Foetal Bovine Serum – a challenging future

Serum and other blood-derived products have been widely used in the research and pharmaceutical arenas for many years. The use of this material has contributed widely to the many and varied advances in medical and veterinary health and these products continue to have an important role in research and drug development.

Foetal bovine serum has had a very specific role in the culture of mammalian cells for over 60 years. It has proved to be a very useful tool based on the broad spectrum of applications and the ability of the product to support a large range of differing mammalian cell types.

The Directive 2010/63/EU of the European Parliament and of the Council of 22nd September 2010 on the protection of animals used for scientific purposes (3Rs) has had a significant impact on the use of both animals and animal derived material within the scientific community with a focus on developing new methods for the testing of compounds together with replacement products to minimise the use of products such as foetal bovine serum.

Criticisms of the use of serum and, notably, foetal bovine serum, include concerns governing the potential ethical risks surrounding the methods employed for the collection of blood, that there have been multiple instances of fraud within the serum industry and the fact that serum is a non-defined biological material resulting in batch-to-batch variation and subsequent inability to reproduce specific *in vitro* studies and quantify resultant data.

Collection methods are controlled through the slaughterhouse process since foetal bovine serum is only collected at facilities where animals are slaughtered for human consumption. These facilities have veterinary officials who are present to monitor every stage of the process.

Fraud and the potential for fraud has been addressed, vigorously, by the actions of the International Serum Industry Association, the ISIA. Life Science Group (LSG) Ltd is proud to be a Traceability Certified member of the Association. The Association has served to develop the programs to allow customers the ability to challenge origin of product, both by testing for geographical origin and also through the analysis of biomarkers to demonstrate the age of the animals from which material was collected.

Many companies offering foetal bovine serum will talk about their material as being 'defined' but in reality, relatively little is known of the composition of this very complex mix of proteins, growth factors, cytokines, chemicals and other myriad components that constitute serum. It is the very composite nature of serum that introduces variables into cell and tissue culture systems.

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Tel: +44 (0) 1234 889180; Email: sales@lifesciencegroup.co.uk
Web: www.lifesciencegroup.co.uk

Science continues to demand more and more by way of specificity and reproducibility. Serum, particularly foetal bovine serum, is currently failing to meet that challenge and it is the responsibility of serum collectors and manufacturers to understand and support the requirements of the scientific community thereby enabling scientist to make more informed decisions concerning the raw materials they employ for specific studies.

The challenges facing the serum industry are threefold:

1. Demonstrate and certify safe and ethical collection methods for foetal bovine serum are employed at all collection sites
2. Reduce batch-to-batch variation
3. Enhancing the chemical and physical definition of foetal bovine serum, developing test panels that give relevant information allowing customers to understand the composition of the product and to select batches accordingly.

Safe and Ethical collection

Certification, similar to that currently issued by veterinary officers present at slaughterhouses, could be designed and issued confirming the length of time between removal of the foetus from the dam and collection of the blood is beyond the minimum time set to ensure that the foetus cannot experience pain or discomfort during the collection process.

Batch-to-batch variation

Inclusion of information on the Certificate of Analysis such as to collection origin, manufacturing origin, date of collection, date of processing and other processes performed on each batch of serum would enable to customer to identify material not only be physical country of origin of the blood but also any changes in the properties of the batch due to the time of year of collection, the number of manufacturing processes and other factors that contribute to the functional properties of each batch of serum.

Origin

It is a common belief that serum collected from certain origins, such as New Zealand, is of superior quality than material collected from South America. Whilst it is true that origin does have an impact on the price of serum, it does not affect the quality or activity of the product. Foetal bovine serum collected under the same conditions from any country will demonstrate comparable ability to support cell growth. For foetal bovine serum the term ‘quality ‘ is frequently confused with ‘health status’ and it is the ‘health status’ of the country from which the serum is sourced that will dictate the potential use, the availability of material for import and eventually determine the price.

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The health status of a country is determined by the OIE, the World Organisation for Animal Health. The mission of the OIE is to ensure transparency in the global animal disease situation. The Organization issues information concerning the health status of various countries with regard to animal diseases including Foot and Mouth, BSE and other diseases affecting cattle populations globally. The status of a country for animal disease of interest will determine where serum collected within that country may be exported. For foetal bovine serum it is this health status which currently determines the suitability of material for certain applications and this is usually reflected in the price. It is for this reason that traceability within the supply chain for those end users required to use material from specific origin is extremely important. It is for this reason that the ISIA has developed methods by which end users can confirm that the serum they have purchased to be of a specific origin is definitively from that origin.

