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This article presents how the U.S. Pharmacopeia (USP) works to ensure the quality of pharmaceuticals by preparing standards.

The U.S. Pharmacopeia (USP) Responds to Changing Needs of Pharmaceutical Manufacturing

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As the pharmaceutical industry shows continued global expansion, manufacturers and regulators are faced with novel and complex challenges in ensuring the quality of ingredients and finished products. The stakes include both public health and corporate reputations. While it's difficult to quantify with precision, many estimates cite the volume of Active Pharmaceutical Ingredients (APIs) in drugs taken by Americans that are manufactured abroad at up to 80%.[1] China and India have emerged as the pharmaceutical powerhouses, but other up-and-coming sources of APIs include Brazil and Southeast Asia – and there are others. Manufacturers and regulators must deploy all available tools to safeguard quality and safety in the resulting elaborate and far-flung supply chains, and new approaches are required as well. Such approaches must respond to the changing realities of the industry, accommodating requirements ranging from cost, to multi-facility/company laboratory capabilities, to regulatory enforceability.

Pharmacopoeial approaches to help ensure the identity, strength, quality, and purity of medicines and their ingredients have long been a key element of the safety nets that protect the drug supply, along with ethical manufacturers and good regulatory structures. American consumers, patients, and practitioners expect safe and reliable medicines – as they have a right to. However, in recent years, distressing incidents have shaken that confidence, not the least of which was the 2007 to 2008 public health crisis involving heparin (a widely used blood thinner) that was deliberately adulterated with a less expensive substance for economic gain, resulting in adverse reactions and deaths. And there have been other damaging incidents.

The U.S. Pharmacopeial Convention, a nonprofit public standards-setting organization, has been developing and updating quality standards for medicines since 1820. With the passage of the Food, Drug, and Cosmetic Act in 1938, most USP standards became enforceable by the Food and Drug Administration (FDA), and have served drug manufacturers with specifications, methods, and procedures needed to help ensure the quality of their products and that support a regulatory framework for compliance. All medicines marketed in the United States must comply with relevant USP standards for identity, strength, quality, and purity, and USP standards also are used in more than 130 countries. As with any scientific endeavor, USP standards must undergo constant revision and updating to take advantage of developments in methodologies and technology. To that end, USP's volunteers – distinguished scientists, regulators, researchers, and public health officials from around the globe working in Expert Committees and other bodies – have been focused on updating USP quality standards, and this engagement with the industrial and regulatory communities helps keep USP's standards current and relevant.

Modernization

The dissemination of up-to-date scientific knowledge and the application of advanced analytical practices play important roles in the global manufacturing of good quality pharmaceuticals. The USP has undertaken a large-scale modernization of our standards so that they may better reflect current scientific thinking and practices and to fill information gaps where they might exist for some API and excipient standards. In parallel to the USP's efforts, the FDA has established a monograph

modernization task force that is assisting the USP in setting modernization priorities. In addition to developing standards for small-molecule drugs that dominate the pharmaceutical market, the USP also has been focused on novel approaches for creating standards that are useful for the manufacture of the growing array of complex biologics.

Broadly speaking, USP standards come in three forms: monographs, general chapters, and reference materials. Monographs are documentary standards (specifications) for individual drug substances or products. General chapters are documentary standards that are broadly applicable procedures and methods (required when referenced in monographs and numbered from 1 to 999) or informational (numbered from 1000 to 1999). Reference materials are physical samples against which manufacturers test their own materials. Documentary standards are made public in the USP's official compendia, most notably the *U.S. Pharmacopeia–National Formulary (USP–NF)*. While the USP's modernization activities span both individual monographs and general chapters (that are either called out in particular monographs or applied as specified in *General Notices* of the *USP–NF*), this article focuses on the USP's revisions of general chapters that may have an impact on manufacturers and regulators worldwide.

Validation, Verification, and Method Transfer

Validation and verification of analytical procedures both play critical roles in a manufacturer's quality control activities in the laboratory. While similar, these are applied for different purposes, and the USP is re-assessing its related guidelines in the *USP–NF*.

The *USP–NF* specifies in its *General Notices* section that only results obtained by methods and procedures in the compendia are conclusive.[2] For those wishing to use alternative methods and procedures, the *USP-NF* does provide guidance on validating non-compendial procedures. Validation demonstrates that the accuracy, sensitivity, precision, selectivity, etc., of an analytical procedure are suitable for its intended use.[3] For example, when working with aspirin in a tablet form with the intent to run an assay on the aspirin, the user who is not using a compendial method must first validate that the method being applied does, in fact, accurately and precisely measure the quantity of aspirin in the tablet form.

Verification, on the other hand, is the user's demonstration that an article is suitable to be analyzed using the method in the *USP–NF*.[4] Scientists applying procedures described in the *USP–NF* to a compendial article are not required to validate the accuracy and reliability of those procedures. However, a laboratory employing a USP procedure for the first time, for example, should verify that it performs as intended.

Closely related to validation and verification is the concept of method transfer. As with verification and validation, the transfer of a procedure associated with a method looks at suitability in a specific context.[5] Transfer refers to the documented process that qualifies a laboratory to use an analytical procedure that originated in another laboratory, ensuring that the results of the transferred method are reliable. Factors to be taken into consideration during method transfer include the procedural knowledge of the laboratory personnel receiving the method and their ability to perform that procedure as intended.

