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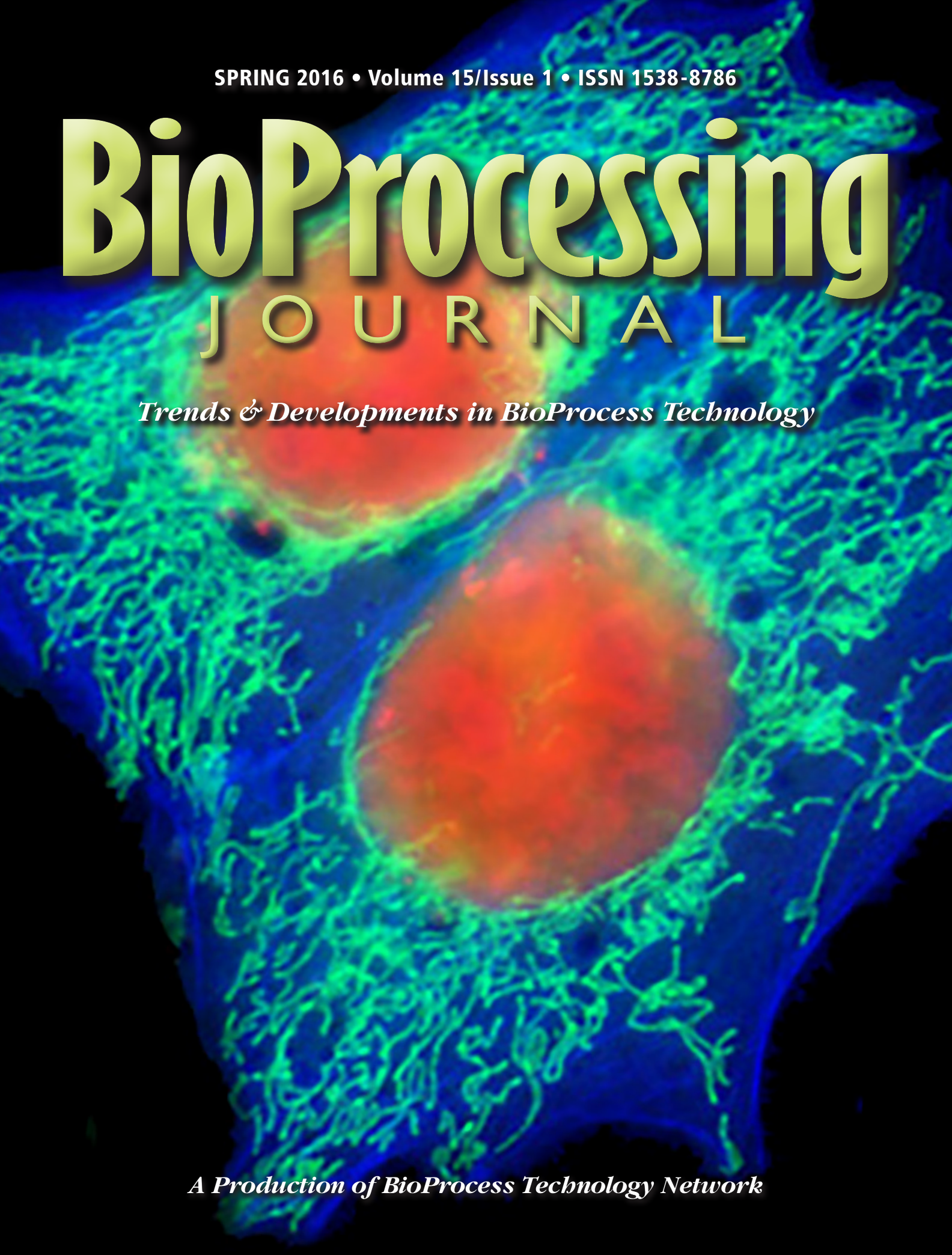
Trends & Developments in BioProcess Technology



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TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Fetal Bovine Serum: Risk Management

By William Siegel

Introduction

Safety is typically viewed, perhaps unconsciously, as the result of a collection of factors, conditions, or behaviors. For example, consider "safety" in the context of personal, financial, or travel. With each, safety is defined as a set of component risks that have been managed to satisfactory levels for a particular situation. The same is true for product safety and risk, whether it be for raw materials or finished goods.

The "safe" use of fetal bovine serum (FBS) is achieved by the management of controllable risks to a level that is acceptable for each particular application. For example, risk reduction requirements for research applications are not as stringent as for diagnostic, therapeutic, or manufacturing applications. Each end-user must decide on the level of risk reduction that is appropriate for their application.

Manageable risks occur in the following areas, and begin at the point of collection.

- **Geography:**
  - disease prevalence profile
  - importation laws restricting your choices of origin countries
  - robust, trustworthy infrastructure in country of origin
  - adequate supply of material available from countries selected
- **Supplier Transparency:**
  - audited and reputable vendors
- **Product Manufacture:**
  - adherence to cGMP guidelines
  - validated sterile filtration
- **Product Testing:**
  - viral infectivity screening
- **Post-Manufacture Treatment:**
  - validated irradiation

Geography

As one of several interrelated risk management topics, Leland Foster and I addressed FBS issues that focused on geography in our previous *BioProcessing Journal* article, "Fetal Bovine Serum: The Impact of Geography."[1] In this current article, I want to emphasize the overall collective view of safety and risk reduction, which also includes geography. This is intended to enhance reader awareness of relevant and critical issues that lead to "good" decisions for a particular application.

