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Pall Corp is developing membrane filtration technologies that are designed to reduce potential bovine spongiform encephalopathy (BSE) contamination in biologicals and biotherapeutics.

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Impact of BSE on the biotechnology industry — detection and risk assessment

Edited by Simon Atkinson

This feature briefly looks at filtration technologies that are being developed by Pall Corp to reduce the potential risk of ‘Mad Cow Disease’ in biological products and drugs. It also provides details of proprietary technology that is designed to reduce prions from blood prior to a transfusion.

Pall Corp is developing membrane filtration technologies that are designed to reduce potential bovine spongiform encephalopathy (BSE) contamination in biologicals and biotherapeutics.

Fatal disease

BSE, also known as ‘Mad Cow Disease’, is one of a family of invariably fatal, progressive, neuro-degenerative diseases widely believed to be caused by infectious ‘rogue’ proteins known as prions.

Recent data demonstrate that Pall membrane technologies, validated to remove a host of viral and bacterial pathogens, can also remove prions for a range of applications. These include removing prions from animal growth factors and serum that are used to manufacture drug therapies, as well as removing them from breathing filters used in medical procedures and from blood prior to transfusions.
Impact
Jerold Martin, Senior Vice President and Global Technical Director, Pall, provided details of developments in biological purification at BIO 2004, which was held recently in San Francisco, USA. His presentation, entitled ‘Impact of BSE on the Biotechnology Industry — New Developments in Detection and Risk Assessment’, was part of a risk assessment panel investigating the impact of BSE on the biotech industry.

BSE in North American
Since the discovery of ‘Mad Cow Disease’ in North American cattle during 2003, public concern has grown about the transference of BSE to humans, including the related ailments Creutzfeldt-Jakob Disease (CJD) and its variant (vCJD).

While attention has focused on protecting the food supply and donor blood from BSE contamination, preventing transmission of infectious prions is as important to ensure the safety of biological products and therapies, many of which are manufactured from animal sources.

Although biotech companies are striving to develop protein-based therapies that are serum-free, the reality is that many products currently use bovine serum-supplemented culture media,’ said Martin.

‘As concerns grow about the potential for BSE contamination, membrane filtration technology is increasingly being recognized and used as an effective method to remove prions to significantly reduce the risk of BSE contamination.’

Membrane filtration technology
Martin’s presentation detailed applications of Pall technology for prion removal. Pall Ultipor VF grade DV20 and DV50 filters, currently used for removing viral and bacterial contaminants during drug processing, have also demonstrated effective removal of four logs of prion proteins.

Approval
The European Agency for the Evaluation of Medicinal Products (EMEA) has qualified and approved the Ultipor DV50 filter for prion removal for Redimune immunoglobulin, manufactured by ZLB Bioplasma AG of Bern, Switzerland, and sold widely throughout Europe. The US Food and Drug Administration (FDA) is currently considering prohibiting the use of bovine materials suspected of BSE contamination in the manufacture of regulated products.

Based on both Western Blot assays and initial results of studies, it has also been found that a new filter technology under development from Pall removes prions to below the level of detection from scrapie-infected red blood cell concentrates. This technology, which combines leukocyte (white blood cell) reduction with prion removal in one small device, holds potential to increase transfusion safety.

Breathing system filter
In addition, the Pall Ultipor 25 Breathing System Filter, used in anesthesia and respiratory procedures, has been validated as a prion transmission barrier, significantly reducing the risk of cross contamination from prions as well as other infectious agents.

The Ultipor filter is also recommended to help stop the spread of Severe Acute Respiratory Syndrome (SARS) in hospitals for both anesthesia and respiratory care. Last year the Taiwan Respiratory Society and the Ministry of Health and Long-Term Care in Ontario, Canada (two locations hit hardest by SARS) issued directives on the use of high-efficiency breathing filters to help prevent disease transmission.

According to Martin, Pall has taken the lead in developing technologies that remove and, in some cases, detect prions from biologicals and blood products. He says that the company’s expertise in membrane filtration is helping to improve the safety of medical and biological products for human use.

Prion reduction
At the annual meeting of the International Society for Blood Transfusion (ISBT), which was held recently in Edinburgh, Scotland, UK, Pall unveiled a proprietary technology that reduces prions from blood prior to a transfusion.

The Leukotrap Affinity Prion Reduction Filter will provide the dual benefit of reducing harmful white blood cells while also reducing infectious prions, the rogue proteins that cause vCJD. The company presented the latest animal model research results in anticipation of launching the new filter in Europe during early 2005, where the problem of vCJD, the human form of BSE, is most critical.

Multi-targeted approach
The prion reduction technology will provide a multi-targeted approach to blood safety by reducing leukocytes and infectious prions that are either cell associated or non-cell associated.

