SEPTEMBER 2023

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Advancing Drug Supply Chain Management, Strategic Sourcing and Supplier Collaboration

- Optimizing Operations Excellence
- Top Five Sourcing Challenges
- Pharmacopoeia Compliance Case Study
- Upstream Processing and Biochemicals
- Sourcing Precautions and Improvements

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Optimizing Operations Excellence Post-COVID

Biopharmaceutical companies should consider establishing partnerships with an Operations Engineering team equipped to respond efficiently and quickly to supply chain issues.

Jesse Rendon
Director of Operations
Spectrum Chemical Mfg. Corp.

Q. What are the biggest challenges and issues for Operations when responding to customers in 2023?

A. The bottlenecks caused by international shipping issues, unpredictable global weather, geopolitical events, material shortages and the complexities of handling and moving hazardous materials are challenging in regard to both the availability and expediency of receiving high quality raw materials and shipping them.

Adding to the logistics challenges that directly impact customers is the labor shortage of drivers on the transportation side of the business. The widespread driver shortage leads to

carriers not picking up products on time, or at all. Obviously, this must be overcome or worked around.

We aim for agility throughout our whole organization and deal with any supply disruptions responsively and efficiently. We are expanding our resources and forecasting well into the future to counteract ongoing post-COVID disruptions and international unsettledness. Fortunately, Spectrum Chemical already has a strong, established global supply chain network that is dedicated to working collaboratively with us in fulfilling our customers' needs.

Q. What does Spectrum Operations do to ensure strong resiliency, agility and flexibility in meeting biopharma customer demands?
A. Spectrum Chemical has the advantage, and our customers benefit from our highly diversified supply base. We are prepared to respond to customer requirements by calling on multiple sources – we can second, third and fourth source, if necessary. We have strong alternatives because we work with such a broad list of supply chain partners, product suppliers and logistics providers. This makes it possible for us to respond as quickly as possible.

Q. What is the importance of providing full transparency in sourcing raw materials for biopharmaceutical customers?
A. There is tremendous responsibility and workload in ensuring that the right orders are received, and they meet customers' requirements as well as regulatory requirements. We are overseeing customer orders for raw materials, APIs, intermediates, solvents, cell-culture media, excipients, production materials, manufacturing equipment, packaging materials and much more.

The full documentation and data sharing that source transparency and traceability require is especially important for raw materials. The goal is to preserve the integrity of raw materials purity with source documentation to protect biopharma drug development processes, save customers time and money, deter the creation of counterfeit drugs and product recalls, and safeguard the supply chain.

"The full documentation and data sharing that source transparency and traceability require is especially important for raw materials."

Q. What about the question of "just in time" versus "just in case" product inventory?
A. Both scenarios should be taken into consideration when planning inventory levels. Having the right amount of inventory, at the right time, for the right order is always our goal. Spectrum Chemical partners with customers and ensures the needed material is readily available. We plan to store additional inventory for specific crucial products and work with multiple suppliers in stocking critical materials.

Q. What impact has Continuous Improvement had on Spectrum Chemical Operations?
A. Spectrum Chemical has implemented Kanban (visual signal) systems for customers who order on a more frequent basis. Having the ability to level load our production schedule while meeting customer demand gives us the advantage of reacting quickly and efficiently to any disruptions that might occur.

Q. Has Spectrum Chemical implemented LEAN practices? If so, has that improved general operations?
A. Spectrum Chemical started our LEAN journey some years ago. We have trained 100% of our Operations on the basics of LEAN fundamentals and have implemented several projects. The goal for Spectrum Chemical is to apply LEAN to all facets of the organization. We want to add value to the customer experience and eliminate waste.

"Whether identifying automation opportunities or improving manual processes, the future is bright."

Q. What is new for Spectrum Chemical Operations?
A. Spectrum Chemical is creating a culture of continuous improvement through innovation and engineering. Whether identifying automation opportunities or improving manual processes, the future is bright. We have established the Operations Engineering team, which is demonstrating a positive impact on general operations, flow, shipping and more.

Our engineers collaborate cross-functionally and support all processes throughout the organization. They focus on removing bottlenecks and assist with the maintenance of a robust cGMP environment. We are also proud of the success of our summer intern program that began three years ago.

Q. What does the future look like for Spectrum Chemical?
A. There will invariably be both improvements and innovations in supply operations as well as disruptions globally, no matter what year it is. As a well-established company with well-secured supply operations, Spectrum Chemical stays vigilant to be capable of acting quickly in dealing with supply chain challenges. Our goal is to supply biopharmaceutical manufacturers with the highest quality raw materials, products and supplies that support drug development and can help speed time to market.

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Top Five Challenges Sourcing Biopharma Raw Materials in 2023

1. GLOBAL MARKETS COMPLIANCE

Global variations in compliance can occur between mature and emerging markets as well as dissimilar interpretations and leadership approaches to quality, safety and risk. This is particularly challenging in addressing cross-site cGMP inconsistencies in multi-site international companies.

To be globally compliant, biopharmaceutical manufacturers have to know and thoroughly follow the ever-expanding regulatory requirements of the FDA, EMA and other regulatory agencies. To manage the complexity of international regulatory demands and exercise best

practices, manufacturers need to partner with the right supplier who can provide:

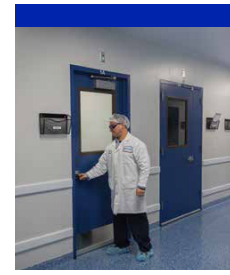
- high-purity raw materials
- an established global distribution network
- vigilance in cGMP manufacturing procedures
- extensive analytical testing
- the quality customer service necessary to help manage compliance challenges

2. SUPPLY CHAIN TRANSPARENCY

Going into full effect this year, the Drug Supply Chain Security Act (DSCSA) is designed to improve transparency, security and responsiveness for U.S. prescription drugs. An electronic system will identify and trace prescription drugs and their ingredients. The purpose of the system is improved contaminant detection as well as speeding recalls of potentially problematic drugs.

By the end of 2023, the entire supply chain must be DSCSA compliant. Complete unit-level traceability, including aggregation, will be mandatory. It will be necessary for manufacturers to provide documentation for each step of the drug supply chain and that includes all raw materials, intermediates and packaging materials.

Spectrum Chemical supports biopharma manufacturers in maintaining product integrity through our in-house testing of raw materials and finished goods in cGMP-compliant facilities to ensure that chemicals and ingredients meet stringent quality standards for the various locations of multinational drug developers. In addition, we provide documented change controls and sourcing to confirm transparency and accelerate speed to market while ensuring a consistent pipeline of raw materials.



WHITE PAPER

Feeding the Cellular Factory: Managing Supply Chains in the Biopharmaceutical Industry

3. RAW MATERIAL TRACEABILITY

Being able to trace raw materials back to their original source if problems occur is an important part of quality control and compliance to help ensure quality and safety in the development and manufacturing of biopharmaceuticals. Traceability refers to tracking and documenting all raw materials and finished goods throughout the manufacturing process. Raw material product traceability consists of tracking inventory from end-to-end, through every operational step and including tracing raw materials to where they were shipped.

In the last several years, many biopharmaceutical manufacturers have adopted blockchain technology to improve traceability. Blockchain technology consists of a distributed ledger that provides permanent and verifiable recording of contracts and transactions.

Not only does traceability help improve quality and compliance, but it also provides biopharma manufacturers with more efficient monitoring and visibility that can help save expenditure and speed time to market by preventing research obstacles, clinical trial failures, product recalls and the development of counterfeit drugs. To be compliant with the DSCSA, end-to-end traceability is also now a requirement as of November 2023.

