



Monograph Development: How to Participate; How to Harmonize

This article details the more operational aspects of monograph submissions, answering the question of how to participate.

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A previous article in this series focused on the questions of why and when a company would submit a monograph to the pharmacopoeias (1). This article details the more operational aspects of monograph submissions, answering the question of how to participate. This question, in turn, is best approached by considering the following: who in the company is responsible for monograph submission and follow-up; what information and materials are needed to enable the elaboration process; and which pharmacopoeias the company will interact with for monograph elaboration. These questions also help when considering how to approach the development of monographs that are harmonized across multiple pharmacopoeias.

CONSIDERATION OF WHICH GROUPS SHOULD HAVE RESPONSIBILITY TO SUBMIT THE MONOGRAPH

After a company decides on its approach to monograph elaboration (i.e., if it will participate—the why and when) (1), the company needs to define who is responsible for preparing the documents for submission to the compendial authorities, as well as providing responses to questions received from the pharmacopoeia during the elaboration process. The company must take many factors into consideration

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when deciding which functional group will be responsible for this activity.

Monograph elaboration responsibilities could fall to many different groups in a company. The responsible group must have the breadth and experience to work externally with the pharmacopoeias, as well as internally across several functional areas and have a clear understanding of post-approval regulatory and quality changes that a new or revised monograph may cause. The compendial affairs group may seem the most logical choice to have the responsibility because they should have well-established connections

to the pharmacopoeias, already understand the pharmacopoeia processes, and have connections to the scientific liaisons that drive the monograph elaboration process. The compendial affairs group should also have a network of contacts already established in many functional areas across the company due to the nature and impact of their pharmacopoeia surveillance activities (2). There are other departments, however, that could be considered to have the responsibility for monograph submission, including the chemistry, manufacturing, and controls (CMC)/regulatory affairs group, because they are responsible for submissions to health authorities that would be impacted by the creation of a new monograph. This group also has the breadth to interact with many functions in a company. The responsibility could fall to the analytical development function or a quality group within a company since much of the information needed is typically owned by one of these groups and they may be most familiar with current methods and specifications for the drug substances or drug products.

Understanding the pharmacopoeia monograph elaboration process should be considered when choosing a responsible function within a company. Each pharmacopoeia has its own requirements for monograph submission and the preferred timing when a company should submit a monograph. The function will need to define a strategy for monograph submission centered around timing and global harmonization, if desired. Not all functional areas have the proper global focus to ensure these are considered in the overall strategy to ensure the best outcome for a company entering this process.

The monograph elaboration process can take several years to be completed. Therefore, project management and communication skills are important for the responsible function. The chosen group needs

to know the current status of the project and be able to deftly handle questions that will inevitably come from the compendial authority. It must ensure a prompt turnaround time for obtaining answers from any affected department, so the monograph elaboration process is not delayed. The responsible department must ensure adequate resources are available for each affected department to fulfill the requests for additional information when they arrive. A connection to the tracking tools available to the compendial affairs group, detailed previously in this series (2), would be important for the chosen function given the lengthy process for monograph elaboration. Attention should be given to the complexity that exists within the industry as a result of joint ventures, collaborative business partnerships, and

A Practical Guide to Pharmacopoeia Compliance: A Series

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 to establish effective processes, partnerships, and tools to maintain appropriate and timely compliance across the bio/pharmaceutical industry to the benefit of patients.

The following articles can be found within this ebook and online at www.BioPharmInternational.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

Table I: Groups involved with monograph elaboration.

Group	Role
Compendial affairs	Communications with compendial authorities; understands the compendial processes; understands company's products
Quality assurance/control	Confirms information sent to compendial authority is aligned with currently used methods and specifications for that region
Analytical support and microbiology function	Knowledge of specification and method changes since product approval; understanding of method nuances needed for successful execution
Research & development	Knowledge of development activities for the drug substance and drug products
Chemistry, Manufacturing, and Controls/regulatory affairs	Knowledge of registration filing status and specifications for company's products in a specific country or region; owns information contained in product registrations that may be included in monograph submission, including method validation summaries, justification of specifications, etc.
Legal	Knowledge of patent information and agreements with other companies for the drug substances or drug products
External partner or joint venture partner	Need to be involved in the decision to create a monograph, what information will be shared, and questions received during the elaboration process for a new or revised public standard
Supply chain product director	As commercial lead for the drug product, has view on importance of regions of the world for a product
Stability group	Provides data from post approval shelf life studies for a drug substance or drug product; provides storage requirements
Packaging development group	Provides storage and distribution requirements

agreements. Appropriate consideration is needed for engagement across these functions and business(es) in establishing who has responsibility for the development of compendial monographs.

