An evaluation of real-world biotechnology product viral clearance via chemical inactivation and virus filtration unit operations

Ajayi Opeyemi, Johnson Sarah, Lute Scott
Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Biotechnology Products, Division of Biotechnology Research and Review 2

Introduction

The production of recombinant therapeutic protein drug products, such as monoclonal antibodies (mAbs) is typically performed in mammalian host cell lines. All mammalian cell lines produce endogenous retroviral-like particles (RVLPs) and other impurities alongside the target pharmaceutical molecule. Additionally, adventitious contamination of the production stream by external viral agents is possible. Therefore, to ensure product safety, the purification unit operations of the manufacturing process must be capable of removing endogenous and adventitious viruses from the production stream (i.e. achieve viral clearance, VC). In typical purification operations, chemical inactivation (CI), and virus-retentive filtration (VRF) are dedicated primarily to inactivate and remove viruses from the product stream, respectively. VRF removes viruses by size exclusion mechanisms, while CI denatures viral envelopes in acidic conditions (low-pH) or disrupts lipid bi-layer in solvent/detergent chemical reagents.

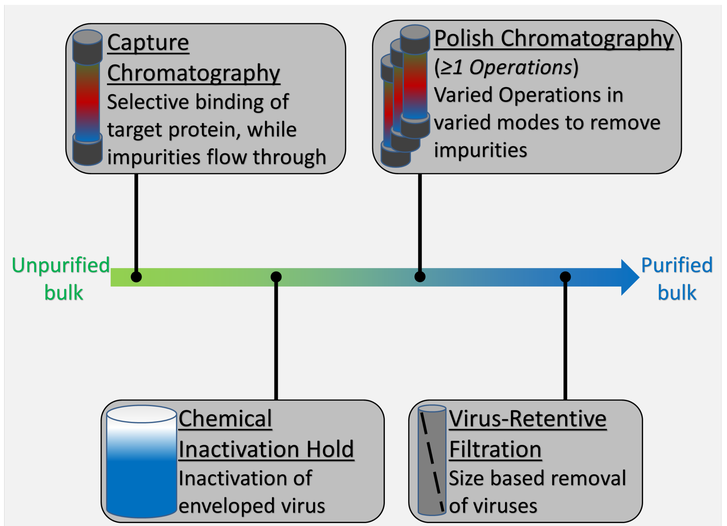

Figure 1. Outline of typical downstream purification unit operations utilized in biotechnology product manufacture.

To validate VC, studies with scaled down models of unit operations are performed with surrogate viruses[1]. Study results are submitted in biological license application (BLA) or investigational new drug (IND) submissions. To enhance Agency knowledge, a VC database was created to understand the impact of manufacturing process parameters and technological advancements on VC. Earlier work has assessed manufacturing operations in BLA submissions[2]. Our goals are to: (1) identify and understand key VC process parameters and (2) aid assessment of viral clearance data via real-world examples.

Materials and Methods

Data Source: eCTD Module 3 section of IND submissions.

Extracted Data: Where possible, the following information was recorded:

1) General product information and identity parameters.
2) Virus retentive filtration data including virus filter make/model, transmembrane/inlet pressure and flow rates/flux.
3) Chemical inactivation data including process type, pH value, solvent/detergent concentration, conductivity, incubation time, incubation temperature.
4) Viral safety report data including unpurified bulk viral particle concentration, dose-safety factor, assay method per study, logarithmic clearance value (LRV) and virus tested. Here we present data for murine leukemia virus (MuLV) – a model virus for endogenous retrovirus, pseudorabies virus (PsRV) – a large enveloped virus, and mouse minute virus (MMV) – a small virus used to model filtration capabilities.

Data Capture and Processing Software: Mathworks® MATLAB and Microsoft® Excel.

Table 1. Current IND viral clearance database entries. *Data contains IND submissions from 01/1980 up to and including 12/2015.

Description		Count
IND Submissions*		712
Chemical Inactivation Data	Low-pH	3834
	S/D	660
Virus-Retentive Filtration Data		4,249