4. RAW MATERIAL VARIABILITY

The challenge of raw and starting material variability is particularly complicated in cell and gene therapeutic discovery and development. Product approvals for cell and gene therapies are continuing to increase. Cell and gene therapy products are expected to be in the foreground of future biopharmaceutical and pharmaceutical development. The FDA has moved to facilitate the speed of development of these promising new therapies through clinical trials, and approval, when warranted.

Living cell-based drug products are highly vulnerable to various quality setbacks as well as supply chain disruptions. Cell-therapy manufacturers and their suppliers must contend with the fundamental variability of living cells and tissues. The increasing number of cell and gene therapies advancing through development to commercialization place an even greater emphasis on the critical importance of choosing the right supplier, a supplier with an established global supply chain network who can be depended upon to provide the highest purity, multi-compendial materials with a readily available supply on demand.

5. JUST IN TIME TO JUST IN CASE

Post-Covid, biopharmaceutical manufacturers are focused on increasing resilience and agility in their supply chains, including planning for raw materials supply from their suppliers as early as possible. The move is from a “just in time” to a “just in case” approach. The goal is to have critical inventory components such as raw materials in place as a stock buffer against supply chain disruptions.

An important part of achieving greater agility is selecting the right supplier to assure the quality of purchased materials. In addition to dependable quality of materials, the right supplier provides comprehensive documentation that meets regulatory compliance, plus additional and customized testing to help control the successful execution of the final manufactured product.

Partnering with the right supplier is both cost- and timesaving in avoiding non-conformities, deviations, potential reputation damage and loss of customer confidence.

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A Case Study in Pharmacopoeia Compliance: Excipients and Raw Materials

By J. Mark Wiggins, Joseph A. Albanese

The authors present a case study with raw materials and excipients, where a consistent, cross-functional approach is needed to ensure the appropriate selection, sourcing, testing, and filing of the materials used to manufacture bio/pharmaceutical products in a global environment, ensuring compliance with applicable compendial and regulatory requirements.

Courtesy of Sartorius

Throughout this series of articles, it has been emphasized that the bio/pharmaceutical industry must comply with requirements published by pharmacopoeias around the world. Several considerations have been presented to illustrate that pharmacopoeia compliance can be difficult. A previous article (1) highlighted compliance challenges resulting from the elaboration of monographs for drug substances and products. These challenges can be considered externally-based, driven by decisions made by the pharmacopoeias during the monograph development process. There are other compliance challenges that are internally-based, resulting from decisions made by one functional area in the company without consideration of the broader impact to other functional areas throughout the organization. One such example can be found with raw materials and excipients, where a consistent, cross-functional approach is needed to ensure the appropriate selection, sourcing, testing, and filing of the materials used to manufacture bio/pharmaceutical products in a global environment, ensuring compliance with applicable compendial and regulatory requirements. This case study is based on the experience of one of the authors (2) but is applicable to all companies across the broader industry, illustrating the potentially surprising point that some compliance difficulties may be of the company's own making.

THE CHALLENGE OF COMPLIANCE

During early development in the product lifecycle (3), various raw materials are used to prepare the drug substance, with the goal of consistently providing this active pharmaceutical ingredient (API) with appropriate quality and purity. Many of the raw materials are completely consumed during the manufacturing process, serving as building blocks that are converted into intermediate materials prior to the ultimate drug substance. Other materials may not be completely consumed, carrying over into the drug substance or drug product as residual materials or impurities. These residual materials may be an especially important consideration for complex biotherapeutic products (BTP). Continuing in the product lifecycle, the subsequent development of the dosage form involves the addition of excipients to the drug substance, with the goal of providing safe and effective delivery of the API in the drug product to achieve the intended therapeutic outcome. Appropriate product development information, along with safety, clinical, stability, and other data, are provided to regulatory agencies around the world to gain marketing approval for the drug product.

This article focuses on the raw materials and excipients used in the manufacture of drug substances and drug products. A company must comply with their approved product registrations and with appropriate compendial requirements, according to the expectations of regulatory agencies (3). The pharmacopoeias also provide information about the need for compendial compliance. For example, the General Notices in the European Pharmacopoeia (Ph. Eur.) indicate that drug substances and excipients must

comply with all the requirements stated in the applicable monograph (4). The General Notices in the United States Pharmacopeia-National Formulary (USP–NF) state, "Official products are prepared … from ingredients that meet USP or NF standards, where standards for such ingredients exist" (5). Clearly, APIs and excipients used to manufacture the drug product must meet compendial requirements. The USP General Notices continue, stating that the drug substances and excipients are themselves prepared "from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs." Again, the active ingredients and excipients clearly must meet the monograph requirements. Information is lacking, however, as to the ingredients used to prepare the drug substances and excipients. In particular, what are the appropriate specifications for the raw materials that will ensure compendial compliance for the resultant APIs and excipients?

This lack of clarity about the control of the raw materials may lead to compliance challenges. The drug development/approval process takes many years and involves a large number of wide-ranging functional areas across the entire company, including research and development, procurement, supply, quality, and regulatory. It is essential for these groups to remain connected and aligned throughout the entire process, with sustained communication and appropriate documentation, to deliver an effective and efficient outcome for the company overall. It can be especially important for decisions made early in the development process to be communicated and understood across all departments. Equally important, the responsible groups making early decisions should have visibility, or line-of-sight, to the strategy and expectations of other groups involved later in the product lifecycle, as part of an end-to-end approach to the overall process (6). The situation is made even more complex as more bio/pharmaceutical companies outsource the production of drug substances, and contract manufacturers work with many customers having different material requirements.

ARTICLE

Fast Pharma: Balancing Risk & Quality with Time to Market

There are important and fundamental questions about the materials used in product development and manufacturing that need to be considered throughout the product lifecycle. How does a company ensure the suitability and compliance of the raw materials and excipients used to support a broad product portfolio in a global environment? Are acceptable materials being used? Is appropriate testing being performed? How is this information communicated internally, across impacted functional areas? How is the information communicated externally, to external

partners and suppliers, as needed? How is the information communicated externally to regulatory agencies around the world? These important questions can be expressed in simpler terms, as follows:

- What do you need?
- What do you buy?
- What do you test?
- What do you file?

These questions relate to the selection, sourcing, testing, and filing for excipients and raw materials, and the interplay among them is shown in FIGURE 1. Each area is connected to, and impacts, the others, but one key aspect is the potential disconnect that can occur between what is sourced and what is filed for these materials. A consistent, cross-functional approach is necessary for a company to answer the questions in a way that ensures compliance with appropriate regulatory, compendial, functional, and quality requirements. Without a consistent approach that is understood and followed across the entire company, compliance problems can emerge.

WHY DIFFERENCES EMERGE

The level of understanding about the materials used to prepare drug substances and drug products increases as a company moves through the product lifecycle (FIGURE 2). Beginning in early development, the focus is on ensuring the materials are "fit for purpose", with appropriate functionality of the materials ("what do you need?") to support their intended use in the drug substance or product. At this stage, there are also questions about possible sourcing of the materials ("what do you buy?") and appropriate quality ("what do you test?"). As development continues toward product registration, launch, and supply, the functionality of the material is better

FIGURE 1: Excipients and raw materials: Interplay of selection, sourcing, testing, and filing. (Figure courtesy of the authors)

