



Surveillance Process for Industry: Monitoring Pharmacopoeia Revisions

An effective surveillance program for monitoring the activities of pharmacopoeias around the world requires processes, people, and tools from across a company.

J. MARK WIGGINS AND JOSEPH A. ALBANESE

The pharmacopoeial revision process and the resulting publication of proposed and official updates were described in a previous article in this series (1). To maintain ongoing compliance with current pharmacopoeia requirements as expected by regulators around the world, it is essential for bio/pharmaceutical companies to be aware of these periodic updates, so they can determine the potential impact and implement appropriate changes to their quality and regulatory documentation, as well as impacted processes and procedures. This article details the surveillance activities carried out by industry to monitor pharmacopoeia revisions so that companies can establish effective, efficient, sustainable, scalable,

and successful processes to address these compliance challenges.

COMPENDIAL AFFAIRS ORGANIZATION, ROLES, AND RESPONSIBILITIES

At a high level, effective surveillance is comprised of processes, people, and tools. These factors were described in an article written 15 years ago (2), and what is, perhaps, remarkable is that the issues and challenges have not substantially changed since then. Before delving into the details anew, it is helpful to look

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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

Upcoming articles in this series will include the following:

- 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

at one particular group that carries out key steps in the overall process.

Although identified by a variety of names, in many companies there is a group or function known as compendial affairs. The activities carried out by the compendial affairs group were described using the end-to-end framework in the second article of this series (3). The compendial affairs responsibilities include surveillance of the pharmacopoeial revision process, which may include publications for both proposed and official updates; advocacy, through responses to proposed changes; and compliance, through involvement in change control to enable implementation of official updates within the company. Another potential advocacy role for compendial affairs is through the submission of new or revised monographs to provide quality standards

in the pharmacopoeias for a company's drug products and ingredients. This activity may also involve coordination within the company and with the pharmacopoeias to provide samples and standards to support monograph elaboration. Direct engagement with the pharmacopoeias and participation in industry trade association activities provide other avenues for advocacy and sharing of best practices and perspectives on compendial issues. In this role, the individuals in compendial affairs also serve as the single point of contact (SPOC) in interactions with the pharmacopoeias. Finally, the compendial affairs group should serve as the internal support for the entire company, providing knowledge and experience in all things related to the pharmacopoeia.

Considering the numerous responsibilities listed above, each

company's approach to resourcing the compendial affairs function can be very different. Benchmarking of the bio/pharmaceutical industry revealed that some major multi-national companies have three to five full time employees in a compendial affairs role. The more common approach, however, is that a single individual or a couple of individuals with part time responsibility comprise the compendial affairs functions. Of course, the fewer the resources available in a company's compendial affairs function, the more challenging it becomes to consistently carry out all the responsibilities necessary to ensure ongoing compliance. One company utilizes an outsourcing model for monitoring pharmacopoeia revisions, establishing a SPOC in the company to manage the surveillance process that is carried out by external contractors. This approach can reduce the cost of using internal resources for that part of the effort, which is considered largely administrative. The external team can execute the review and filtering process and then assign the identified items with potential impact to a company's internal groups for complete assessment.

Another consideration is where within a company the compendial affairs function should reside (1). Key to this organizational decision is realizing that many functional areas in a company may be impacted by pharmacopoeial requirements. In one sense, it can be argued that compendial affairs could fit anywhere within a company, while the practical reality is that this function does not seem to fit well anywhere. Benchmarking has shown compendial affairs to be organized within the quality, regulatory, or research and development functions, or even at a corporate level due to the broad impact. There is no right or wrong organizational approach, but

the key consideration is that compendial affairs functions are critical to ongoing compliance. The individuals or group assigned these responsibilities need to have management support across the company to effectively address the impact of pharmacopoeia revisions, ensuring the necessary tasks are assigned the appropriate priority.

INDUSTRY SURVEILLANCE PROCESS: PURPOSE AND SCOPE

Perhaps the most important of the compendial affairs responsibilities is surveillance of pharmacopoeial revisions. A detailed description of the industry surveillance process is provided in the **Sidebar** to this article. The purpose of this surveillance is to identify, communicate, and enable assessment of the potential impact resulting from updates to pharmacopoeial requirements within a company in order to plan and execute implementation and help ensure ongoing compliance (see **Sidebar**, pp. 30–35, **Figures 1–2**). This activity also provides an opportunity to influence the compendial requirements through comments submitted in response to proposed revisions. The number of individual compendial changes to be reviewed for potential impact to a company is staggering: more than 3000 new or revised monographs and general chapters per year in the global pharmacopoeias alone. This number increases as a company scales up to bring additional national pharmacopoeias into the process. Considering this large volume of work, the crucial decisions to be made are which pharmacopoeias and which part of the revision process a company will monitor. These decisions on the scope of compendial affairs activities may differ for different companies.

The first decision—which pharmacopoeias to monitor—is dependent on where the compa-

ny's products are registered and distributed. For a large multi-national company with globally distributed products, surveillance of the global pharmacopoeias—*European Pharmacopoeia (Ph. Eur.)*, *British Pharmacopoeia (BP)*, and *United States Pharmacopoeia–National Formulary (USP–NF)*—would be necessary, along with monitoring several of the important national pharmacopoeias, including the *Japanese Pharmacopoeia (JP)* and those in China, Russia, and India. For a smaller bio/pharmaceutical company focused on products in clinical development, surveillance of only *Ph. Eur.* and *USP–NF* may be sufficient to remain compliant.

The second decision—whether to follow proposed and/or official revisions—depends on several factors such as company resources, commitment to advocacy, and conscious choices to be proactive or reactive to achieve compliance. Some companies only follow official revisions to reduce the burden of the compendial process. Monitoring and implementing only pharmacopoeia changes that are official is the minimum a company must do to comply with current requirements. Following both proposed and official changes allows a company the opportunity to be more proactive, potentially influencing the outcome of a proposal through advocacy. Either approach is acceptable and will allow a company to comply; however, following only official items drives the company to be more reactive, potentially making them ill-prepared when implementing the changes that occur.

