

Is your serum a forgery? The painful truth about the importance of the origin of Fetal Bovine Serum (FBS) in research

We all know that counterfeit products can appear anywhere; cosmetics, luxury brand goods, foods and even pharmaceuticals, but did you know that the fetal bovine serum (FBS) that you use for your research can also be counterfeit?

FBS is an overlooked but crucial reagent used in research and it is an increasingly expensive commodity. In the past there have been incidents where companies have been found to be adulterating serum or being deceitful about the origin or type of product. Such instances can result in wasted time and money, invalid scientific results, and damage to reputations. These effects are similar to those experienced when research is performed using misidentified cell [1] lines and need to be given serious consideration.

The ISIA

The International Serum Industry Association (the ISIA) was formed in 2006 to provide a focus to ensure that such incidents would not be repeated. The Association mission states that the ISIA *shall establish, promote, and assure compliance with uncompromised standards of excellence and ethics in the business practices of the global animal serum and animal derived products supply industry.*

The ISIA is an association comprised of collectors, producers, distributors, and end users of animal-derived products. The prime objective is to promote ethics within the industry and to focus on the safe sourcing and safe use of serum and animal-derived products. The ISIA is also committed to providing education to stakeholders on the various aspects of sourcing and use of serum.

The Importance of Cell Culture

Cell culture is one of the most important techniques in cellular and molecular biology as it provides a platform to investigate the biology, biochemistry, physiology (e.g., aging), and metabolism of wild-type and diseased cells. The interaction and route of infection between wild-type cells and pathogenic agents (e.g., bacteria and viruses) can also be studied in specific co-cultures. Furthermore, immortalized cancer cell lines have given researchers insight into the biology of cancer and through the selective treatment of wild-type cells with UV radiation, viruses, and toxins, causative agents of tumorigenicity have been identified. Finally, human-induced pluripotent stem cells (hiPSCs) have been derived from individuals with inherited disorders and differentiated toward the affected cell type in which the disease manifests. These hiPSC-derived somatic cells are suitable platforms for the studying molecular mechanisms of a disease in a dish. [2]

FBS is crucial to cell culture. Being sure of the origin and treatment of FBS used in cell culture research is equally important as in vaccine and biopharmaceutical manufacturing.

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Counterfeit pharmaceuticals and adulteration of chemicals is nothing new. Rx360, The International Pharmaceutical Supply Chain Consortium, has developed supply chain audit programs to mitigate the risks in pharmaceutical manufacturing. The life science community needs to adopt similar strategies.

Authentication of Cell lines

The authentication of cell lines in research has long been a cause for concern [3]. Researchers are now aware of the issues that can be caused by Tom popping down the corridor and borrowing cells from Dick, who, in turn, inherited them from Harry. Cell lines, when maintained in culture for too long, are subject to genetic drift and may exhibit reduced or altered key functions. A lack of diligence in the choice of a cell line can result in a lack of publication or a lack of funding. Maintaining the integrity of a cell line has never been more important.

The issue of cell line integrity was recognised some 20 years ago, when academia and industry joined together to ensure that funding was only given to projects where the integrity of the cell line was guaranteed. Equally important, publication of academic literature could be refused if it was determined that due diligence had not been carried out on the choice of cells used for the research.

In 2015 the National Institutes for Health (NIH) stated:

NIH expects that key biological and/or chemical resources will be regularly authenticated to ensure their identity and validity for use in the proposed studies.

*These include, but are not limited to, **cell lines**, specialty chemicals, antibodies, and **other biologics**.*
[4]

Based on this statement, why should the choice of serum used in research be any different than the cells, when the potential for contamination could be equally devastating? As noted above the NIH has been advising researchers to consider authentication of their serum since 2015.

Potential Issues

The majority of FBS suppliers demonstrate truth in labelling. It is a requirement of the ISIA that the country of collection is shown on the bottle label and that both country of collection and manufacturing be clearly demonstrated on the accompanying documentation provided with each bottle.

It is possible to purchase serum labelled simply as “Research Grade” or “South America.” This might sound okay, but what does it really tell you about where the product comes from? Can the supplier demonstrate traceability from the source?

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Viral Contamination

Viruses are infectious agents that rely on host cells for their own replication. Owing to their small size they are very difficult to detect. While some viruses may induce morphological changes in cultured cells (cytopathic effects), other species may integrate into the cellular genome and alter the phenotype of the investigated cell line. The presence of viral contaminants can be challenging to confirm but generally relies on PCR, ELISA, immunocytochemistry, or electron microscopy [2]. Viruses can enter cell cultures through the cell culture serum. The use of FBS from unknown and untraceable sources introduces a serious risk as this can present a serious health concern, not only for the individual laboratory workers, but also to animal health populations in the importing country.

Regulatory Compliance

The movement of animal-derived material around the globe is very highly regulated, surprisingly more so than the movement of human derived-material.

Veterinary Health Certification regulations vary widely across the globe. It is the status of a country, regarding the presence of an animal disease of concern, together with interagency government agreements, that will determine where serum collected within that country may be exported. Individual countries have varying requirements for importation of serum from the same geographies based on the animal health status of the region from which the serum was collected. These requirements are extremely complex and are continually changing as regulations evolve. [5].