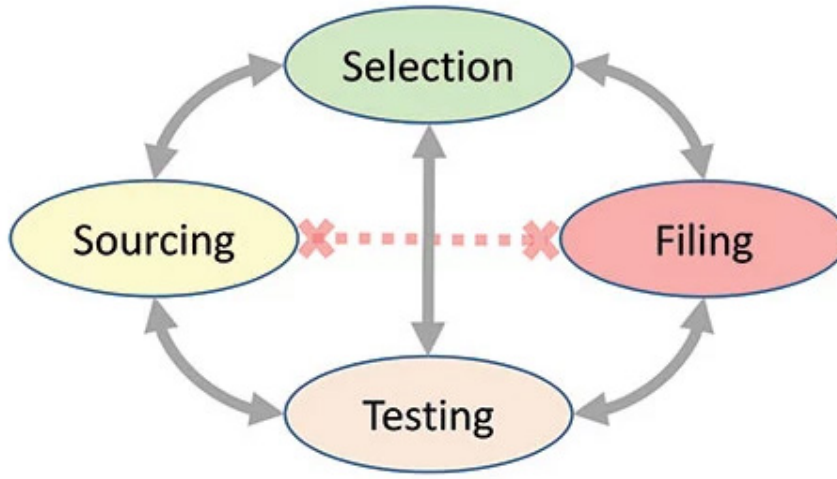
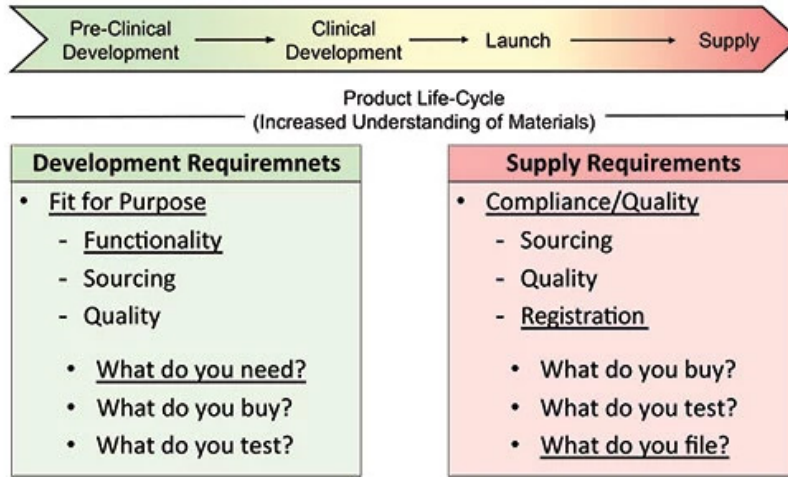


FIGURE 2: Excipients and raw materials: Considerations across the product lifecycle. (Figure courtesy of the authors)



understood, and quality and compliance considerations now become most important. The situation is increasingly complicated in today's global industry, with additional regulatory expectations arising in important markets. Appropriate sourcing and testing are still key considerations ("what do you buy?" and "what do you test?") that bridge product development to supply, but a critical focus now surrounds the specific details that will be included in the product registration ("what do you file?").

The differences that emerge in this case study are internal to the company, based on misalignment of expectations and requirements for raw materials and excipients between different functional areas. Without a line-of-sight or end-to-end perspective across the product lifecycle, different areas will likely have different understanding and definitions for the materials used during development, continuing into product launch and supply. Although a definition is provided in the International Council for Harmonization (ICH) Q6 guidelines for an excipient used in a drug product, there is no information about the ingredients that are used in the preparation of the drug substance (7). To enable a consistent process for the selection, sourcing, testing, and filing of excipients and raw materials, it is critical to have clear, practical, and specific definitions (see **TABLE 1**), not just for the materials themselves, but also for the grades that may be available. The definitions used for materials throughout this article are listed in Table I and are summarized as follows:

- Raw materials are used in the manufacture of the drug substance and should not be present in the final drug product.
- Residual materials may be used during the manufacture of the drug substance or drug product, but may not be completely

TABLE 1: Material definitions.

Table I: Material definitions.

Raw material	Any material intended for use in the manufacture of a drug substance including: ◦ Organic starting materials, reagents, catalysts, etc. (for small molecules). ◦ Biological media, buffers, resins, etc. (for complex biotherapeutics).
Residual material	For small molecules: ◦ An ingredient added during manufacture of the small-molecule drug substance or drug product, but intended to be removed (e.g., granulation solvent). For complex biotherapeutics: ◦ An ingredient added during manufacture of a complex biotherapeutic drug substance or product that is not removed from the final product (e.g., culture media used in fermentation, etc.).
Excipient	An ingredient, other than the drug substance, added during the manufacture of a drug product (both small-molecule and complex biotherapeutic products), which is intended to be present in the final product, providing appropriate functionality/efficacy, such as: ◦ To aid the processing of the drug product ◦ To enhance stability of the drug product ◦ To provide bioavailability or patient acceptability ◦ To assist in product identification, etc.

TABLE 2: Material grades.

Table II: Material grades.

Compendial grade	A material grade for which a compendial monograph exists. ◦ The material meets the specific requirements in the monograph and is manufactured under appropriate GMPs.
Multi-compendial grade	A material grade for which more than one compendial monograph exists. ◦ The material meets the specific requirements in the multiple monographs (e.g., *United States Pharmacopeia—National Formulatry, European Pharmacopoeia., Japanese Pharmacopoeia*) and is manufactured under appropriate good manufacturing practices (GMPs).
Supply grade	A material grade that ensures visibility to supply chain and change control. ◦ The material is manufactured under appropriate GMPs or controlled conditions to ensure consistent quality
Reagent grade	A material grade for a procured commodity that is not always intended for use in the bio/pharmaceutical industry (e.g., ACS or food grade).

removed, and as a result may still be present in the finished product.

- Excipients are ingredients added to the drug substance during manufacture of the drug product and intended to be present in the final product.

While these terms and definitions may differ between different companies, the important point is to have the discussion and reach a common understanding within a company to establish a consistent, cross-functional approach to compliance.

The definitions for materials are based on their use in the manufacture of the drug substance and drug product. The definitions for material grades are based on the materials that are purchased and the testing performed on them. The definitions for grades used in this article are listed in TABLE 2 and include compendial grade, multi-compendial grade, supply grade, and reagent grade. Compendial and multi-compendial grade relate to the availability of one or more monographs for the material in the pharmacopoeias. Supply grade is a term used when there is a need for a company to have visibility to the supply chain and change control for the material. As an example, for a material purchased from a distributor, a company may need to be notified if the distributor changes their supplier of the material, as this could have an impact on the drug product manufacture.

Similarly, for a material purchased directly from a manufacturer, a company may need to be notified if changes are made to the manufacturing process of the material as this may also impact the manufacture and quality of the drug product. The notification from distributors and manufacturers can be very important for control of the materials used in the highly-regulated bio/pharmaceutical industry. Finally, reagent grade applies to materials not covered by the criteria above. The use of reagent grade materials should be carefully considered to ensure their acceptability in the manufacture of a drug substance or product, from a quality and regulatory perspective.

It is now possible to look at the four questions posed earlier in greater detail, with the common understanding provided by the definitions for materials and grades given above. The underlying questions will enable discussion and drive decisions that are consistent across the various functional areas. Many of the underlying questions are the same but are examined from different perspectives by different functional areas. The goal is to align on the approach used throughout the product lifecycle for the selection, sourcing, testing, and filing of the materials.

Functionality: What Do You Need?

The question, "what do you need?", arises at the very beginning of development, and the answer depends on how the material will be used. Is it an excipient used in the drug product, or is it a raw material used in the drug substance? This is a fundamental question that should be easy to answer.

If the material is intended as an excipient, its safety must be confirmed. Is safety or toxicology data available in the literature? Does the material have generally recognized as safe (GRAS) status? Is it listed in the FDA Inactive Ingredient Database showing the maximum level that has been approved in drug products for a particular route of administration or dosage form? When looking at the functionality of the material, it is important to identify the unique characteristics that contribute to its suitability for the intended use. What specific materials and grades should be considered? Will the material support a quality-by-design approach to manufacturing? Is viscosity or particle size important? Are there impurities that can impact the overall quality of the material itself or the quality of the product that will be made from it? Are there residual solvents or elemental impurities present? Depending on its use, is there a need to consider microbiological quality or sterility?