The challenges of monitoring proposed and official revisions published by global and national pharmacopoeias can make it difficult to achieve on-time compliance with updated requirements. This situation is further complicated by complex

global supply chains in the bio/pharmaceutical industry, including multiple manufacturing sites, external manufacturing sites, and excipient/component suppliers that may be impacted by updated pharmacopoeia requirements. Based on the experience of one of the authors, to address these challenges, a large multi-national company assembled the compendial affairs group and a wide range of impacted stakeholders in an international, cross-divisional, multi-site, multi-day Kaizen event with the specific aim of mapping the existing process for compendial review and implementation to identify possible improvements. This enabled the company to develop a new process for pharmacopoeia surveillance that emphasized monitoring pharmacopoeia revisions starting at the proposal stage, stressed the importance of a comprehensive tracking tool, and created new cross-functional teams to assist in the impact assessment for the company. The enhanced process was more effective, efficient, and sustainable in helping to ensure ongoing compliance with new and revised pharmacopoeial requirements.

INDUSTRY SURVEILLANCE PROCESS: PEOPLE

As noted earlier, the industry's surveillance of pharmacopoeia revisions is comprised of processes, people, and tools. Throughout the detailed description of the process (see **Sidebar**), the key players have been identified, and what emerges is the broad network that is required to accomplish this work. It is helpful to focus briefly on the people involved in an effective surveillance process, as follows:

- Compendial affairs group
- Internal stakeholders/subject matter experts (SMEs)/teams
- Local contact group/In-country partners

Table I. Pharmaceutical industry associations engaged in surveillance of pharmacopoeia revisions.

Acronym	Association name
United States	
NJPQCA	New Jersey Pharmaceutical Quality Control Association
MWCDG	Mid-West Compendial Discussion Group
WCDG	Western Compendial Discussion Group
PhRMA	Pharmaceutical Research and Manufacturers of America
BIO	Biotechnology Innovation Organization
AAM	Association for Accessible Medicines
CHPA	Consumer Healthcare Products Association
United Kingdom	
ABPI	Association of the British Pharmaceutical Industry
Europe	
EFPIA	European Federation of Pharmaceutical Industries and Associations
EBE	European Biopharmaceutical Enterprises
Japan	
JPMA	Japan Pharmaceutical Manufacturers Association
China	
RDPAC	R&D-Based Pharmaceutical Association Committee
International	
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IGBA	International Generic and Biosimilar Medicines Association
IPEC*	International Pharmaceutical Excipients Council
GSCF	Global Self-Care Federation
PDA	Parenteral Drug Association

* The IPEC Federation is a global organization consisting of IPEC Americas, IPEC China, IPEC Europe, IPEC Japan, and IPEC India.

- Company leadership/functional area management
- Pharmaceutical industry associations.

The critical role played by the compendial affairs group in the overall process was presented earlier. The internal stakeholders, working individually as SMEs or as part of a team, and those functional areas that are impacted by specific pharmacopoeia

revisions are also necessary in the process. These resources reside over the entire company, as identified earlier in the detailed description of the surveillance process. These SMEs must clearly understand their role in the compendial process, whether it be technical assessment or driving the implementation of a change across the company. Without clearly defined roles and responsibilities,

items may not be properly assessed or implemented. The engagement of internal SMEs and impacted stakeholders is critical to the effectiveness and sustainability of the compendial affairs process. Additionally, to effectively manage changes in the national pharmacopoeias, engagement with the local contact group or in-country partner is vital, due to the challenges of irregular revision schedules and the potential need for translation. To be truly successful in the overall effort, the entire process and all the people involved need the support of company leadership and functional area management, who must be aware of the time commitment needed to properly assess a revision, develop appropriate comments, or drive implementation of the change that potentially affects multiple sites, products, and registrations. This time commitment is not trivial and adequate resources need to be available to ensure ongoing compliance with pharmacopoeial requirements.

All of the groups mentioned are internal to a company, but the discussion of people that support the surveillance process is not complete without consideration of a key external connection: pharmaceutical industry associations. These associations may be found in many countries and regions around the world and a list of some key industry groups that monitor the pharmacopoeias are included in **Table I**.

The value gained by a company through connecting with the compendial interest or discussion groups in these industry associations should not be underestimated. It should be noted that these groups do not talk about pharmacopoeia changes that impact only one or a few companies, such as specific monographs for drug products or ingredients. Rather,

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Bio/pharmaceutical industry surveillance of compendial changes: Process in detail

The process used in the bio/pharmaceutical industry for surveillance of compendial changes (**Figure 1**) starts with publication of proposed changes by the pharmacopoeias and continues to the publication of official updates. The first steps of the industry surveillance process are the same for proposed and official revisions: monitor pharmacopoeia publications, filter for potential impact, and communicate the changes. Having an effective process for these initial steps is crucial to the ultimate success of complying with pharmacopoeia updates. The subsequent steps involve a deeper look into proposed changes to assess the impact and develop an implementation plan, followed by evaluation of the official changes and execution of the implementation plan. The process also provides opportunities to respond to proposed changes and submit revision requests for official changes, if needed.

Monitor pharmacopoeia publications. The compendial affairs function needs to have access to the publications it intends to monitor (i.e., new editions, supplements, and forum publications). For official editions and supplements to the global pharmacopoeias, this can be done mainly on-line by purchasing the appropriate licenses. For proposals in the global pharmacopoeia forum, access is available through free on-line website postings. Because the global pharmacopoeias are published in English, the compendial affairs function in many multi-national companies can review the table of contents (TOC) in the publications/website postings to identify relevant items. This work may be more difficult for companies where English is not the primary language. Many companies monitor and filter the items in the TOC when each publication is received; alternatively, this may be done on a monthly basis to capture revisions in all publications identified within that time frame.

National pharmacopoeias present challenges for the compendial affairs function due to less regular publication schedules and the fact that revisions may not be available in English. To successfully monitor these pharmacopoeias, the compendial affairs function needs a strong tie to the company's local responsible group in that country, if available. This local group could reside in the quality, regulatory affairs, or other area, or in a local manufacturing site in that country. With well-defined roles and responsibilities, this local contact group (or in-country partner) monitors the local language pharmacopoeia publication or website to identify new items for review and impact assessment by the company. Once identified, the local group would determine the urgency for a complete and accurate translation into English, based on the time allowed for commenting on proposals or implementation of official changes. The roles and responsibilities are best defined in a cross-functional process with agreement between the partners and should be reviewed periodically to ensure it is working effectively.

Filter for potential impact. Reviewing the TOC in a pharmacopoeia publication represents the first in a series of "filters" through which changes are passed to determine if it applies to a company. To perform this filtering properly, the

compendial affairs function must have a way to identify all excipients, APIs (procured or manufactured internally), and drug products across their entire supply chain. Gathering this information can be overwhelming and inefficient, as many business systems are not designed to provide this comprehensive "where-used list". This information must be combined from several sources within a company, a time-consuming activity that is repeated each time the TOC filtering needs to occur, as the list needs to be current.

