A QBD Perspective: Sterile Filtration Process For Sterile Pharmaceutical Drug Products

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FDA and EMA Regulatory Requirements

- The Committee for Proprietary Medicinal Products (CPMP) Guidelines EU Annex 1 (2009) recommends use of dual filtration systems using two 0.2 μm filter membranes
- The FDA's Aseptic Guide (2004) recommends the use of redundant or serial 0.2 μm rated membranes respectively
- The EMA-CPMP Guidance on Manufacture of the Finished Dosage Forms (1996) states " the maximum acceptable bioburden prior to sterile filtration must be10CFU/100 mL, if this requirement is not met, it is necessary to use a pre-filtration through a bacteria retentive filter"
- PICS guidance(2010), bioburden limit prior to sterile filtration should be justified

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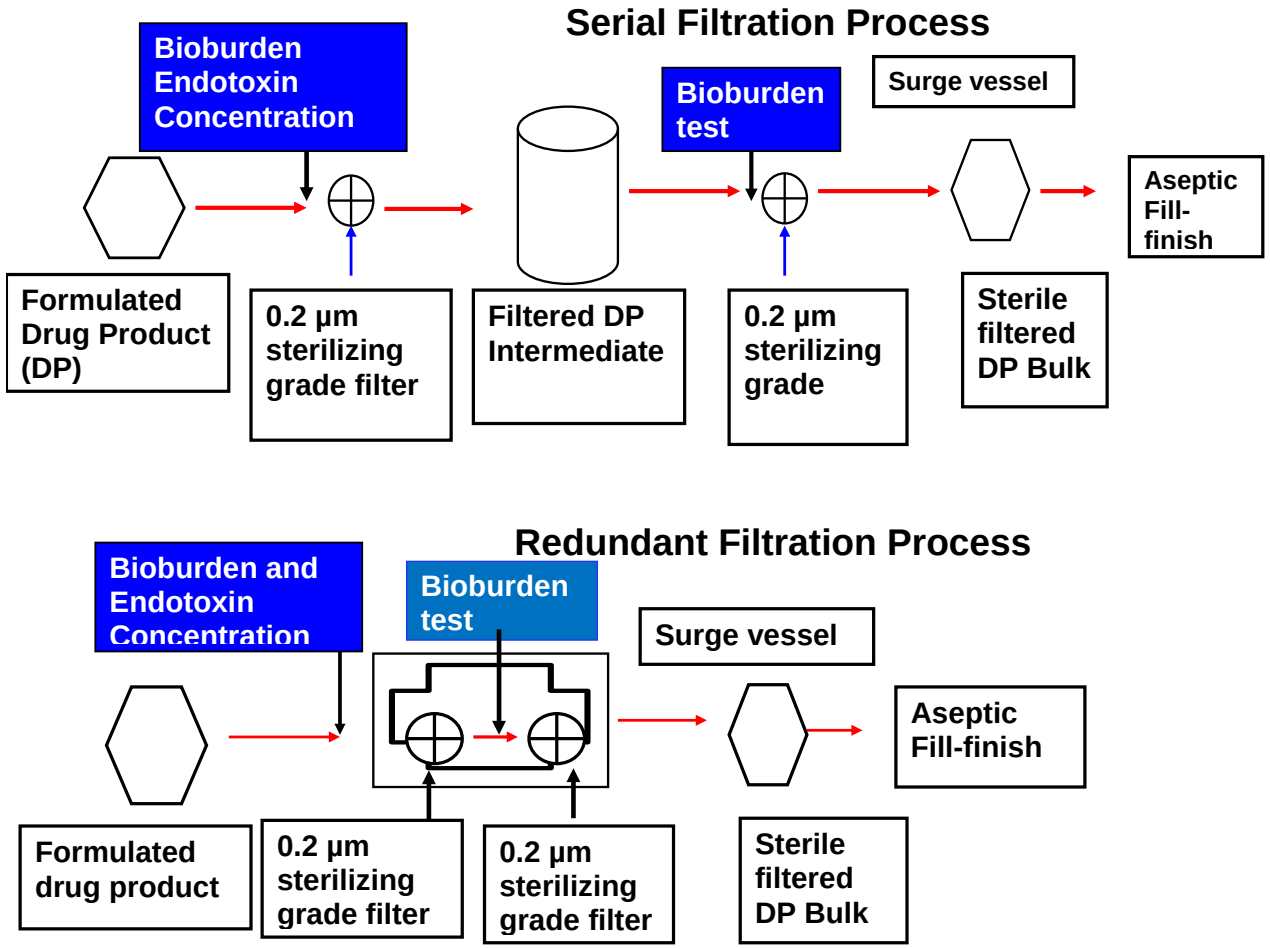
Multi-filter Arrangements Provide Pre-filter and Final filter Effect To Produce Sterile Filtrate