The functional and quality requirements for the materials determined during development are important to other groups involved later in the product lifecycle. These requirements will be tested by the quality groups to ensure the identity, purity, and performance of the materials. The requirements may eventually be listed and justified in product registrations, with potential impact on post-approval change control. At a certain point, questions arise

as to the availability of the material. These sourcing considerations are not necessarily fundamental during early development but are critical in late development and commercialization.

Sourcing: What Do You Buy?

The question, "what do you buy?", builds on the decisions made in new product development and evolves throughout the product lifecycle. Again, you start with the question of how it is used because that, in many ways, determines what you buy. The development scientist may pull a raw material or excipient off the laboratory shelf to start their work. The material may have been purchased through a chemical catalog or it could be a promotional sample from a potential supplier. The scientist might check what is available in the chemical stock or manufacturing area that can be used in development studies.

There is still a need to understand the critical quality attributes (CQAs) for the material to enable discussion with potential suppliers. At this stage, there is a focus on what is available. Is there only one supplier or are there multiple sources that can provide the material? Is visibility to the supply chain or change control necessary and possible for the material?

As product development proceeds, considerations of the cost and available quantities become important. If there are multiple sources for the material, what is the basis for choosing one supplier over others? Is there a need to qualify more than one supplier in case of material shortages? What experiments are needed to ensure suitability of materials from different suppliers for use in the specific formulation? Have the suppliers been previously audited by the company? Were the audit findings acceptable? Are specific materials with different characteristics available (e.g., hydroxypropyl cellulose with different molecular weight and viscosity properties) and is one better suited for the intended function? All of these questions lead to the ultimate determination of the materials and suppliers that will be used in the manufacture of the drug substance and product. These decisions also impact the testing performed and provide information about what may be filed in product registrations. Typically, the purchased materials should be compendial, multi-compendial, or supply grade. In some cases, reagent grade materials may be considered, although the ability to use reagent grade materials in drug product manufacture is fairly limited due to quality and regulatory concerns, in the authors' experience.

Quality: What Do You Test?

The question, "what do you test?", depends again on how the material is used. If the material is used as an excipient and there are applicable monographs, the quality groups need to ask whether they will perform all tests in one or more pharmacopoeias. In which countries will the product be filed? This determines which pharmacopoeias may be applicable when

ensuring compendial or multi-compendial compliance. What if the material is used as an excipient but is non-compendial, meaning there is no monograph for the material in the pharmacopoeia?

"Understanding CQAs for the intended use is again important so that quality testing can be performed to control these characteristics in releasing the material."

Understanding CQAs for the intended use is again important so that quality testing can be performed to control these characteristics in releasing the material. What tests are performed by the supplier? What are the supplier's acceptance criteria? One key point in going through the exercise at this stage is that there must be discussion and agreement with the supplier for any additional tests or different limits that will be required based on the use of the material. A company making these decisions in a vacuum or without interaction with the supplier can put the availability of the material at risk and create potential challenges for the company. Release tests should include analytical and microbiological controls to evaluate overall quality, ensuring the identity, purity, and functional suitability of the material. Control of specified impurities is a key consideration. Some tests for the functionality-related characteristics of the material may be performed as "internal tests" and not included in the product registration. These internal tests are performed for release of the material but do not represent a regulatory commitment. This leads to the final question to be considered.

Registration: What Do You File?

The question, "what do you file?", also depends on how the material is used because this determines what may be listed in the product registration. One key lesson is that the answers to the prior questions ("what do you need, buy, test?") do not necessarily have to correlate with what you file. What is listed in the registration does not have to match what is sourced or even tested. This returns to the potential disconnect that was presented earlier in FIGURE 1.

At a practical level, how the material is used determines which section of the Common Technical Document (CTD) will contain the information about the material that is provided to regulatory agencies. Recall that the bio/pharmaceutical company must comply with approved product registrations, including applicable compendial requirements. What is listed in the registration becomes a regulatory commitment. Based on how the material is used, does the company need to commit to compendial testing in the registration per the applicable monograph? If used as an excipient, the answer is "yes." For which pharmacopoeias is the company claiming compliance? It is recommended that compliance with only

one pharmacopoeia be listed in any product registration, according to which particular pharmacopoeia is applicable for the specific country to meet regulatory expectations in the filing. This idea will be further detailed in the following strategy section. Are there additional tests, such as quality attributes and functionality testing, that are critical to product manufacture and should be included in the registration?

In determining what to list in the product registration, a company must choose wisely because the decision essentially locks you in. Considering what may be an extreme example, imagine an ingredient used as a "raw material" as defined in this article, and that it is an important component in the preparation of the drug substance. Imagine further that the company wishes to control the particle size of this material, not as a CQA, but to aid in processability during manufacture of the active ingredient. In this example, because it is an important component in the manufacturing process, visibility is needed for the supply chain and change control of the raw material. This situation is consistent with the use of "supply grade" material.

Imagine, however, that the supplier will only assure supply chain visibility if the company purchases "compendial grade" material. It must be stressed that procuring compendial grade material does not mean that compendial compliance must be listed in the registration; nor would particle size testing necessarily need to be included.

Perhaps the company has determined that only assurance of the identity of the material is required for quality testing and in the registration to support the material's intended use in manufacturing. The particle size might be an additional internal test for control, while the company gains more experience with the manufacturing process. If, however, there are disconnects between the different functional groups in the company and in their decisions, it is conceivable that the registration might list compendial compliance (based on the material procured) and the particle size test (based on the testing performed) because a consistent approach was not followed.

The result is an unnecessary regulatory commitment with which the company must now comply. This situation can create challenges for many groups, including quality ("why do we now have to perform testing per the compendial monograph?"), manufacturing ("after scale-up, we no longer need to control particle size for the material"), and procurement ("we would like to change to a lower-cost supplier who provides supply chain visibility for the material without reference to the monograph"). Any changes to address these challenges will require that the company make updates to the product registrations, with the associated difficulties typical of the change control process. This situation illustrates the intersection of the four questions considered and enables discussion of principles and strategies that can help avoid the potential challenges.

ALIGNING ON PRINCIPLES AND STRATEGIES

The goal is for a company to establish a consistent, cross-functional approach for the selection, sourcing, testing, and filing of materials used to manufacture drug substances and products, in compliance with applicable compendial and regulatory requirements. Consistent principles and strategies should be established that will be followed throughout the product lifecycle by all functional areas in the company. Using the definitions provided earlier, the following principles are proposed:

Principles for excipients

- An excipient should be compendial grade, unless a monograph for that material is not available in the pharmacopoeia.
- If there is more than one applicable monograph in the multiple pharmacopoeias, the material may be multi-compendial grade.
- An excipient without a compendial monograph should be supply grade

Principles for raw materials

- A raw material should be supply grade.
- Even if there is a monograph in the pharmacopoeia for the material, its use as a raw material does not require sourcing, testing, or filing as compendial grade.
- A raw material may be procured as compendial grade (to have supply-chain and change control visibility), but the filing should only include the minimum requirements to ensure the quality and suitability of the material. The filing should not reference the compendial monograph.