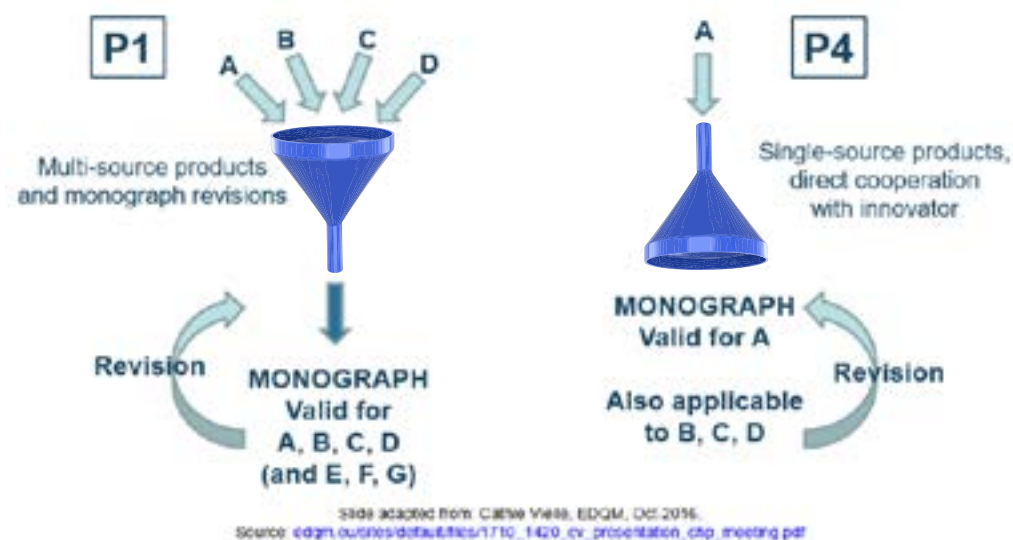
The data needed for monograph development are owned by many departments within a company. Choosing a specific business function that owns or has technical oversight for the product development data could be a possibility to take ownership of the submission process. **Table I** summarizes the various departments and their role in monograph elaboration. The functional area that owns the elaboration process must be able to address questions outside its own area of expertise, interacting with other functional areas to ensure the company is speaking with one

voice. The submitter of the information for monograph elaboration needs to act as a single point of contact (SPOC) for all questions that will come from the pharmacopoeia scientists. This means that if an analytical group is chosen to be responsible for the monograph submission, they need to collaborate with other groups such as microbiology, quality, and regulatory when questions are received. Product knowledge and experience with the drug substance or drug product are also important considerations for the selection. The monograph submission is expected to include reports from the entire lifecycle of the drug substance and drug product from early development that resulted in a specific control strategy for that material, through the current mar-

keted product stability data, and everything in-between. The chosen group for the elaboration process should be closely connected to several stakeholders that provide input for the needed information to create a monograph, including approved limits for the country or region of the intended pharmacopoeia, as well as microbiological controls, storage and distribution requirements, shelf-life data for that region, all necessary method descriptions, validation reports, and justification of specifications. Understanding the breadth of responsibility to act as the SPOC will drive the choice for the company. This in turn will help the monograph elaboration process to run more smoothly because there should be better flow of information between the company and the compendial authority.

Although there are many potential owners for this responsibility, in the authors' experience the compendial affairs function is best suited to lead a cross-functional team required for monograph elaboration. One significant reason is the length of the elaboration process, with the pharmacopoeial focus that the compendial affairs function brings throughout this period of time. Given that many companies frequently change their organizational structure, the interactions with the pharmacopoeia could stop if the focus of a different group with monograph elaboration responsibility changes due to a company reorganization. If a company has chosen to proactively work with global pharmacopoeias to establish monographs, the responsibility to drive elaboration or revision is best placed with a function that operates well across the matrixed environment that exists in most companies.

Figure 1. Difference between multi-source and single-source products for *European Pharmacopoeia* monograph elaboration.



CONSIDERATION OF WHICH PHARMACOPOEIAS TO PARTNER WITH FOR MONOGRAPH DEVELOPMENT

A company needs to decide where they will submit the monograph, and this is determined by several factors. A pharmacopoeia may communicate their interest to the company to develop a monograph for a specific drug substance or product. Alternatively, the company may approach the pharmacopoeia proactively to indicate their interest in developing a monograph. As detailed in an earlier article (1), the preferred timing of the pharmacopoeia to develop the monograph or the specific considerations for a company regarding the particular drug substance or product will enter into the decision. For many products, the monograph will first be developed in the *United States Pharmacopoeia (USP)* or *European Pharmacopoeia (Ph. Eur.)* due to their preferred timing for monograph elaboration, as well as the likelihood of earlier regulatory approvals achieved by a company in the United States and Europe. The geographical location

of the company may also influence where the monograph is first submitted, but the global nature of the industry and the availability of channels for communication with the pharmacopoeias should minimize this being a significant factor.