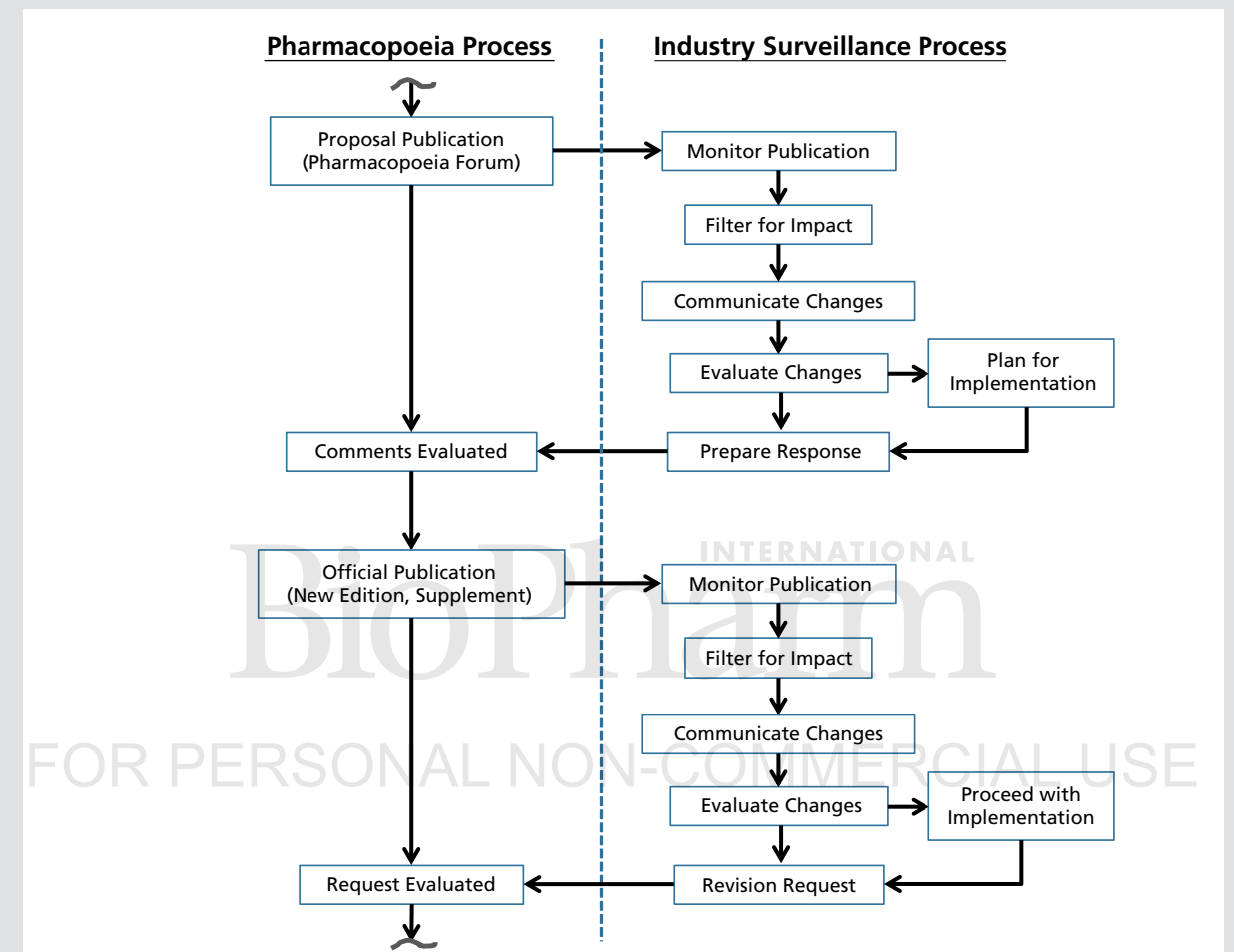
This list of materials and products is used to filter the TOC in the pharmacopoeia publication to identify individual monographs of interest to the company. One complicating factor is the nomenclature used by the pharmacopoeias and by a company for materials, with a single material potentially having multiple names. It is important to know how each material is named in a pharmacopoeia publication and how it may be named in your company's systems (e.g., trade name, chemical name, or some other abbreviated name due to field-size limitations in the enterprise system, such as SAP). See the following examples:

- Avicel PH-102 (DuPont) = Microcrystalline Cellulose
- Glycerin (*USP*) = Glycerol (*Ph. Eur.*)
- Dibasic Sodium Phosphate (*USP*) = Disodium Phosphate Dihydrate (*Ph. Eur.*)

Another complex task is identifying which general chapters in the pharmacopoeias apply to the company. Combined, there are over 2000 general chapters contained in the global and national pharmacopoeias that need to be considered. There is redundancy in several of the chapters across the many pharmacopoeias, but the compendial affairs function needs to identify the respective chapter in each. For example, the harmonized chapter for uniformity of dosage units appears as *United States Pharmacopoeia (USP)* <905>, *European Pharmacopoeia (Ph. Eur.)* 2.9.40, and *Japanese Pharmacopoeia (JP)* 6.02, while the non-harmonized chapters for weight/mass variation and content uniformity appear as *Ph. Eur.* 2.9.5 and 2.9.6, *Indian Pharmacopoeia (IP)* 2.5.3 and 2.5.4, and *Chinese Pharmacopoeia (ChP)* 0101 and 0941. It is important to establish this list to filter the TOC for general chapters, so time and resources are only spent on further assessment of those items that impact your company. The publication of a new general chapter requires a company to determine whether to add this to their TOC filter list. A company must also decide whether to monitor and comment on non-mandatory, informational chapters in the pharmacopoeia (e.g., chapters above <1000> in *USP* or above 9000 in *ChP*). There is an additional factor in considering these informational chapters: some of the "non-binding" information may be critical and should possibly be monitored and/or adopted, especially because the chapters may be referenced in other chapters that are mandatory, and regulatory agencies may decide to enforce certain aspects contained within the chapters, even

Bio/pharmaceutical industry surveillance of compendial changes: Process in detail (cont.)

Figure 1. Industry Surveillance Process Steps.



though listed as informational. To minimize the risk of missing a general chapter with potential impact to the company, essentially all new and revised chapters in a pharmacopoeia publication may need further assessment.

