A Case Study in Pharmacopoeia Compliance: Excipients and Raw Materials

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In this series of articles, the authors provide an understanding about the need for pharmacopoeia compliance and practical guidance to assist those who perform this work. Published articles in this series are available online at www.PharmTech.com/compendia:

- Why Pharmacopoeia Compliance Is Necessary
- Why Pharmacopoeia Compliance Is Difficult
- A Brief History of Pharmacopoeias: A Global Perspective
- Global Pharmacopoeia Standards: Why Harmonization is Needed
- Harmonization Efforts by Pharmacopoeias and Regulatory Agencies
- Revision Process for Global/National Pharmacopoeias
- Surveillance Process for Industry: Monitoring Pharmacopoeia Revisions
- Monograph Development: Why and When to Participate
- Monograph Development: How to Participate; How to Harmonize
- A Practical Approach to Pharmacopoeia Compliance
- A Case Study in Pharmacopoeia Compliance: Excipients and Raw Materials
- Pharmacopoeia Compliance: Putting it All Together; What is on the Horizon

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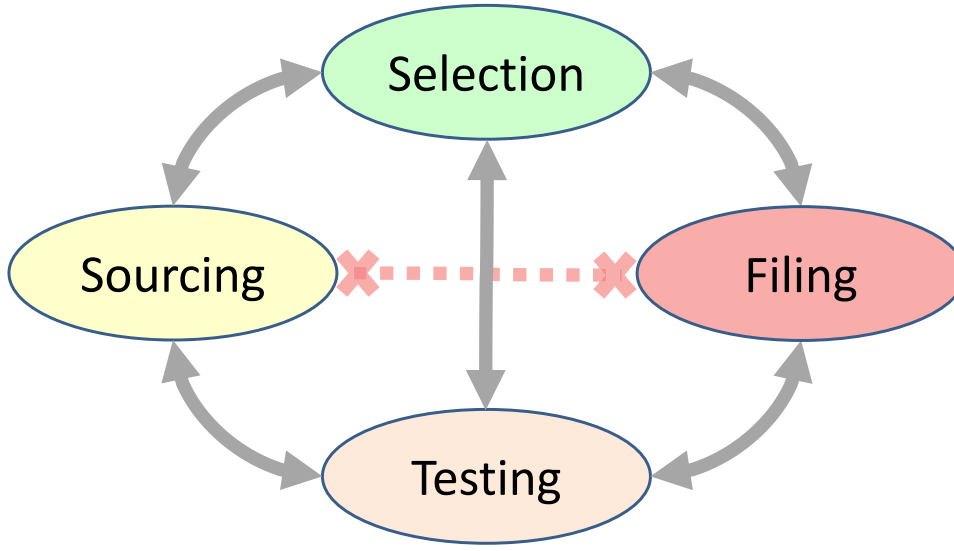
Throughout this series of articles, it has been emphasized that the bio/pharmaceutical industry must comply with requirements published by pharmacopoeias around the world. Several considerations have been presented to illustrate that pharmacopoeia compliance can be difficult. A previous article (1) highlighted 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

Figure 1. Excipients and raw materials: Interplay of selection, sourcing, testing, and filing.



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.

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

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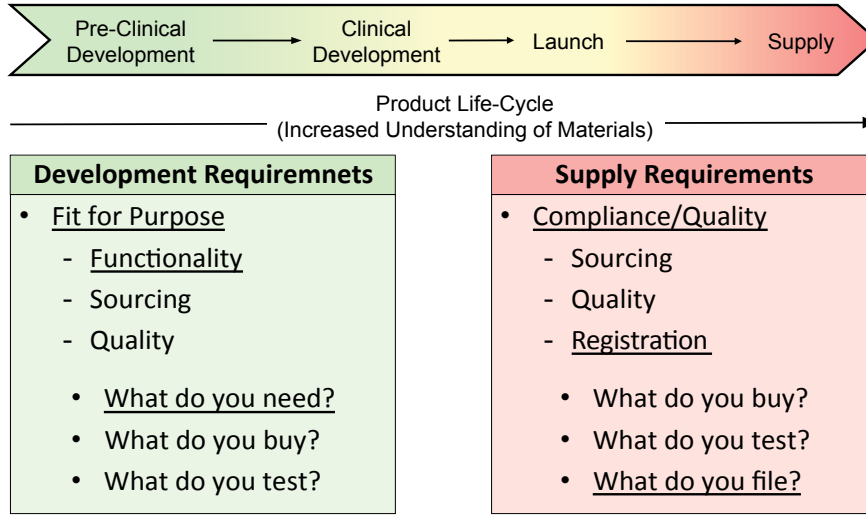
Figure 2. Excipients and raw materials: Considerations across the product lifecycle.



