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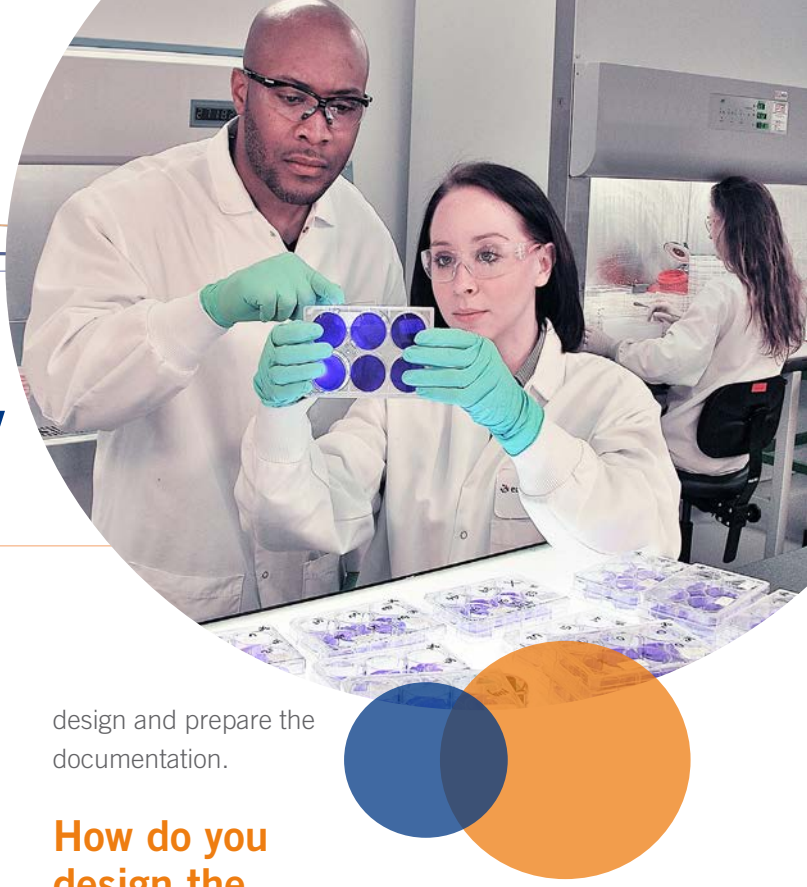

Planning The Execution Of A Viral Clearance Study

by Doug Rea, Research Fellow

Viral clearance studies are a necessary component of any regulatory submission for clinical trials or commercial product approval for all biopharmaceutical products. These studies are performed to evaluate the capability of the purification process to remove or inactivate viruses that could potentially contaminate the starting material. They are complex studies that require substantial financial and personnel resources, as well as specialized scientific expertise to perform. As such, viral clearance studies are often performed at a qualified contract testing laboratory rather than in-house. When multiple parties are involved in this process, clear communication and a comprehensive understanding of the approach and timeline is critical.

It is important to get a viral clearance study done right the first time in order to avoid costly delays. Knowing the right questions to ask and establishing a detailed plan with close communication among all parties involved are key in completing a successful viral clearance study.

There are some common questions to ask up front when planning a study, including which steps of the process to test with which viruses and what the spiking percentage should be. However, there are other critical questions and details to address early in the planning process to ensure that there are no surprises during the execution of the study.

How soon do you need to begin planning?

As early as possible. Decisions made during development of the purification process can have an impact on the design and results from the viral clearance study. If you proactively consider the needs for your viral clearance study in these early stages, you will be in a good position when it is time to conduct the study.

Who is responsible for what?

Will you be performing the study, or will the contract lab be performing it? Who is performing the scale-down purification validation? Make sure roles are clearly defined. If the contract lab will be performing either part, they will need detailed information on the process steps. They will also need time to develop the study design and prepare the documentation.

How do you design the scale-down process?

Regulatory guidelines require that the scale-down process be validated, i.e. that the scale-down process match the manufacturing process as closely as possible given constraints of different sizes. This match should take into account both execution parameters and results.

The first question is, what size unit operations to execute during the study? There are a number of factors to consider. For instance, consider the column diameter. Traditionally, the scale down is done by maintaining the column height and the linear flow rate the same and decreasing the column diameter. However, as column diameter decreases, the wall effects increase. Also, as the volume of the column decreases, the relative volume of the extra-column volumes increases, increasing extra-column volume effects. Either one or both of these factors can distort a chromatogram, potentially rendering it non-representative, and therefore unsuitable for the study.

As another example, consider an ion exchange membrane filter. Scaling down strictly by filter volume may not be adequate; it may also be necessary to take into account the flow path through the filters and the number of filter layers that make up the overall membrane. These considerations may limit the selection of sizes that can be used for the viral clearance study.

