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Fetal Bovine Serum: The Impact of Geography

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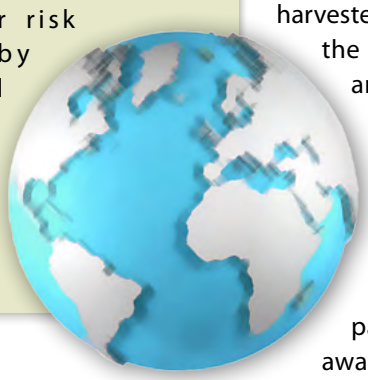
Introduction

Misunderstandings persist regarding geographic origin when sourcing fetal bovine serum (FBS), particularly as it affects quality and cost. This brief communication provides an overview of FBS and sourcing considerations, and direction to resources for further research on related questions.

A key concept in evaluating quality in animal-derived raw material is that it is impossible to fundamentally improve the quality by means of *any* processing. Quality must begin at the source.

The importance of geographic origin in suitability assessment is too often overlooked. Global geographic incidence of bovine disease or adventitious agents presents an opportunity for risk management by selecting material from geographic areas with the most limited disease/agent profiles.



General Overview of Serum and Its Uses

The primary application of FBS is to fortify cell culture media. It is the most common media supplement used for cell culture. No other supplement has been found to provide the same degree and universality of cell growth stimulation. This cell growth stimulation comes from the abundance of blood-associated biochemicals responsible for the rapid cellular development inherent in fetal maturation. Although other types of serum may be used (*e.g.,* calf serum) equivalent performance cannot be expected. Alternative sera lack the full range and concentrations of powerful growth stimulants present in FBS.

FBS can be used with virtually all mammalian cells grown *in vitro* for research and production. This includes applications in cell-based research, drug discovery, diagnostics, toxicity testing, cell therapy, *in vitro* fertilization, human and animal vaccine production, as well as biopharmaceutical manufacture. Each of these applications carries a different risk profile with regard to potential adverse effects stemming from the use of serum. For example, serum used in research typically involves negligible risk. In contrast, the potential risk is somewhat greater, yet manageable, for serum applications in cellular therapy products, vaccines, and biopharmaceuticals destined for licensure in animals or humans. These applications require additional risk management strategies focused on quality testing and geographic source verification.

FBS is derived from whole blood obtained from normal bovine fetuses harvested from healthy cows at abattoirs. Governmental inspectors assess the health of each cow, and fetuses are collected only from those animals deemed fit for human consumption. Therefore, FBS is a by-product of the meat processing industry.

After aseptic collection, the blood is further processed under carefully controlled conditions. Representative samples from pools are taken and subjected to a battery of tests including sterility (bacterial, fungal, and mycoplasmal), endotoxin, immunoglobulin (IgG), hemoglobin, viral screening, biochemical panels, and electrophoretic profiles. Finished product is frozen to await sampling for quality control release to buyers.

Sterile-filtered FBS may also be treated using gamma irradiation or heat-inactivation and should be labeled to indicate the post-filtration treatment. These treatments provide additional security in controlling potential adventitious agents such as viruses.

FBS Market Economics

Volatility in the pricing of FBS causes widespread frustration and can make budget forecasting very difficult. The reasons for this are manifold. As finished goods, FBS prices essentially follow standard supply and demand economics. However, this is only a secondary factor in its pricing dynamics. The primary factor and main market-driver is the beef processing industry, since FBS is produced as a by-product of this industry. Animals are not raised and prepared solely for the harvest of fetal blood. Therefore, the intersection of the primary cost-driver, meat supply-demand, and the demand for FBS, often clash to cause a whirlwind of cyclical and unpredictable FBS pricing.

The number of pregnant animals coming to slaughter is determined by a multitude of events independent of the serum market. These include:

- Weather-induced cattle sell-offs—drought and harsh winters
- Cattle retention—ample forage and government intervention in the agriculture market
- Dairy cow buy-outs to reduce milk production
- Increasing milk and meat demand due to exports often precipitated by adverse weather or animal health conditions elsewhere globally

Additionally, erratic and seemingly unplanned industry demand for FBS contributes to pricing turmoil. Large-volume consumers may make requests for quotations from multiple suppliers giving the false impression that demand has suddenly increased. This induces a rush to find supply, and bidding wars for fetal bovine blood may result. These pricing disruptions do not create more serum but only determine which supplier will have the inventory to sell. This impact can be magnified if more than one buyer acts in a similar time frame.

Pricing becomes even more complicated when overlaid by the fact that some buyers can only use serum produced in certain geographies. In these situations the supply and demand pressures are intensified and cause even more pronounced swings in FBS pricing.