Principles for residual materials

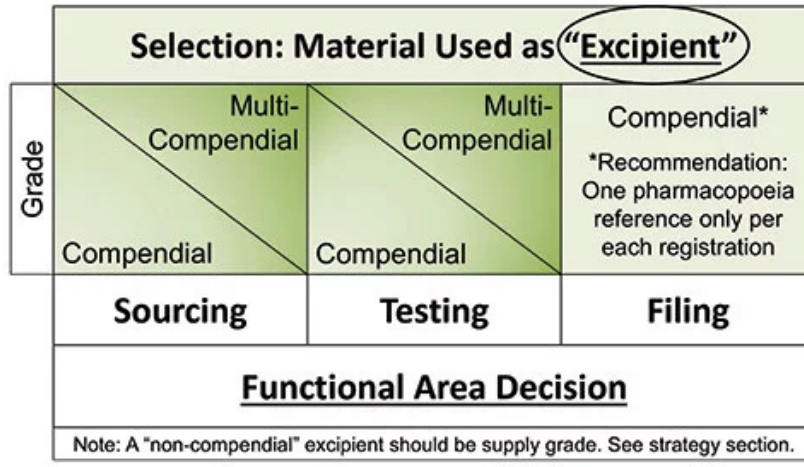
- A residual material may not be applicable in all small-molecule or complex biotherapeutic processes. Whether the material needs to be compendial grade or supply grade should be addressed on a case-by-case basis.
- The strategy for a residual material would generally align with the raw material strategy.
- Testing and filing should reflect appropriate, minimum requirements for the material.

As stressed before, in establishing the principles within a company, it is important to have the discussion with colleagues from all functional areas involved throughout the drug product lifecycle to develop a consistent approach for the appropriate selection, sourcing, testing, and filing for the materials used.

STRATEGIES FOR EXCIPIENTS: COMPENDIAL VS. MULTI-COMPENDIAL

The principles given above enable a company to establish their strategy based on the fundamental use of the material as an excipient or raw material. **FIGURE 3** shows an appropriate strategy for the case where the selection process determines an ingredient will be used as an excipient. The other functional area decisions for sourcing, testing, and filing are shown in the three columns, with the corresponding choices for material grade shown in the colored boxes. Assuming there is an applicable monograph

FIGURE 3: Strategy: Material used as excipient. (Figure courtesy of the authors)



in one or more pharmacopoeia, the sourcing decision for an excipient is either compendial or multi-compendial. The testing decision is also compendial or multi-compendial. The filing decision is compendial, with the recommendation that only one pharmacopoeia is referenced for the material in any registration. The decisions in this strategy can be better understood by looking more closely at specific situations.

It is instructive to look at the interplay of the decisions for sourcing and testing when considering whether compendial or multi-compendial grade is the better choice for an excipient used in a particular drug product. It will cost more for a company to purchase an excipient sold as multi-compendial grade because the supplier of the material must perform additional testing to ensure compliance with more than one monograph. The user of the excipient may be able to leverage the multi-compendial testing performed by the supplier to reduce their own testing of the material, by accepting some results from a qualified supplier's certificate of analysis (COA). This can be done provided the user of the excipient performs at least one specific test to verify the identity of the material. Additionally, the user must establish "…the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals", as stipulated in the US *Code of Federal Regulations* (8).

Alternatively, the excipient user can perform all testing needed to ensure multi-compendial compliance for the material. This can be accomplished even if the material is purchased to comply with the monograph in only a single pharmacopoeia. This approach is not "testing into compliance". To be considered compendial grade, a material

must be prepared according to recognized principles of good manufacturing practice (GMP) and meet the requirements in the pharmacopoeia monograph, as noted in the *USP* General Notices (5). With this understanding, a material may be purchased, for example, as "*Ph. Eur.* grade", meaning it has been manufactured under appropriate GMPs and meets the *Ph. Eur.* monograph requirements. This material can be further tested by the user of the material according to the *USP* monograph. If the material meets the additional *USP* requirements, it can be considered to be multi-compendial, because it has been prepared under appropriate GMPs and complies with the monograph requirements in both *Ph. Eur.* and *USP*. With this approach, there is a potential business risk that must be understood by the quality and procurement functions in the company. The excipient user may be unable to return material to the supplier if they obtain a failing result for an additional test in the *USP*, when the supplier has not indicated that the material complies with the *USP* monograph requirements. Alternatively, there is no need to reject the material if it fails *USP* testing, but the company would need to control the material inventory, so it is not used where *USP* compliance is required.

There are, in fact, a wide range of options that a bio/pharmaceutical company may take to ensure multi-compendial compliance for an excipient intended to support global product registrations (9). The most conservative approach is to perform full testing according to the specific tests, methods, and acceptance criteria contained in each monograph. Full multi-compendial testing demands significant resources and time, and, accordingly, will not be the preferred approach in many instances, particularly once the product has reached the supply stage of the lifecycle. There are earlier times during the product lifecycle, however, where this might be a good approach to take. For an excipient used in a drug product biobatch or formal stability batch, demonstration that the material has been tested to comply with applicable pharmacopoeia monographs for the United States, Europe, Japan, and China markets, for example, enables this information to be communicated to regulatory agencies in these countries and may avoid delays in product approval. Obviously, testing would not be required for a national pharmacopoeia if there is no intention to file in that particular country.

Other approaches involve reduced testing as noted earlier, by accepting some results from a supplier's COA or establishing an appropriate skip-lot testing program. A company may be able to leverage the outcome of excipient harmonization completed by the Pharmacopoeial Discussion Group (PDG) to perform testing per one monograph in the *USP*, *Ph. Eur.*, or *Japanese Pharmacopoeia (JP)* to ensure compliance with all three. There is also a strong case to be made for a company to leverage their own "internal harmonization" for excipient testing to ensure multi-compendial compliance. This concept was presented in a different context

in the previous article for a drug substance (1), where a company demonstrates equivalency between their currently approved method and a different method published in a new monograph. In the case of excipients, internal harmonization would demonstrate and document that the same results would be obtained using different methods in the different monographs for a particular quality attribute, to reach the same overall accept/reject decision for the excipient. This determination of method equivalency between the different monographs enables a company to perform testing per one pharmacopoeia to ensure compliance with the others used in the equivalency studies. The use of a method other than the one in *Ph. Eur.* requires prior approval from regulatory agencies in Europe (10). In the case of internal harmonization of excipients, it is recommended that the *Ph. Eur.* test method be performed to ensure multi-compendial compliance while avoiding this regulatory burden.

Turning to the strategy for the regulatory decision, it is important to keep in mind that a company must comply with pharmacopoeia requirements to which they have committed in their product registrations. To ensure global acceptance for compendial grade excipients used in a drug product, a company should demonstrate compliance with *USP* and *Ph. Eur.* monograph requirements, at a minimum. These global pharmacopoeias are accepted by many regulatory agencies well beyond the geographical boundaries covered by the pharmacopoeia (11).

A few additional points are necessary. If the product will be marketed in Japan and there is a *JP* monograph for the excipient, then compliance with the *JP* is required for Japan. Filing *USP* or *Ph. Eur.* in this case would not be accepted by the Japanese health authority. A similar situation is now clear for China. If there is monograph for the excipient in the *Chinese Pharmacopoeia (ChP)*, then compliance with the ChP is mandatory for the excipient used in product going to China. The situation for other countries with their own national pharmacopoeia should also be considered, although the broad acceptance of *USP* and *Ph. Eur.* standards may be suitable to regulators in these countries.

"Turning to the strategy for the regulatory decision, it is important to keep in mind that a company must comply with pharmacopoeia requirements to which they have committed in their product registrations."

Looking more closely at multi-compendial compliance with *USP* and *Ph. Eur.* monographs for excipients, what should the company actually file in their product registration? This question relates to the pharmacopoeia reference listed for excipients in CTD section 3.2.P.1 for the composition of the drug product. In an effort to maintain a single product registration for use globally in 150 or

more countries, some companies choose to indicate multi-compendial compliance by some combination of the applicable pharmacopoeias, such as *"USP/Ph. Eur.,""USP, Ph. Eur.,"* or even *"USP or Ph. Eur.,"* perhaps with a footnote indicating compliance with one or the other "as applicable to the particular country". While the meaning of this regulatory commitment may be apparent for the US and European countries, it is not as clear to regulators in many other countries around the world. Nor is the meaning necessarily clear to the quality group in a company that needs to test an excipient for use in a product intended for one of these countries. Recall that for Japan and China, compliance with the *JP* and *ChP*, respectively, is required if they contain a monograph for the excipient. This means the goal of a single registration is not possible for a global bio/pharmaceutical company.