Figure 2 depicts the filtering process used in monitoring pharmacopoeia revisions. A typical year may see the publication of 3000 or more total items that are new or revised in the global pharmacopoeias, which must be filtered. Using the lists of materials, products, and general chapters described previously, the compendial affairs function filters the TOC for each publication to identify items that may impact the company. For large multi-national companies, the initial TOC filter may identify approximately 500 items with potential impact. These constitute the set of items each year that may require change control when the items become official. Following the TOC filter, the compendial affairs group or another specified function in the company then carries out a deeper dive to further filter the identified items and determine if they have major impact to the

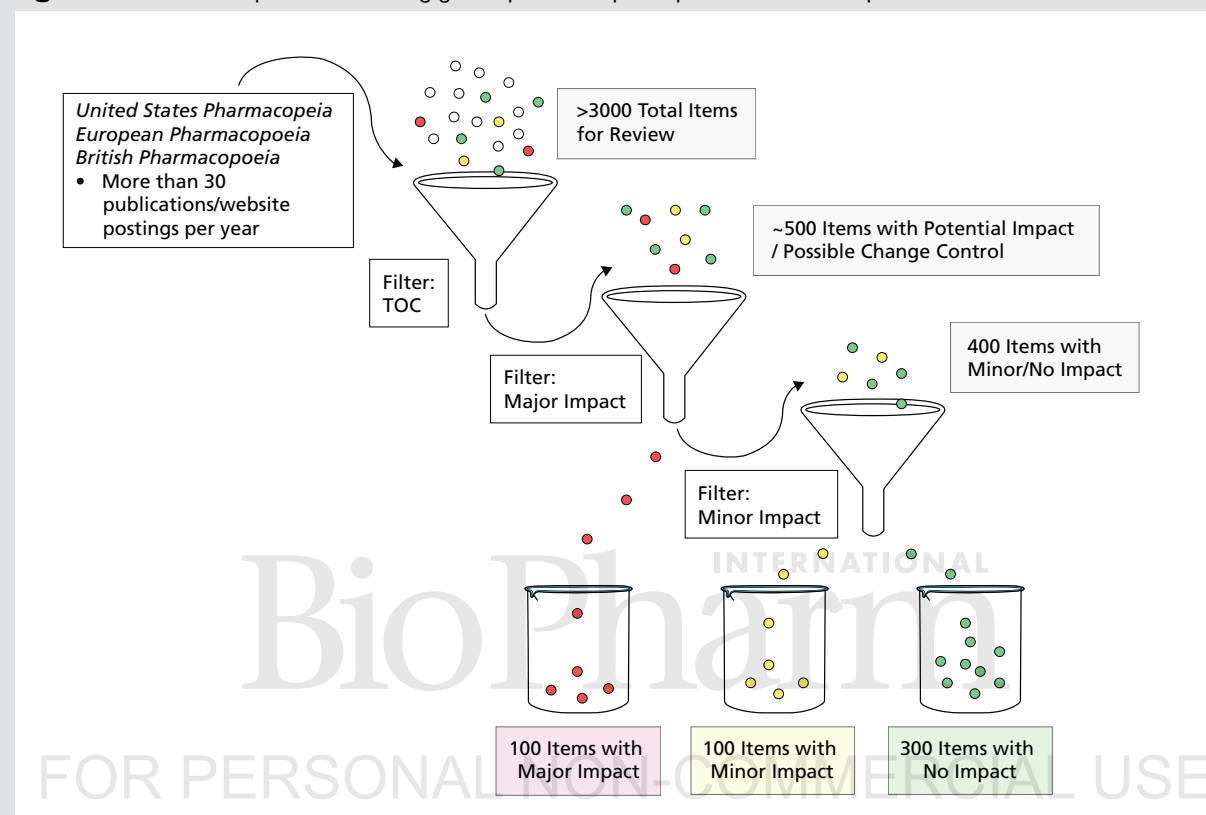
company. Pharmacopoeia updates with the greatest potential impact include the following:

- New or significantly revised general chapters
- New monographs including specifications/limits and methods, which may be different than the company's product registration
- Revised monographs with changes to specifications/limits
- Revised monographs with new or significantly updated methods, which may require new procedures, equipment, columns, or reagents
- Changes that may impact labeling, packaging, storage, and/or distribution.

This determination of major impact can be accomplished in several ways, but it is often true that input from multiple groups is required, because of the potentially broad impact of pharmacopoeia updates. A company may have the subject matter expert (SME) for the topic (general chapter) or material (monograph) review the change. In some cases, a specified group of company SMEs may review all changes and assess the potential impact. For the

Bio/pharmaceutical industry surveillance of compendial changes: Process in detail (cont.)

Figure 2. Surveillance process: Filtering global pharmacopoeia publications for impact.



company mentioned in the main article that held the Kaizen event, the improved procedure created a new team, called the “central triage team”, to meet on a regular (bi-weekly) basis and assess each individual compendial change published during that time period to determine those with the greatest potential impact. As suggested by the name, this team is comprised of representatives from central functions within the company, including: compendial affairs; quality control/assurance; external quality assurance; regulatory/chemistry, manufacturing, and controls (CMC); bio/analytical sciences; microbiology; and stability. For a large multinational company, as many as 100 new or revised items per year may be identified in pharmacopoeia updates with potentially major impact. Whichever way the surveillance process is designed, this triage step to assess major impact is important because it will allow more resources to focus on these changes, reflecting the complexity and urgency needed. The remaining items identified—400 in this example (**Figure 2**)—will fall to the minor or no impact category and require further assessment to determine if they can be closed with minimal additional input from the business.

For national pharmacopoeias, as mentioned earlier, it is important to have a connection with the local contact group in that country. After the publication of a new edition or supplement (i.e.,

official changes), or forum (i.e., draft proposals for comments), the local group would perform the TOC filtering of items based on the drug products registered and distributed in that country. The list of affected materials or general chapters could be smaller than the global lists for the entire company. If there are products or formulations specific to that market, any unique excipient, API, or drug product monograph needs to be identified and added to the local filtering list. The determination of major impact for these items in the national pharmacopoeias can be accomplished by the local contact group or via the process established for items found in the global pharmacopoeia publications.

