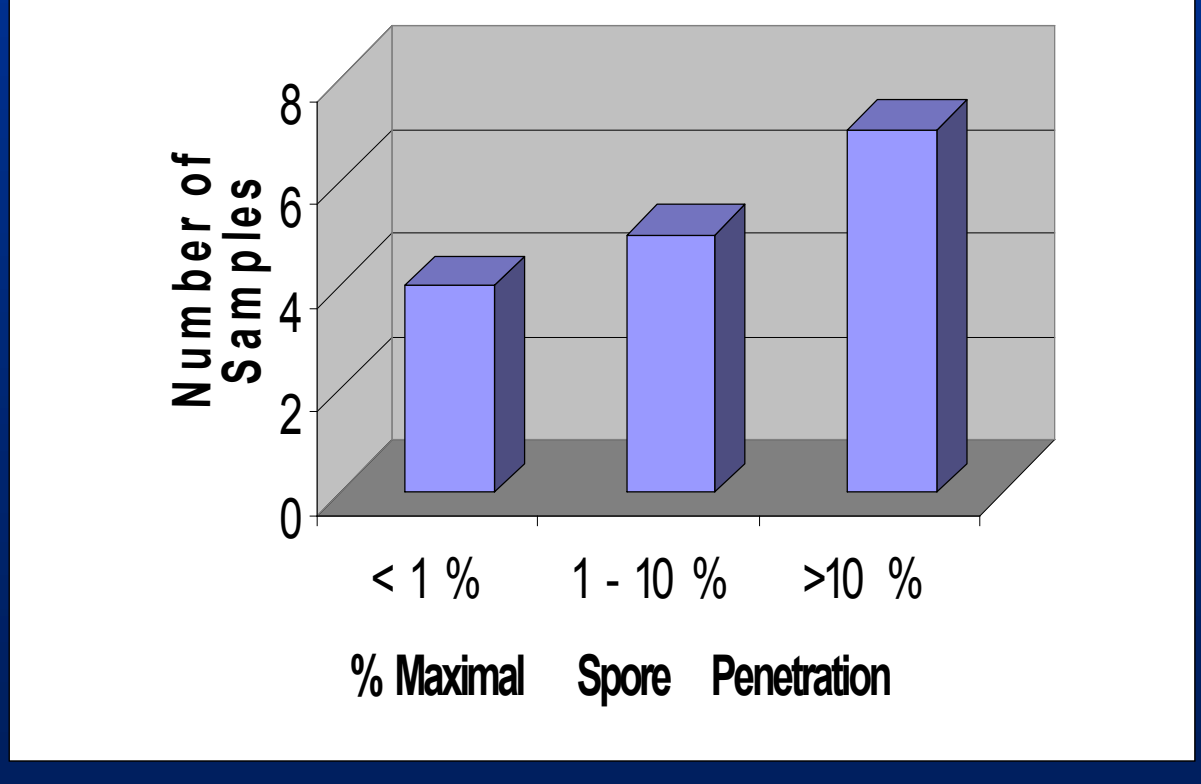
- Temperature range
- Pressure range, …
- Maximum rate of change of the above. …
- Bioburden.

The property of the microbial barrier of the packaging material shall be evaluated.

*) ISO 11607-1, 2006, subclauses 5.1.3 - 5.1.6

Microbial barrier efficiency: 16 commercial porous medical packaging materials*

$10^3/cm^3$ airborne bacterial spores; flow rate of 2 cm^3 min^{-1} cm^{-1}



* Sinclair CS, Tallentire A 2002 PDA J Pharm Sci Tech 56:11-19

Validation of the compatibility of the sterile barrier system with the airborne microbial challenge

Performance parameter

Airborne microbial retention capacity

Relevant factors to be considered

Level and relevant sizes of airborne particles bearing microorganisms

Flow rate of air through the layers of packaging material

Validation of the compatibility of the sterile barrier system with the environmental challenge by airborne microbes

p x V = const.

