A Quick Guide for Sourcing Biopharmaceutical Raw Materials

by Douglas Bowman

Before the ratification of regulatory guidelines from The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8–Q11 (**1–4**) — whose scope includes raw materials for biopharmaceutical production — many drug manufacturers chose the most cost-effective and readily available raw materials sourcing options without specifically considering the provenance of those materials. Depending on the chosen supply chain, such materials could be of widely varying quality and not necessarily suitable for a destined application. Raw-material sourcing for bioprocesses is not a one-size-fits-all operation.

Why Source Matters

When sourced materials exceed quality standards, excessive cost is the main issue. However, in the case of substandard materials, patient-health risks become the primary cause for concern. Perhaps the most well-known example of the detriment that substandard materials can cause is the 2008 heparin incident. A contract laboratory sourced what it thought was adequate-quality porcine heparin from China. It turned out to be contaminated with oversulfated chondroitin, which was not identified until it was too late. The laboratory's client had already used the ingredient in formulated drug product administered to patients. The end result was 80 patient deaths and hundreds more patients reporting adverse health effects.

The heparin incident (and other contamination incidents) led to more stringent regulations to prevent such sourcing-derived problems from reoccurring. Those requirements are enshrined in the ICH Q11 guideline (**4**), which biopharmaceutical manufacturers are now striving to implement for their manufacturing processes.

By extension of the ICH Q11 requirements and stipulations placed on drug manufacturers, raw materials suppliers should provide a number of data points to support risk-management and control strategies. Such data include whether a material is of biologic or synthetic origin, in which facility a material was made, how it was handled and packaged, and any change-control elements. Suppliers also should include information about any potentially toxic substances that were used during their manufacturing processes, such as heavy metal catalysts and solvents. This list is not exhaustive; any other information that could affect a raw material's quality also should be included.

Do: Determine What Level of Quality Is Required

There is a misconception that every raw material used in a biopharmaceutical process must be US Pharmacopeial (USP) or good manufacturing practice (GMP) verified, or both. Although requesting prices for GMP material might seem simple when contacting potential suppliers, providing all documentation demanded for a GMP ingredient may be unnecessary, particularly for certain raw materials used in early stages of fermentation. This is why a careful risk assessment of the entire process is essential.

Don't: Assume That "GMP" Means the Same to All Suppliers

GMP is a generic term applied to many different industries, not all of which may meet the needs of a bioprocess. To a supplier whose business is focused on the production of active pharmaceutical ingredients (APIs) and late-stage intermediates for small-molecule drugs, GMP would mean something very different than it does to a company specializing in ingredients destined for the food-manufacturing sector. API GMP standards usually far exceed what is necessary for bioprocess raw materials — and thus add unnecessary cost. By contrast, food-grade (or other grade) materials are unlikely to come with the supply chain traceability that is necessary for a bioprocess. Although no general definition yet describes exactly what level of raw material traceability and control is suitable for a bioprocess, the GMP standards demanded for excipients are being recognised as broadly appropriate. The joint International Pharmaceutical Excipients Council – Pharmaceutical Quality Group (IPEC-PQG) GMP guidelines for excipients are the most useful set of rules to reference.

Don't: Assume That "USP Quality" Will Be Suitable or Even Available

USP also can have different meanings. An ingredient should claim to meet USP requirements only if it has met the analytical standards laid out within the USP compendium and has been processed under conditions that meet GMP standards. Yet some suppliers omit those processing conditions and claim USP compliance if an ingredient meets the analytical criteria alone. Some suppliers provide no indication about the conditions in which their ingredients were made, handled, and packaged. So a given ingredient actually might not be suitable for a bioprocess. Demanding that USP standards be met for all raw materials is pointless, because many ingredients used in biopharmaceutical manufacture are not listed in the USP compendia or other compendial listings and thus cannot (by definition) be supplied in USP or other compendial quality.

Do: Find Out Whether a Supplier Has Internal Bioprocess-Specific Standards

Many big chemical suppliers that are active in the biopharmaceutical sector already have developed a set of internal standards for raw materials destined for bioprocesses. Those suppliers will cherry-pick the most relevant parts of GMP, USP, IPEC, and other quality systems organizations while omitting

those parts that are unnecessary. The result is a set of cost-effective raw materials that are designed for bioprocessing. In such cases, a supplier can help you determine whether a material indeed will be suitable for a specific bioprocessing step. If it is not, the supplier can suggest what might be acceptable to balance quality and cost.