Both general and specific information is available for companies interested in learning more about *USP* and *Ph. Eur.* monograph submissions. Monographs in the *USP* are developed by the scientific staff and appropriate expert committees (3, 4). Monographs in the *Ph. Eur.* are elaborated by the European Directorate for the Quality of Medicines and HealthCare (EDQM) staff and experts using two processes. The difference between the two processes is the number of manufacturers involved during the initial elaboration of a monograph. This is an important difference for companies to understand. One process—actually the fourth approach established for *Ph. Eur.* monograph elaboration—is called P4, in which a single company, typically the innovator company before patent expiration, initiates the collabora-

tion with EDQM to establish a monograph for a drug substance or drug product (5). With the P4 process, the innovator provides their methods and specifications for review and evaluation by EDQM. A draft monograph is published that will be applicable to all subsequent manufacturers once they receive approval from the European health authorities. The other process—the initial approach used to develop *Ph. Eur.* monographs—is called P1, in which EDQM invites all currently approved manufacturers to participate in the monograph elaboration process (6). With the P1 process, the patent for the drug substance or product will have expired or will expire soon and generic-drug manufacturers have entered or will soon enter the market. The companies that choose to participate using the P1 process provide their methods and specifications, and the EDQM scientists develop and publish the draft *Ph. Eur.* monograph that will be applicable to all current and future manufacturers of the drug substance or drug product. The differences between the two processes

and their applicability are illustrated in **Figure 1**.

To assist companies who wish to participate in monograph development, the pharmacopoeia authorities have published documents to detail what information is required. EDQM has several technical guides (7) available to help the responsible function in a company gather the needed information for development of *Ph. Eur.* monographs. The *Technical Guide for the Elaboration of Monographs* (8) provides useful information applicable to monographs for small-molecule drug substances, as well as excipients. EDQM has additional guides covering a wide range of monograph types, including finished products containing chemically defined active substances, synthetic peptides, recombinant DNA proteins, herbal drugs, and vaccines (7). The technical guides provide information that may be used for the P4 (single-company) or P1 (multi-company) monograph elaboration processes. *USP* similarly provides specific monograph submission guidelines covering chemical medicines, excipients, dietary supplements, and food ingredients (3). There is also information about *USP*'s approach to biologics standards (9) and on their pending monograph process (10), which allows for development of monographs for articles awaiting approval by FDA. Supplementary Chapter III in the *British Pharmacopoeia (BP)* provides their requirements for submission of monographs to the *BP*. The *Japanese Pharmacopoeia (JP)* posts instructions on their website related to monograph submission, including what information is required (11). For other national pharmacopoeias (e.g., those in China, Korea, India, Russia, and Brazil), the monograph elaboration

process is less clear and typically occurs well after the *USP*, *Ph. Eur.*, and *BP* monographs have been developed.

HOW TO ACHIEVE HARMONIZATION

An important consideration when elaborating monographs with multiple pharmacopoeias is the concept of prospective or informal harmonization (1). The *Good Pharmacopoeial Practices (GPhP)* guidance published by the World Health Organization (12) suggests that as new monographs are developed, harmonization of the requirements across the pharmacopoeias could be achieved. This approach to monograph development has been gaining acceptance across the pharmacopoeias for drug substances and products. This initiative has been undertaken through a collaboration between the bio/pharmaceutical industry and the pharmacopoeias (*USP*, *Ph. Eur.*, and *BP*) with visibility provided to other pharmacopoeias, including those in Japan, China, Korea, and India. The effort has resulted in the successful completion of several new, prospectively harmonized monographs for small-molecule drug substances and products. However, it is important to understand that monograph harmonization will not occur on its own, and specific commitment and actions are required of the company to achieve this goal. Separate questions may be received from each of the pharmacopoeias involved in the elaboration process, potentially increasing the effort for a company to develop the monograph. More material will be needed to establish the reference standards required by the multiple pharmacopoeias. The process of elaborating harmonized monographs may also be more challenging for the phar-

macopoeias. If a company wishes to pursue monograph harmonization, it is critical to communicate this intent at the beginning of the process to each pharmacopoeia that will be involved. Timely, effective, and sustained communication with the pharmacopoeias is also required throughout the elaboration process.