Volume flow based on air pressure change:

Volume flow based on temperature change:

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

Calculation of compatibility:

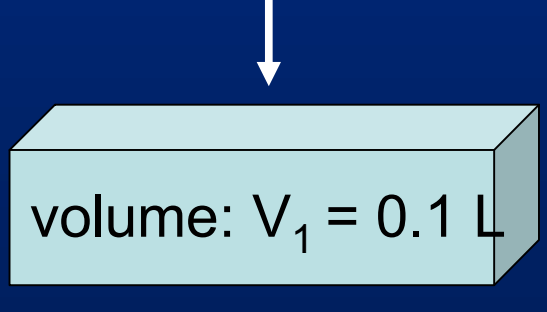
$$N_o \times \frac{100 - Filtration\ efficiency\ (\%)}{100} \times n \leq 10^{-6}$$

n = number of events compatible with SAL

Airborne bioburden (< 3 µm):
20 CFU/m³

Room temperature: 20 °C

Filtration efficiency: 99.6%

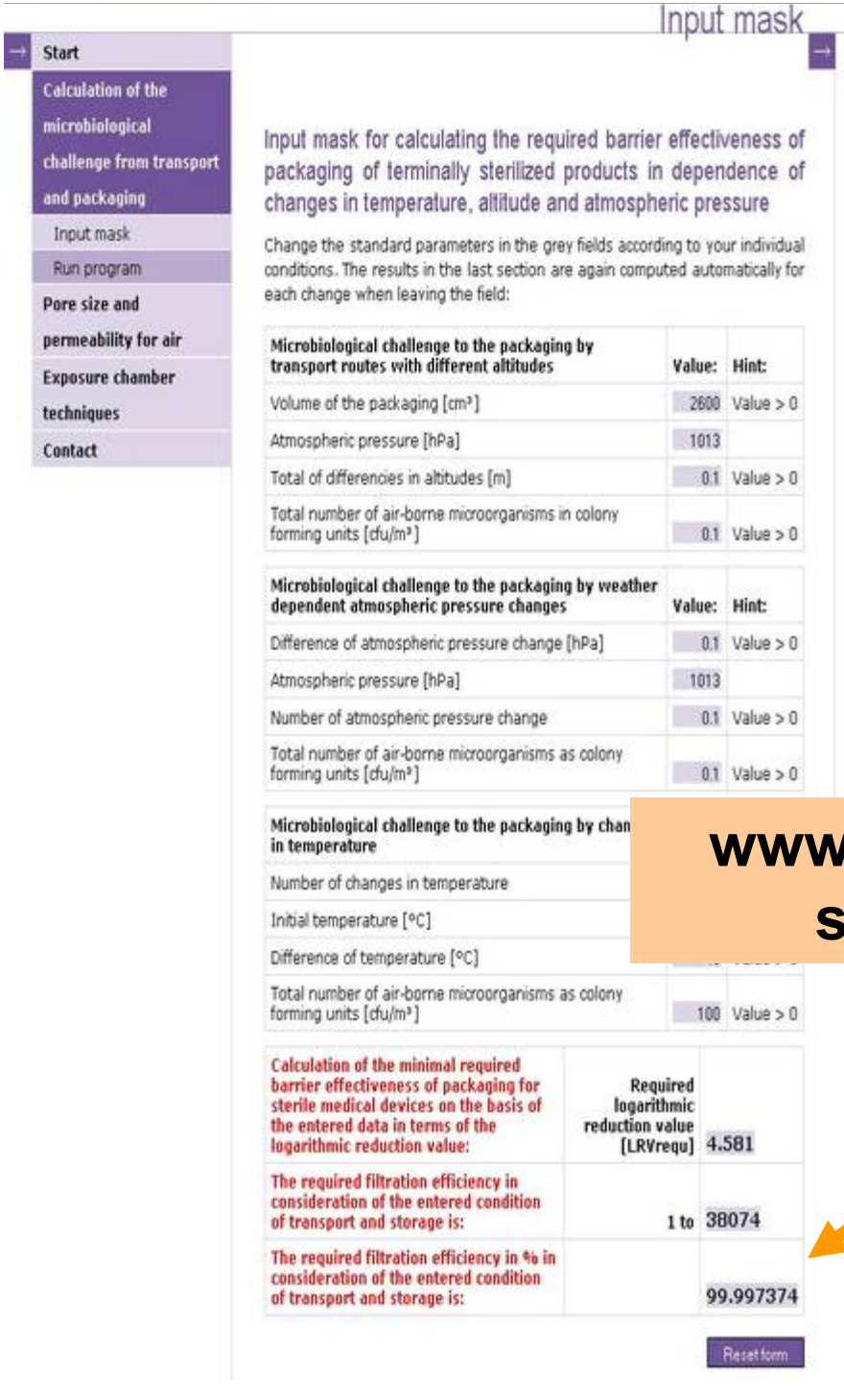


Microbial challenge per event:
$N_0 = \Delta V_{t+p}$ x 20 CFU/m³

number of events per week		
	scenario A	scenario B
Δt = 2 °C	1	7
Δp = 10 hPa	1	7
bioburden sized < 3 µm	20 CFU/m³	20 CFU/m³

Calculation of the number of events (n) and shelf life compatible with the SAL (package volume: 0.1 L; filtration efficiency per wrapping layer: 99.6%)

wrapping method	number of events (n)	1 event per week scenario A	7 events per week scenario B
		shelf life	shelf life
single wrapping	7.5	7.5 weeks	1 week
double wrapping	1871	36 years	5.1 years



www.microbiological-evaluation-of-sterile-barrier-systems.com/

required filtration efficiency

Consequences of the validated shelf life calculation for transport and storage of sterile products

