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Biologics QbD case study: Characterizing a final sterile filtration step

Parker domnick hunter outlines the process of quality by design and how it can be used within a bioprocess to ensure consistency of a final product using the example of a final sterile filtration of a drug product.

The International Committee on Harmonisation defines quality by design (QbD) as: "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [1]."

In a seminal paper on the subject[2], Rathore & Winkle (Nature Biotechnology, 2009) builds on this definition and adds the need to understand raw materials variability and the relationship between this and product quality attributes. The authors propose a process for QbD, starting with the identification of a product's critical quality attributes (CQAs), from which a reliable manufacturing process capable of delivering the CQAs is then developed. This is achieved by performing a risk assessment on each attribute for its potential impact on the final drug's safety and efficacy.

A risk-based approach to quality

The A-Mab case study published by CASSS & ISPE[3] proposed that each quality attribute can be ranked on a continuum of criticality rather than a binary critical/non-critical classification.

Once identified, CQAs can be monitored and controlled through the process to ensure a consistent product of the required quality. During the development of each operation within the manufacturing process a further risk-assessment is required to ensure the operation will deliver a product with the required quality attributes.

Take, for example, a final sterile filtration of a drug product (Figure 1). Here, bulk drug substance is blended with a prepared excipient and refiltered to remove particulates to protect the second sterile filter from blockage and to reduce bioburden levels.

A fishbone-type diagram can be used to identify every process parameter that might affect the CQAs of a step in a process. An

Figure 1: *Final sterile filtration*

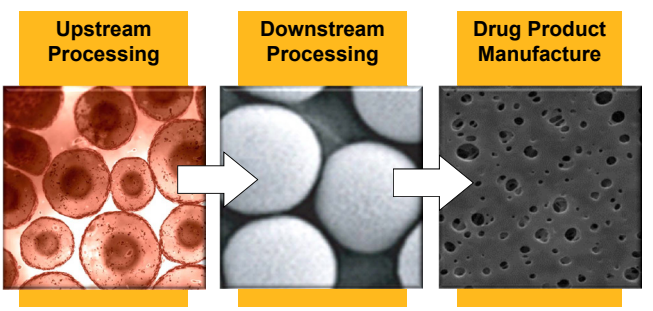
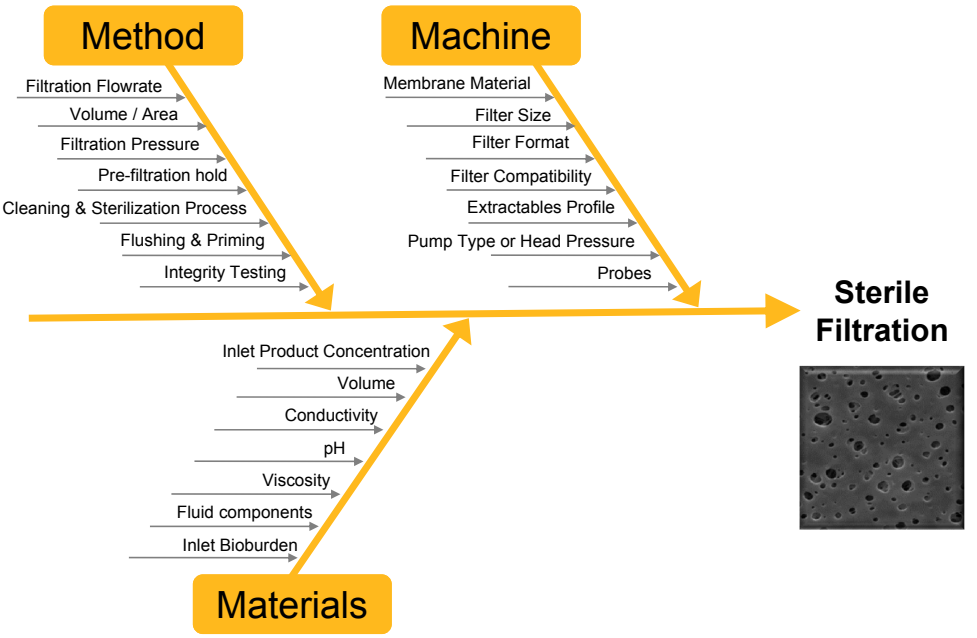


Figure 2: Identification of process parameters



example of this for a final sterile filtration is shown in Figure 2.

The use of a multidisciplinary team will ensure no process parameters are missed. This analysis can also be used in the regulatory submission. Each process parameter can then be given a risk score - based on experience and literature - for the likelihood that the parameter will affect each individual CQA. Figure 3 shows one approach that has been proposed where the parameters identified in the fishbone diagram are given an overall criticality ranking derived from multiplying all of the scores from each CQA.

We would argue, however, that a parameter should be considered critical if it impacts even a single CQA to a significant level, irrespective of its impact on other CQAs. Figure 4 shows an example of a risk assessment using this second approach where a greater number of parameters would be considered more critical.

Once the ranking has been made, options for mitigating the risks at this step of the process can be identified. This may be as simple as the specification of consumables in batch records or through further study of parameters by multivariate experimentation.

Defining a design space

Such experimentation can be costly in the early product development cycle, especially as sub-operations may need two design of experiments (DOEs) to determine a design space. The first experiment is typically a scouting experiment using a method such as a full factorial design but this will only identify which parameters exert an impact on the attribute over the range studied. The identified parameters should, therefore, be carried forward into a second multivariate experiment which models the relationships between parameters - on their own or in combination with one another - and quality attributes.