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The desire to establish harmonized monographs may also meet with internal resistance in a given company, due in part to the potential impact on approved limits. Some tests based on general chapters that are already harmonized, such as uniformity of dosage units, are easily harmonized in a monograph. There are some limits, however, which cannot be easily harmonized based on what has been approved by different health authorities for a test. For example, the assay limits for a drug product may be 90.0–110.0% in the US and 95.0–105.0% in Europe. Impurity limits are usually the most difficult to harmonize. Although these limits should be safety-based, the regulatory review process sometimes drives impurity limits to be

FIGURE COURTESY OF THE AUTHORS. FUNNEL IMAGE/MCCARONEY/STOCK.ADOBE.COM

Table II: Tests to be considered for a small-molecule drug substance monograph.^a

Tests		
Assay (Active Moiety)	Impurities	Color/clarity of solution
Identity (HPLC, IR, etc.)	Sulfated ash/residue on ignition	Water (KF or LOD)
Identity (Counter Ion)	Chiral purity	Microbial limits. Bacterial endotoxins, sterility (as appropriate)

^a not meant to be an all-inclusive list.

HPLC is high-performance liquid chromatography. IR is infrared spectroscopy. KF is Karl Fischer titration. LOD is loss on drying.

Table III: Tests to be considered for a small-molecule drug product monograph.^a

Tests		
Assay (Active Moiety)	Impurities	Characteristics
Identity (HPLC)	Uniformity of dosage units (UDU)	Water (LOD)
Dissolution	Specific tests required by a dosage form general chapter	

^a not meant to be an all-inclusive list

HPLC is high-performance liquid chromatography. LOD is loss on drying.

based instead on process capability. As a result, it is not uncommon to have differences between the acceptance criteria for impurities approved in different regions. Monograph harmonization could require a decision to tighten an impurity limit in a region, based on reevaluation of the company's process and safety data to ensure the proposed limit makes sense to protect patients without putting undue burden on the manufacturer. It may be a challenge to convince impacted areas within a company that it is appropriate to tighten already approved limits solely to achieve harmonized monographs in the pharmacopoeias. The challenges of compliance with harmonized monographs that differ from approved product registrations will be detailed in another article in this series.

CONSIDERATION OF INFORMATION AND MATERIALS NEEDED TO SUPPORT MONOGRAPH DEVELOPMENT

The responsible function in a company needs to clearly understand what information is required by a global or national pharmacopoeia for monograph elaboration or revision. As noted in the *GPhP* guidance, "Pharmacopoeial standards are public standards that are science-based and data-driven and based on sound analytical measurement and accompanying validation data" (12). To achieve science-based monographs, existing specifications—the list of tests, references to analytical procedures, and appropriate acceptance criteria—that have been approved by the health authorities based on International Council for Harmonization (ICH) Q6A (small

molecule) (13) and ICH Q6B (bioterapeutics) (14) guidance documents are an appropriate starting point. It may be a challenge to prepare monograph submissions for older products that may not have been developed under ICH guidance documents. A similar challenge is encountered when an existing monograph will be modernized by the pharmacopoeia. As discussed in another article (15), the health authorities' expectations and pharmacopoeial requirements constantly evolve to remain consistent with current technology. This requires a manufacturer to complete a proper evaluation for older products to determine if it can meet the current regulations and guidance documents in order to develop a monograph for the drug substance or product, regardless of when the product was developed.

The tests, methods, and acceptance criteria sent to the pharmacopoeia should align with the approved filing for the drug product, including information regarding the drug substance, in that country or region. However, not all tests in the approved filing may be appropriate for the monograph. Additionally, because the monograph submission typically occurs many years after first product approval, the documentation should include specifications that reflect all strengths and formulations for the drug product, even if some of these have only been recently developed and approved. The official monograph for that dosage form will apply to all strengths marketed, regardless of when the product was approved by the health authority. If the specifications provided for the monograph are different than what is filed for that country or region, a sound justification must be

made since the pharmacopoeia will consult the health authority to verify the specifications are consistent with those approved. Specifications should also conform with the requirements in applicable general chapters for the specific dosage form included in the particular pharmacopoeia.

The acceptance criteria set by the pharmacopoeias are typically based on shelf-life specifications that are approved by the health authority in that region. The *GPhP* guideline indicates, "Specifications that limit market access by, for example, favoring one manufacturer to the exclusion of others should be avoided" (12). Stated another way, the pharmacopoeia standard should not override a health authority approval. The monograph acceptance criteria are meant to encompass all manufacturers of the material, including differences between synthetic schemes for drug substances or different formulations for drug products. It is a daunting task for the pharmacopoeia to achieve a sound scientific monograph that does not block a manufacturer.

