EXECUTIVE SUMMARY

In today's volatile sera market, it is critical for sera users to understand the complexity of the product they purchase. BioProcessing Journal, a quarterly publication covering technological advancements and best practices for the development and production of safe and effective biologics, recently published two articles that address important points to consider when evaluating sera products and suppliers. The articles titled "Fetal Bovine Serum: What You Should Ask Your Supplier and Why" and "Fetal Bovine Serum: The Impact of Geography" highlight the market dynamics currently driving price volatility, product availability, supply chain disruptions, and regulatory changes. These articles also outline for sera users what actions to take to successfully navigate current market conditions and how to ensure their cell culture work flows are safe guarded.

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FETAL BOVINE SERUM: 
WHAT YOU SHOULD ASK 
YOUR SUPPLIER AND WHY

By DEVIN DAVIS and SHERRIE DRAKE HIRSCHI

INTRODUCTION

In today’s volatile sera market, it is critical that sera users worldwide thoroughly review their supply relationships and update sourcing and risk mitigation strategies. BioProcessing Journal’s recent article by Siegel and Foster highlighted the impact of selecting the appropriate country of origin as one criterion for purchasing decisions.[1] Many more vital selection criteria exist to ensure a sera supplier provides long-term assurance of supply and integrity of supply. This article identifies critical questions sera users should ask their suppliers and explains why they should ask them.

CHANGING MARKET DYNAMICS NECESSITATE REVIEW

The sera industry has experienced substantial changes in the last year. Mergers and divestitures have introduced instability to, and turnover of, once-stable supply relationships. The first mass recall of fetal bovine serum (FBS) in history for adulterated product affected a large number of sera suppliers and users.[2] The World Organisation for Animal Health (OIE) announced the risk status of bovine spongiform encephalopathy (BSE) upgrade in the United States to “negligible risk,” establishing US-origin FBS as equal in safety to that of Australia and New Zealand.[3] In addition, new industry standards for quality and traceability have been established to inform, protect, and support sera users in selecting a sera supplier.[4]

These historic changes—combined with reduced availability of sera due to historically low cattle inventory levels[5]—demonstrate that the traditional paradigm for sourcing sera is no longer valid. Sera users can use the following discussion points to kick-start a conversation with existing and potential sera suppliers to ensure their research or production requirements are uninterrupted by these dynamics.

DISCUSSION POINT #1: ASSURANCE OF SUPPLY

Assurance of supply resides at the source—the abattoirs where the raw materials for sera products are procured. Sera suppliers attempt to provide sourcing stability to their customers by establishing strong relationships at the source. Many of these relationships have shifted due to the merger and divestiture activity of the past year, and those shifts have altered the ability of suppliers to provide long-term supply stability.

Similarly, a sera supplier’s relationships at the source have a dramatic impact on the quality of products they supply. Product quality indicators—such as endotoxin and hemoglobin levels—are driven by the care and attention given to the raw materials when initially collected and processed. Not all abattoirs, collection techniques, and raw material processing steps are created equal.

Reputable sera suppliers take the time to educate their customers about their supply relationships, collection and processing steps, and any changes that have occurred as a result of the market dynamics previously mentioned. Sera users should thoroughly investigate the ability of a supplier to provide long-term assurance of supply. This investigation may validate current sourcing practices or uncover sourcing risks that were not previously known.
ASSURANCE OF SUPPLY

WHAT QUESTIONS TO ASK | WHY IT IS IMPORTANT
---|---
• Describe your supply relationships at the source. | • Allows the supplier to articulate their story
• Where do you collect? Which beef packers do you work with? Why do you work with them? | • Quantifies the scope of their supply chain and why they are organized that way
• Are you single-sourced or multi-sourced? | • Quantifies risk of interruption; given reduced product availability, multi-sourced is more secure
• Do you do the work yourself or involve a partner? Why do you do it that way? | • Pros and cons exist for both vertically integrated or outsourced supply chains. Find out why the supplier prefers their approach and which certified partners they work with
• What kind of agreements are in place? | • Understand what type and length of contracts are in place to reduce risk of supply interruptions
• Has any of this changed recently? | • Assurance of future supply may be at risk due to supply realignment; reputable suppliers support full transparency and will be forthcoming about impact of any changes
• Can we make a site visit? Perform an audit? | • Demonstrates transparency and standards compliance, provides opportunity to validate supplier claims; go where you want to go, see what you want to see

DISCUSSION POINT #2: INTEGRITY OF SUPPLY

Integrity of supply means that all aspects of product quality and traceability are well-documented, validated by independent audit, and completely transparent. In their recent article, Siegel and Foster[1] emphasized the importance of “exercising extra vigilance in confirming the integrity and authenticity” of information provided by a supplier and performing “due diligence in vendor qualification of all serum suppliers.” They encouraged sera users to do a “thorough audit of the traceability system,” to “know your vendors,” to conduct “proper and periodic on-site audits,” and ask for the appropriate “credentials.” These recommendations underscore the fact that strategic, quantifiable differences exist between suppliers, their products, and their operations.

The International Serum Industry Association (ISIA) has established industry standards and certification programs to aid sera users in substantiating integrity of supply.[4] Five years ago, the ISIA developed and implemented a rigid program of independent audits to verify compliance with traceability standards. Elite status as an ISIA Traceability Certified supplier is awarded to those who demonstrate full compliance with ISIA guidelines and are the subject of a successful audit. Further, it has established strict guidelines for product quality testing and reporting on documents like certificates of analysis (CoA). Sera users should source exclusively from ISIA-certified companies to ensure traceability and product quality. A list of certified suppliers, filtration partners, and raw material providers is maintained on the ISIA’s website.[6]

Product quality and traceability is also enhanced by validated technology enhancements in the manufacturing process. Implementation of single-use, disposable filtration technology eliminates cross-contamination risk from lot-to-lot and maintains true traceability – a technology that is widely used downstream in bioproduction environments. Additional measures such as maintaining the cold chain during filtration ensures that the bioburden of the sera is unchanged during processing and final packaging.

Sera users should use the above standards, programs, and technologies to comprehensively examine
Suppliers' integrity of supply, conduct on-site audits, and identify and discuss any points of non-compliance. Any hesitation in this regard on the part of a supplier is a serious cause for concern.

CONCLUSION

Changing market dynamics have altered the historical paradigm for sourcing sera. Sera suppliers may be hesitant to explore the impacts of these dynamics with sera users, as it exposes problems that, to their point were overlooked or ignored. However, the exercise serves the long-term interests of both sera suppliers and users. The responsibility to scrutinize the supply strength and product integrity of a supplier rests squarely on the shoulders of sera users. The discussion points outlined in this article will facilitate sera users in the discharge of that responsibility and lead to a stronger, long-term relationship with their ideal sera supplier.

REFERENCES


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FETAL BOVINE SERUM: THE IMPACT OF GEOGRAPHY

By WILLIAM SIEGEL and LELAND FOSTER

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.

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.
FBS Market Economics

Volutility in the pricing of FBS causes widespread frustration and can make budget forecasting very difficult. The reason 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. 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.
- 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

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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. 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. Additional measures of safety and supply chain confidence are obtained by requiring that suppliers are ISIA Traceability Certified.

**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.

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**References**


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