Application Summary

Filter Use for Bioburden Reduction and Sterilization in Drug Formulation and Filling

The absolute necessity of assuring a sterile product in pharmaceutical drug manufacturing is most often accomplished by employing bioburden reduction and/or sterilizing filters at critical points in both upstream and downstream processes. Using the proper filters will ensure product quality and patient safety. This application summary addresses the different roles, locations and choices of process filters designed to reduce and/or remove bacteria in drug production.

Sources of Bacteria

Bacteria can enter a process stream in different locations and from multiple sources.

- Ingredients brought into the facility may be contaminated
- Delivery systems for these ingredients might not be adequately sterilized
- Bacteria may be present in the water used in manufacturing
- Maintenance operations (filter change, component replacement, etc.)
- Plant air - even in clean rooms - may have airborne bacteria

Installing the appropriate filters at each step of the process can reduce or eliminate bacteria buildup, while sterilizing filters installed at the filling step ensures complete removal of bacteria from the product.

Upstream Processes

Upstream processes are everything leading into the formulation tank.

- Delivery of bulk liquid ingredients
- Storage of ingredients
- Transfer of ingredients into the formulation tank
- Water treatment for use in the final formulation
- Compressed gasses

Depending on criticality, upstream processes may employ either bioburden reduction or sterilizing filters. To decide which, several factors must be considered:

- Likelihood of bacterial contamination in products delivered from a vendor
- Level of contamination that might be encountered
- Adequacy of cleaning/sterilizing procedures for the delivery and holding tank system
- How much of a burden might be placed on downstream sterilizing filters if a bioburden reduction filter is employed
- How conducive the formulation is to bacterial growth? If bacteria can easily propagate in the product, then a sterilizing filter is the best choice. If not, a less expensive bioburden reduction filter could be employed.

Prefiltration requirements - whether incorporated as a layer in the bioburden reduction / sterilizing filter or as a stand-alone filter - also need to be assessed to optimize process performance and filter costs.

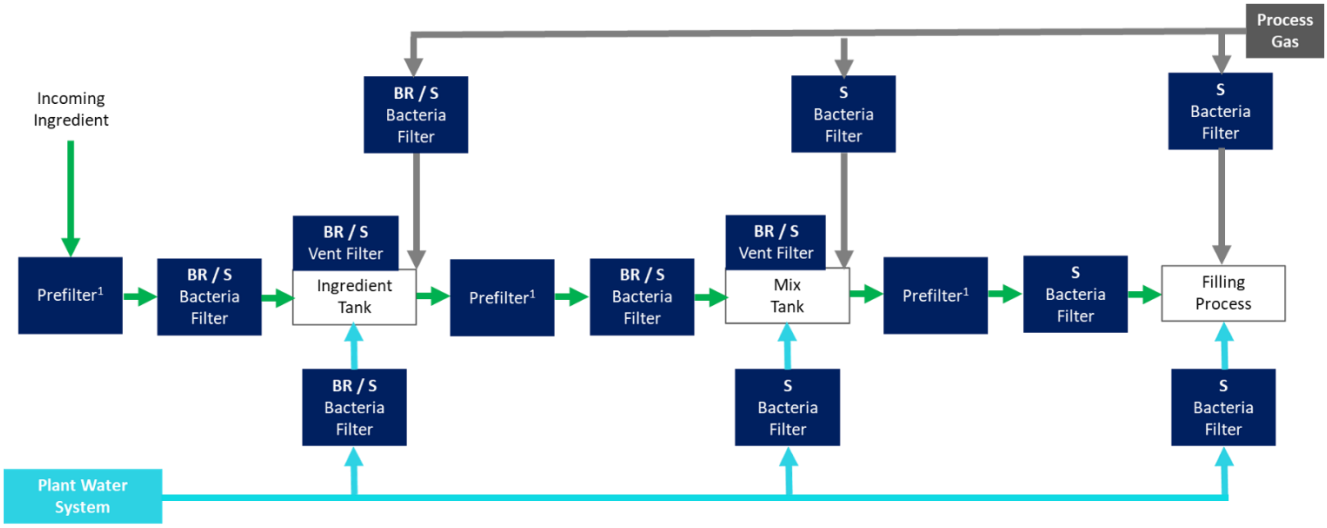
Downstream Processes

Downstream processes are everything between the formulation tank and the filling system. Unless an alternate disinfection method is employed (heat sterilization, addition of a preservative, etc.) these processes will always require sterilizing filters.

