VIRUSURE
VIRUS & PRION TESTING

Recent years have seen a shift in the paradigm for virus safety, away from an assumption that each pillar of the safety tripod (see Figure 1) contributes equally to the overall virus safety profile of a product, towards a view that virus inactivation and/or removal may play a more important role in assuring product safety. This shift in paradigm has played an important role in the how virus clearance studies are perceived, and therefore the degree of regulatory scrutiny that such studies receive. Ensuring therefore that such studies are performed in anticipation of such scrutiny, and that the design reflects current regulatory requirements, takes on great importance.

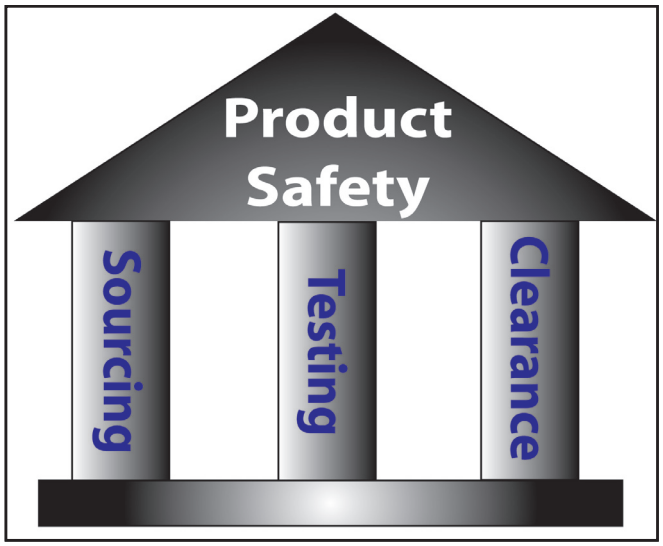
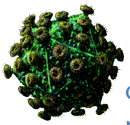


Fig. 1: The Safety Tripod: The virus safety of biopharmaceutical products is assured through a combined approach of sourcing, testing and virus clearance. But how equal are the contributions of each pillar?

Robustness: The robustness of any virus removal/inactivation step is today a critical component in the design of the virus validation study. The issue of robustness has been slightly confused by different definitions given



Of Parity and Virus Safety: The extent of the move away from a paradigm where each pillar of the safety tripod contributes equally to virus safety is product dependent, and has been most noticeable in the human plasma products industry. For human plasma-derived products, the actual contribution to risk reduction by donor selection, donor screening and virus inactivation/removal can be mathematically modelled and such studies have shown that donor screening and donor testing contribute in the order of a 1-2 $\log_{10}$ reduction in measurable risk for viruses such as HIV or HCV. In contrast, the incorporation of two steps into the manufacturing process, each providing in the order of 5.0 $\log_{10}$ inactivation or removal, can provide a risk reduction in the order of 10 $\log_{10}$. Such data has resulted in ever increasing scrutiny of the manufacturing process, in particular on ensuring that the design of the virus inactivation studies and the presentation of data is such that the reduction factors claimed can be relied upon.

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in the CPMP Note for Guidance on Virus Validation Studies and that given in the ICH Q5A guidance document on the Viral Safety Evaluation of Biopharmaceutical Products. The CPMP document defines robustness as "… parameters which influence the effectiveness of a process step to remove/inactivate viruses …" whereas the ICH document defines robustness in relation to the ability of the manufacturing process in general to removal specific or non-specific model viruses. For the purposes of regulatory review, the issues of robustness are discussed in light of parameters which influence the effectiveness of a process step to remove/inactivate viruses, although the value of the ICH definition should not be disregarded.

For inactivation steps, the kinetics of inactivation remains the most important information regarding the robustness of the step. Inactivation steps that provide for rapid and complete inactivation, or complete inactivation within 50% of the total exposure time, will provide a higher level of assurance than inactivation steps where virus is still detectable out to near the end of the process incubation.

For more information about our virus clearance testing services, please contact us either by email at Andy_Bailey@virusure.com, or using the contact details shown on the front page of this fact sheet.

Virus Selection for Clearance Studies

Target Virus Class	Example Model Viruses	Genome	Size (nm)	Envelope?	Resistance
Retroviruses*	Murine leukaemia virus	2x ssRNA	80-110	Yes	Low
Pestiviruses	Bovine viral diarrhoea virus	ssRNA	50-70	Yes	Low
Paramyxoviruses	Paramyxovirus type 3	ssRNA	100-200+	Yes	Low
Herpesviruses	Pseudorabies virus Bovine Herpesvirus	dsDNA	120-200	Yes	Low-Med
Reoviruses*	Reovirus type 3	dsRNA	60-80	No	Med-High
Polyomaviruses	Simian virus type 40	dsDNA	40-50	No	High
Parvoviruses*	Mice minute virus Porcine Parvovirus	ssDNA	18-22	No	High

The selection of viruses for virus clearance studies is dependent on the risk profile of the product. The selection should cover a range of physico-chemical properties, including those viruses with the high resistance to inactivation, and include those viruses which are potential contaminants. The viruses marked with an * are almost universally selected for the validation of virus clearance in recombinant biopharmaceutical products. Other virus types may also be considered if the risk profile of the product suggests potential contamination with members from that particular virus family.

All of the above listed viruses are available for use in spiking studies at ViruSure. This list however is not intended to be an all inclusive listing. Please enquire if there is a specific virus model you require for your studies.