- Two filter arrangements are commonly used



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Serial Filtration Multi-filter Arrangement Offers Significant Advantages Over Redundant Filtration

Serial Filtration	Redundant Filtration Process
The Serial Filtration produces the same result as redundant filtration.	Redundant Filtration does not double the LRV.
Provides better overall process control since the filter integrity data for the first filter is available before sterile filtration	Integrity testing of the redundant filtration is not possible until the filling operation is complete.
Significantly minimizes the risk of bioburden build-up prior to sterile filtration by assuring that the inherent bioburden is removed or significantly reduced.	May not be possible in all cases.
Improves bioburden characterization, understanding of bioburden control, biburden build-up risk and pre-sterile filtration bulk hold time since tank containing filtered DPI can be incubated at 2-8°C for microbial control.	May not be possible in all cases due to lack of separation with the sterile filter.
Ease of reducing the distance between the sterilizing filter and fill machine.	May not be possible in all cases.
Provides opportunity to better optimize manufacturing resources, capacity and cost	May not be possible in all cases.
May not be possible.	May reduce cost of bioburden testing.

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Factors Affecting Microbial Retention

- Product chemical nature and formulation
- Pore-size rating and membrane material, filter capacity
- pH, viscosity, osmolality, surface tension and temperature (T_{max}) Absolute Pressure or Maximum filtration pressure (P_{Max}) and Differential pressure (ΔP)
- Flow rate/unit surface area (flux)
- Upstream bioburden quantity and composition
- Volume of the Liquid (throughput)
- Product hold time
- Filter Flush Volume (filter wetting) and Product Flush

Filter compatibility, characterization, and sizing studies should be performed to select right filter for ensuring the filtrate sterility

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Sterile Filtration Performance Parameters: Parameter Definitions

- **Non-key Performance parameters:** These parameters do not assure process consistency. Variables are shown to be well controlled within wide range and at extreme of the range may have an impact on process performance. Have low influence on the bioburden control on the subsequent steps
- **Key Performance parameter:** Ensures operation reliability when maintained in a narrow range and have significant bioburden controls capability. May impact on control on the subsequent steps. These parameters assure consistency
- **Critical Performance parameters:** Ensure operation reliability within a very narrow range. A variation beyond the narrow range affects product quality and have no further processing steps that can control the bioburden

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Drug Product Sterile Filtration Operating and Performance Parameters Classification

- Operating Parameters

Non-key	Key	Critical
Viscosity[1]	Volume of liquid to be filtered	Absolute pressure
Temperature[2]	Minimum volume of wetting fluid	pH
	Bioburden prior to filtration	Product API concentration
		Minimum volume of formulated drug product flush

1 Viscosity is a drug product characterized parameter
2 Temperature is a non-key due to wide range of control (4-20°C)

- Performance Parameter

Non-Key	Key	Critical
Temperature (T_{max})	Bioburden content	Filter integrity
	Filtration time	Product specifications or Critical quality attribute
	Filtered drug product hold	Differential pressure (ΔP)
	Volume of liquid to be filtered	Minimum filter wetting time (Drug product flush)
	Yield*	

*Yield can be justified as key parameter based on scale and risk assessment and manufacturing historic data

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Bioburden Limits Are Filter Performance Parameter and Measure Effectiveness of Operational Parameters