Companies handling animal-derived materials are required to be registered by their local authorities in the country of manufacture and the movement of material between facilities is stringently controlled

Origin

The origin of serum is important. Origin determines the health status of the animals from which the serum is collected. The health status then determines how the serum may be used. For example, for pharmaceutical use, FBS of New Zealand, Australian, and USA origin is the serum of choice today [5]. Serum from a number of other geographies is permitted for import and manufacture for other applications, including research use. Individual countries have different regulations for importation and these regulations are based on the health of the cattle populations within the exporting country.

The health status of a country is determined by the World Organization for Animal Health (WOAH previously known as OIE). Their mission is to ensure transparency of global animal diseases. WOAH issues information concerning the health status of various countries with regard to animal diseases of concern, including foot-and-mouth disease, bovine spongiform encephalopathy (BSE) and other diseases affecting cattle populations globally [6]. It is therefore clear that knowing the country of origin of the serum you are using can be of vital importance.

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Unfortunately, it is possible to cloud the origin of a product by moving raw material from one country to another or even by moving the adult animal from one country to another. The ISIA have developed origin testing techniques, together with Oritain Global Ltd. (<https://oritain.com>), that can determine the country of origin of serum through trace element testing (7). By using this method, origin may be determined to 99% accuracy and lots where serum of a variety of different origins have been mixed can be identified.

It is also possible to determine whether the FBS originated from an area of a specific country that is free from specific disease and which is permitted to export product. This is particularly important in areas such as Brazil, where Foot and Mouth Disease together with other notifiable bovine diseases are endemic in certain regions.

Traceability

There is a single, simple mitigating step that can be taken to ensure the safe sourcing of FBS for research use. Traceability. Specifically, ISIA Traceability.

In 2009 the ISIA developed a Traceability Audit Program to assist serum collectors, manufacturers, and end users to determine the origin of the product they are using. In 2014, an article was published in Bioprocessing Journal entitled 'Fetal Bovine Serum: What You Should Ask Your Supplier and Why'. [8]. This article discusses the need for traceability of serum supply as it affects further manufacturing.

The Traceability Program developed by the ISIA and adopted by the membership is wide reaching. This program looks, in depth, at material coming into a facility for processing and material leaving the facility post processing. It looks at mass balance; serum may not be 'created' during production. It looks at the supply chain surrounding the collection and handling of the raw material. It looks at the regulatory pathway and the required certification for importation. There is a physical on-site audit, there is also random sampling of serum for origin testing. It is a robust program ensuring that customers, sourcing their FBS from ISIA Traceability Certified companies, have the assurance that what they are paying for is sourced from the origin stated on the label.

The Traceability Program is being increasingly adopted by global regulators. Large pharma now routinely requests traceability information concerning the lots of serum purchased for further manufacturing. Researchers need to be asking those same questions of their serum suppliers.

Supply Chain Concerns

Collectors of serum that are ISIA Traceability Certified have an obligation to ensure standards of collection of FBS at the facilities in which they operate. This involves ensuring the welfare and veterinary supervision of the animals, but it also involves ensuring the welfare of the operatives involved in the process. In these facilities, where animals are being slaughtered for human consumption, there are regulatory standards to

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protect individuals from exploitation. FBS can be collected in some of the poorest regions of the world as these are where there are the largest cattle populations

FBS collected from unregulated operators does not offer this level of comfort. The FBS may be collected in completely unregulated slaughterhouses, from areas where the export of material is not permitted and where specific bovine pathogens are endemic. It is vitally important that everybody concerned with the supply chain recognises their role in maintaining social standards and equality throughout the process.

Conclusion

There is always going to be cheap material to purchase. There will always be those deals that seem too good to be true. It is always a case of 'buyer beware' but there are things that the research community can do to protect themselves, their research and, most importantly, their credibility.

Purchasing from trusted suppliers with robust traceability programs in place is one way of ensuring that research is robust, reproduceable, and publishable. Do not hesitate to ask for traceability documentation and, in the case of FBS, proof of adherence to the ISIA Traceability Certification program.

Using serum or cell culture media from an unknown and unsafe origin is like using those cells that Tom sourced from Dick who inherited from Harry. You just don't know where it has come from, nor do you know what contaminants lie hidden that are affecting your results. You have no control over the potential for viral contaminants or over the collection methods and the welfare of the animals and of the individuals involved in the collection processes.

FBS should be sourced from a serum supplier who is a member of the ISIA, adheres to the ISIA Traceability program and sources material from ISIA Traceability Certified suppliers.

Just because an accident hasn't happened yet doesn't mean that it won't happen in the future. No individual wants to lose their research program or be responsible for the introduction of a significant pathogen into a country hitherto free from disease. Fetal bovine serum is an important, valuable resource. It is important to research and important to the worldwide health of humans and animals. Take the time and ask your serum suppliers about traceability and about the ISIA. Your research is worth it.

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