Don't: Assume That All Raw Materials from China Should Be Avoided

The heparin incident has led to a misconception that Chinese suppliers should not be trusted to supply quality raw materials and that supply chain problems will vanish if China is avoided. This is simply not the case. Although a great deal of small molecules are easy to source from multiple suppliers in many countries, some specific raw materials (e.g., sugars, salts, amino acids, and trace metals) are predominantly produced in China. An internal blanket-sourcing ban would leave very few options, if any, for those essential components.

Do: Identify Reliable Chinese Suppliers

With so many Chinese companies offering raw materials to the biopharmaceutical industry, ostracizing an entirely competent segment of suppliers would be counterproductive to finding a solution. In some cases, a company selling ingredients might also be the original manufacturer, but it is more likely that a third-party exporter (providing no clue about where materials were made) is selling them. Carrying out visits and audits to check whether production standards meet requirements is an expensive and onerous task. Often, the best way forward is to engage a trusted supplier based in the United States or Europe that has the resources to identify potential sources in China and carry out audits through its own Chinese procurement and audit specialists. That supplier should also be able to provide important traceability documentation and, if necessary, reprocess sourced material in its own facility so it meets correct quality standards.

Don't: Assume That if It's Made in the West, Then It Will Be Safer

Conversely, there is a similar misconception that anything sourced from one of the big Western chemical conglomerates is guaranteed to meet quality requirements. That is not the case. Big chemical companies make the vast majority of their money selling large volumes of chemicals into sectors such as oil exploration or plastics manufacture. Even if one of their products happens to be required in a bioprocess, it is unlikely to meet the stricter quality standards for pharmaceutical manufacturing. Worse, because biopharmaceutical manufacturing could represent such a minuscule proportion of sales for that chemical, the company is likely to be unwilling to put in the effort to complete the necessary paperwork and analytical work to satisfy biopharmaceutical regulators. A Western chemical supplier also may have insufficient microbiological control in the handling and packaging processes or a lack of appropriate change-control systems.

Do: Use a Pharma-Dedicated Third-Party Supplier

All of the above drawbacks can be prevented if you use a trusted third-party supplier. Such a supplier can have several customers looking for bioprocess-specific materials, and their combined volume demand puts those customers in a much better position to persuade big chemical companies to meet all additional requirements of the biopharmaceutical sector. Such suppliers also can process materials further (e.g., by using distillation, recrystallization, or salt formation) to reduce levels of contaminants such as heavy metals or solvent residues and to meet targeted biopharmaceutical specifications. A trusted third-party supplier also can carry out all analytical testing the original manufacturer is unable to perform.

Don't: Assume Materials Must Be Sourced from Original Manufacturers

A recent update to the European Union's (EU's) GMP guidelines **(6)** states that, when possible, raw materials should be procured from the original manufacturer. Although the reasoning behind that statement is sound, in practice it is not feasible to purchase every chemical component directly from myriad manufacturers. The intent of the guideline is to ensure full traceability of all materials back to where they were actually made and to prevent complex supply chains of traders where the identity of the original source is obscured. The guideline should not be interpreted to dictate that all third parties are to be avoided. When dealing directly with an original manufacturer, a biopharmaceutical manufacturer that wants to purchase only a few grams of a substance can find it very difficult to extract the necessary documentation and to gain audit access. As with sourcing from chemical conglomerates, using an experienced large third-party supplier will facilitate such tasks, because the increased purchasing power gives the supplier greater weight to request information. It also can significantly expedite the entire process, both for materials manufacturers (that now need deal with only one customer) and for biopharmaceutical companies (that will now not waste months verifying that the material meets all FDA and EMA requirements).

Safety First

Sourcing all individual components that go into a bioprocess and ensuring that such materials meet quality requirements is a huge task. By preventing the pitfalls and misconceptions (and using a trusted third-party supplier where appropriate), you can make that task more manageable while keeping costs down. All of this contributes to the development of a safe and efficient product, backed up by a reliable raw materials supply chain.

References

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4 ICH Q11 *Development and Manufacture of Drug Substances. Fed. Reg.* 77(224) 2012: 69634–69635.

5 *The Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients* 2006; http://ipec-europe.org/UPLOADS/IPEC_PQG_GMP_Guide_2006(1).pdf.

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