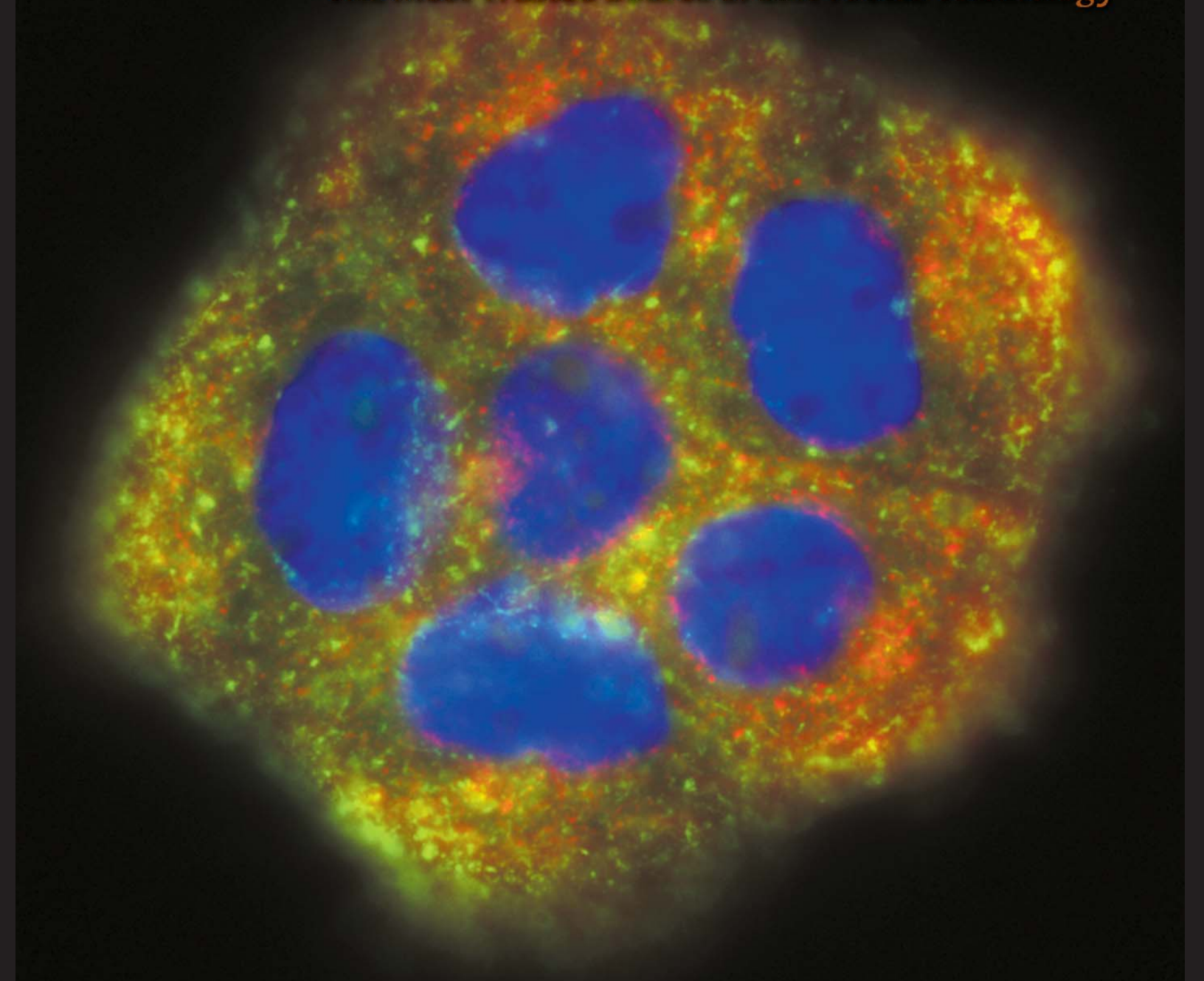
A publication of
The Williamsburg BioProcessing Foundation

