Life Sciences

## Application Note

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# Safety Considerations for Gas Filtration in High-Temperature and Oxygen Enrichment Applications

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Gas filtration using sterilization-grade filters is a key part of the production, manufacturing and packaging process of biopharmaceuticals and other products. While it may seem a simple step, there are major safety considerations that have to be taken in to account to protect staff, equipment and facilities from hazard, particularly when working in high temperature and oxygen enrichment applications.

## The Need for Gas Filtration

Sterilizing gas filters are used in high temperature air and oxidizing gas applications including:

- High temperature air applications include autoclave, fermentation inlet air, aseptic packaging/blow-fill-seal and hot Water For Injection (WFI) tank vents
- Oxidizing gas applications include ozonated water tanks, high temperature and ozonated-water venting, and oxygen enrichment of air for bioreactors

These gas or air filters typically consist of a polypropylene core, cage and end-caps, with polypropylene drainage layers, surrounding and supporting PTFE filter membranes.

### Oxygen Enrichment of Bioreactors

Bioreactors are used for the production of proteins, peptides and other biologics from cultured mammalian, bacterial and yeast cells for biotechnology and biopharmaceutical applications. The cells are cultured in a nutrient rich broth. As the cells produce more and more metabolite, the mixture of cells, fermentation media and end products proteins becomes thicker, making it harder for essential supplies of oxygen to reach the cells. One approach is to bubble pure oxygen or oxygen-enriched air through the mixture. This increased supply of oxygen can improve cell densities and increase the yield of often very high value products.

The gases introduced into bioreactor systems must be of very high levels of purity to protect the cultures from bacteria and other contaminants. An option is to use liquid challenge-validated sterilizing grade filters to remove impurities. The gas then escapes from the bioreactor through a vent fitted with a second gas filter. This prevents the culture from becoming contaminated, reduces loss of fermentation media, and protects operators and the environment from escaped live cells or microorganisms. This latter precaution is especially important when dealing with genetically-modified organisms (GMOs).

### Ozonated Water Tanks

When ozone is dissolved in water it creates a potent and very fast-acting antimicrobial agent, and is used in part of the process to manufacture water for injection (WFI) and purified water[1]. The ozone, or its breakdown product, oxygen, is then vented through a filter. The resulting sterile purified water and WFI is stored in high purity water holding tanks. Sterilizing-grade entry and vent filters ensure that the stored water remains protected from contamination from particulates or bacteria.

## The Safety Issues

One of the safety issues with gas filtration systems for oxygen, ozone or oxygen-enriched air is the risk of fire. The fire triangle describes the three components that are required for combustion – fuel, heat and an oxidizing agent. A fire can start if all three of these are present in the right proportions, and will continue until the fuel is exhausted or the fire is extinguished[2].

Gas filtration systems can provide all three components. Gases such as oxygen and ozone are oxidizing agents, and high levels increase the risk of organic materials, plastics and polymers, and even metals, catching fire. Materials used for filters, for example polypropylene filter supports and drainage layers, can fuel a fire, as can organic contaminants on the filter, including dust from the air and fibers from clothing, and lubricants and sealants used on or around the filter cartridge.

Polypropylene components have a low oxygen index, meaning that low oxygen concentrations can support combustion. A low auto-ignition temperature makes them more likely to catch fire, and their high heat of combustion could cause serious damage to the surrounding equipment, and be hazardous for operators.

While materials like PTFE (polytetrafluoroethylene), used for filters, are much less flammable, the surface of the filter can become hot and this could trigger ignition of the polypropylene hardware in the filter. The surface area of the filter can build up a static charge, and when this is discharged it can also trigger a fire. Alternatives to PTFE filters that would avoid the static issue include metal filters, but these are not validated for liquid sterilization, and cannot be tested by the water intrusion test (WIT), a standard tool to assess the in situ integrity and bacterial retention rate of a filter. All-fluorocarbon filters also have potential, but these are very expensive.

Inorganic particles on the filters, for example rust or pipe scale deposited from steam cleaning lines also have potential to increase the risk of static discharge, and the particles themselves may also combust if temperatures are high enough. Because of this it is vitally important to ensure that the environment is kept as clean as possible. Steps to this include working in a clean environment, as well as ensuring that operators wear appropriate clothing, and are trained in appropriate handling techniques and cleaning steps for the gas and air filters and any other equipment.

Fire isn't the only safety issue, however. Because oxygen and ozone are highly oxidizing, they can damage the filter cartridges, particularly the filter supports, used in the gas inlets and vents. As inlet air or WFI vent filters may be held at 80-120 °C, and as the air flows through the filters under some degree of pressure, this can accelerate the damage process.

Filters that are damaged by oxidation are less effective and could allow genetically modified organisms to escape, putting operators at risk. They could also allow otherwise sterile products to be contaminated, which if not detected could be hazardous, particularly for vulnerable patients. Oxidized filters will need to be replaced more often, and the corrosion process could create particles which may also contaminate products, potentially meaning that that production lines have to be halted or finished products discarded.

## Building a Better Filter

To deal with these kinds of environments, filters need to be specially designed. The ideal filter would have a sterilizing-grade membrane, and the filter, supports and hardware manufactured from non-oxidizing and/or antioxidant materials in a controlled environment.

Pall's solution has been to create its range of Emflon HTPFR filter cartridges based on a proprietary hydrophobic 0.2 µm sterilizing grade, double layer PTFE filter membrane. This is held within support and drainage layers made from oxidation-resistant polyphenylene sulfide (PPS) polymer and surrounded by polypropylene hardware that incorporates antioxidants, and can remain stable under heat exposure. The filter cartridges can be used in inlets and vents up to 100°C for longer periods, and up to 120°C for shorter periods.

In more extreme environments, or where more-exacting particle removal ratings are needed, the PTFE filters can be replaced with all-fluoropolymer or metal filters.

The filters are validated using liquid bacterial challenge tests and water intrusion tests. The filters have been designed to comply with ISO 9001-certified quality management system requirements, and meet cGMP sterilizing-grade filter requirements. They are manufactured meeting ISO Class 8 room standards and Pall's internal manufacturing and quality controls.

## References

1 Cohen, N. Understanding Dissolved Ozone and its Use in Pharmaceutical Water Systems. Pharmaceutical Engineering. May 2013. Available from: www.ispe.org/knowledge-briefs/dissolved-ozone.pdf

2 A Reporter's Guide to Fire and the NFPA: All About Fire. National Fire Protection Association. Last Accessed: 7 February 2015; Available from: http://www.nfpa.org/press-room/reporters-guide-to-fire-and-nfpa/all-about-fire

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