Once a company has selected the specific pharmacopoeia(s) and whether harmonization will be a goal, the company needs to provide a significant amount of data and documents to start the monograph elaboration process. The information sent to the compendial authority would include the following:

- Specifications, as defined by ICH Q6A (13) and Q6B (14):
 - A list of the tests proposed for inclusion in the monograph (Table II and III). These tests should be appropriate for the public standard and will be applicable to all manufacturers and materials covered by the monograph. Not all methods

included in the product registration are necessary or appropriate for the monograph. No tests that are internal only should be submitted, such as particle size or bulk density, for a drug substance, or an assay for preservatives in a drug product.

- Analytical methods and associated validation reports used for release and stability/shelf-life testing.
- Microbiological purity methods and associated validation reports if they differ from compendial methods.
- Appropriate acceptance criteria, which should be stability/shelf-life limits since the monograph applies throughout shelf-life for the material or product. The limits should include registered limits only (i.e., no in-process or in-house limits for that market or region).
- Information about the drug substance, including chemical structure, molecular formula, formula weight, nomenclature (generic and International Union of Pure and Applied Chemistry [IUPAC] names), Chemical Abstracts Service (CAS) number, description, solubility, hydration, crystalline structure, and polymorphism. For complex bioterapeutics, this would also include the peptide map of the protein or peptide and its approximate formula weight.
- Information about each specified organic impurity and degradation product, including chemical structure and IUPAC nomenclature.
- Information about residual solvents and elemental impurities, which may be present in the material.

- Justification of specifications, as typically included in the product registration.
- Stability/shelf-life data report, typically covering the last four to five years of production.
- Certificates of analysis from three recent lots of drug substance and three lots of each strength of drug product. A batch overview from recently released lots may also be provided (typically, not less than 10 batches).
- Information related to storage and labeling requirements.

Companies have different approaches to providing the monograph submission to the compendial authorities.

Companies have different approaches to providing the monograph submission to the compendial authorities. Some companies will provide a draft monograph following the pharmacopoeia's respective format and style, with proposed specifications for each test and method descriptions to communicate only enough details as needed in the monograph. Other companies will submit specifications, methods, and validation reports as they exist in quality and regulatory documents, with no redaction prior to providing them to the compendial authorities. It is suggested that a company define its approach to monograph submissions in a procedure or job aid

given the volume and complexity of the information and materials needed to be provided to the pharmacopoeia.

Each elaboration process is different and brings to light different questions and approaches for establishing the monograph.

Regardless of the approach taken to submit information, the compendial scientists will thoroughly review all the documentation provided to prepare their own draft of the monograph. For the validation information, a good practice is to prepare a method validation summary for critical methods such as assay or chromatographic purity as this can result in fewer questions from the pharmacopoeia. This is especially true when there are different synthesis schemes used for a drug substance or multiple strengths for a product that were developed and validated at different times by the company.

After the documentation has been initially reviewed by the compendial authorities, the company will be requested to provide physical materials to support the elaboration of the monograph, including samples of drug substance, drug product(s), and available impurities, all of which will be used for testing performed in the compendial authorities' laboratories. It is extremely helpful to anticipate this request from the

compendial authority, with the samples gathered by the company while the documents required for the submission are first being collected. For complex biotherapeutics, the in-house standard that is used in the company's assay should be provided, as well as any other qualified materials that are used as controls in an assay.

Reference standards must be provided for the active ingredient, any specified impurity for the drug substance, and any specified degradant for the drug product. The impurity standards are typically used to identify the impurity peaks observed and ensure system suitability in chromatographic procedures. If specified impurities are not available, a suitable "dirty" batch of the drug substance may be used as the reference standard, provided the individual impurities present can be satisfactorily identified. Each material should be provided in sufficient quantity to allow for testing and for the compendia to establish their reference standard for the material. Each material requires a certificate of analysis that will enable the pharmacopoeia scientists to qualify it as a reference standard that can be used by any company. The pharmacopoeia may also request a Safety Data Sheet (SDS) and other supporting data (e.g., infrared [IR] spectra, Raman spectra, nuclear magnetic resonance [NMR] spectra, mass spectra [MS], X-ray powder diffraction [XRD] spectra, differential scanning calorimetry [DSC], chromatograms, etc.) and a bovine spongiform encephalopathy/transmissible spongiform encephalopathies (BSE/TSE) statement for materials provided by the company. It is common for the pharmacopoeia to request additional quantities of reference standards that they can qualify and

provide for other laboratories to use as suitable reference standards. The pharmacopoeia may request assurance from the company that sufficient amounts of material will be available to establish their second batch of compendial reference standard; this becomes a commitment from the company to support the continued use of the monograph once it has become official.

