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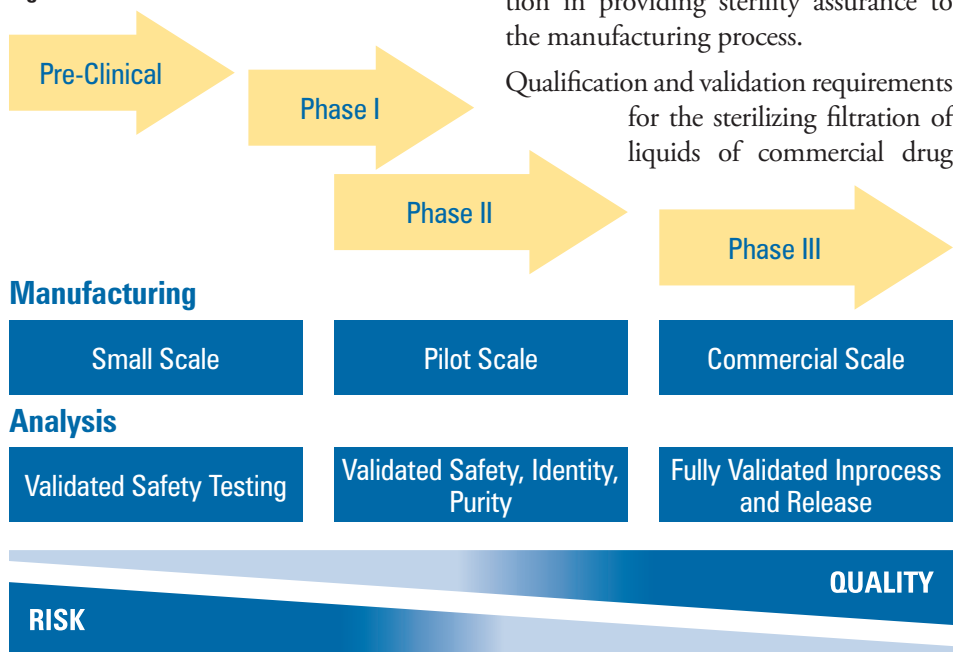
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## Validation and Qualification of Sterile Filtration for INDs

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The manufacture of investigational medicinal products presents additional challenges and complexity in comparison to commercially manufactured and marketed products. By definition, the word “investigational” implies that there is an effort to achieve a further understanding through additional knowledge. It is the acquisition of process understanding and process knowledge that drives a development effort to build quality into the process and product by effectively mitigating risk and unknowns. The application of QbD is intended to eliminate risk and build a foundation of quality into the product and process as it moves along the development continuum (**Figure 1**). Therefore, patients participating in clinical trials are exposed to higher risks as compared to patients treated with marketed products.

**Figure 1** QbD Continuum



Regulatory guidance on investigational products is intended to minimize this risk. This recommendation involves evaluating the manufacturing setting to identify potential hazards and take appropriate actions to eliminate and mitigate them with the intention to safeguard the quality of the investigational drug (**1**). Some patient safety risks such as toxicity, unintended side effects or the efficacy of the product are inherent to the nature of drug development, and exist as a result of the lack of process understanding and validation at early phase development. Per the U.S. FDA, “Product sterility is a critical element of human subject safety, you should take special precautions for phase I investigational drugs that are intended to be sterile” (**1**). For aseptically prepared drug products, the sterilizing filtration process is a critical unit operation in providing sterility assurance to the manufacturing process.

Qualification and validation requirements for the sterilizing filtration of liquids of commercial drug

products are clear and well understood. *PDA Technical Report No. 26 (Revised 2008) Sterilizing Filtration of Liquids* is a valuable reference which clearly details how sterile filtration validation should be conducted in order to comply with regulations. Determining the appropriate qualification and validation activities and methodologies for the filter sterilization of investigational medicinal compounds is an area of much less clarity and greater complexity. Complexity arises from the lack of process definition and the very limited quantity and volume of product formulations during early development phases. A risk-based and phase-appropriate strategy for the qualification and validation of filter sterilization is a sound mechanism to overcome these challenges and to ensure that as a product advances through development stages, risk is continually displaced by a foundation of quality. Therefore, one can look to regulatory guidance documents to better understand the requirements for validation of sterilizing filtration of early phase medicinal products. Two such documents that can be referenced in this case are the FDA’s *Guidance for Industry: CGMP for Phase 1 Investigational Drugs* and *Eudralex Vol. 4 Good Manufacturing Practice Guidelines*.