Risk Mitigation

As discussed earlier, foetal bovine serum does not differ from country to country in terms of the ability to support cells. What differs is the health status of that country and the risk of disease transmission. There are steps that can be taken to mitigate some of these risks. These steps include filtration and gamma irradiations. Filtration to 0.1 micron or below can remove bacteria and some mycoplasma. Gamma irradiation may be employed to control the viral load in all types of sera although this may have an effect on the functionality of the serum. There is currently no process available to remove prions from serum commercially for serum collected from BSE affected areas although it has been shown that prions are not present in blood and blood products.

Barrier-free Trade

It is an industry dream that serum, collected under supervised and controlled methods and from facilities where animals are slaughtered for human consumption, would share the same status and be able to be shipped globally and without barriers. In reality this is unlikely to happen since the OIE will continue to monitor animal health and to suspend areas during outbreaks of animal disease and, currently, gamma irradiation is not considered to be a sufficient risk mitigation step to avoid the potential for transmission of disease. Additionally international trade agreements for the export of meat from certain areas and the associated political pressures will all impact the ability of serum to move freely.

The ISIA understands that it is the duty of the Association to work with regulators globally in order to help them understand the importance of these products and to understand the actual risk as opposed to the perceived risk of transmitting disease through blood derived materials. The ISIA will continue to work to develop treatments for the manufacture of sera and to slowly, through scientific argument, open some of these barriers to allow the free movement of material in what is becoming an increasingly global economy.

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Defined FBS

The industry, through the ISIA, could work with the global customer base for FBS to understand the concerns and requirements for physical and chemical parameter testing in order to set an industry minimum standard of testing for FBS to enable customer to have a clear understanding of the composition of each batch, and the likely effects of the serum on their study or manufacturing process. These tests could include a much larger panel of functional assays, increased number of antibody profiles, hormone profiles, antibiotic tests, growth factor determination and chemical profiles as standard.

It should be understood that the challenges faced by the serum manufacturers are not challenges to them alone. Manufacturers of any biologically active material destined for use in cell and tissue culture face these same issues.

Alternatives to FBS

There has been a great deal of time and effort spent in the search for the 'Holy Grail' – the single alternative to replace foetal bovine serum in cell culture. To date, this has not been achieved although there are many 'serum-free' media available and these are not without issue. Formulations are not made public for commercial reasons in order to protect IP so scientist are, effectively, in the same position as with the use of foetal bovine serum.

Excipients within formulations, such as insulin, have a similar issues with batch-to-batch variability as any other biological with the exception that these differences are hidden within a 'standardised' formulation. Home-made media, even when the formulation is known, will show variation unless identical excipients from identical lots of raw material are used within the manufacture.

Plant-derived materials can introduce both animal and plant derived adventitious agents into cell cultures and are also subject to the same issues of lack of definition and batch-to batch variability.

Human serum is also used for the support of cells in culture and this, also, is not without problems. There are concerns over ethical collection, the impact of the use of human serum for cell culture competing with serum required for clinical needs, the viral risk inherent in batches of human material pooled from a large number of donors. Human serum has, of course, the same unknown composition as foetal bovine serum.

Human serum is also currently widely used in cell therapy to support cells prior to transplantation.

Conclusion

It is clear that it is not so much the origin of the material used to support cell and tissue culture that is the issue but the understanding of the composition of the material of choice. This will always be a

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fundamental issue with artificially designed 'serum-free' media formulations since companies will be unwilling to share commercially sensitive information. This will result in the scientist being in the same position as with foetal bovine serum currently, in the dark.

Biologically derived material, such as foetal bovine serum, can be made more acceptable to the scientific community by enhanced testing, thereby opening the 'black box' which is currently foetal bovine serum and resolving the issues caused by the lack of physical and chemical definition of the product.
It would seem, therefore, that it is in the best interests of both the scientific community and serum manufacturers to achieve a greater understanding of this amazing resource.

Jennifer Murray
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International Serum Industry Association
www.serumindustry.org
jennymurray@lifesciencegroup.co.uk