VIRUSURE
VIRUS & PRION TESTING

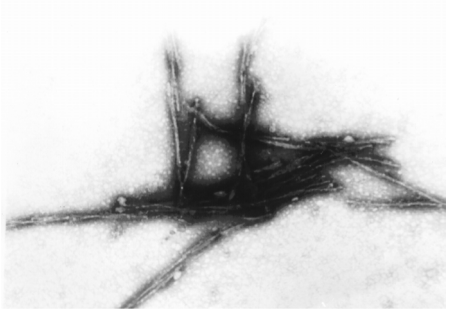
Prion Clearance Studies

With the trend in new vCJD cases occurring at a higher rate now in non-UK residents, reflecting most likely the later peak exposure to BSE in Europe and other areas of the world, the probability of finding vCJD plasma or blood donors who have contributed to plasma pools used for the manufacture of plasma derived medicinal products is also increased. As of early 2009, cases of vCJD outside of the United Kingdom have been reported in France (23 cases), Spain (5), Ireland (4), USA (3), Netherlands (2), Portugal (2), Canada (1), Italy (1), Saudi Arabia (1) and Japan (1). Furthmore, the rececnt confirmation that vCJD is was transmissible via clotting factor preparations prepared from a vCJD implicated plasma pool, has refocussed attention on the requirements to ensure sufficient prion clearance in plasma-derived products.

With the revised EMEA position statement on Creutzfeldt-Jakob disease (CJD) and the safety of plasma and urine derived medicinal products (EMEA/CPMP/BWP/2379/02 Rev. 1), there is a requirement for the manufacturers of human plasma derived products to perform prion clearance ("investigational") studies.

The term "investigational studies" used in the revised position statement on CJD and plasma-derived medicinal products accurately reflects the nature of the studies performed to demonstrate prion clearance. Validation studies, as virus clearance studies are often termed, implies a level of understanding of the infectious agent which in turn allows the type of studies that can produce in depth data relating to the robustness of a process step to remove or inactivate virus, It is clear that for prions, we do not yet have the level of understanding of the nature of infectivity in blood that would allow such certainty of study design and interpretation. It is therefore not appropriate to use the term validation in the context of prion clearance studies.

The EMEA guidance document on the investigation of manufacturing processes for plasma-derived medicinal products with respect to vCJD risk provides a framework assisting the design of prion clearance studies, and applies many of the principles that have served virus validation studies well over the years. Investigations for prion removal or inactivation however still present challenges not encountered with virus studies. Inactivation studies are one such example where study design can have a significant impact on the results and the interpretation of results.



Scrapie Associated Fibrils, a characteristic of prion contamination in high titre brain derived preparations (picture kindly provided by Dr Robert Somerville, Institute for Animal Health, Edinburgh, UK).

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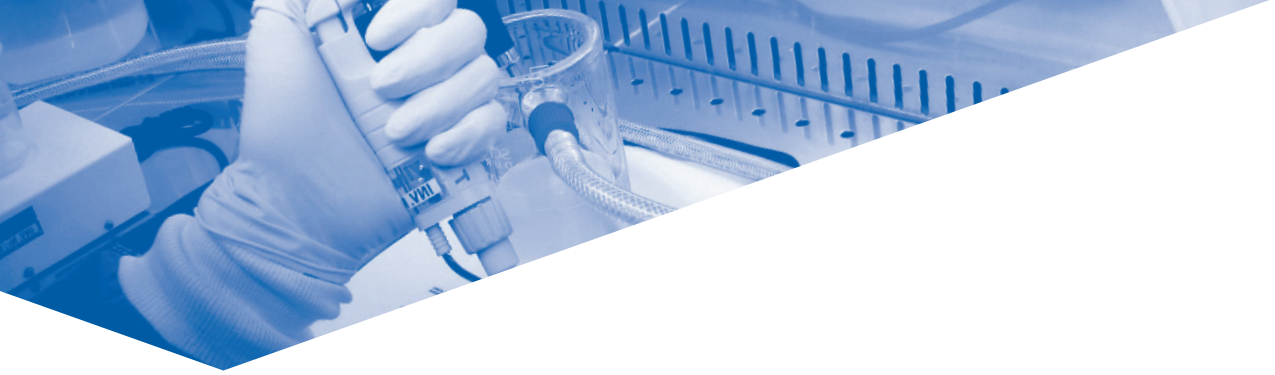

Prion Sanitisation

Published studies with prions have demonstrated that qualities of the spike preparation and microenvironment of the agent can have a dramatic effect on the capacity of an inactivation procedure to inactivate prions. Procedures which result in "fixing" of the prion agent, such as drying, treatment with organic solvents or cross-linking with aldehyde based disinfectants results in an increase in the proportion of prion protein demonstrating resistance to inactivation.

The observation of increased resistance to inactivation following certain procedures has implications for the disinfection of biopharmaceutical equipment or surgical instruments suspected of CJD contamination. Current practice for the GMP cleaning of biopharmaceutical equipment require that potential for carry over of product and contaminants must be minimised, that cleaning procedures are validated, and where components with an identified risk from TSEs are used, then prion cleaning/inactivation data may be required. Sanitisation therefore becomes a significant topic for discussion for multi-product facilities, for slaughterhouses collecting raw components for subsequent manufacture and where re-dedication of equipment previously exposed to potential risk material is performed.

ViruSure Prion Clearance Services

We are able to offer a number of services to assist you in meeting your prion removal requirements:

Western blot testing services

With our fully validated quantitative Western blot assay for 263K hamster adapted Scrapie, we can perform investigational studies on the ability of manufacturing processes to remove or inactivate prions in compliance with EMEA, FDA and JMHLW requirements.

In vivo prion bioassays

We operate a fully validated BSL-2 animal facility equipped for working with rodent adapted prion strains. We can therefore also perform *in situ* cleaning studies, using stainless steel wires exposed to high titre prion agents (based on the procedure as described by Flechsig et al. (Transmission of scrapie by steel-surface-bound prions.Mol Med. 2001 Oct;7(10):679-84)

TSE Model Agents Available at ViruSure

We are able to work with all available rodent adapted prion strains, but currently most studies at ViruSure are designed and performed using the 263K hamster adapted strain of scrapie. This agent has been widely used in prion inactivation/removal studies, and is widely accepted as a suitable model for other TSE agents in such studies.