A review of these documents for guidance specific to the qualification and validation of the sterilizing filtration of liquids provides numerous insights.

The FDA document (**1**) proceeds to list out a number of manufacturing controls that should be considered; this list includes controls such as media process simulation,

environmental monitoring, sterilization of components and devices, aseptic technique training and quality control requirements for product release. The topic of liquid sterilization by filtration, however, is not directly addressed or emphasized as a process control that should be focused upon during phase 1. One could conclude that validating the efficacy of the filter's ability to produce a sterile effluent is not required at this stage.

In contrast to the FDA guidance, the European guidance (2) makes a strong recommendation that liquid sterilization by filtration should be validated to the same standard as commercially marketed products. During early development stages such as phase 1 this could be difficult to achieve due to product volume limitations that could prevent the normal course of work that is a prerequisite to filter validation such as filter capacity and sizing trials.

It can be concluded that neither the FDA nor EU guidance provides detailed insight on how the critical operation of sterilization by filtration should be handled in development phases. In reality, from the perspective of a sterilizing-grade filter supplier and validation service provider, we see sterile filter validation occur at a variety of development stages from as early as phase 1 and up to late phase 3. Thus, the question is often raised "what is the right time to validate the sterile filtration process." The answer, like most validation questions, is, "it depends." In general, many drug manufacturers' lifecycle management processes require filter validation to occur in phase 2.

There are of course exceptions, however, such as difficult to filter sterilize formulations which could warrant validation at an earlier time or development of a highly similar products where the acquisition of existing knowledge can be leveraged. Still, filter validation can be considered as a lifecycle process in and of itself and not as a discrete action. This concept will be elaborated upon with recommended actions to mitigate risk from the sterile filtration process as early as practically possible to align with the concept of quality by design and the overall objective of producing safe clinical products. The recommendations

that follow will focus on the three main facets of sterilizing-grade filter validation: chemical compatibility, bacterial retention, and Extractable and Leachable substances evaluation. The objective of each recommendation is to acquire as much knowledge as practically possible in regard to the efficacy of the filtration process, and thus remove risk and unknown and build quality into the process. In essence, the activity of sterilizing filtration process design and validation should be treated as a lifecycle process not an event that occurs at a single point in time.

### Early Phase Development

**Chemical Compatibility:** It is critical even as early as phase 1 to start the evaluation of chemical compatibility because a non-compatible fluid and filter combination has a much higher likelihood to result in particulate or leachable contamination and/or bacterial passage both of which are unacceptable. The successful use of a sterile filter in early phase as defined by product quality and filter integrity testing is not a suitable replacement for evaluating chemical compatibility. The reason is, with small batch sizes the filter/product contact time could be a very short duration, and therefore, evidence of a noncompatible filter may only be detected during full validation at a later stage of the product development. Once the process has become more defined and fixed, the replacement of a critical device with a large product contact surface area becomes a greater challenge.

Drug product availability may not afford a full compatibility test of the filter device. Therefore, a paper-based assessment is the optimal starting point were the product solvent, active ingredient and excipients can be assessed against material handbooks and supplier-published information, as well as knowledge obtained from the development and qualification of highly similar product formulations. If a paper-based assessment points toward any suspected incompatibility, testing should follow. This could be testing of only membrane coupons in order to limit use of valuable drug product or testing of a full device using a placebo if the compatibility concern is related only

to the solvent or excipients. Despite the fact that the filtration process may not be well defined, a compatibility testing design space could be easily arrived at by assuming that the total filter/product contact time would not exceed the length of time that an aseptic filling process is qualified for, and a similar design space decision could be made for temperature assuming the maximum temperature of a typical filling suite for products filtered at ambient temperatures or just below the maximum temperature at which a product would remain stable for a product that is heated prior to filtration.

The lack of a fixed final product formulation is another challenge of determining compatibility during early development. Design space strategy, however, can be implemented to overcome this challenge. Here, a hypothetical product could be formulated on the basis of the maximum quantity of individual ingredients and pH limits and thus serves as a basis for a worst-case formulation from which compatibility of a filter device can be evaluated.