As shown in **FIGURE 3**, it is the authors' recommendation that only one pharmacopoeia is referenced for the excipient in any registration. This means listing *USP* compliance for excipients in one registration, which may be filed in 75 or more countries that accept *USP* compliance. Another registration would list *Ph. Eur.* compliance for excipients, to be filed in another 75 or more countries, including all of Europe. The benefit of this approach becomes clear when considering the potential impact on global product registrations resulting from an update to the pharmacopoeia monograph. Executing the change control process to implement the monograph update typically requires some degree of regulatory impact assessment by the chemistry, manufacturing, and controls (CMC) function of a company to determine if any actions are necessary. Assume, for example, the update is to the *USP* monograph. If the company has filed the somewhat ambiguous *"USP/Ph. Eur."* compliance in 150 countries, then the company will need to complete regulatory impact assessment for product registrations in all 150 countries. By contrast, if the company has filed specific compliance to *USP* in 75 countries, then the impact assessment is only needed for the registrations in these 75 countries. No change control or impact assessment is needed for the other 75 countries where *Ph. Eur.* compliance has been filed. This approach reduces by half the number of regulatory impact assessments needed by a company as a result of compendial updates. This workload reduction is significant given the time and complexity of looking at so many individual product registrations. Adding the country-specific registration needed for Japan that lists *JP* excipient compliance and for China that lists *ChP* excipient compliance, there are a total of only four different registrations needed for global use, acceptable in essentially every country in the world.

There are other approaches that may be taken to ensure appropriate compliance for excipients with monographs in the pharmacopoeia. In Europe, the excipient supplier can apply for Certification of

Suitability to the Monographs of the *European Pharmacopoeia* (CEP). The CEP procedure has been in place for more than 25 years to provide assessment of the manufacturing and quality controls used for an excipient (12). Another approach introduced by USP, the Ingredient Verification Program for Excipients, provides a complete evaluation of an excipient company's quality system to ensure control of the material's quality and includes review of manufacturing batch records and release data, a GMP audit, product testing, and continuous surveillance monitoring (13).

"There are some instances where there is no monograph in the pharmacopoeia for an excipient that will be used in a drug product."

STRATEGIES FOR EXCIPIENTS: NON-COMPENDIAL

There are some instances where there is no monograph in the pharmacopoeia for an excipient that will be used in a drug product. These so-called "non-compendial" excipients could be novel materials that have not previously been approved in a drug product or simply a material where a pharmacopoeia monograph has not been established. Non-compendial excipients introduce another set of considerations to help guide a company's strategy. As noted previously, the safety, toxicology, and/or GRAS status must be assessed for the non-compendial excipient. Because compendial grade is not an option, the sourcing decision defaults to supply grade to ensure visibility to the supply chain and change control for the excipient.

The questions now center on the appropriate testing and filing for the material. Looking first at testing, how does the excipient user establish appropriate specifications when there is no compendial monograph for the material? The starting point is the supplier's specifications, but there are additional questions to be considered. Should the excipient user include all tests from the supplier's specifications? Should the same methods be used, if they are available from the supplier? Are there tests or methods in the general chapters of the pharmacopoeia that could be used for the material? Should the company apply the same acceptance criteria to the material, or is there a particular range for a quality attribute that is needed for their manufacturing process? Are there other functional requirements that should be added to ensure appropriate control for the excipient? Because the excipient supplier will likely have no visibility to the specific use of the excipient in the drug product, the user must ensure agreement with the supplier on any additional tests or limits for the material. Not doing so could result in the supplier being unable to consistently provide material that meets the user's specifications, putting the supply of the drug product at risk. The ultimate goal, as emphasized previously, is to establish overall testing requirements that ensure the excipient has appropriate quality,

is fit for purpose in the drug product, and can be procured on an ongoing basis.

Once the specifications have been established for the non-compendial excipient, consideration turns to the product registration. In this case, there is not the ability to make the simple but specific reference to quality requirements listed in a monograph for the material. Which of the tests established for the non-compendial excipient should be included in the filing? Clearly, there are tests that are required for the excipient that should be listed, becoming regulatory commitments to control the quality of the material. There may also be some tests that can be maintained as internal tests, as described earlier. Additional information, beyond quality requirements, will also be needed in the registration for a novel excipient.

An interesting situation experienced by one of the authors helps to illustrate the subtlety of the considerations that can enter into a company's strategy for excipient testing and filing. A new product under development included an excipient that had not been previously used by the company. On searching, the CMC group found there were no monographs for the material in either the *USP* or *Ph. Eur.*, but there was a monograph in the *French Pharmacopoeia (Ph. Fr.)*. The CMC scientist wanted to take the simple and seemingly appropriate action of filing the excipient to comply with the *Ph. Fr.* monograph. In discussion with the compendial affairs group, however, it was pointed out that the *Ph. Fr.* was not included in the company's pharmacopoeia surveillance process, for a variety of reasons, including available resources and the need for translation. This raised the risk that any future change to the *Ph. Fr.* excipient monograph could jeopardize the company's compliance for the material, as committed in the registration. Should the material be filed with the *Ph. Fr.* reference, which would likely be acceptable throughout Europe, but perhaps not as widely accepted by other countries? Is there another approach that could be taken? The compendial affairs group recommended the material be filed as a non-compendial excipient to avoid the compliance risk. However, the specifications listed in the *Ph. Fr.* monograph at the time of filing would be used to establish the tests, methods, and acceptance criteria to control the material, becoming manufacturer's specifications rather than compendial specifications. If questioned upon review by a health authority, the alignment with the *Ph. Fr.* monograph could be shown. By listing the requirements as manufacturer's specifications, however, the compliance risk was removed with no additional surveillance activities required by the company to monitor potential changes to the *Ph. Fr.* monograph. It is conceivable that another company would have made a different decision and filed the excipient to meet the *Ph. Fr.* requirements. This points to the reality that, taking all considerations into account, there is not always a single decision that is best for all companies. The

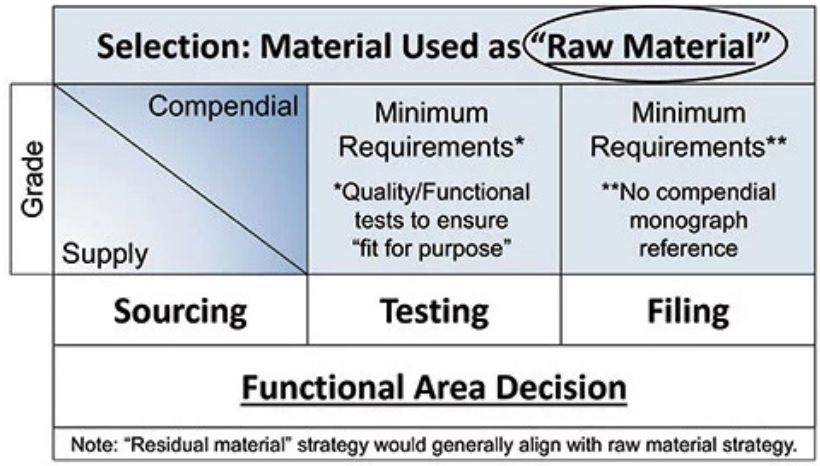
lesson is that the affected groups should come together and discuss the functional requirements, quality requirements, and regulatory expectations for the material to determine the appropriate strategy.