Communicate the changes. Once the specific materials and general chapters of interest to a company have been identified, an in-depth assessment is needed for the specific changes, with tasks assigned to the appropriate SME or business function. The notification of pharmacopoeia updates to a company’s impacted stakeholders may be provided individually, with each change sent to the specific SMEs for assessment, or as a compilation of all the changes identified in a particular pharmacopoeia publication or over an established time period. Some companies use both approaches—individual notification and a consolidated list—to ensure visibility and awareness for a wide range of stakeholders,

Bio/pharmaceutical industry surveillance of compendial changes: Process in detail (cont.)

and to increase the chances that all functional areas have an opportunity to consider the potential impact of the changes.

A key part of this communication is determining who in the company needs to receive the information, as well as what tool is used for notification and monitoring the tasks. The compendial affairs function needs to establish the list of SMEs to review/assess each new and revised item found during the filtering step of the process. This is not an easy task, because SMEs reside in multiple functions across a company (e.g., quality, regulatory, analytical, research and development, supply chain, packaging development, labeling, logistics for distribution, and external manufacturing). Once established, the list of SMEs needs to be maintained with updates to reflect turnover in personnel and changes in responsibilities for these areas. Maintaining the engagement and commitment of the SMEs is also challenging, but crucial to the success of the surveillance process. When the compendial affairs function requests assessment of pharmacopoeia updates by SMEs from the business units, a common response is, “it’s not my job,” among others that were touched upon in the second article of this series (1). Given the span of control where SMEs reside across the company, the understanding, commitment, and support by executive leadership and functional area management across the company is important in ensuring routine SME participation in this surveillance process to ensure compliance. The ongoing effort to keep all stakeholders involved and up to date with ever-changing pharmacopoeial requirements is quite a task and should not be underestimated in resource planning for the compendial affairs group.

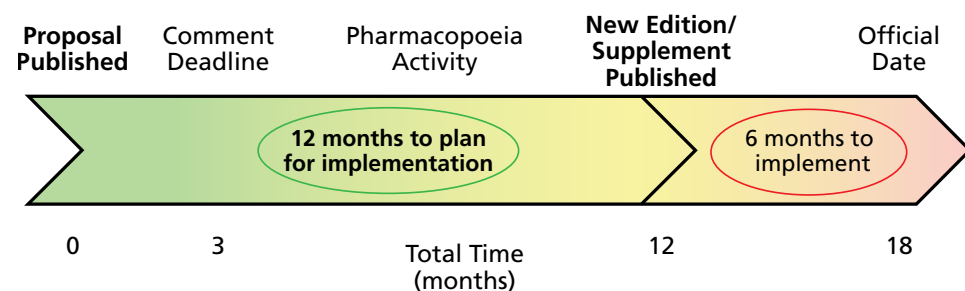
Proposed changes: Evaluate, develop a response, and plan for implementation. Typically, for global pharmacopoeias as well as many of the national pharmacopoeias, new and revised requirements are first published as proposals, with an opportunity for public review and comment prior to becoming official. At the pharmacopoeia proposal stage in the industry surveillance process, two important actions are undertaken, usually in parallel, for items with potential impact to the company: develop a response to the proposal and plan for implementation of the changes (**Figure 1**). Submitting comments to pharmacopoeia proposals requires a company decision to pursue this proactive approach to the overall process. There are clear benefits in doing so, but the trade-off is the resources needed by the company to perform this work. Not every revision proposed by the pharmacopoeia requires a response; indeed, the vast majority do not. The assessment step in the surveillance process helps to identify the changes where a response may be beneficial. For these proposed changes, developing appropriate comments can require significant time and effort. This is particularly true, for example, when laboratory work is needed to evaluate a proposed change to an analytical method, or when data-mining of release and stability information is required to determine whether a company can comply with a proposed tightening of an impurity limit.

For the first action, when a response is needed, the compendial affairs function works with SMEs and impacted stakeholders to evaluate the change and prepare scientifically-based comments to submit to the pharmacopoeia authority. In most companies, the compendial affairs function is responsible for this advocacy, aimed at influencing decisions about the official content that will be published in the pharmacopoeias. The compendial affairs advocacy may be associated with a company’s larger regulatory intelligence activities. Effective advocacy requires the compendial affairs function to clearly define what is needed from the SME assessment of a change and in what manner the information is provided back to the compendial affairs group (e.g., comments, suggestions, data). The compendial affairs function must let the SME know when the assessment is due, typically at least 14 days before the response is due to the pharmacopoeia. This allows the compendial affairs function to work through and follow up on internal comments received. It is important that SMEs understand that sound scientific rationale and data (where appropriate) are required to support a request for change to a proposed general chapter or monograph. It is not enough for a scientist to disagree with a statement or requirement without offering the reason for the objection, a suggestion for a change in the statement or requirement, and the appropriate rationale for the suggestion. To enable effective and appropriate commenting, it is recommended that the compendial affairs function develop a training program to help their SMEs in this work. Without this training, the compendial affairs group may spend significant time rewriting or interpreting the comments from SMEs prior to sending them to the pharmacopoeia authority. One possible outcome of the rewrite is that the original intent of the SME comments could be lost. After these internal comments have been received, potentially from multiple stakeholders, the compendial affairs function then shapes the information into a consistent, coherent, and hopefully compelling response that is provided to the pharmacopoeia agency before the established comment deadline. For commenting to the national pharmacopoeias, the connection to a company’s local contact group is essential so comments can be translated into the local language prior to submission. For countries such as China, where turn-around times for review and commenting can be short, this process and expected roles must be well-defined ahead of time to maximize the chances for the company to be successful in their advocacy.

At this stage in the surveillance process, a company has usually filtered and determined which proposed changes may have the greatest potential impact. These major changes often benefit from the effort required by a company to develop and submit comments in response to the proposal. For the remaining items identified with potential impact, an assessment serves to look further into the details of the change to determine whether there is minor impact or no impact to the company. It may be surprising, but true, that this deep dive into details is needed to make this final determination of impact. As illustrated in **Figure 2**, the

Bio/pharmaceutical industry surveillance of compendial changes: Process in detail (cont.)

Figure 3. Typical timeline for pharmacopoeia revisions to move from proposal to official.



remaining 400 items each year are assessed and filtered to find about 100 with minor impact, and the remaining 300 items with no impact. A simple example of a proposal with no impact is a change to a detail in an analytical procedure, when it is found on further assessment that the specific detail is not listed in testing standards or product registrations for the company. Another example is a change proposed by USP to the monograph for a pharmaceutical ingredient, when it is found upon assessment by the manufacturing site that the associated product is only marketed in Europe. It is helpful to also have confirmation from the regulatory group that USP requirements are not listed in the product registrations for that ingredient. It is worth noting that input from multiple functional areas across the company helps to increase the effectiveness of this deep-dive to determine the impact of proposed pharmacopoeia revisions; one group usually does not have all the necessary information.