Summer 2006

BioProcessing™ JOURNAL

The Most Trusted Source of BioProcess Technology™



Vol. 5 No. 2

www.bioprocessingjournal.com

Current Challenges in Raw Materials Control Programs

By PAULA J. SHADLE

A program for control of biopharmaceutical raw materials is a critical quality system that helps assure patient safety and contributes to product quality. The systems for testing and acceptance must be scientifically based, and meet global regulatory requirements and standards. When a new raw material is sourced, it is important to quickly establish the quality profiles for the supplier and the raw material. Among the numerous challenges that confront a company attempting to establish an effective, compliant, raw materials program, this paper will address the following:

- Challenges in sourcing and tracing raw materials that are suitable for use in human therapeutics
- Challenges and obstacles in qualifying suppliers
- Special challenges faced by a firm that has outsourced its manufacturing and/or quality control (QC) testing

Biopharmaceutical companies must meet these challenges while also meeting business requirements of cost-effectiveness, speed to market, and development of a regulatory strategy that will triage the inevitable process changes. A balanced perspective, the ability to perform risk assessment, and prioritize resources are important components of a company's raw materials program.

Challenges in Raw Materials Traceability and Sourcing

We live in a global economy, with pharmaceutical raw materials coming from all over the world, yet we are required to be able to trace each material we use, not only within our firm, but also back through the supply chain to the original manufacturer. As the supply chain gets longer, this becomes very challenging.[1]

When the material is purchased from a repackager or vendor, the company may not receive adequate information on the origin of the material. The advantage of buying from a few vendors should be balanced against the cost of obtaining adequate information from the primary suppliers. Challenges may include:

- Negotiating with a vendor which, for business reasons, does not wish to disclose its sources
- Confirming that all materials can be traced
- Coping with a vendor having multiple suppliers, not all of whom meet your company's standards
- Obtaining agreements for site visits and audits

Contracts and supply agreements are very helpful in surmounting these challenges. Such agreements should be negotiated with the assistance of those trained in that area, such as purchasing or supply chain experts—not only by scientists—to ensure that they are workable, legal, and enforced.[2–4]

Animal-derived raw materials are a special case in this category. Because of the risk of diseases such as transmissible spongiform encephalopathies (TSEs) and viral diseases, the controls over sourcing and traceability have additional safety value. Animal-derived raw materials can introduce adventitious agents into a pharmaceutical process, and sourcing controls are a major means to prevent contamination. Treatments such as irradiation are also helpful in some cases.[5,6]

Challenges in Supplier Qualification

The first challenge in supplier qualification may lie in the sheer number of different raw materials and suppliers to be qualified. Priorities must be set, based on an assessment of the relative risks between suppliers and materials. Many materials will be accepted based on a certificate of analysis (COA) and confirmation of identity. The supplier's data are used to assess whether each material conforms to specifications.

Risk lies in relying on a supplier's QC laboratory if it has not been audited or verified by independent testing. This risk can be mitigated by such strategies as:

- Sourcing from suppliers that are

Paula J. Shadle, Ph.D. *(shad1357@aol.com), is principal consultant, Shadle Consulting, Lafayette, CA.* *This article is based on a presentation given at the Williamsburg BioProcessing Foundation's Raw Materials and Disposable Process Systems for Mammalian Cell Products meeting held in Kansas City, MO, July 18–20, 2005.*

known to have pharmaceutical experience

- Performing a brief supplier evaluation, including a financial assessment and a quality questionnaire
- Retaining samples that are sufficient to perform full COA testing
- Identifying one test which serves as an indicator of lot quality

A company may select one test from the COA list that is stability indicating, and perform it on a material known to degrade. Alternately, a use test can be employed; for example, to test a cell culture media additive whose chemistry is not well understood. Such tests, although difficult to develop and perform, can detect unsuitable materials before they are placed into manufacturing use.