STRATEGIES FOR RAW MATERIALS

The strategies and functional area decisions for the case where the selection process determines an ingredient will be used as a raw material for the preparation of the drug substance are presented in FIGURE 4. As shown in the columns, the recommended sourcing decision is supply grade or compendial grade, either of which can provide the desired supply chain and change control visibility for the material. Sourcing compendial grade for the raw material does not mean it would be tested or filed as compendial grade. It is unnecessary to consider multi-compendial grade material as this will simply be more costly to purchase.

If compendial or supply grade material is not available, or if it is otherwise suitable for the material to be purchased as a commodity, then reagent-grade material can be considered, with the cautions mentioned earlier taken into account. The testing decision is to include only the minimum requirements that are needed to ensure the raw material is fit for purpose, in terms of its quality and functional attributes. The filing decision is also to include only the minimum requirements necessary, with no reference made to a compendial monograph, if one is available for the material. In establishing the specifications for the material, some tests from an available monograph or from general chapters in the pharmacopoeia might be included, since these can be useful. There should be no commitment to comply with the monograph, however, because that is neither necessary nor appropriate for the intended use of the raw material

FIGURE 4: Strategy: Material used as raw material. (Figure courtesy of the authors)



in drug substance manufacture. Recall the product lifecycle can span many years from development to registration to supply, with many functional areas involved in decision-making throughout the process. With this in mind, in the authors' experience, the decisions made for raw materials pose the greatest risk of internal disconnects between what is filed and what is sourced or tested, as represented in **FIGURE 1**. Committing to more than is necessary for the raw material in the product registration has unfortunate practical and long-lasting impact to other functional groups in the company.

STRATEGIES FOR RESIDUAL MATERIALS

As noted in **FIGURE 4**, the strategy for a residual material would generally align with the raw material strategy. Similar to raw materials, the decisions made for residual materials pose a risk of disconnects between what is filed and what is sourced or tested. Consistent application of the principles and strategies described in this article can help avoid these disconnects, ensure appropriate testing, and reduce the potential compliance burden and risk.

CONCLUSION

Principles and strategies have been provided to help companies develop a consistent, cross-functional approach for the appropriate selection, sourcing, testing, and filing of raw materials used in the preparation of drug substances and excipients used in drug products. Having a common understanding of definitions based on how the materials are used and for material grades based on what is purchased and how it is tested can facilitate appropriate decisions by impacted groups across the product lifecycle. The decision of what is included in the product registration is particularly critical. The often-complex answers to seemingly simple questions- What do you need? What do you buy? What do you test? What do you file?- help guide a company's decisions that can provide less complexity and ensure compliance with applicable compendial and regulatory requirements.

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Upstream Processing: Biochemicals and Raw Materials

By Meg Rivers

Experts reveal how to identify the "right" biochemical, the process of sourcing biochemicals, sourcing challenges, and what industry professionals should know about the space.

Sourcing biochemicals adds a layer of complexity on top of an already complex process of sourcing raw materials. Development lifecycles must be considered in addition to good material specification and supply chain risks. *BioPharm International* interviewed Ryan Crisman, chief technical officer; Sarah Gould, associate director of MSAT (manufacturing science and technology); Jessica Freeman, MSAT process engineer III; David Mandeix, associate director of supply chain; and Christopher Lewis, senior director of quality, all of Umoja Biopharma, on biochemicals and raw materials in upstream processing.

According to Crisman, Umoja Biopharma specializes in immunotherapy, specifically in reprogramming T cells *in vivo*, which allows a patient's immune system to target cancer cells.

UPSTREAM PROCESSING AND BIOCHEMICALS

BioPharm: Where do biochemicals come into the pharma development and manufacturing process? What does this look like for upstream processing, specifically?

Gould: Biochemicals define the final drug product; their quality and composition can impact the critical quality attributes (CQAs) significantly. Biochemicals do not so much come into the process as they are the process, having a prominent role in the identity, purity, and strength of the final drug product. The quality of the biochemicals is one of the most important factors in creating safe and effective drug products. For upstream processing, the cell line dictates the mode in which we run the upstream process. Thus, having the right producer cell for our lentiviral process can really make or break process performance—and, by extension, our ability to intensify the process to commercially-relevant scale.

IDENTIFYING THE RIGHT BIOCHEMICAL

BioPharm: How do you determine what biochemical type is best?

Gould: We want a high quality and reliable vendor who can partner with us to develop new solutions for lentiviral manufacturing and ensure consistent supply. Most of what is commercially available was designed for other virus types. We have the opportunity to apply some strategies or materials from AAV (adeno-associated viruses) to LVV (lentiviral vectors), but it does not always transfer successfully. Therefore, there is a significant opportunity for biochemical developers to partner with lentiviral development companies.

SOURCING BIOCHEMICALS VS. RAW MATERIALS

BioPharm: How does selecting biochemicals compare to raw materials sourcing in biopharma?

Freeman: For many biochemicals, you not only have to evaluate the performance in your process but also how it will be characterized. In some cases, this requires a release method to demonstrate clearance of the biochemical. Sometimes, analytical support is available from the same vendor—an ELISA (enzymelinked immunosorbent assay), for example— to show clearance in your process. Thus, you are often evaluating both the utility of the biochemical in your process and your analytical ability to demonstrate removal in the process. These requirements necessitate locking arms with vendors to ensure appropriate execution of specialized work. Furthermore, much of that custom work has less clear guidance and practices. Critical industry standards (like a multi-compendial grade) do not currently exist for biochemicals. Biochemicals often make up such intrinsic components of the process (plasmids, cell line, etc.); as such, it is more difficult to ensure a universal standard, such as multi-compendial grades

for raw materials. In addition, biochemicals are actively being developed and improved upon, which also makes their standardization more difficult compared to raw materials.

DEFINING CGMP

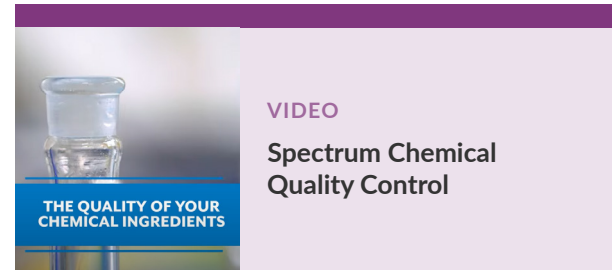
BioPharm: How do you define current good manufacturing practices (CGMP), specifically as it relates to biochemicals? What does that entail?

Lewis: When we refer to CGMP for biochemicals, we would expect suppliers to adhere to GMP requirements in the manufacturing, documentation, testing, release, and distribution of those materials. This would include quality systems that adhere to regulatory requirements and industry standards to provide the appropriate level of control and oversight for their (our) intended use. These systems and processes should be appropriately robust and auditable. When someone claims CGMP, they should have their act together to meet all requirements and standards defined by the agencies.

SOURCING RAW MATERIALS

BioPharm: What are best practices for sourcing biochemicals? For raw materials?

Mandeix: The cost of poor-quality materials—raw or otherwise—cannot be understated. This issue often rears its head when trying to source things fast or cheap. Best practices for sourcing raw materials start with having a good material specification, a robust supplier qualification system, and an understanding of how your needs compare to that of the market at large. Sourcing biochemicals adds complexity to this process, as companies must also account for a development cycle (or sometimes several) and can then be called upon to help your CDMO [contract development and manufacturing organization] de-risk their own supply chains in order to facilitate the production of your biochemical. In either case, strong relationships with your suppliers and an in-depth knowledge of your material are table stakes for any company's sourcing process.



BioPharm: What does the process of sourcing raw materials look like for your company?

Mandeix: As a relative newcomer to the biotech space that had to deal with the challenges of the pandemic shortly after its founding in 2019, Umoja has had to develop some extremely flexible sourcing strategies. Raw material is sourced with phase-appropriate control and supplier scrutiny (i.e., the specifications for both raw material and supplier tighten as we move from Phase I to Phase III). These systems are still being built out, with an eye towards an end state of commercial compliance for the quality systems. The best practice is to identify several suppliers that can provide

what we need within a reasonable timeline and then work with them as we tighten our specifications or change what we need out of the material.