What has been achieved by the process at this stage? A company has been able to take a total of 3000 changes published per year by the global pharmacopoeias, and through a series of filters and further assessment, determine that only about 200 of these truly have impact. The effort needed to identify the revisions with impact is neither quick nor easy, but it is beneficial as it enables the company to then focus on the 100 major changes and the 100 minor changes to determine next steps to maintain ongoing compliance. For major changes, which typically have broad impact across the company, the impact assessment benefits from a “targeted compliance team,” ensuring input from all potentially impacted areas regarding the specific, targeted pharmacopoeial revision. This team is comprised of representatives from appropriate functional areas, including the supply-chain function and impacted manufacturing/stability sites, since no single group can identify the impact of a major change to every area in a company. The targeted compliance team has the responsibility to provide input on the proposed change to help in the development of a possible response to the pharmacopoeia, and equally important, to develop the company’s implementation plan for the specific compendial update being evaluated. Any lab work and data mining performed to support the company’s response to the pharmacopoeia is also valuable in the second

action at this stage—determining the implementation plan for the proposed change. Each proposed revision with major impact to the company will affect different stakeholders to different degrees, and it may be questioned who has the decision rights for such a team. The answer is that decisions about the implementation plan must be made in the best interest of the company overall, with input from each area weighed in the determination, and the ultimate benefit to patients firmly in mind. For minor changes, a cross-functional team may not be required to develop the implementation plan, but a similar decision process can be used to determine how best to proceed.

It is important to understand that proposed changes must not be implemented, because they are not yet official. Though it may seem premature to begin planning for implementation at this stage, doing so increases the likelihood that the changes can be put in place by a company in the relatively short time between the subsequent publication and designated official date for the pharmacopoeia revisions. This is shown in **Figure 3**, which represents a typical timeline for a proposed revision to become official. Time zero is set as the publication of the proposal, with three months allowed by the pharmacopoeia for public review and comment. Once the comment deadline ends, the pharmacopoeia organization continues their process, leading to publication of the official change in a new edition or supplement. The minimum time taken by the pharmacopoeia to accomplish this is about nine months, although it often takes longer. Once the update is published in the new edition or supplement, six months is usually allowed for its implementation. Starting to develop the implementation plan at the proposal stage provides a minimum of 18 months to accomplish this important work and help maintain ongoing compliance, a full year longer than the six months available after the updates are published in the new edition or supplement. This extra time can be invaluable in making the necessary updates to a company’s procedures, documentation, and product registrations, especially for those changes that have been identified to have major impact.

The impact assessment for proposed pharmacopoeia updates enables effective planning for implementation if/when they become official. Most revisions proposed by the pharmacopoeia

Bio/pharmaceutical industry surveillance of compendial changes: Process in detail (cont.)

move forward from proposal to official without significant change from what was initially proposed. In the authors’ experience, 90% or more of proposed changes move forward 90% of the time with no major change to the proposal. If there are significant changes, as sometimes seen with proposals for new or significantly updated general chapters, the pharmacopoeia will typically publish another draft for review and comment before becoming official. Given this situation, the sooner a company can assess the impact of a pharmacopoeia revision (i.e., at the proposal stage), the better they are able to plan for a smooth implementation of the change, especially given the challenges associated with official change control processes in many companies. This evaluation also enables the submission of comments to the pharmacopoeia, when necessary, advocating in regard to changes that may be unacceptable or unachievable for the company.

Official changes: Evaluate and proceed with implementation. The pharmacopoeia process to introduce new and revised monographs and general chapters continues from the proposal stage to the subsequent publication of updated requirements that become official through new editions and supplements. The publication of these updated requirements triggers the final phase of the industry surveillance process. The specific steps performed by a company at this official stage are essentially the same as described for the proposal stage: monitor the publications, filter for impact, communicate, and evaluate the changes. The ultimate goal, however, shifts to focus on implementation. If the revision was previously evaluated at the proposal stage, a re-evaluation is performed by SMEs or responsible groups to identify changes that may have been introduced from the proposal to the official publication. Any changes from proposal to official are taken into account to adjust the implementation plan that was developed at the proposal stage; changes from proposal to official are also documented in the change control process to properly implement the official revision. The work then progresses to execution of the implementation plan, thereby providing compliance with the updated official pharmacopoeial requirements. If the pharmacopoeia revision was not previously evaluated when it was proposed, this is the first time a company will identify the update, and all the steps of the impact assessment detailed earlier in the process must be accomplished in the six-month timeframe typically allowed between publication of the new edition or supplement and the official date. The evaluation must now focus on what has changed from the previous official requirements, including how these are reflected in the company’s documentation, to the newly updated official requirements. Failure

to accomplish all this activity on time, including any laboratory evaluation or data-mining, culminating in the completion of change control, results in a potential compliance gap for the company, which may be revealed upon inspection by regulatory agencies.

A change control process is challenging at best but is a critical part of the compendial process to ensure compliance with current pharmacopoeia requirements. The change control process ensures input from impacted stakeholders, including the quality and regulatory groups, which is especially important when the change will impact multiple sites, multiple products, and potentially hundreds of product registrations around the world. The timing necessary to submit registration updates and receive any needed approvals from the health authorities, potentially over a time horizon of many years, must be considered and managed properly during this interim period.

Although the functional organization and details of the overall surveillance process may vary from one company to the next, there are common elements among the approaches that are effective: having multiple SMEs assist in the assessment; starting at the proposal stage; providing responses to the pharmacopoeia; and planning for implementation of updated requirements. Even in the best compendial affairs programs, there are occasions when a company may have difficulty complying with some of the specific, updated official pharmacopoeial requirements. To address this situation, the last step of the industry process, when needed, is for a company to submit a request for revision to the pharmacopoeia authority, advocating for further revision of the general chapter or monograph that was just made official. This request may not be received favorably by the pharmacopoeia if the company did not provide any comments when the revision was first proposed. Similar considerations as those for developing a company’s response to a proposal also inform the development of a request for revision to an official update, complete with scientific rationale and data needed to support the requested change. This input from a company starts the entire pharmacopoeia revision process from the top, which again triggers the industry surveillance process. As noted before, pharmacopoeias continually evolve and given all the different viewpoints of the impacted stakeholders in a company, one can begin to get an appreciation of the challenges and complexity faced by all.