Results

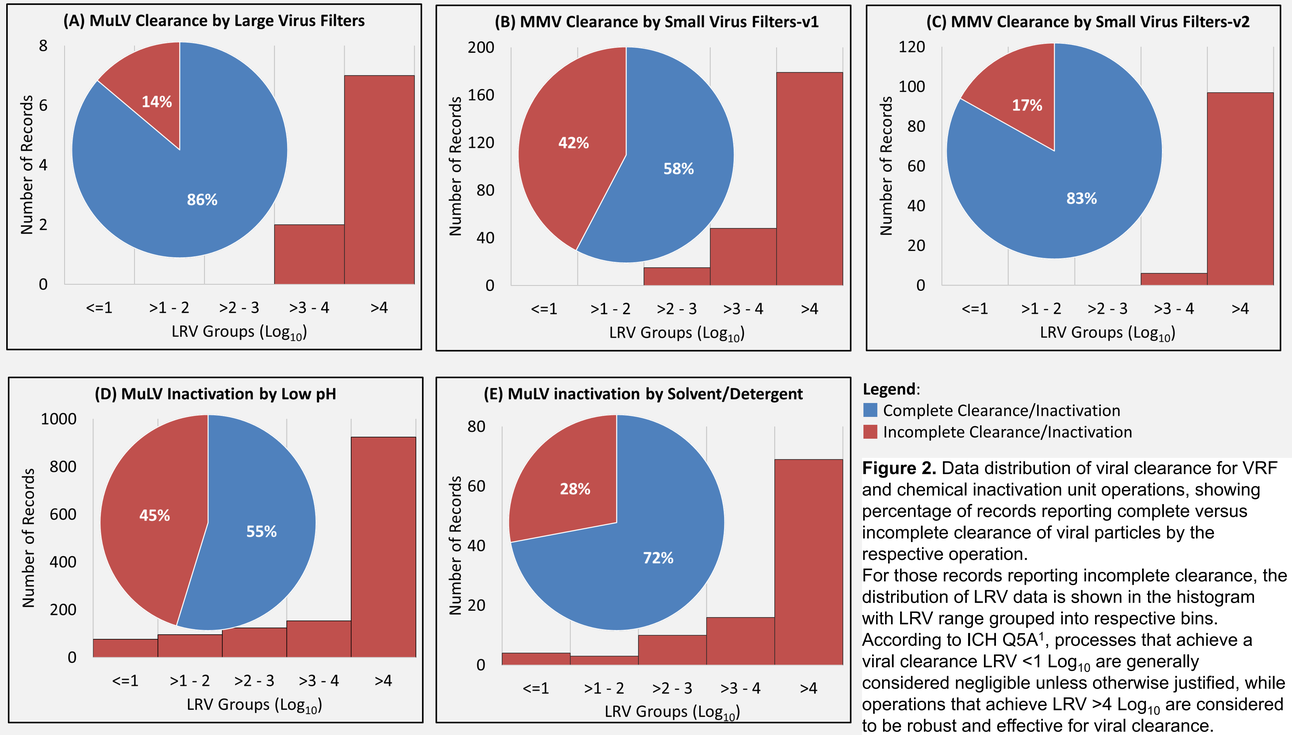

Figure 2. Data distribution of viral clearance for VRF and chemical inactivation unit operations, showing percentage of records reporting complete versus incomplete clearance of viral particles by the respective operation.
For those records reporting incomplete clearance, the distribution of LRV data is shown in the histogram with LRV range grouped into respective bins.
According to ICH Q5A[1], processes that achieve a viral clearance LRV <1 Log_{10} are generally considered negligible unless otherwise justified, while operations that achieve LRV >4 Log_{10} are considered to be robust and effective for viral clearance.

Discussion and Conclusion

Cumulatively, for the VRF process, >80% of records report complete clearance of MuLV for all filter types (for clarity only large virus filter data shown). However, an increase in the percentage of complete clearance for MMV is observed for first- versus second-generation small virus filters. For records where incomplete clearance was observed, there is a general improvement in clearance capabilities of the second-generation small virus filters over other types. This suggests that process parameters such as transmembrane pressure, volumetric throughput, etc.), may have an impact on the VRF process , which corroborates earlier work[3]. For chemical inactivation, the data shows that ~55% and >70% of low pH and solvent/detergent studies, respectively, on MuLV report complete inactivation. However, of the records reporting incomplete inactivation, the distribution range observed shows that process parameters like inactivation duration and temperature do impact inactivation capabilities which corroborates other reported data[4]. Overall, trends observed support current recommended CDER/OPQ/OBP practices for the dedicated viral clearance unit operations of chemical inactivation and VRF. Next steps include completion of data mining , evaluating the impact of process parameters on the observed viral clearance trends for both VRF and chemical inactivation. IND submissions also offers the opportunity to investigate how process parameter changes along the phases of drug development impact the viral clearance capabilities of unit operations.

References

1) ICH-Q5A(R1), (1999). Quality of Biotech Products: Viral Safety Evaluation of Biotech Products Derived from Cell Lines.
2) Ajayi et al. (2022). An updated analysis of viral clearance unit operations for biotechnology manufacturing.
3) Johnson et al. (2021). Virus filtration: A review of current and future practices in bioprocessing.
4) Brorson et al (2003). Bracketed generic inactivation of rodent retroviruses by low pH treatment for mAbs and recombinant proteins.

The opinions expressed in this poster are those of the authors and not necessarily those of the Food and Drug Administration or the U.S. Government.