BIOTECH

Technical Regulatory Topic

USTR 3489

Regulatory Framework for Virus Safety

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1 Introduction

Any pharmaceutical process that involves the use of biological materials must implement measures to mitigate the risk of contaminating viruses from potentially reaching a patient.

Although the first regulatory requirements for virus safety were directed towards plasma based products[1,2], as knowledge of potential virus contaminants has increased, there has been appropriate regulatory guidance issued to assure virus safety for monoclonal antibodies and recombinant proteins[3,4], biological medicinal products[5,6], and more recently, to address the rapidly growing market of Advanced Therapeutic Medicinal Products (ATMPs).[7,8]

2 Regulatory Framework for Virus Safety

Patient safety from contaminating viruses has largely been assured through the application of three virus safety strategies by biopharmaceutical manufacturers.

1. Careful sourcing and a thorough screening of all components to the bioreactor (e.g. master cell banks and raw materials), as well as elimination of the use of animal derived ingredients wherever possible. Pre-treatment of raw materials (e.g. virus filtration, gamma irradiation) to prevent the possibility of contamination by adventitious agents should be practiced where appropriate.
2. Implementation of appropriate virus removal or inactivation steps in the manufacturing process.
3. Appropriate testing of product throughout the manufacturing process to confirm the absence of contaminating viruses.

This three-tiered approach has provided a solid foundation for assured viral safety in the production of biopharmaceuticals. However, there is also a regulatory expectation that end-users implement the principles of quality by design into any virus clearance step. This means that end-users must demonstrate through the application of solid science and in-depth risk assessments that the manufacturing process will consistently remain in a state of control and ensure that the Quality Target Product Profile (QTPP) of the final product is met each and every time[9].

To determine how much virus clearance is needed in a process, the end-user must evaluate the maximum potential level of virus contaminants in the process, following the steps outlined in Figure 1. By working with suppliers, and performing prior knowledge assessments, as well as scaled down bench trials to determine the most suitable virus clearance methods, the end-user can optimize their process with respect to virus safety. The expectation is that at least two orthogonal steps be implemented for virus safety assurance.

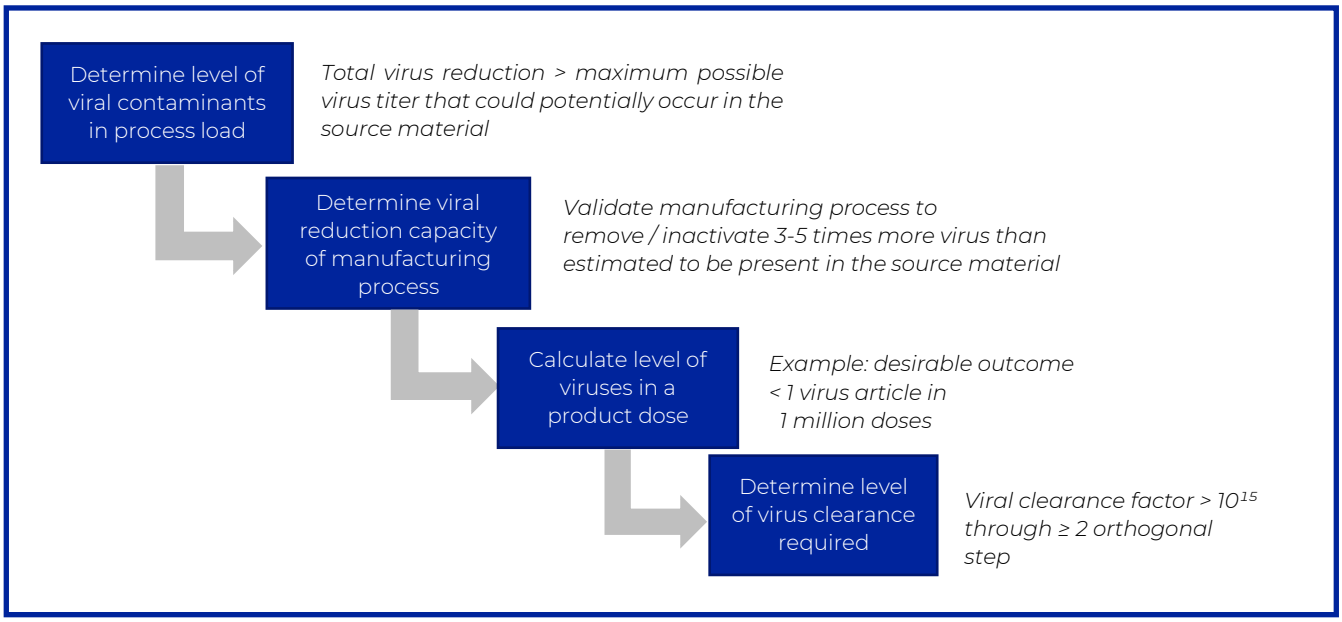
There is a regulatory requirement that virus clearance testing is performed with appropriate mammalian viruses prior to producing product for clinical trials, but also as the manufacturing process details are finalized, typically at Phase 3 of clinical trials. During these validation studies, it is critical that the worst-case manufacturing conditions are simulated for each virus clearance step implemented. In addition, the late stage validation studies must use a range of different viruses to demonstrate the robustness of the manufacturing process to remove or inactivate viruses that could be present (based on a risk assessment), as well as potentially unknown viruses.

An in-depth description of relevant mammalian viruses to use in virus clearance validation studies is provided in the International Council for Harmonization ICH Q5A[10], and can be categorized as:

- Relevant viruses (identified viruses or of same species, or likely to contaminate)
- Specific model viruses (virus closely related to known or suspected virus with similar physico-chemical properties)
- Non-specific model viruses (viruses used to characterize the robustness of the manufacturing process to remove or inactivate a range of viruses with different properties)

Figure 1.

Evaluation of level of virus clearance required



Finally, the overall virus reduction factor is defined as the sum logarithm of individual virus inactivation / removal steps, with only steps showing > 1 log removal of viruses being considered.

3 References

[1] EudraLex, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 14: Manufacture of Medicinal Products Derived from Human Blood or Plasma (2011).

[2] EMA Guideline On Plasma Derived Medicinal Products (2011).

[3] FDA, Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997).

[4] EMA Guideline On Development, Production, Characterisation And Specifications For Monoclonal Antibodies And Related Products (2008) / 3R's Technical update (2016).

[5] EMA Guideline on the Use of Porcine Trypsin used in the Manufacture of Human Biological Medicinal Products (2014) (EMA/CHMP/BWP/814397/2011).

[6] EMA Guideline on the adventitious agent safety of urine derived medicinal products (2015) (EMA/CHMP/BWP/126802/2012).

[7] EMA Guideline on the Quality, Non-Clinical and Clinical Aspects of Gene Therapy medicinal Products (2015).

[8] Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2020).

[9] ICH Q8 (R2) Pharmaceutical Development (2009).

[10] ICH Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnological Products Derived from Cell Lines of Human or Animal Origin (1999).

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