Additionally, the compendial authority may ask for clarification of steps provided in a method or for additional shelf-life data amongst other questions from their first review. These may include robustness data using other instrument brands to perform the analysis, questioning or tightening system suitability criteria, and adapting gradient profiles for separations. The pharmacopoeia authorities prefer to have a single high-performance liquid chromatography (HPLC) analysis that can be used for drug substance, drug product, and associated impurities or degradants. If a content uniformity analysis is needed for the product, it is preferred that it is run with the same method as the assay.

Each elaboration process is different and brings to light different questions and approaches for establishing the monograph. The following highlight different scenarios that have been encountered by the authors during monograph elaboration.

Impurity limits

It is the authors' experience that impurity limits for drug substances and drug products have the most challenges. Monographs on pharmaceutical substances and products should take account of the principles defined in the ICH Q3A (16) and Q3B (17) guidelines and follow regulatory decision-making. However, there are

Table IV: Tests to be considered for a complex biotherapeutic monograph.^{a, b}

Tests		
Identity	Bioassay	Protein concentration
Glycans analysis	Residual DNA	Charge heterogeneity test
Purity (CE-SDS)	Purity (SEC)	Residual host cell proteins
Impurities related to viruses and prions	Mycoplasma and virus testing	Bacterial endotoxins
Sterility	Microbial Limits	Oxidation or deamidation assays
Deamidation analysis	Specific tests required by a general monograph	Peptide mapping

^a not meant to be an all-inclusive list

^b some tests included in "production" section

SEC is size-exclusion chromatography. CE-SDS is capillary electrophoresis sodium dodecyl sulfate.

also practical considerations that emerge in the transition of a company's private standard into the public standard embodied in the monograph. For example, drug substance methods typically focus on identifying synthesis impurities and API degradants, whereas drug product methods only focus on degradants due to the formulation or API degradation. It can be challenging to ensure that a chromatographic procedure for a drug product can distinguish a degradation product from a synthesis impurity present in the drug substance. An inability to identify a particular impurity peak in a chromatogram may lead to it being an unspecified impurity in the monograph, even if it is listed as a specified impurity in approved product registrations. If there are requirements needed for purity, especially in the case of significant degradation, this information must be shared with the pharmacopoeia authority.

Tests that are dependent on route of synthesis

There are some tests where the method or acceptance criteria are tied to a specific material, making it difficult to establish the monograph. To address this situation, the *Ph. Eur.* monograph may include modifications to what is filed in Europe, in order to make the monograph applicable to all materials and manufacturers. The *USP*, on the other hand, has introduced the flexible monograph (18) approach for drug substances that use different synthetic routes, when a "one-method-fits-all" approach cannot be easily achieved. For drug substances, the impurity profile can be completely different depending on starting materials, solvents, and catalysts used upstream in the synthesis route. One method may not be able to capture all synthesis impurities so the *USP* flexible monograph allows for additional methods for assay and chromatographic purity for these materials.

Tests that are dependent on product formulation

Dissolution testing for solid oral dosage forms presents a challenge for the pharmacopoeia monograph. Differences in formulations often result in different release profiles when a specific dissolution medium and sampling time point(s) are described. The *USP* flexible monograph approach allows for more than one dissolution test to be included in the monograph. This may also be true for other tests in the monograph. For the dissolution example, manufacturers provide their dissolution method and acceptance criteria that are specific to their formulation to *USP* since the initial method published may not be suitable for that company's formulation. By including the formulation specific test as "Test 2", the *USP* provides flexibility for the manufacturer to select the appropriate test to be used. However, there are some products where the flexible approach seems to be carried to an extreme: the *USP* monograph for Diltiazem HCl Extended Release capsules contains more than 15 different dissolution test options. With these options, it is the responsibility of the manufacturer to ensure their drug product labeling reflects which test is used, if it is not Test 1. If there is no designation in the labeling, it is assumed the product uses Test 1 listed in the monograph. Other pharmacopoeias are considering different approaches to dissolution testing in monographs, which will be explored in a later paper in this series.

