BIOTECH

Technical Regulatory Topic

USTR 3474

How to Select Worst-Case Parameters for Process-Specific Filter Validation Studies

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1 Introduction

Parenteral drug formulations are administered sterile. Sterile administered liquids are typically injectable formulations and ophthalmic formulations. The preferred method of drug sterilization is by terminal sterilization, for example large volume parenterals (LVPs – fill volume is >100 mL) [1]. However most parenteral drug formulations are heat sensitive and alternate sterilization methods are acceptable, if appropriately validated. Sterile filtration is one of the common methods of (cold) sterilization considered in biopharmaceutical industries worldwide for these heat sensitive formulations. Sterile filtration is a process of removing microbes from a fluid stream without adversely affecting the drug product and plays a pivotal role in assuring final product sterility.

Drug manufacturers can claim the drug formulation as sterile by filtering through a pre-sterilized (by gamma irradiation or autoclave/ sterilization-in-place (SIP)) sterilizing grade filter (pore rating of 0.2 micrometer less) and following aseptic practices downstream. For a product that is sterile filtered, regulatory agencies expect filter validation studies to be performed as part of process validation applying Quality Risk Management (QRM) and Quality by Design (QbD) principles [2] [3].

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice [4], ISO 13408-2: Aseptic processing of health care products – Part 2: Sterilizing Filtration [5], Parenteral Drug Association Technical Report Number 26 on “Sterilizing Filtration of Liquids” [6], and Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (EMA/CHMP/CVMP/QWP/850374/2015), 2019 [1] provide guidance on how to validate a sterilizing grade filter. The general objective of performing filter validation studies is to answer the following questions:

- Does the filter affect the drug product formulation?
- Does the drug product formulation or process conditions affect the performance of the filter?

A filter validation program includes, but may not be limited to, the following studies under worst-case process conditions:

- Product Wet Integrity Test (PWIT)
- Chemical Compatibility Test
- Filter Adsorption Test
- Bacterial Viability Test (BVT)
- Bacterial Challenge or Retention Test (BCT/BRT)
- Extractables (and Leachables)

Regulatory agencies expect filter validation studies should be conducted using the worst-case conditions. “Worst-case” refers to a set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure [6].

The worst-case parameters considered for each filter validation test with respect to product characteristics and process parameters are tabulated in the below tables, against which filter validation studies are carried out to establish the filter design space.

Table 1

Consideration of worst-case parameters for sterilizing grade filter validation

Filter Validation Test	Description	Worst-Case Parameters	Rationale for Worst-Case
Product wet integrity test	Product characteristic	Surface tension	The lower the surface tension, the lower the test pressure or bubble point values would be, and similarly, higher surface tension values will result in higher test pressures or bubble points values.
	Process parameters	Temperature	Forward Flow (FF) Test: The lower temperature of a range is considered worst case. The diffusive flow rate is lower at lower temperature and will result in a lower limit which has not to be exceeded during FF test. This will provide an increased safety factor.
			Bubble Point (BP) Test: The lower temperature of a range is considered worst case. The BP depends on the surface tension of a liquid but here the surface tension decreases with higher temperature. The higher BP at lower temperature as the minimum limit will serve as the safer limit.
Chemical compatibility test	Product characteristic	pH	pH is an important characteristic to select the right filter media based on prior knowledge assessment (PKA).
		Components	Product components with higher concentration are considered worst-case due to the potential for increased chemical reaction.
		Solvent	Organic based formulations are more aggressive on membrane polymers and filter hardware compared to aqueous solvent.
	Process parameters	Temperature	Higher temperature is considered worst-case since the rate of chemical reaction increases with temperature.
		Sterilization	Moist heat sterilization: Filters can be sterilized by autoclave or steam in place. Higher temperature and duration are considered as worst-case due to higher thermal stress on membrane polymers and filter hardware. Gamma irradiation: Higher irradiation dose is considered as worst-case due to higher ionic excitation, and the potential formation or breaking of chemical bonds from the polymers used.
		Duration	Longer duration of product exposure is considered as worst-case due to increased chemical reaction.
Adsorption test	Product characteristic	pH	The pH may have an impact on adsorption, but due to the different isoelectric points (IEP) of the components of a liquid it will not be possible to define a worst-case pH for the liquid. It will vary from product to product.
		Ionic strength	Higher ionic strength is considered worst-case because of greater competition to bind to adsorptive sites.
		Viscosity	Low viscosity is considered worst-case because of better wetting of filter membranes.
		Components	Lower components concentration is considered worst-case since a higher opportunity exists to bind to the adsorptive sites. However, if adsorption is observed with lower concentration of components, it is recommended that further evaluations are performed with higher concentration components.
	Process parameters	Temperature	Lower temperature in the range is considered as worst-case since there could be change in product physio-chemical properties which can have an effect of adsorption of product components.