WHAT INDUSTRY PROFESSIONALS SHOULD KNOW

BioPharm: What is one thing you wish the pharma industry knew about biochemicals and raw materials?

Freeman: Companies in the pharma industry should be less fearful of implementing new biochemicals and raw materials into their processes. Companies often fall back on tried-andtrue technology 'because the FDA has seen it,' and it will make their regulatory submissions more easily digestible. But that doesn't foster process innovation and is not always the best material for the given use. Larger companies have the advantage of resources to take on that risk instead of falling back on what has worked historically without investigation of new novel solutions

UP-AND-COMING TRENDS

BioPharm: What trends do you see on the horizon for biochemicals and raw materials? Are there any up-and-coming technologies we should be aware of?

Gould: Expect to see process intensification for lentiviral processes that are starting to mirror what continuous mAb [monoclonal antibodies] processes look like. This means there is a lot of interest in other biochemicals and raw materials to enable intensification, such as continuous filter setups and producer cell lines instead of transient transfection. Producer cell lines and continuous processes enable the higher process throughputs required to meet the expected growth in demand in the gene therapy space.

Originally published as M. Rivers, "Upstream Processing: Biochemicals and Raw Materials," *BioPharm International* 35 (11) 20–21 (2022).

Materials Sourcing: Precautions and Improvements for Cell and Gene Therapies

By Lauren Lavelle, BioPharm International

Growth in cell and gene therapies puts pressure on the raw materials supply chain.

Materials sourcing for cell and gene therapies is a complex, precise process that requires organization and adherence to pharmaceutical guidelines. Experts discuss the challenges developers must work to overcome while suggesting steps for further improvement, less risk, and better cooperation with the supply chain.

SOURCING PRECAUTIONS AND CHALLENGES

When discussing the precautions needed when sourcing materials for cell and gene therapies, vice-president of

Scientific Affairs and Business Development for TrakCel, Matthew Lakelin, stresses the importance of following best practices. "These include ensuring that those suppliers have adequate stocks to maintain your peaks and troughs in demand and also ensuring that those suppliers have the ability to hold specific batches for your batch numbers and lot," he says. "There is a paucity of viral vector manufacturers at the moment, putting real pressure on supply lines associated with these raw materials. Finding and obtaining these products can be challenging especially due to the custom nature of the manufacturing exercise."

EBOOK

Biopharma/Pharma Analysis: Don't Leave Change Control to Chance

Lakelin notes that the collection process is crucial. "For autologous products, it is important to ensure consistency in the collection process used to obtain starting material. [Consistency] can be achieved by providing standard operating procedures at collection centers and using orchestration software to manage the process," Lakelin says. "For allogeneic products where a key raw material will be human cells, it is recommended to use a recognized sourcing partner. Using a specialist significantly decreases the risk associated with these raw materials and also gives you the widest number of options available for these products."

Ezequiel Zylberberg, PhD, vice-president of Product Development and Planning at Akron Biotech, suggests cell and gene therapy developers take a risk-based approach to sourcing ancillary materials while keeping industry guidance documents in mind.

"[Sourcing] entails the systematic identification, analysis, evaluation, reduction, and acceptance of different risks in the supply chain," Zylberberg said. "For instance, animal-derived materials are generally considered to be high risk. Neutralizing potential pathogens by irradiation or nanofiltration or replacing these materials with xeno-free alternatives (where feasible) are attractive risk-mitigation steps. Human-derived products can also present challenges, which is why shifting towards virus inactivated raw materials can effectively mitigate risk while still enabling the use of critical materials like Human AB Serum and Human Fibronectin."

Other challenges cell and gene therapy developers face while sourcing materials have to do with time to market, according to Nandu Deorkar, vice-president of R&D for Biopharma Production at Avantor.

"The demand for reducing the time that a therapy reaches the market is pushing manufacturers to implement lab-scale processes and the research-use-only

grade of materials used within them into commercialization levels that are neither efficient nor effective," Deorkar explains. "Unlike in monoclonal antibody manufacturing, materials in use for cell and gene therapies are required in smaller scales. Many of the materials available today are for research-use only and need to be adapted to meet current good manufacturing practices (cGMP) as well as other regulatory standards (e.g., non-animal derived sources)."

Zylberberg notes that demand for materials continues to grow. "More than 50 percent of biomanufacturers expect to experience moderate to severe capacity constraints at commercial scale by 2025," he says. "Pressure on the supply base is likely to grow, with more than 1,000 regenerative clinical trials underway globally."

He adds that suppliers need to grow to support this demand. "The cell and gene therapy supply chain has expanded considerably in the last few years, but must continue to grow, consolidate, and standardize to support the industry moving forward," Zylberberg says. "Building greater cGMP-compliant ancillary material manufacturing capacity and supporting developers and regulators with robust Drug Master Files will be important in ensuring that ancillary materials are suitable for clinical and commercial manufacturing use."

SUGGESTED IMPROVEMENTS

Deorkar suggests partnerships between raw materials suppliers and biopharma manufacturers are beneficial in terms of improving workflow and enhancing materials sourcing activities.

"Raw materials suppliers can partner with biopharma manufacturers to help them gain efficiency in raw materials management for their cell and gene operations in several areas, with customized packaging being a large area of opportunity," he says. "Additionally, the requirement for biological activity to be retained in cell and gene therapies limits the use of harsh purification methods. This adds a special sensitivity that potentially harmful or adventitious agents cannot be introduced through the raw material supply chain. This is another area that benefits from partnership between manufacturers and their suppliers of raw materials: understanding the requirements for cGMP materials and implementing them early in the therapy development and manufacturing process."

Using smaller package sizes improves efficiency and reduces risks, says Deorkar. "Packaging materials in smaller, single-use bags is not only more effective from the standpoint of helping to eliminate material waste and remove process steps, allowing for immediate use in operations, but [these packages] are also nimbler to transport between facilities that may be undertaking different steps of the scale-up process for a therapeutic," Deorkar says. "Ready-to-use solutions, like buffers in single-use packaging configurations, can also help with streamlining operations, eliminating extra

process steps such as opening/closing/reopening containers under hoods and sub-dividing from bulk containers."

Lakelin adds that software platforms can benefit organizations by reducing supply chain risks. "For autologous therapies, do not underestimate the advantages of using cellular orchestration platforms," Lakelin says. "These software solutions have been designed specifically to manage all aspects of starting material collection and movement. A good orchestration system will minimize risk in the supply chain whilst maximizing efficiency, [aid] coordination of collection centers with manufacturing centers, and ensure utilization of manufacturing assets whilst permitting starting material donation only when it can be used."

A CASE FOR PARALLEL SOURCING

Securing materials from more than one main source, referred to as parallel sourcing, is often used to lessen risks during emergencies, such as during the COVID-19 pandemic. While Zylberberg recognizes that parallel sourcing can add expense, he says it is necessary.

"Qualifying secondary suppliers is costly and time-consuming. It requires that quality assurance, purchasing, manufacturing, and planning teams collaborate to identify suitable alternate sources of critical inputs to production," he said. "However, it is vital to ensure that these activities have been properly executed. The time and effort placed on secondary supplier qualification up front will be rewarded with the availability of options if and when bottlenecks present themselves."

"Beyond identifying suitable alternatives, biomanufacturers need to properly assess their options, audit their facilities, and qualify them per their quality management systems," Zylberberg says. "It is incumbent upon biomanufacturers to adopt and implement a risk-based approach to sourcing that recognizes the exceptional circumstances we find ourselves in and mitigates potential issues accordingly."