MONOGRAPHS FOR COMPLEX BIOTHERAPEUTIC PRODUCTS

As mentioned earlier, the ICH Q6B guideline (14) for biological/biotechnological products (BTP) is a

Table V: Example case for method comparability for a biotherapeutic monograph.

Test – Charged Variant	Methodology	Peaks having acceptance criteria
Company A	Liquid chromatography–weak cation exchange	<ul style="list-style-type: none"> Sum of isoforms 1 and 2 Isoform 5 Sum of isoforms 3, 4, and 6
Company B	Capillary isoelectric focusing with carboxypeptidase B	<ul style="list-style-type: none"> Sum of acidic peaks Sum of basic peaks Peak X No new peaks greater than XX%

good starting point for a company elaborating a BTP monograph with the pharmacopoeia. However, the concept of product specific monographs for complex BTPs, such as monoclonal antibodies (mAbs), is still subject to vigorous debate between health authorities, pharmacopoeias, and industry. The biggest challenge is the ability to fully characterize a complex biologic material with the available analytical technologies. Given differences in the manufacturing processes and limitations in analytical capabilities, exact copies of complex BTPs cannot be produced, only biosimilars can be manufactured. This is unlike small-molecule drug substances and drug products where full characterization is expected and can be readily achieved.

As a result, there are only a few monographs for complex BTPs with multiple manufacturers published in the *Ph. Eur.* and one published in the *Chinese Pharmacopoeia (ChP)* for an orphan drug (single manufacturer). As of this writing, the other global and national pharmacopoeias, including *USP*, have not published any monographs for BTPs; indeed, the *BP* and *USP* are exploring alternate approaches to product-specific monographs for establishing pharmacopoeia standards for BTPs. With the limited

availability of monographs at this time, the approach to harmonization of BTP monographs is limited for these types of products. The EDQM has published a technical guidance document for *Ph. Eur.* monographs for biotherapeutics (19).

Consideration for specific tests to be performed on complex biotherapeutics are outlined in the general monographs located in the pharmacopoeias, including *Ph. Eur.*, *ChP*, and *Indian Pharmacopoeia (IP)*. All pharmacopoeias have been publishing general chapters for the tests employed for BTP analysis and more chapters are currently being elaborated. General chapter elaboration for BTP products offers one of the best opportunities for prospective harmonization across the pharmacopoeias today.

Tests to consider for inclusion in a BTP monograph are listed in **Table IV**. These include identification of product-related impurities resulting from oxidation or deamidation or mechanisms that cause aggregates to form. The impurities are measured by a wide range of analytical technologies, so it is important that specific methods are provided to the pharmacopoeia authorities. Additionally, there is significant attention given to process-related impurities that can adversely impact a patient if present. Testing is required for bacterial

endotoxins, host cell proteins, and host cell DNA. Risks from impurities related to viruses and prions must also be considered if using cell culture or media supplemented with components of animal or human origin. Many of these more common tests are typically covered by existing general chapters in the pharmacopoeia.

Setting strict acceptance criteria for tests in a monograph for complex biologicals (e.g., mAbs) can be extremely difficult. As noted earlier, generic mAbs are “similar” and not an exact copy, as is the case for small-molecule entities. Given that each product is “similar” and uses a unique control strategy, a single set of acceptance criteria would be inappropriate to list in a monograph for many of the tests. If specific ranges were published, the approach would not be capturing the entire class of “similar” materials and could essentially block manufacturers from the market. This would be contrary to the approach advocated in the *GPhP* that monograph “specifications that limit market access ... should be avoided” (12).

The flexibility introduced by the general chapters in the pharmacopoeias also creates some complexity when trying to find a method that is suitable for all complex biotherapeutics covered by a product-specific monograph. The *Ph. Eur.* general monograph 2031 for monoclonal antibodies allows for many techniques to analyze a required attribute of a BTP. An example of this is given in **Table V** for the Charged Variants test in the infliximab concentrated solution monograph that became official in January 2019. Two companies’ specifications are shown for the test. It would be impossible to decide which of these techniques is best suited for the

Table VI: Tests to be considered for a vaccine monograph.^{a, b}

Tests		
Identity	Adjuvant	Aluminum
Assay	Residual host cell proteins/DNA	pH
Antigen content	Free formaldehyde	Water
Antimicrobial preservative	Bacterial endotoxins	Sterility
Bovine serum albumin	Virus concentration	Mycoplasmas
Degree of adsorption	Extraneous agents	Bacterial and fungal contamination
Specific tests required by a general monograph		

^a not meant to be an all-inclusive list

^b some tests included in “production” section

analysis, and there is no way to compare the acceptance criteria established for each technique to demonstrate they provide “comparable” results. This is not like comparing the use of different columns for a reverse-phase C18-based HPLC method typically used for small-molecule drug substances and drug products.