- Low variations of temperature and low rates of their changes reduce the microbial challenge,
- Transports (containership, transport plane) with relevant temperature changes and atmospheric pressure changes raise the microbial challenge,
- Outsourcing of sterilization can increase the risk of recontamination through transport routes with convulsions, temperature variations, changes in air pressure (different altitudes).

Annex B: “Standardized test methods and procedures that may be used to demonstrate compliance with the requirements of this part of ISO 11607-1”

DIN 58953-6:2010: subclause 2.15: Testing for germ proofness with passage of air

Mixture of 0.25 g quartz powder (40-150 µm) and bacterial spores (2.5×10^5 CFU)

Acceptance criterion (pass/fail decision):
≤ 15 CFU/ 10 samples

Quality standards for drinking water and medical packaging material

WHO 1958

"That water intended for human consumption must be free from chemical substances and micro-organisms in amounts which would provide a hazard to health is universally accepted."

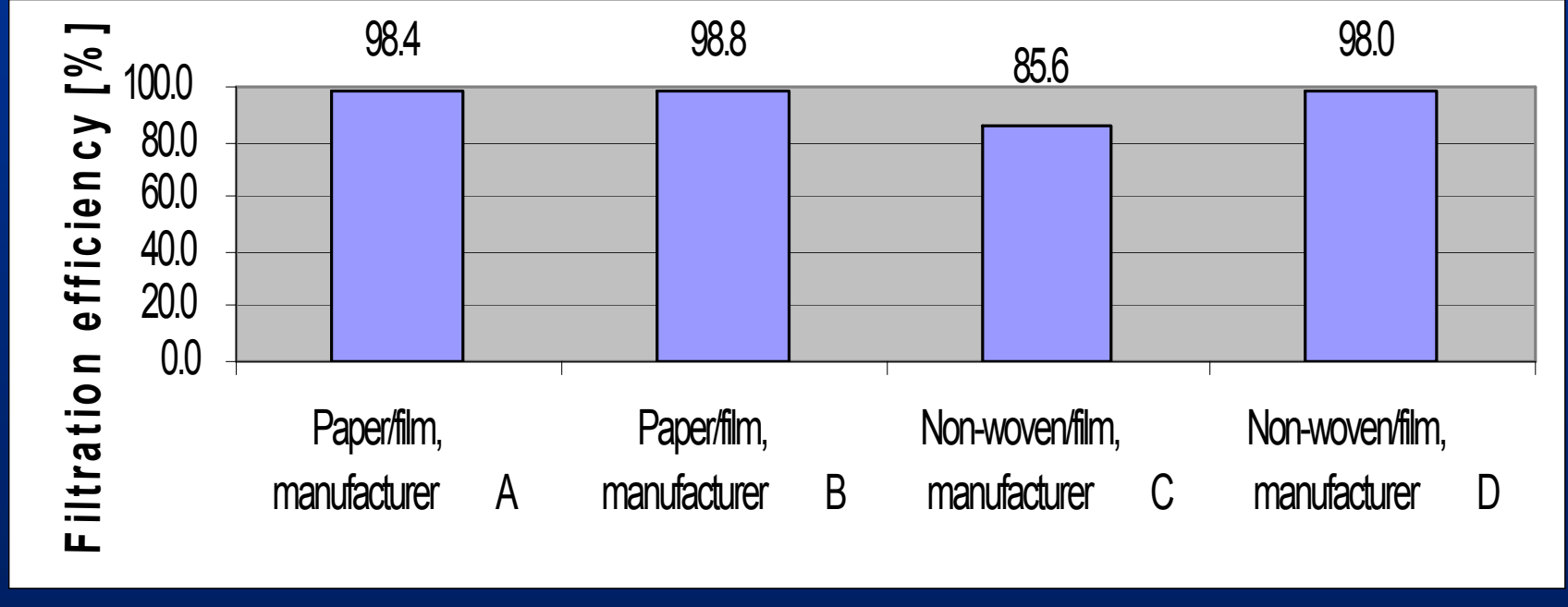
„… that coliform organisms be absent from each 100-ml sample of water entering the distribution system."