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.

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.

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 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, not just for the materials

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).

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 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 II** 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?

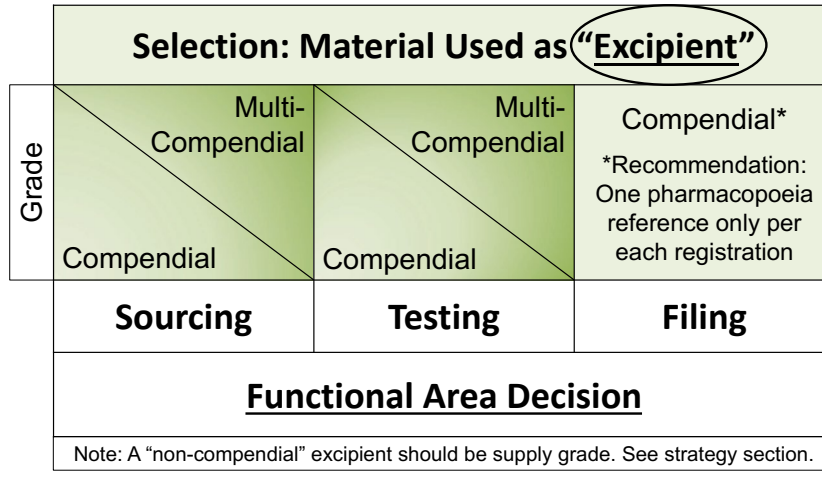
Understanding CQAs for the intended use is again important so that quality testing can be performed to control these characteristics in releasing the material. What tests are performed by the supplier? What are the supplier's acceptance criteria? One key point in going through the exercise at this stage 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,

Figure 3. Strategy: Material used as excipient.



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 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.

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).

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.

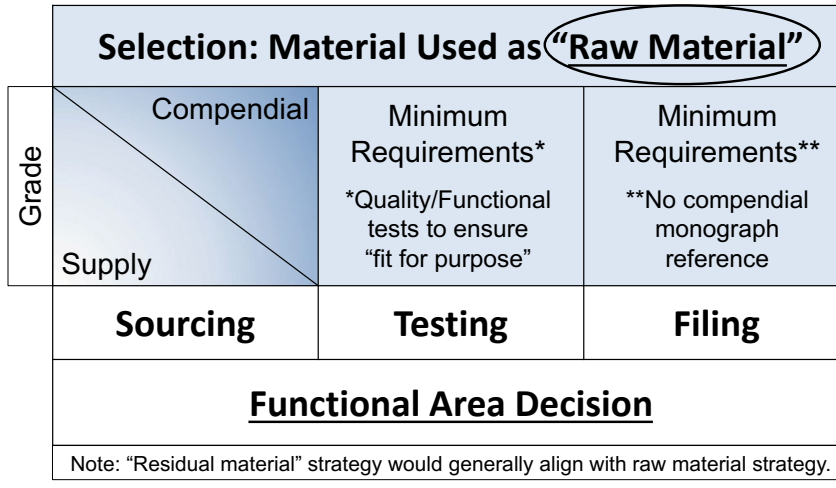
Once the specifications have been established for the non-compendial excipient, consideration turns to the product registration. In this case, there is not the ability to make the simple but specific reference to quality requirements listed in a monograph for the material. Which of the tests established 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 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.

Figure 4. Strategy: Material used as raw material.



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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