The output of the multivariate experiments can be used to create a design space which, if operated within, generates a product of the required quality. The use of design spaces may allow a manufacturer additional flexibility and reduce the need to deploy resources investigating out-of-specification occurrences that may not be detrimental to quality.

It is of critical importance that the experiments can be demonstrated to be representative of large-scale manufacturing.

All this effort should be part of a holistic plan to characterize an entire process. Linker studies must be performed to show that, if a design space is operated within for each process step, the final product will achieve its target quality consistently. ▸▸

Figure 3: Ranking of parameters

Process Parameter	Sterility	Endotoxin	Leachables	Vis- & Non Vis- Particles	Product Concentration	Aggregation	Risk Ranking
Filter Size	10	7	10	10	7	5	245000
Membrane Material	10	5	10	10	7	5	175000
Filter Format	10	7	10	10	5	3	105000
Volume / Area	10	5	10	5	7	3	52500
Filtration Flowrate	10	7	5	7	1	7	17150
Filtration Pressure	10	7	5	7	1	7	17150
Flushing and Priming	5	7	10	10	3	1	10500
pH	7	7	7	3	1	5	5145
Cleaning and Sterilization	10	7	10	7	1	1	4900
Filter Compatibility	10	1	10	7	1	5	3500
Fluid Components	5	5	5	5	1	5	3125
Conductivity	5	5	5	3	1	5	1875
Volume	7	5	7	7	1	1	1715
Inlet Bioburden	10	10	1	1	3	3	900
Inlet Product Concentration	1	1	1	5	10	10	500
Pre-filtration hold	7	10	1	1	1	3	210
Integrity Testing	10	10	1	1	1	1	100
Pump Type or Head Pressure	3	1	3	3	1	1	27
Extractable Profile of Filter	1	1	10	1	1	1	10
Probes	1	1	1	1	1	1	1

Process Parameter

Risk Ranking Score

Figure 4: Ranking of parameters

Process Parameter	Sterility	Endotoxin	Leachables	Vis- & Non Vis- Particles	Product Concentration	Aggregation	Risk Ranking	Max Risk Score	Min Risk Score	Comments
Filter Size	10	7	10	10	7	5	245000	10	5	Specify in batch record based on max and min volumes
Membrane Material	10	5	10	10	7	5	175000	10	5	Specify in batch record
Filter Format	10	7	10	10	5	3	105000	10	3	Specify in batch record
Volume / Area	10	5	10	5	7	3	52500	10	3	DOE 2 (Sterility, Endotoxin, Leabables & Particulates Responses)
Filtration Flowrate	10	7	5	7	1	7	17150	10	1	DOE 2 (Sterility, Endotoxin, Leabables & Particulates Responses)
Filtration Pressure	10	7	5	7	1	7	17150	10	1	DOE 2 (Sterility, Endotoxin, Leabables & Particulates Responses)
Flushing and Priming	5	7	10	10	3	1	10500	10	1	DOE 1 (Sterility, Endotoxin, Leabables & Particulates Responses)
Cleaning and Sterilization	10	7	10	7	1	1	4900	10	1	DOE 1 (Sterility, Endotoxin, Leabables & Particulates Responses)
Filter Compatibility	10	1	10	7	1	5	3500	10	1	Compatible if all Quality Attributes can be met
Inlet Bioburden	10	10	1	1	3	3	900	10	1	Use TR26 challenge levels for DOEs
Inlet Product Concentration	1	1	1	5	10	10	500	10	1	DOE 2 (Sterility, Endotoxin, Leabables & Particulates Responses)
Pre-filtration hold	7	10	1	1	1	3	210	10	1	Use worst case for DOE2
Integrity Testing	10	10	1	1	1	1	100	10	1	Validated procedure
Extractable Profile of Filter	1	1	10	1	1	1	10	10	1	DOE 2 (Sterility, Endotoxin, Leabables & Particulates Responses)
pH	7	7	7	3	1	5	5145	7	1	Use worst case for DOE2
Volume	7	5	7	7	1	1	1715	7	1	Specify in batch record max and min volumes to be filtered
Fluid Components	5	5	5	5	1	5	3125	5	1	Product Specification
Conductivity	5	5	5	3	1	5	1875	5	1	Product Specification
Pump Type or Head Pressure	3	1	3	3	1	1	27	3	1	No actions required
Probes	1	1	1	1	1	1	1	1	1	Routine calibration

Process Parameter

Risk Ranking Score

QbD forms part of a much larger control strategy incorporating GMP controls, in process testing and control of raw materials. This control strategy must be reviewed regularly as part of the post-approval lifecycle management plan.

QbD requires a significant investment in resource early in the product lifecycle, however, effort in the early days to determine a target product profile and create a process that addresses and controls the CQAs within a design space will pay dividends by preventing rework during the critical and expensive process validation phases. ■

[References]

1. *International Committee on Harmonisation (2009), Guidance for Industry Q8(R2) Pharmaceutical Development.*
2. *Rathore, A.S. & Winkle, H. (2009) Quality by design for biopharmaceuticals. Nature Biotechnology,27, 26-34,.*
3. *CMC Biotech Working Group (2009) A-Mab: A Case Study in Bioprocess Development. CASSS & ISPE.*