		Flow rate	There are many competing physical processes that can affect how the flow rate impacts the adsorption of product components. Some can enhance while others can diminish the degree of adsorption. Due to this fact it is not possible to define a general worst-case flow rate for the purposes of laboratory-scale filter adsorption studies. Flow rates will be determined by practical levels to facilitate the operation of the study. It is recommended to confirm the results by full production scale tests.
		Sterilization	Sterilization conditions could potentially have an impact; hence the mode of sterilization must be simulated as worst-case.
Extractables test	Product characteristic	pH	The pH extremes (higher or lower) are considered as worst-case due to greater extraction potential.
		Solvent	Organic solvent-based products are considered worst-case since they are more aggressive for generating potential filter extractables.
	Process parameters	Temperature	Higher temperature is considered as worst-case due to higher extraction potential.
		Duration	Longer duration is considered worst-case due to longer fluid/filter contact time, resulting in potentially higher quantities of extractables.
		Sterilization	Moist heat sterilization: Filters can be sterilized by autoclave or steam in place. Higher temperature and duration are considered worst-case due to higher thermal stress on filter polymers resulting in different chemical entities and profiles. Gamma irradiation: Higher irradiation dose is considered as worst-case due to higher ionic excitation resulting in different chemical entities and profiles.
Bacterial viability test and bacterial retention or challenge test	Product characteristic	Surface tension	Product with lower surface tension is considered worst-case due to a potentially greater chance of penetration of the challenge organism (based on studies with highly penetrative fluids).
		Viscosity	Higher viscosity is considered worst-case as higher pressure is required to filter the product which could affect filter media retention capabilities.
		Osmolarity	Higher osmolarity is considered worst-case since challenge cell size may decrease over prolonged exposure.
		Components	Product components with higher concentration is considered as worst-case because higher concentrations may have increased potential for any interaction with the filter membrane and/or bacteria affecting bacterial retention. However, conversely, lower component concentrations may allow different bacterial viability results, so should be evaluated on a case-by-case basis.
		Bioburden	*Brevundimonas diminuta* ATCC 19146 has been the micro-organism of choice for bacterial challenge test. If other bacteria are used, they should be small enough to challenge the retentivity of the sterilizing grade filter and should simulate the smallest microorganism found in the production.
	Process parameters	Temperature	Higher temperature is typically considered as worst-case due to the increased potential for any interaction of the process fluid on the filter membrane and/or bacteria. However, for very broad temperature ranges (e.g. 4 – 30 °C), testing should be performed at both temperature extremes.
		Duration	Longer process duration is typically considered worst-case due to the increased potential for any interaction of the process fluid on the filter membrane and/or bacteria.
		Pressure	Higher pressure is considered worst-case due to a potentially increased risk of bacterial penetration.

		Throughput	Higher volume throughput is considered as worst-case due to potentially higher stress on the filter membrane due to clogging.
		Flow rate	Higher flow rate is considered as worst-case due to a potentially higher risk of bacterial penetration.
		Intermittent cycles	Filtration process consisting of intermittent cycle like pump stop-start cycles, represents the worst case.
		Sterilization	Moist heat sterilization: Filters can be sterilized by autoclave or steam in place. Higher temperature and duration are considered worst-case due to higher thermal stress on filter polymers and could potentially affect retention capabilities of test filter media. Gamma irradiation: Higher irradiation dose is considered as worst-case due to higher ionic excitation and could potentially affect retention capabilities of test filter media.

2 Conclusions

Agencies expect sterilizing grade filter validation studies to be conducted using the worst-case processing conditions. This document outlines the product characteristics which should be considered or evaluated and process parameters which represent worst-case conditions for filter validation studies. It is difficult to define the worst-case generically, and it should be evaluated and justified on a case-by-case basis. The process parameters mentioned are critical process parameters (CPPs) which are validated to establish filter design space. Within the design space, end-users would determine normal operating parameters, which should be well balanced within the filter design space so that sterile filtration is always in control. It is advantageous for end-users to create an appropriate balance between the validated filter design space and filter operational space to minimize the risk of a process requiring post-approval changes.

Pall can provide technical consultancy and assist with selection of worst-case parameters for specific applications.

3 References:

(1) Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (EMA/CHMP/CVMP/QWP/850374/2015), 2019

(2) ICH Q9, Quality Risk Management, 2006

(3) ICH Q8 (R2), Pharmaceutical Development, 2009

(4) FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, 2004

(5) ISO 13408-2: Aseptic processing of health care products – Part 2: Sterilizing Filtration, 2018

(6) PDA Technical Report No. 26, Sterilizing Filtration of Liquids, PDA J. Pharmaceutical Science and Technology, 62, No. S–5, 1–60, 2008

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