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1. J. M. Wiggins and J.A. Albanese, “Why Pharmacopoeia Compliance Is Difficult,” *BioPharm International Regulatory Sourcebook eBook*, 26–34 (September 2019).

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the focus of their discussion is on changes that have broader impact to the entire industry, as seen with

general chapters, which are used by many companies. Key benefits of engaging with industry groups include recognizing you are not in this alone; that it is helpful having

many eyes look at the information; and there is power in numbers.

Participating in these groups as part of the compendial process increases a company’s abil-

ity to identify all changes with potential impact and to be more successful in the resulting advocacy efforts. During the proposal stage, through discussions in the industry associations, it is often found that the compendial affairs function in one company has identified a potentially major revision, when other companies may not yet have made that determination. This heightened awareness enables greater assurance that a major change is not missed, and the resulting discussion can focus on how the change may impact the broader industry. If the particular industry group charter allows, and the proposed change warrants, comments can be sent to the pharmacopoeia authorities by the association, representing the input of many companies to bring added weight to any concerns identified. Again, these comments need to be scientifically based and supported by data where appropriate.

Being connected to industry trade organizations is invaluable in these situations because the organization represents companies that have similar opinions. For high-impact changes, such as elemental impurities, it is important to have this connection to trade organizations to help consolidate the industry point of view. Leveraging this critical mass through comments to proposals can influence the final outcome of the official revision. Investing time to participate in these organizations is a simple yet effective way to leverage the power and influence they have when engaging with the pharmacopoeias. For their part, the pharmacopoeia authorities have demonstrated their willingness to engage with industry to discuss issues that are identified.

INDUSTRY SURVEILLANCE PROCESS: TOOLS

The final piece of the industry surveillance process is focused on the tools that help the compendial activities run smoothly and enable the people to remain actively engaged. This piece of the puzzle is as crucial as the process and people in ensuring a compliant system. Investing in appropriate tools allows for comprehensive tracking, ease of communication, implementation of revisions, and generation of metrics on the effectiveness of the process.

Being connected to industry trade organizations is invaluable because the organization represents companies that have similar opinions.

The most important tool for a compendial affairs program is the one to track the pharmacopoeia changes identified with impact to the company and the current status of these items. The tracking can be done using various tools, from a simple spreadsheet/database or a SharePoint (Microsoft) team site with simple functionality to a specially configured out-of-the-box quality solution or a customized in-house system specifically designed for tracking. Each of these options have been used by a number of companies and are viable solutions to enable proper tracking of the compendial process. As a company works to establish a compendial affairs program, an approach of “crawl, walk, run” can be applied. At the begin-

ning, the process may use a simple spreadsheet to track items of interest. As the program matures and the processes become more defined, a database or a SharePoint team site may be appropriate. The latter offers an opportunity to add automatic notifications and due-date reminders for assessment tasks. It also allows for export of the data to enable metrics (monthly, quarterly, or annually) to be generated. If configured properly, the application will allow for the connection of proposal items and official items to help aid the assessment and change control processes needed for compliance.

Other tools critical to the success of compendial surveillance were mentioned in the filtering stage of the detailed process (see **Sidebar**): the lists of drug products and related materials, including pharmacopoeia general chapters used by a company. The challenges of trying to pull all the necessary information on materials used, where they are used, and if they are still active are significant. Rarely is a single system available to accomplish this; rather, it requires the aggregation of information from multiple systems throughout the company. Requests may need to go to the various business systems across a company with the resulting information combined into one list by the compendial affairs function to ensure all materials are captured for the filtering process. This is a time-consuming and people-intensive process step, but it may be the only approach to ensure all materials are captured for a company, in the absence of a single, integrated business system. Another important determination is which general chapters need to be assessed by a company. Investing the time to develop a grid of “similar” chapters across the pharmacopoeias and which general chapters are used by the company will ensure a

robust filter and reduce the number of items that require further assessment. Typically, a spreadsheet can be used to establish this matrix of general chapters across pharmacopoeias, with an indicator if the chapter is applicable to the company. The list requires periodic follow up to add new general chapters and remove others that have been made obsolete.

Communication tools are also important for a successful surveillance program, to provide the findings of the ongoing pharmacopoeia filtering process throughout the company and enable assessment for potential impact. This includes communication of individual items and an overview report sent at a regular frequency (per publication, monthly, or quarterly). Microsoft Word programs and Microsoft Excel spreadsheets are the typical tools used for such reports. The compendial affairs function needs to keep up-to-date lists of SMEs and other stakeholders for email distribution of necessary reports or task assignments. Having a dedicated email box for the compendial affairs function is also a recommended best practice for communication. This alleviates individuals in the company from having to know a specific person in the compendial affairs role and allows for people changing their roles and responsibilities. Most people can remember a well-named email address (e.g., Compendialsupport@company.com) more easily than a specific individual’s name. This generic email address allows all members of the compendial function to monitor requests and questions that may be sent to them from any group in the company.

If a company’s compendial affairs function submits responses to pharmacopoeia proposals, then a process for this needs to be defined. Typically, responses

are submitted on company letterhead and sent via email to the pharmacopoeia authority or a specific scientific liaison in the pharmacopoeia organization. The file is usually submitted in portable document format (PDF) with electronic signature to maintain the integrity of the file, which also serves as the official record of the company’s position on the particular issue.

All appropriate functional areas within a company must assess the impact of pharmacopoeia changes and determine implementation steps for the site or global function, including possible updates to product registrations.

Some pharmacopoeias have online platforms that allow comments to be directly uploaded to that site. It is expected that other pharmacopoeias will follow suit in the coming years. Also, it is recommended that the tracking system, mentioned before, be configured so that submitted comments can be tracked to enable follow-up as needed. This also allows a determination of whether the comments and suggested changes submitted by a company were

taken into account in the official version for implementation. This also provides the compendial affairs function with the ability to generate metrics on the company’s efforts to influence the pharmacopoeia authorities.