It is well known that serum originating from New Zealand and Australia is higher in price when compared with United States and Canadian origins. Further, serum from these four countries is priced significantly higher than that from most South American countries. This price stratification results from the demand placed on FBS from preferred geographies by manufacturers of medicines who consume serum in large volumes. These price differentials reinforce the need to be vigilant in evaluating certificates of origin (COO) for accuracy.

Assessing Quality

The most important step in assessing serum quality is to determine its intended use. The determination of the serum quality necessary to comply with good laboratory practices (GLP) in research can be very different from that required for human medicines (good manufacturing practices [GMP]). Research applications permit significant flexibility in serum characteristics. However, there are commonalities of basic quality testing to which FBS should be subjected. These include those tests mentioned previously. Virus screens are also common. Additionally, an electrophoretic profile can provide assurance that the FBS IgG levels are characteristically low, thus establishing differential identity from other bovine sera. For further information regarding suggested quality testing, including specifications, visit the International Serum Industry Association (ISIA) website.[1]

Geography of Origin

This is often the most overlooked factor, yet a very important parameter when considering quality for intended use. The issues to consider are summarized below.

- Global geographic variation in disease history and currently prevalent bovine diseases, or adventitious agents, allows risk reduction by restricting purchases to those geographic areas with the most limited disease/agent profiles.
- The World Animal Health Organization (OIE) website contains comprehensive animal disease status reports from around the world.[2] This site is invaluable in assessing the risk associated with bovine adventitious agents that may occur in the raw product. The fewer diseases prevalent in the country of origin, the lower the risk of disease agents being present in the serum.
- Certain bovine viruses such as bovine viral diarrhea virus (BVDV) occur worldwide while other bovine diseases display distinct geographic prevalence. For example, neither foot-and-mouth disease (FMD) nor bovine spongiform encephalopathy ([BSE] "mad cow disease") has ever occurred in New Zealand. Many of the countries where both FMD and BSE have been identified have successfully implemented eradication measures while disease control in some other countries is just beginning. There are countries in which FMD, for example, is an ongoing problem.[2]
- Restrictions placed on the importation of animal-sourced material by agriculture regulators must also be taken into consideration. Often industrial-scale buyers of FBS have manufacturing plants in countries where the domestic supply is limited or of unsuitable quality. The serum, therefore, must be imported. The specifications as to acceptable supplying countries must, of necessity, be harmonized between the buyer and the respective

government import regulators. These regulations are often based on the same animal disease status profiles as presented by the OIE. Therefore, it remains critical to consider the geography of origin when sourcing serum.

Geographic Origin—Verification Issues

Again, the decision to specify geographic origins are dependent on the intended use of the serum. It is paramount for applications leading to manufacture of a licensed product for human or animal use. All quality parameters can be determined by testing except for the geographic origin. This leaves the buyer to rely only upon documentation for verification of origin. One should exercise extra vigilance in confirming the integrity and authenticity of the certificates of origin.

To that end, the ISIA recently implemented traceability standards and an auditing system to verify the authenticity of the country of origin claims made by any serum supplier.[3] The system sets industry standards for the documentation trail and product preparation from the abattoir to the buyer:

- Most importantly, a rigid program of third party audits is used to verify standards compliance.
- ISIA Traceability Certified status is awarded to suppliers who adhere to ISIA guidelines and are the subject of a successful audit.

Trust but Verify

All buyers are encouraged to use due diligence in vendor qualification of all serum suppliers. While most of the audit procedures used in routine supplier audits will work with serum suppliers, a thorough audit of the traceability system is not routine. For those unfamiliar with audit procedures that are customized for serum suppliers, consult the ISIA website for help.[4] Additional measures of safety and supply chain confidence are obtained by requiring that suppliers are ISIA Traceability Certified.

Photo courtesy of Thermo Fisher

Summary

Serum is a unique product not only due to its composition but also because of its volatile pricing and its complex, regulated sourcing. Establishing appropriate specifications based on intended use is critical. Trust suppliers to provide serum that meets your specifications and maintain that trust through proper and periodic on-site audits.

Quality cannot be tested into FBS. Verifiable quality starts from the moment of harvest and continues until the moment the bottle is sealed, frozen, and shipped to the buyer:

- Verification of traceability documentation of the serum to its specified geographic origin is often overlooked as a critical part of quality audits.
- Country of origin has a material impact on the product risk profile with regard to the potential lack of adventitious agents.
- Governmental import-export restrictions for both raw materials and finished goods are inextricably linked to geographic country of origin.

This is especially true for biopharmaceutical manufacturers. Those working in research have fewer concerns, but many times the lines between research and manufacturing can change. Know your vendors. Specify ISIA Traceability Certified credentials. Request certificates of analysis (COA) and COOs.

References

[1] http://www.serumindustry.org/documents/ISIAStandardizationdocument081.pdf
[2] http://www.oie.int/en/
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