ISO 11607-1:2006:

"5.2.3 Porous materials shall provide an adequate microbial barrier to microorganisms.

… . There is no universally accepted method of demonstrating microbial barrier properties."

Capacity of 4 types of pouches (15x15 cm) to remove airborne microbes (30 pouches per group) *



*) presented by H. Dunkelberg on 14th World Sterilization Congress & 8th National Sterilization Disinfection Congress of Turkey, 6-9 November 2013, Antalya, Turkey

Risk of infection when using sterilized products contaminated with a low count of environmental microbes

Infection/outbreak	Cause	Remarks
Aspergillus meningitis outbreak in 2 hospitals in Sri Lanka after spinal anaesthesia for caesarean section [1]	"sub-optimal storage of sterile devices for over 6 months after tsunami was most plausible reason"	No infections when syringes are used for other injections. Unopened syringes showed growth.
Outbreak with 80 cases of BSI in 6 US states after use of heparinized saline flush syringes [2]	Syringes were prepared as compounded medical products.	P. fluorescens was identified in unopened syringes; The specific source of contamination could not be identified.
Exposure to propofol in 7 hospitals was associated with postoperative infections[3]	Risks: "use syringes of propofol that had been prepared up to 24 h beforehand", "prepare multiple syringes …at one time for use throughout the day."	

1) Guaratne et al.: Ceylon Medical Journal 2006;51:137-42; 2) Gershman et al.: Clinical Infectious Diseases 2008;47:1372-9
3) Bennet et al.: N Engl J Med 1995;333:147-54

Recommendations for parenteral applications to reduce the risk of microbial growth

- From a microbiological point of view, the product should be used immediately[1]
- Replace tubing used to administer blood, blood products, or fat emulsions (…) within 24 hours of initiating the infusion[2]
- Propofol: use strict aseptic technique … discard within 12 hours of opening[3]

[1]) CPMP (Commitee for proprietary medicinal products), 1998
[2]) CDC, 2011: Guidelines for the prevention of intravascular catheter-related infections
[3]) Labeling text of the manufacturer

Sporadic device-associated infections caused by compromised packaging integrity are difficult to identify

- because the microbiological status of the unopened device can no longer be examined,
- because the cases occur isolated in time and location.

Summary

- The establishment of suitable standard methods as mandatory for testing the airborne microbial filtration efficiency is a precondition for assessment sterility up to the point of use.
- The assessment of the compatibility of sterile barrier system with the environmental airborne microbial challenge can help prevent hospital acquired infections.
- A suitable Sterility Maintenance Policy should be practised consistently according to International Standards.

Thank you for your attention