According to Pall, in blood about 60% of prion ‘infectivity’ resides in leukocytes (cell-associated) and about 40% percent in plasma (non-cell associated). Research results show that the new filter has an affinity to all types of prions, including aggregated, denatured and normal.

‘This is a major milestone in the quest to protect the public from this insidious and always fatal neuro-degenerative disease,’ said Eric Krasnoff the company’s Chairman and Chief Executive Officer. ‘We are moving this technology forward rapidly. This is a seminal event in the international effort to stop the spread of vCJD. Blood centres and hospitals will soon be able to combine both prion and leukocyte reduction in a single, simple step.’

Blood transfusion
Prion transmission from human-to-human via a blood transfusion came to the forefront during December 2003 when a case of vCJD was identified in a person who received a blood transfusion six years earlier from a donor who later died of the disease.

Since vCJD has an unknown, albeit lengthy, incubation period that is asymptomatic, there is no way to know how many people already have the disease and how many could have already transmitted it via blood transfusion.

Studies
With support from the New York Institute of Basic Research, Pall is studying the new filter using three different assays — Western blot assay, bioassay and animal models of prion disease — to validate reduction of infectious prions.

An endogenous ‘infectivity’ study evaluated the efficacy of a prototype filter for the removal of scrapie-infected prions from red blood cell concentrates. After a 300-day incubation period, none of the hamsters (20) that received the filtered red cells developed scrapie, a transmissible spongiform encephalopathy. During the same period, two out of the 18 hamsters that received unfiltered red cells developed scrapie, exhibiting the clinical signs and symptoms of the disease.

Gold standard
It was found that the prototype Pall prion removal filter removed infectious prions from red cell concentrates below the limit of detection of the Western blot assay, the gold standard used to determine the presence of prions.

A bioassay was also used to quantify the amount of prion removal. It was found that the filter removed approximately 4 logs of scrapie-infected prions. The evidence to date, as demonstrated in the animal model, suggests the reduction of prions, both free and leukocyte bound, may provide a higher margin of transfusion safety.

Storage periods and procedures
Graham Rowe, head of Laboratory Services of the Welsh Blood Service, also reported at ISBT the results of a study he conducted to determine what, if any, effects the new filter may have on red blood cells following the usual storage periods and procedures.

This study evaluated the filter using three commonly used but different anticoagulants and
their associated storage times. He compared the effects of prion and leukocyte filtered red cells with leukocyte-only filtered red cells, and also compared these results to historical data. These preliminary results have demonstrated that blood filtered with the Pall Leukotrap Affinity prion reduction filter is substantially equivalent to control blood units from a safety and efficacy point of view.

Blood centres
Since a majority of blood transfused in the industrialized world is currently leukocyte reduced, a filtration approach can swiftly and easily fit into routine operating (cGMP) practice already in use in blood centres around the world. It is expected that the new technology will meet the requirements of the Council of Europe for a CE mark and will be ready for operational trial in Europe beginning in early 2005.

The company continues to study the new technology and will release additional results on the animal model research in the coming months. It says that it is also planning to conduct clinical surveillance studies after receiving the CE mark to continue to add to the knowledge about transmission of prion diseases.

Boon to public health and safety
Although the incidence of new cases of vCJD have appeared to slow down over the past few years, many experts believe that we should not be lulled into a false sense of security.

Since the disease has an unknown incubation period without clinical sign or symptoms, a proportion of the population could be harbouring vCJD and acting as blood donors. The existence of sub-clinical prion carriers raises concerns of a human-to-human wave of transmission, posing a potential threat to the safety of the blood supply.

These experts contend that the possibility of further increases in the number of cases, even a human epidemic of vCJD, cannot be dismissed. Since the risk of vCJD is not restricted to the UK, the examination of the history of blood donation may be required in other European countries and elsewhere.

Pall is also studying the new technology as a potential detection device to identify ‘Mad Cow Disease’ in cattle, as a means to help protect the food supply. According to an April 2004 Consensus Conference on Transmissible Spongiform Encephalopathies, there is currently no reliable or practical way available to determine the presence of BSE and vCJD in food or in living asymptomatic animals or people.

Prion diseases
Prion diseases are fatal, neuro-degenerative diseases, referred to as Transmissible Spongiform Encephalopathies that affect both humans and animals. They include scrapie in sheep, bovine spongiform encephalopathy in cattle and vCJD in humans.

It is estimated that the incubation period (prior to clinical symptoms) for vCJD may be anywhere between 10 to 20 years. Since the first human case of vCJD was identified in 1994, there have been 154 confirmed cases worldwide with the vast majority (143) in the UK. On 17 December 2003, the Secretary of Health of the UK announced the first case of a patient dying from vCJD, received from a blood transfusion during an operation.

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