EDQM recognized this difference and placed these types of tests, which are variable based on allowable techniques and results generated, in the “production” section (20) of their *Ph. Eur.* monograph. The “production” section of the monograph constitutes mandatory requirements for a manufacturer, including in-process testing or tests to be performed on the final drug product. EDQM also introduced the approach where an example method (19) is provided in the monograph, but a manufacturer may instead use their own method, subject to approval by the competent health authority. This approach allows the requirement to be present in the mono-

graph but gives a manufacturer flexibility in meeting it. This flexible approach also ensures that no manufacturer will be blocked from the market.

Additionally, for BTP methods, there is little robustness information being generated by manufacturers across instruments from different vendors. Most companies tend to pick a platform technology and then employ it across the organization allowing for smoother method transfers and decreased method variability. This makes the monograph elaboration process more complicated because manufacturers, pharmacopoeia scientists, and government testing laboratories will most certainly not standardize on a single vendor’s instrument.

The understanding of what is required for BTP monographs has been under discussion between industry and the pharmacopoeia for many years. Industry’s concern was recognized by EDQM and is evident in the flexible approach used to complete the first *Ph. Eur.* monographs for monoclonal

antibodies with multiple manufacturers. It remains to be seen if other pharmacopoeias will follow this approach or not. This is new territory for the pharmacopoeia authorities since this is the beginning of monograph elaboration for these types of therapeutic entities. As analytical capabilities are enhanced and technology advances, the required tests and appropriate techniques to analyze mAbs will evolve and so will the future requirements in the pharmacopoeias. There are sure to be other hurdles to overcome as industry, health authorities, and pharmacopoeia authorities gain more experience with complex BTP monographs.

MONOGRAPHS FOR VACCINES

Consideration of specific tests to be included in monographs for vaccines for human or veterinary use are outlined in the *Ph. Eur.* general monograph 0153, *BP* Appendix XV J, and *USP* chapter <1235>. There are also specific technical guides from the EDQM regarding human and veterinary vaccine monographs (21, 22). Vaccine monographs in the *Ph. Eur.* often contain a “production” section, as was described for other complex biotherapeutic products. Like other drug types, there are general chapters available to describe tests and what should be considered to execute the methods appropriately. Tests to be considered for inclusion in monographs for vaccines are listed in **Table VI**.

MONOGRAPHS FOR EXCIPIENTS

Excipient monographs are elaborated or revised in a similar fashion as drug substance and drug product monographs. Typically, an excipient manufacturer will drive the elaboration process with

the specific pharmacopoeia. In *Ph. Eur.* excipient monographs, the control of additional properties (e.g., functionality-related characteristics) may be included. The draft monograph will be available for commenting, and a drug product manufacturer will have to comply with the monograph when published as official. Other than performing surveillance and providing comments on proposals, there is not much for a bio/pharmaceutical manufacturer to do for this type of monograph.

GENERAL CHAPTERS

General chapters are created or revised in a similar fashion as drug substance and drug product monographs, except it is usually the pharmacopoeia that drives the process. Elaboration of a new chapter is driven by regulatory changes (e.g., implementation of ICH Q3D) or new analysis techniques that become more routinely used by industry (e.g., methods for biotherapeutics analysis mentioned above). Typically, the pharmacopoeia will establish a working group including stakeholders from industry, academia, and regulatory agencies for the elaboration of a specific new chapter. This is another great opportunity for a company to participate with the pharmacopoeia to influence the outcome of the chapter. The draft general chapter will be available for commenting and bio/pharmaceutical manufacturers will have to comply with the chapter (unless it is informational) when published as official.

CONCLUSION

Pharmacopoeia monographs are science-based public standards that are data-driven and built on sound, validated analytical measurement or microbiological prac-

tices. If a company decides to participate in the elaboration process, having clear responsibilities to ensure the elaboration process is followed and driven to completion is necessary if the outcome is to be appropriate for the company. Regardless of which type of monograph, a company must recognize that the elaboration process is essentially taking private standards for each manufacturer and making it a single public standard for all companies to follow, so some flexibility is needed. Additionally, being proactive and having a strong collaborative relationship with the pharmacopoeia scientists enables a company to more effectively advocate for changes in the proposed monograph should conflicts arise. The same advocacy approach also applies to the elaboration or revision process for general chapters. The next article in this series will illustrate how pharmacopoeia compliance can be a challenge even when a company participates proactively, since the monograph may differ from product registrations.

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