Inactivation unit operations such as low pH and solvent/detergent treatment require special planning. Control samples are usually included to provide an untreated sample for comparison to the treated samples. But you cannot create a control by spiking virus into an inactivation sample and neutralizing immediately, since

some degree of inactivation may occur and the integrity of the control could be questioned. There are several ways to address this issue; none of them are ideal and all require careful planning. In addition, it is desirable that the viral spike for the control and inactivation samples be the same percentage of the starting material volume. If they are not, viral clearance can still be calculated, but the calculations are more complex and the results may be questioned as non-representative. Similarly, it is desirable that both the control and inactivation samples be diluted in the same way during the execution of the clearance unit operation.Again, if this is not possible, a viral clearance can still be calculated, but the calculations are more challenging.

Although the scale-down process is intended to model the full scale process closely, constraints of size and assay requirements may require some deviations from the manufacturing process. Therefore, any differences between production and the viral clearance scale down model should be evaluated and justified during the planning process. This will ensure that there are no deficiencies in the scale down that could impact the acceptability of the results.

What materials are needed?

Samples and solutions are often pulled from a Pilot GMP purification run that may occur months before the clearance study. It is necessary to ensure that there is enough sample to load the unit operations to the target goal. But to do that, you must have determined your scale-down parameters (as suggested above). In addition, you must also ensure that the amounts collected are enough to provide an adequate sample volume to be used for the assay. You must also take into account viral assay sampling losses and sampling for cytotoxicity/interference testing. In addition, it is prudent to collect extra samples for possible repeat tests.

Running out of solution during the study could result in costly delays and rework. Take into account not only the amount needed for the runs themselves, but also include additional volume for priming lines of chromatography instruments, for dilutions (e.g. A280nm buffer blanks) and for extra runs, as well as extra to cover unforeseen accidents like cracked bottles.

What supplies will be needed?

Your viral clearance lab will probably provide standard lab supplies.However, if your process requires special items, such as filters or housings, don't assume the testing lab has them. It is important to check.

What are the execution parameters of the scale-down process?

Discuss your process with the viral clearance lab, especially if the lab will be executing your process. But do so even if your staff is going to the viral clearance lab to execute the process. The viral clearance lab will need to know volumes used and generated during the process in order to calculate clearance. Often these volumes are obvious, but not always. This is especially true for inactivation steps—they may be simple to execute, but planning can be challenging.

If the viral clearance lab staff will be executing some or all of the unit operations, remember, they have not lived with the process as you have.Details of specifications, limitations, and quirks in your process need to be communicated. If there are any solubility, stability or special handling issues for the samples you will be using, let the lab staff know.Also, include any adjustments that need to be made to samples before they are used and any testing to be done beyond the viral assays.Finally, if you have any procedures important to you in the setup and/or cleanup of the process, don't forget to communicate these as well. Another important consideration is to provide ranges for all critical parameters. Any critical factor, be it capacity, flow, pressure, etc, should have an acceptable range specified if you cannot be 100% sure of hitting it exactly. For example, suppose the capacity of a column is ≤ 30 mg/mL bed volume. So, is a load of 1 mg/mL bed volume acceptable? Technically, yes. However, it is unlikely that any regulatory reviewer would find this an acceptable model.Another consideration is whether or not you wish to pursue an "average" model, or a "worst case" model.Therefore, plan your specifications carefully and thoroughly and be sure everyone involved understands them.

What is your schedule for performing the study?

It is important to share your daily schedule with your testing lab. The viral plaque assays used for most clearance determinations require growing indicator cells, which must be used within a fairly narrow timeframe. Knowing how long the unit operations take will allow the sponsor and the viral clearance lab to develop a schedule to provide the resources needed for the assays.

How much information should you communicate?

Every company has its own jargon. Don't assume that just because doing something a certain way is standard for you and your company that everyone understands that this is the way you do it. Communications of details are important for success. Even when flexibility is acceptable, the viral clearance laboratory needs to know this. The more the viral clearance laboratory knows and understands about your process, the smoother your study will run.

What if you don't know how to answer some of these questions?

If you are unsure about what information to provide or how to answer these questions, ask your viral clearance lab. An experienced laboratory sees almost every conceivable situation, and these experts can be a useful resource in the design of your study. Do not be afraid to ask them for advice.

Summary

The two most important factors of a successful viral clearance study are communication and attention to detail. Establishing effective communication between the sponsor and the testing lab will ensure that all parties are following the same path throughout the duration of the study. Understanding the intricate details involved and knowing what questions to ask your viral clearance lab will also help this process go smoothly.

In the end, the more information the testing lab has about the process and the requirements of the sponsor, the better equipped they will be to develop a precise plan that reviewers will deem controlled and accurate. Following these guidelines can help ease this process and lead to a successful viral clearance plan.