- **Control limit**: Monitors the shift or trends during routine manufacturing. Actions taken to correct the trends or excursions prevent/minimize the incidences and microbial counts reaching action or rejection level excursions. Control limits are internal limits and adjusted annually based on historic data
- **Action limit**: Controls potential deviation from the established parameter and may have a potential impact on the product quality. These limits are filed regulatory bindings Therefore, product impact assessment and efficiency of CAPA should be performed. If assessment concludes product quality impact, then lot is rejected
- **Reject limit**: Reject limits measure the critical quality attribute and are based on product efficacy and safety. Violation of these limit results into lot rejection. These are filed specification and legal regulatory bindings

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Bioburden Limits: Purpose, Establishment, Investigations and Quality System Requirements

Purpose	Bioburden Limits, Functions, Establishment and Investigations		
	Process Control	Action	Reject
	Monitors process shifts and measurement facility dependent	Measures acceptable performance of process and quality	Measures Quality and Safety
Approaches to set limits depends on process step and process	Statistical or 2 fold below the Action limit or Rejection limit	Based on process step, effects of bioburden on process step and risk assessment	Based on product Quality and Safety or regulatory requirements
What to investigate	Trends	Each excursion	Each excursion
Quality systems requirement	Root cause and CAPA	OOS, root cause and product impact assessment (PIA) and CAPA	OOS, additional studies as required, root cause, PIA and effectiveness of CAPAs

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EMEA 10 CFU/100 mL Bioburden Limit is Not Only the Prudent Approach for Producing Sterile Filtrate

Durapore 0.22 µm Filter Description	Filter Nominal Area (m^2)	Validated Bacterial Challenge	Worst Case Batch Size (L)	Filter Retention Efficiency at 10 CFU/10 mL (%)
Cartridge (4inch)	0.1765	1.0×10^7	200	99.88
Cartridge (10 inch)	0.69	1.0×10^7	200	99.71

- A Pragmatic wider Action limit for sterile filtration than 10CFU/100mL can be applied
- A 10CFU/10mL can be justified without risk to sterile product quality and safety

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Comparison of Bioburden/cm^2 Of The Effective Filter Area At 10 CFU/100mL and 10 CFU/10mL

- Bioburden/cm^2 of the Effective Filter Area (EFA) for a validated microbial filter retention

0.22 µm Filter Description	Filter Nominal Area (m^2)	Worst Case Batch Size (L)	Theoretical Bioburden (CFU) /cm^2 of EFA	
			Action limit (10 CFU/100mL)	Action limit (10 CFU/10mL)
Durapore Cartridge (10 inch)	0.69	200	3	29

An Action limit of 10 CFU/10 mL can be applied prior to sterile filtration because a 6 log reduction of bioburden is demonstrated as compared to filters validation challenge at 10^7 CFU/cm^2

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Conclusions

- All dual filtration and multi-filter arrangements containing 0.2 µm sterilizing grade filters produce sterile effluent
- Thorough filter characterization studies for the sterilizing grade and their validation must be performed
- Bioburden Action limit prior to sterile filtration should be justified considering the product characteristics, product growth supportive properties, filter characterization and filter validation studies
- Scientific rationale and justification are warranted for EMA requirement for pre-sterile filtration bioburden limit of 10 CFU/100mL
- EMA requirement for validated sterile filtration process unnecessarily increases the cost of quality of biotechnologically derived products
- A pragmatic wider pre-sterile filtration bioburden limit such as 10CFU/10mL can be justified

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Back-up Slide

Formula For Calculating Filter Retention Efficiency at the Assigned Action Limit

- Filter Retention Efficiency

$$\text{Filter Factor} = \frac{(\text{Action Limit in mL} \times 1000) \times (\text{worst case liquid volume})}{(\text{Filter Area in cm}^2) \times (1 \times 10^7\ \text{CFU/cm}^2)}$$

Percent Filter Retention Efficiency = (1- Filter Factor) ×100

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Formula for Calculating Bioburden/cm^2 Of The Effective Filter Area (EFA) At 10CFU/100mL and 10 CFU/10mL

Formula for calculating Bioburden/cm^2 of Effective Filter Area at the assigned Action Limit

Bioburden/cm^2 = Bioburden in bulk at Action Limit ÷ Filter nominal area (cm^2)

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