Raw Material Myths:
Separating Fact from Fiction

Douglas Bowman, Program Manager, PharmaGrade at SAFC

Prior to the recent establishment of clearer regulatory guidelines for the raw materials used in biopharma production processes, easy accessibility of materials would often trump quality during the sourcing phase. While it is undoubtedly important to have a ready supply of all materials needed to complete a bioprocess, it is even more important that the materials meet specific integrity requirements to ensure the quality of the final active drug.

Since a bioprocess can easily include 100 or more individual chemical components in media and additives, there must be a clear understanding of the quality and provenance of each material. Failure to build this understanding increases the risk of adverse events, such as the well-publicized heparin incident of March 2008, when tainted product resulted in the deaths of at least 85 patients and serious health concerns for hundreds of users of the anticoagulant.1 This incident, among others, ultimately became a catalyst for the creation of more stringent regulations, ratified in 2012, which the biopharma industry is still working to fully implement today.

These regulations, culminating in the ICH guideline Q11, require manufacturers to conduct a risk assessment of their manufacturing process, identify critical control parameters, and determine the criticality of each raw material based on where and how it is used in each specific process. When auditing, regulators can demand a full picture of the supply chain for all raw materials and require the drug manufacturer to justify its risk assessment that led to the decision to use a particular source and grade. The raw material supplier provides risk assessment information that includes, but is not limited to, elements such as manufacturing location, origin of the material (biological/synthetic), packaging and handling environment employed, details of any toxic substances such as solvents or heavy metal catalysts used during manufacture, and change-control elements.

As the industry continues to transition under the new regulatory environment, suppliers and biopharma manufacturers continue to learn how to work within the guidelines. Even as the industry responds to this paradigm shift, a handful of common myths remain.

Myth: All Raw Materials Must Meet GMP Standards
There is a common assumption that the new regulations mean every raw material used in a biopharma manufacturing process must meet good manufacturing practice (GMP) standards and/or be of USP quality. Certainly, submitting a request for quotation and stating that the chemical must be GMP or USP seems clear and concise, and both of these terms are good indicators of high levels of product quality and control. However, the reality is subtler than that. For example, GMP is a generic term, and there are many different GMP standards grouped under that heading.

Different suppliers receiving a simple request for a GMP product could reply with very different offers. For instance, one could offer an API quality product and another might offer a food-grade product. Neither supplier would be incorrect, as these are both GMP standards, but GMP products designed to meet API standards are often over-engineered for what is needed in a biopharma process and may well exceed the customer requirements, adding unnecessary cost to the product. On the other hand, the food-grade chemical will not provide an adequate level of transparency and control. In general, GMP standards designed for excipients, such as IPEC guidelines, are being adopted as a good proxy quality standard for biopharma raw materials.

USP can also be a minefield. By definition, USP compliance should only be claimed when the chemical both meets the compendial analytical specification and has been processed and handled under GMP conditions. Many suppliers declare USP compliance when only the analytical requirements have been met; this is no real indication of the environment in which the chemical has been manufactured or packaged. In addition, many chemicals commonly used in bioprocessing are not listed in the USP compendia, and no monograph specification exists, so a blanket “USP-quality” request is null and void.

Finally, several suppliers who specialize in serving the biopharma industry have developed internal quality systems to deliver products specifically designed to meet biopharma raw-material requirements. These quality systems incorporate the important aspects of GMP standards without the superfluous elements and can offer more nimble, cost-effective solutions. The best option is to use a risk-based approach to establish the desired quality for each raw material in each application; work with proven preferred suppliers to identify the product grade with best fit; and find the right balance between quality and cost.

Myth: Raw Materials From China Should Always Be Avoided
The 2008 heparin scandal was connected to counterfeit raw materials sourced from China. Unfortunately, this led to a belief within the biopharma industry that future problems might be prevented if Chinese ingredients are avoided. This is an overreaction that can cause real supply chain fulfilment problems. While it might be relatively easy to find a small-molecule product from a non-Chinese source, for many of the key components of a bioprocess, this is not the case. Most of the world’s supply of numerous raw materials—from amino acids and sugars to salts and trace metals—come from China, so eschewing that country entirely is problematic.

The key here is identifying reliable Chinese manufacturers. This can be challenging, given that there are hundreds of alternative manufacturers, mostly fronted by third-party commercial exporters. For drug manufacturers, one answer is to use a trusted supplier who can: 1) identify suitable sources; 2) conduct audits using its own local Chinese procurement and quality assurance specialists; and 3) provide any necessary traceability documentation. Ideally, the supplier will also have the capability, where necessary, to reprocess the Chinese raw material in facilities in Europe or the U.S. to ensure it meets the necessary quality standards, dramatically reducing any risk in sourcing raw materials that were originally manufactured in a Chinese factory.

Myth: Chemicals from Western Industrial Manufacturers Are By Default Fit for Purpose
In contrast to the concerns about Chinese manufacturers, there is a perception that if a chemical is supplied by one of the large global chemical companies, its quality will automatically be acceptable. But bulk chemical manufacturers are geared up for supplying large volumes to customers involved in plastics manufacturing, or oil exploration, for example. While their product range includes some chemicals that are also important components of biopharma processes, this application represents only a fraction of a percent of overall output and sales. The production line may be dedicated to this specific chemical, so the process and quality will be optimized and standardized for general purposes. However, the levels of documentation, impurity analysis and microbiological control, for instance, often fall below the acceptable standards expected by the biopharma industry.

These manufacturers can also be reluctant to enter into separate quality and supply agreements with such small-volume customers, as it would commit them to significant extra expense and documentation that is unnecessary for the vast bulk of their business. They also typically do not have sophisticated change-control tracking and notification systems in place and therefore rarely provide the change control needed for raw materials going into regulated applications.

Sourcing through a dedicated third party can resolve these issues, because the supplier has enough volume to persuade the manufacturer to put biopharma requirements in place. In addition, the third party can carry out further processing, such as distillation, recrystallization or salt formation to ensure impurity profiles meet specific requirements. Analytical techniques such as residual solvent and heavy metal analysis can provide an additional layer of reassurance. Risk is thus reduced because changes are limited with a more standardized supply chain, and access to these commercially available chemicals is reliable.

Myth: It Is Essential to Source Directly From the Original Manufacturer
This myth arises because a recent update to an EU regulation states that, wherever possible, raw materials should be procured directly from the original manufacturer. The aim is to ensure traceability back to the site where the raw material was originally manufactured, rather than passing through a complex chain of traders with no clear information about the source.

However, it can be difficult for a small-volume end-user to obtain the required documentation, even if the quality of the material meets biopharma needs. A large intermediary supplier, with greater purchasing power, will be in a much better position to have the requisite documentation and auditing already in place. Regulations do not demand that raw materials be procured from the original source. As long as full traceability is available, the documentation from a reputable intermediary supplier justifies to the FDA or EMA that the drug manufacturer has carried out due diligence and is using fully audited quality products. A documentation package from the raw-material supplier provides this information and can decrease timelines by months.

SAFC Raw Materials
As a trusted supplier of raw materials, SAFC recognizes the importance of having access to the right grade of material for each step of bioprocessing. Because materials are either developed in-house or sourced from verified providers, SAFC has the ability to meet volume and grade requirements. A dedicated customer support staff offers guidance based on expertise in the most recent regulatory requirements, as well as the implications each material selection may have on a bioprocess.

To learn more about how SAFC can reduce supply chain risk in biopharmaceutical manufacturing, visit: sigmaaldrich.com/safc-pharmagrade.