Disease prevalence in FBS-origin countries is an ongoing and serious concern for regulators who oversee FBS importation, and also for those who monitor licensed product manufacture and diagnostics. As an example, the US Department of Agriculture (USDA) website states, *"The Animal and Plant Health Inspection Service (APHIS) is a multi-faceted agency with a broad mission area that includes protecting and promoting US agricultural health. If, for example, foot-and-mouth disease was to become established in the United States, foreign trading partners could invoke trade restrictions and producers would suffer devastating losses."*[2]

One might say that a certain degree of mandatory risk management is imposed on end-users by governments and regulators. Each country restricts available choices of FBS-origin countries that can be imported to the point of use. Although a single incident of viral disease is not equivalent to an epidemic outbreak, regulators must be continuously vigilant in monitoring global outbreaks and then take appropriate action. Preventing avoidable animal and human disease, as well as catastrophic economic losses, is a significant responsibility.

The robust and trustworthy infrastructure in FBS-origin countries is key to high levels of confidence in supply chain security. An unbelievably low price may come at the expense of adulteration and/or misrepresentation. Political instability sometimes accompanies low trust

Image courtesy of Beef + Lamb New Zealand, www.beeflambnz.com.

environments. This can lead to shipment seizures, criminal charges (perhaps unjust), and supply interruption.

Although certain FBS-origin countries may be satisfactory in all other respects, the FBS harvest output may be inadequate for long-term assurance of continued supply.

Supplier Transparency

Safety and continuity of supply are cornerstones of the Davis and Hirschi *BioProcessing Journal* article, "Fetal Bovine Serum: What You Should Ask Your Supplier and Why."[3] The authors make two main points: (1) the assurance of supply; and (2) the integrity of supply. Supplier transparency for site visit audits is a primary concern.

> ***Key Fact:*** *Available historical data—without exception—supports the safe use of serum in biomanufacturing processes.*

I fully support their views and wish to add that standard audits alone may be inadequate to reveal intentional FBS fraud and concealment of relevant facts. The serum supply chain has many unique facets. This presents a temptation for the potential bad actor to take advantage of auditors who are inexperienced in the serum industry, particularly with respect to traceability.

In addition to rigorous on-site audits, traceability certification audits are now available and are quickly becoming a standard end-user requirement. Since its inception in 2006, the International Serum Industry Association (ISIA, www.serumindustry.org) has promoted the highest level of industry ethics and safety in the animal-derived products supply chain. The ISIA established an industry standard program of traceability audit certification, now widely supported by end-users and suppliers alike. ISIA members provide approximately 90 percent of the serum used in the life sciences market.

Product Manufacture

Electing to purchase from suppliers that adhere to validated cGMP manufacturing guidelines reduces risks related to sterile filtration, adulteration, and mislabeling. Additionally, cGMP manufacturing provides a common framework upon which auditors can conduct site audits.

Product Testing

Risks related to bacterial contamination are probably very low. Validated sterile filtration methods are highly effective. The flexibility inherent in the required testing methods (*e.g.,* 9 CFR, EP, *etc.*) allows vendors to employ differing methods for mycoplasmal and viral screening, and sometimes screen for a reduced number of viruses. The risks of poorly executed adventitious agent screening (mycoplasmal, bacterial, and viral) can be reduced by successful audits that confirm the suppliers' effectiveness.

Post-Manufacture Treatment

Further risk reduction for adventitious agents is obtained by post-manufacture irradiation. Validated gamma irradiation (25–40 kGy) provides the greatest assurance of viral infectivity while retaining FBS performance. Gamma irradiation cannot guarantee the complete and total removal of viral contamination in FBS. A radiation dose sufficient to yield a sterility assurance level (SAL) of 10^{-6} reduces FBS performance to unsatisfactory levels.

Avoid FBS?

Serum-free and non-animal-derived culture media have applicability in certain circumstances, but have limitations and tradeoffs to consider.

- Some cell culture processes cannot be converted to serum-free conditions.
- Time and expense, perhaps considerable, must be invested to determine if serum-free conditions are possible, and if so, how to optimize them.
- Reduction in product yields and growth rates are expected, at least initially.
- Expensive supplements can make the project economically nonviable.
- Plant-derived materials have risk profiles linked to cultivation (*e.g.*, fertilizer) and unique trace contaminants with unknown impact on biological systems.

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Conclusions

Safe sourcing of FBS cannot be attained solely by electing to buy FBS from the country with the lowest number of viral infection incidents. Also, recall that an "incident" is not equivalent to an epidemic "outbreak." "Safe" is a relative term that is now understood to imply acceptable risk management for a given circumstance.

Biologics manufacturers of licensed products favor FBS from the USA, Australia, and New Zealand. This is because there is convergence of factors that minimize overall risk to a satisfactory level for this particular application. The arbiters of "satisfactory levels" are risk managers inside the company, licensing regulators inside the government, and governmental import/export regulators overseeing import of the FBS, and perhaps export of the final product.

Applications for FBS in research and diagnostics have less stringent requirements for satisfactory risk reduction profiles. This does not mean that their FBS is "unsafe." It merely means that, for these applications, satisfactory risk reduction fits a different profile.

Lastly, know your supplier. This is a key factor in risk reduction. There is no substitute for supplier transparency, supplier traceability certification, and supplier audits. Ask the hard questions at on-site audits and expect willing cooperation, veracity, and verifiability. As Davis and Hirschi conclude in their article, *"Any hesitation in this regard on the part of a supplier is a serious cause for concern."*[3] Yea, verily.

Image courtesy of ANZCO Foods Limited, New Zealand, www.anzcofoods.com.

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About the Author

William Siegel is a consultant with 25 years of experience in the serum and cell culture industry. Formerly based in the Washington, DC area, he is now in Sarasota, Florida. For a significant portion of his career, Mr. Siegel worked for the American Type Culture Collection (ATCC) and Cambrex BioScience, now Lonza Walkersville.

Email: siegelwilliamh@gmail.com | **Phone:** 301-514-3235