**Microbial Retention:** It is critical at early development stages to evaluate the risk of not having an efficacious sterile filtration process. When evaluating microbial retention, a drug developer who has experience developing highly similar formulations, such as MABs for instance, has the advantage of relying on the filtration efficacy results of highly similar drug product filter combinations where critical parameters that influence microbial retention can be compared such as surface tension, osmolarity and physical parameters such as: pressure and time. Table 6.3-1 in *PDA Technical Report No. 26 (Revised 2008) Sterilizing Filtration of Liquids* is a good starting point from which highly similar product formulations could be risk assessed in order to use the prior knowledge gained by validation of one or more formulations to assess with some degree of confidence that a new formulation/filter combination is efficacious. At which point a proper validation of microbial retention should commence as the product formulation and filtration design space become more clear and fixed by establishing the

required parameters from which to design a meaningful process and product specific validation: defined product formulation, filter capacity, flux, maximum pressure, maximum contact time, expected bioburden and filtration mode (constant pressure or constant flow rate).

In contrast, the developer of a novel drug formulation with no existing knowledge should make every effort to prove sterile filtration efficacy as early as practically possible. In particular, a new formulation which contains a surface active ingredient that reduces surface tension or a nanoparticulate formulation such as a liposomal vaccine presents additional risk. Per Folmsbee and Moussourakis:

“A review of field and laboratory bacterial retention validation data for a variety of fluids and challenge conditions suggests that low surface tension fluids, such as many adjuvants and adjuvanted vaccines, present a higher risk of the occurrence of a bacterial penetration event during sterilizing filter validation. Among the classified solutions examined, liposome solutions represent the highest risk, followed by lipid and finally surfactant solutions” (3).

During early phase development when product volume is scarce it may not be practical to complete a process and product specific microbial retention test at the same standard as required for marketed products. A modified approach, however, can provide the drug developer with an early indication that sterilizing filtration efficacy will be effectively validated later in the development effort. The typical approach to microbial retention studies could be modified to use only one challenge filter as opposed to the typical set of three or by use of membrane discs that are smaller than the often used 47 mm size. Additionally, filter manufacturers and validation service providers can be consulted for advice on test setups and arrangements that are designed to limit the amount of product volume required. In general, an opportunistic approach should be employed to seize opportunities to acquire additional knowledge of the liquid sterilization process as early as practically possible.

**Extractable and Leachable Substances:** As is the case with chemical compatibility and microbial retention, numerous opportunities exist to acquire knowledge and reduce risk along the development path. Essentially, the E&L evaluation starts as early as initial filter device selection where only devices that meet compendia and other qualification standards should be selected examples include conformance to USP Class VI, materials that meet indirect food additive requirements per 21 CFR 177–82, and are nonfiber releasing. Verifying acceptable compatibility between the process conditions, process fluid, and filter increases the likelihood that selecting well qualified materials will result in an acceptable E&L evaluation that is not additive to the product to an extent that would pose a health risk to the patient.

The practice of performing extractable substances studies with model solvents is an advantage for early phase development because these studies do not require valuable and perhaps nonexistent formulated drug product. In the case where the drug manufacturer is developing highly similar formulations, it is likely that previous model solvent studies utilizing the same filter type would be applicable to new formulations. Additionally, suppliers may publish some basic extractable substances information in the form of white papers or validation guides which can be leveraged at an early stage to assess the expected overall quantity of extractable substances, and also review identified compounds for toxicological assessment and potential to react with the API or other drug ingredients.

A rationalized design space taking into consideration the sterilization process, the maximum expected contact time, and temperature is generally all that is required to select relevant model solvent data from which to evaluate a particular process if unsure of the most appropriate model solvent the worst case one could be selected. Thus, qualification information and extractable substances evaluation will provide a strong indication that the selected filter device will not adversely impact the product. Further confidence is built upon the utilization of the same materials of construction throughout development to ensure through clinical

trials and stability studies that no adverse reaction is occurring between filter leachable substances and the product. Additional evidence of safety and quality can be demonstrated by conducting a leachable substances evaluation during the later stages of drug development when the precise formulation becomes fixed; the filter that will be used in commercial production is selected, sterilization method and process is defined, and any mitigation steps such as preflush of filters has been defined.

## Conclusion

The treatment of filter validation as a lifecycle process and a process validation effort will help to ensure that the right level of quality is being designed into the sterile filtration process. When treated in this manner a drug developer is in a much stronger position from which to demonstrate due diligence in protecting patient safety. This can be a challenge within the context of regulatory guidance that points towards the importance of sterility assurance controls as early as phase 1 but is very nondescript on the manner in which the validation of the sterile filtration process should be conducted at such an early point in the drug development effort.

## References

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## About the Author

**Ross Acucena** has over 13 years of combined experience in pharmaceutical manufacturing and validation. His work experience includes manufacturing of both API and sterile drug products. 