⟨1229.15⟩ STERILIZING FILTRATION OF GASES

INTRODUCTION

Gases, such as compressed air, nitrogen, and atmospheric gases that contact sterile components, containers and closures, and product contact surfaces of processing equipment, such as tanks and piping, must be sterile to prevent contamination of pharmaceuticals and biopharmaceuticals. The sterilization of gases is typically accomplished by passing the gas through one or more sterilizing-grade membrane filters. The filtration process must be designed to ensure that the filtered gas has been sterilized.

GAS VERSUS LIQUID STERILIZING FILTRATION

Sterilizing Filtration of Liquids ⟨1229.4⟩ contains information that is applicable to this chapter, including but not limited to sterilizing-grade filters, retention mechanisms and factors affecting retention, validation, integrity-testing principles and methods, and prefiltration bioburden control. The significant differences between liquid and gas filtration will be discussed in this chapter.

MEMBRANES FOR GAS STERILIZATION

Filters used for sterilization of gases are commonly hydrophobic membranes, although hydrophilic membranes can be employed where membrane wetting during use is not an issue. Wetting may be a factor with filters used for autoclave venting and where vent filters are required to maintain the sterility of tank headspace. Microporous filter membranes that have a pore-size rating of NMT 0.2 µm, which meets the ASTM International standard (see F838-15a *Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration*), are suitable for the sterilization of gases; in fact, these filters are considerably more retentive for gases than for liquids (*1*). Additionally, the filters must be chemically compatible with the gas to be filtered and physically compatible with the filtration conditions (e.g., pressure differentials and flow rates).

RETENTION MECHANISMS

The primary retention mechanisms of membrane filters used in gas sterilization are size exclusion, impaction, diffusional interception, and electrostatic attraction. Size exclusion is effective for particles (microorganisms) that are too large to pass through the pore structure of the filter membrane and is essentially independent of the velocity of gas flowing through the filter. Retention mechanisms other than size exclusion can be effective for particles smaller than the pores they encounter. Retention due to impaction, diffusional interception, and electrostatic attraction is dependent on particle size, flow rate, and relative humidity. For example, particle retention efficiency due to impaction is proportional to the mass of the particle; heavier particles have a greater momentum than lighter ones and are therefore more likely to contact pore walls and subsequently be retained by the filter during tortuous flow. In contrast, the capture efficiency of diffusional interception is inversely proportional to particle size and velocity. Smaller particles influenced by Brownian motion can exit the streamlines, contact the filter matrix, and be retained, and lower velocity increases potential contact time and improves capture efficiency. Electrostatic attraction of particles is reduced by a high relative humidity in the filtered gas. Adsorption, which can be important in liquid filtration, is not a retention mechanism for gases.

VALIDATION

Validation of the processes used in sterilizing filtration for gases, in general, may be divided into two parts: sterilization of the filter and its housing, and the ability of the filter to remove microorganisms from the filtered gas.

Sterilization of the filter and its housing has been addressed specifically in ⟨1229.4⟩ and *Sterilization-in-Place* ⟨1229.13⟩, and generally in *Sterilization of Compendial Articles* ⟨1229⟩.

Membrane filters meeting the requirements of ASTM F838-15a are suitable for sterilizing filtration of gases in terms of microbial retention. Liquid bacterial challenge testing represents a worst-case condition for sterilizing gas filters because the retention efficiency in liquids is lower than in gases (*2*).

INTEGRITY TESTING

Integrity testing requirements and techniques are discussed in ⟨1229.4⟩. The hydrophobic filters typically used for gas filtration can be integrity tested using bubble-point, diffusive-flow, and pressure-hold tests that use a liquid of low surface tension to completely wet the pore structure of the filter membrane. Additionally, integrity testing can be performed by measuring the membrane's resistance to wetting with water as a function of pressure. Water intrusion testing is an example of this type of integrity testing.

REFERENCES

1. Liu BYH, Rubow KL, Pui DYH. Performance of HEPA and ULPA filters. Proceedings, Annual Technical Meeting—Institute of Environmental Sciences. 1985 Apr 29–May 2; Las Vegas, NV.
2. Parenteral Drug Association. Sterilizing filtration of gases. Technical Report No. 40. *PDA J Pharm Sci Technol*. 2005;58(1 Suppl TR40):7–44.