Over time, supplier qualification exercises may reduce the need for such testing as they provide information and assurance. Many companies will subject several supplier lots to complete testing before use. The test results confirm whether the supplier's testing laboratory can be relied upon for future results, and also characterize the raw material.[7,8]

Raw materials are manufactured globally, which brings added challenges. The World Health Organization reports that many countries lack the infrastructure to guard the supply chain against accidental or intentional introduction of substandard, contaminated, or even counterfeit materials. Contaminants such as insects, glass shards, metal shavings, heavy metal contamination, and the like are straightforward to detect, while microbial contaminations or mix-ups may be much more difficult. These can occur at any point in the supply chain. A firm's incoming acceptance, therefore, must include inspection of the package for integrity and identity, and appearance testing of each raw material.[1]

Periodic full testing of the COA tests is especially important to maintain a quality raw material or supplier. Equipment, processes, and personnel do change over time, and testing is a non-specific way to detect a change in quality.[7]

Challenges for the Virtual Firm/Outsourcing

Many companies today contract out manufacturing, QC testing, or both. Outsourcing requires that the business partners share the responsibility for quality, traceability, and controls. Key challenges for the sponsoring firm may include:

- Deciding whether to delegate the entire raw materials program to the contract manufacturing organization (CMO)
- Defining adequate oversight when raw materials are contracted out
- Mediating disagreements

Table 1 lists specific examples of issues that may confront a virtual firm. Because the legal responsibility ultimately lies with the sponsor firm that releases its drug product, careful consideration is needed in formulating the strategy and defining roles. Yet, the sponsor firm may lack expertise in raw materials, for example, and thus depends on its CMO. Risk is created if the less experienced firm makes the critical decisions. At the same time, the sponsor must exercise oversight. This dilemma needs attention that goes beyond "who pays for the rejected material." After all, nobody wants a raw materials issue to be the reason that a product is placed on clinical hold, given a refusal to file, or is recalled from the market.

Table 1. Examples of challenges for a virtual firm.

- CMO is using suppliers you don't approve of
- CMO refuses to let your raw materials into its facility
- CMO accepts on certificates of analysis when you want more testing done
- CMO tests to USP while you want USP/EP/JP
- CMO hasn't fully qualified its suppliers
- CMO doesn't audit any of its suppliers; you have no legal right to audit them
- CMO won't transfer supplier or raw materials information when you are ready to open a second site
- CMO requires that you source, test, and release your own raw materials
- Added cycle time because multiple firms are part of the process
- Expertise may not extend to all needed areas for oversight
- Pressure to use the CMO before it has been fully qualified

REFERENCES

1. World Health Organization. <www.who.int/media-centre/ factsheets/fs275/en>.
2. Shadle PJ. Qualification of raw materials for biopharmaceutical use. *BioPharm International* 2004; 17:28–35.
3. Lubiniecki AS, Shadle PJ. Raw material considerations. In: Brown F, Fernandez J, editors. *Development of Specifications for Biotechnology Pharmaceutical Products*. Basel, Switzerland: S. Karger Publishing; 1997.
4. Del Tito BJ, Tremblay M, Shadle P. Qualification of raw materials for clinical biopharmaceutical manufacturing. *BioPharm* 1996;9:10.
5. European Agency for the Evaluation of Medicinal Products (EMEA). Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. London; 2001 May 31.
6. Shadle P. BSE offers lessons in risk assessment. *BioPharm International* 2004;17: 24–33.
7. Current good manufacturing practices for finished pharmaceuticals. *Code of Federal Regulations*, Title 21, Part 211.80–94, 211.101, 211.184 as amended 1 Apr. 2003.
8. International Congress for Harmonisation (ICH). ICH Topics Q7A — Good manufacturing practice for active pharmaceutical ingredients. Geneva; 2000.