The last essential tool for a compendial affairs program is a global change control system. Items that are published as official by the pharmacopoeias typically have a six-month window for implementation from the time of publication. It is important that all appropriate functional areas within a company assess the impact and determine the implementation steps for the site or global function. Key to the change process is a regulatory impact assessment to determine if any product registrations need to be updated. A simple change in a monograph could still result in updates to registrations in several countries, determined by a company’s filing strategies. To have an effective change control process that drives on-time implementation of a pharmacopoeia change, each site or global function must understand their role and execute it promptly. Also, a responsible person or group needs to be identified that will drive the change control from start to finish. This is a difficult job for multi-site, multi-product changes, or changes that impact multiple registrations. It is important for the responsible person to begin this process shortly after the proposal has been reviewed. If a company begins the implementation process when an item is reviewed at the proposal stage, it will have done most of the assessment and planning before the item becomes official, when there is only six months to complete the implementation (see **Sidebar, Figure 3**).

Taken together, the tools supporting the compendial processes

can potentially identify emerging trends for each of the pharmacopoeias. The trends are identified by reviewing items in the compendial tracking and change control systems and can then be molded to reflect changes that should be made to existing development and commercial product support processes helping to ensure compendial line-of-sight (CLOS) for the company.

MEASURING SUCCESS: ADVOCACY AND COMPLIANCE

Management will often request a report of metrics regarding on-time completion of items for commenting and for implementation. Having described the details of the industry surveillance process, including the people and tools that are necessary, it is appropriate to ask how to measure success for this work. As it turns out, this can be somewhat difficult to do. Pharmacopoeia revisions take place over protracted periods of time. It typically takes a minimum of 18 months from proposal to official, and often much longer—up to several years for some major changes—for the pharmacopoeial revision process to be completed. Because of this, many changes remain open for a long time and the compendial affairs function may have hundreds of items that have not reached the final step in the process. In the end, however, success can be examined from the standpoint of advocacy and compliance.

Advocacy. In monitoring pharmacopoeia revisions, a management decision is required on whether the company will be proactive through advocacy efforts or strictly reactive in compliance. Advocacy is aimed at influencing the decisions of the pharmacopoeia authorities to impact the official content published in new editions and supple-

ments. In advocating for changes to revisions that have been proposed by the pharmacopoeia, there are very few quick wins. For people who have been involved in this work, it is often the case that advocacy does not consistently achieve its intended goal. Rarely are all comments submitted by a company accepted by the pharmacopoeia, to be reflected in the official requirements. A reasonable goal is to nudge the proposal in a meaningful way, hopefully influencing the major issues that have been identified, while accepting that minor issues may go unresolved. For their part, the pharmacopoeias must consider all comments received from stakeholders, who may have perspectives that are diverse and even contradictory. The pharmacopoeia authority balances this information to determine how best to proceed.

Advocacy is a critical part of the compendial process and can result in an official revision that is easier to implement than it would have been if comments had not been submitted.

Another aspect of advocacy is how a company reacts when comments are not accepted by the pharmacopoeia authority. The company can contact the appropriate scientific liaison at the pharmacopoeia to ensure the comments were clear and understood. Having established

connections with the scientific staff in the pharmacopoeias can facilitate these discussions. Any unresolved issues that appear in the official revision can be the basis for the company to request a new revision to the general chapter or monograph, providing additional rationale or scientific data to support the requested change.

The advocacy part of the compendial process can be very rewarding when comments are accepted by the pharmacopoeia authorities. It can be equally frustrating when sound scientific rationale may not be accepted, leaving a potential compliance gap for the company. It can be difficult to explain to company scientists and management that the comments were not accepted, and that procedures and documentation may need to be changed to reflect the official requirements. Another frustrating and challenging aspect of the compendial process may be encountered as a result of differing timelines followed by the pharmacopoeias to make harmonized requirements official, as has been seen with the updated chapters on residual solvents and elemental impurities to align with the corresponding International Council for Harmonization (ICH) guidelines. Still, advocacy is a critical part of the compendial process and can result in an official revision that is easier to implement than it would have been if comments had not been submitted.

Compliance. The ultimate goal of the industry surveillance process for monitoring pharmacopoeia revisions is to maintain ongoing compliance with current requirements, as expected by regulatory agencies around the world. The success of a company's process can be measured by on-time implementation of official pharmacopoeia revisions.

Implementing compendial updates is made more difficult by the large number of revisions that must be addressed, and the assessments needed by many SMEs and functional areas in the company. There are likely instances where a proposed or official revision that impacts the company may not have been identified, or the impact of the change has not been fully assessed by all stakeholders. Even if identified and assessed appropriately, there are times when the change control process is delayed, awaiting key decisions on implementation, as well as assessments by impacted areas, including manufacturing sites and regulatory affairs.

The success of a surveillance process can be measured by the on-time implementation of official pharmacopoeia revisions, a challenge due to the large number of revisions.

Updates to product registrations and gaining approval from regulatory agencies around the world may take a long time due to the complexity of the work. In these situations, a manufacturing site may have to perform duplicate testing, using the old pharmacopoeia requirements and the new ones, managing appropriate compliance in the interim until everything is realigned.

These situations are often noted by leadership as failures in the process, and while this may be a valid perspective, it does not reflect the majority of cases where these “misses” did not happen. Ideally, management expectations of the process will reflect this reality. In the authors' experience, one measure of success for the compendial affairs function is “flying under the radar”, going unnoticed by management because everything is proceeding as expected and no compliance gaps emerge. All this success, however, may be forgotten when a potential compliance gap is found. At this point, the success of the process relates to how quickly and how well the company's stakeholders can come together and address the gap. Sufficient resources are needed for these implementation activities, potentially including method comparability studies, to reach a suitable outcome in a short time while other routine work is also maintained for the functional areas. Learning from these situations can lead to continuous improvement in the surveillance process to minimize the likelihood of another such occurrence in the future.

CONCLUSION

Details of the bio/pharmaceutical industry surveillance process have been provided to help address the compliance challenges resulting from pharmacopoeia revisions. The goal for an individual company is to establish an effective, efficient, sustainable, scalable, and successful process to accomplish the work. It is the people and tools that contribute to the effectiveness, efficiency, and sustainability of the process, and the benefits of advocacy activities are clear. The process can evolve over time, with more people and new tools added as resources are

made available, which can also support the scalability of the process to add more pharmacopoeias or products to the overall monitoring. Consideration of all these details determines the ultimate success of the process.

Recalling the fundamental principle stated in the first article of this series (4), compliance with official requirements published by pharmacopoeias around the world is a legal and regulatory requirement in those countries and regions in which the pharmacopoeia is applicable. However, there is flexibility in how a company complies, and this will be explored in later articles. A future article will describe another advocacy opportunity: collaboration with the pharmacopoeias for the submission and development of monographs.

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