- Sterile filtration of the formulated product
- Water used to wash and sanitize the filling system and other downstream components
- Compressed process gasses

Typical Process Steps

The diagram below shows typical process steps utilized for drug formulation and filling and location of proper filters.



[1] Prefilter optional; May be incorporated as a layer in BR/S filter, **BR** denotes Bioburden Reduction, **S** denotes Sterilizing

Ingredient Delivery

Filtration is used for ingredients used in drug formulation ranging from bulk liquid chemicals (solvents, buffers, etc.) to small volume powders. Installing bacteria removal filters on incoming chemical lines will help prevent continued growth in storage tanks, and will reduce the load on more critical downstream sterilizing filters. The diagram above shows a single Incoming Ingredient line, but there may be multiple lines for a given process. Each line should be individually assessed for the proper filters to be used.

Ingredient Holding Tank(s)

After consideration of the factors discussed under *Upstream Processes* above, it may be desirable to install filters in the transfer lines from the holding tanks feeding into the formulation mix tank. This will be especially important if the formulation will support continued bacteria growth.

Formulation Mix Tank

After the formulation is prepared in the mix tank, sterile filtration is required for the filling and packaging steps. This filter, along with any required prefiltration, must be installed in accordance with in-line sterilization and integrity testing requirements.

Tank Vent

All tanks must be protected with a proper vent filter. These hydrophobic filters allow air to exit the tank during filling, and more importantly prevent bacteria from entering the tank during transfer of contents. The same considerations for deciding between bioburden reduction or sterilizing filters outlined under *Upstream Processes* above also apply to proper selection of vent filters.

Water Purification

Water used in formulating the product or for cleaning/sanitization the process must be properly filtered. Point-of-use filters are installed to ensure any potential bacteria contamination in the plant water system is reduced or removed as necessary.

Pressurized Gas Lines

Any pressurized gasses used in the process must be filtered. Sterilizing grade hydrophobic filters are installed to prevent potential bacteria contamination in the pressurized gas lines from entering the process.

Choosing the Right Filters

Absolute rated membrane filters with pore size 0.22 microns or less are considered to be sterilizing.

Depending on the application or nature of known potential contaminants, 0.1 micron filters can also be employed. Critical Process sterilizing filters have been validated for > 7-log bacteria removal following ASTM-838-15 protocols. CPF will provide a validation guide for the filter(s) chosen documenting test results for bacteria retention, and information regarding filter construction, biosafety and performance. The final choice of pore size often requires validation testing in the actual fluid to be processed and CPF provides that service.

The filter(s) selected must be compatible with the fluid being filtered and process disinfection/sterilizing methods. The filter(s) must be capable of removing target organisms without affecting the composition or activity of the fluid being filtered.

Conclusion and Summary

Drug formulation and filling requires multiple steps, each of which present an opportunity for bacteria to enter the process. Installation of the proper Prefilter, Bioburden Reduction and Sterilizing filters will ensure product sterility, guaranteeing product quality and patient safety. Critical Process Filtration provides validation services and supplies a wide range of filter materials and configurations allowing optimization of your filtration process while minimizing filtration costs. For more information, please contact the Critical Process Filtration Technical Service team.

Cartridge, Capsule & Laboratory Filter Options for Bioburden Reduction and Sterilization in Drug Formulation and Filling

Prefilter Options

- PPD (polypropylene depth filter)
- PGD (fiberglass depth filter)
- BCWPS (high capacity PES)

Bioburden Reduction Options (liquid)

- BPS (PES membrane; High capacity PES prefilter layer optional)
- BNM (Nylon 6,6 membrane)
- BPVWL (PVDF membrane)

Bioburden Reduction Options (gas)

- BTM (PTFE membrane)
- BPVWB (Hydrophobic PVDF membrane)

Sterilizing Options (liquid)

- PPS (Dual layer PES membrane)
- SPS (Single layer PES membrane)
- HPPS (PES membrane with high capacity PES prefilter)
- PNM (Nylon 6,6 membrane)

Sterilizing Options (gas)

- PTM / PTR (PTFE membrane)

Validation

- 0.22 micron membrane filters are validated for > 7-log reduction of Brevundimonas diminuta
- 0.1 micron membrane filters are validated for > 7-log reduction of Brevundimonas diminuta and reduction of Acholeplasma laidlawii (mycoplasma)
- 0.03 micron membrane filters are validated for > 7-log reduction of Acholeplasma laidlawii (mycoplasma)

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