The USP has recently established a new Expert Panel on Validation, Verification, and Transfer of Analytical Procedures, the ultimate goal of which will be to generate proposals for the revision of three USP General Chapters: <1224> *Transfer of Analytical Procedures*; <1225> *Validation of Compendial Procedures*; and <1226> *Verification of Compendial Procedures*. Three new mandatory general chapters on spectroscopy also have been proposed:[6] <852> *Atomic Absorption Spectroscopy*; <854> *Mid-Infrared Spectroscopy*; and <857> *Ultraviolet-Visible Spectroscopy*. Each of these general chapters contains sections on validation and verification with specific acceptance criteria for accuracy, precision, and other performance characteristics. In this manner, the USP is attempting to establish a more precise definition of what is considered to be an acceptable alternative procedure.

Microbiology

As stated, some of the USP's general chapters can apply across many articles. For manufacturers, the extent of microbial contamination in a finished product must always be a consideration. The USP's Microbiology Expert Committee looks at microbial presence and absence in both sterile and non-sterile pharmaceutical products. Non-sterile drugs – such as oral solid dosage forms or syrups – allow for the presence of small amounts of microorganisms in their makeup. Sterile products, on the other hand – which include parenteral drugs – must be manufactured and handled to avoid any microbial presence, given that they are administered into the bloodstream. Microbial contamination in sterile drugs can result in disease and – in some cases – even death. While all products purported to be sterile have to meet the requirements of General Chapter <71> *Sterility Tests*, sterility assurance is gained only through the use of robust and validated sterilization processes.

The USP's General Information Chapter <1211> *Sterilization and Sterility Assurance of Compendial Articles* addresses general principles of sterility assurance as well as information on sterilization processes. The USP has responded to user and stakeholder feedback that greater detail is needed to address specific sterilization processes. With future revisions, <1211> will focus exclusively on sterility assurance, and the USP has initiated the development of several chapters – the <1229.x> series – dedicated to individual processes. General Chapter <1229> will serve as an overarching general chapter covering the general concepts of sterilization. To date, 11 more focused general chapters have been planned, out of which eight will focus on distinct processes for sterilization, how they are to be conducted, and what materials are most suitable for their use:

- <1229.1> *Steam Sterilization by Direct Contact*
- <1229.2> *Steam Sterilization of Aqueous Liquids*
- <1229.4> *Sterilizing Filtration of Liquids*
- <1229.6> *Chemical Sterilization*

- <1229.7> *Gaseous Sterilization*
- <1229.8> *Dry Heat Sterilization*
- <1229.10> *Radiation Sterilization*
- <1229.11> *Vapor Sterilization*

The other three general chapters in the 1229.x series will address areas related to these processes:

- <1229.3> *Monitoring of Bioburden*
- <1229.5> *Biological Indicators for Sterilization*
- <1229.9> *Physicochemical Integrators and Indicators for Sterilization*

Another major consideration for manufacturers with regard to microbial presence is contamination control. General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* has undergone a major revision and will become official in 2012. By changing the focus from evaluation of cleanrooms to key guidance that supports sterile pharmaceutical processing environments, revised General Chapter <1116> addresses ways to help eliminate microbial growth, particularly when introduced by human contact. Guidance in the general chapter as well as monitoring parameters for microbiological evaluation should be applied only to cleanrooms, Restricted-Access Barrier Systems (RABS) and isolators used for aseptic processing. Changes to <1116> include clarification of limitations of counting methods used in microbiological evaluation, including sampling, recovery, data tracking, and trend analysis. The general chapter provides an improved description of microbiological incubation conditions relative to intended recovery (e.g., typical temperature and time, or modification for slow growers). The general chapter also gives guidance on the establishment of sampling plans and sites; microbiological sampling methods (e.g., air sampling, surface sampling); contamination recovery rates, and other important microbiological control parameters.

In the arena of bioburden control for non-sterile pharmaceutical products, very little information is available either in the pharmacopoeias or regulatory guidance documents. Clearly, the quality of raw materials, the surrounding environment during manufacture, and personnel conducting quality control activities are just some of the factors that can contribute to the bioburden of a product. In a draft proposal that will be available for public comment in the USP's *Pharmacopeial Forum* in 2012, the USP will recommend a risk-based approach to bioburden control. By looking at factors that have the potential to affect product quality and patient safety and considering the best ways of addressing these, the user can then identify the risk associated with a product and apply appropriate methods for bioburden control. Points for consideration when assessing potential risk associated with non-sterile drug product manufacture include:

- synthesis, isolation, purification, package, and storage of drug substances
- inherent antimicrobial properties
- water activity
- equipment design and cleaning
- process water production, storage, distribution, and use
- route of administration
- age and general health of the patient population expected to use a drug product

In the case of antibiotics, microbial assays are used to measure a drug's potency by looking at its inhibitory effect on a target microorganism. Because of difficulties associated with conducting this type of assay and the time required for its completion (three to four weeks), the USP is exploring the use of a more rapid High-Performance Liquid Chromatography (HPLC) assay as a replacement. While not all antibiotics have an approved HPLC assay, the USP will look for guidance from its newly established Expert Panel on the topic to recommend validation criteria for replacement of an antibiotic microbial assay by HPLC methods. The USP also will look to manufacturers for information on validated HPLC methods that have been approved by regulators for inclusion in specific antibiotic monographs.

Similarly, current pharmacopoeial microbiology tests – such as sterility tests – rely on the demonstration of microorganism growth. Limitations of these tests include their low sensitivity as well their time- and labor-intensive nature. The USP is seeking to identify new referee tests or procedures (used by the FDA or a third party to assess regulatory compliance) based on modern methods that can detect and enumerate microorganisms in a more rapid and sensitive manner. The USP Microbiology Expert Committee also is working to update General Chapter <1223> *Validation of Alternative Microbiological Methods* to enable the user to validate microbiological methods, including those based on modern technologies.

Modern microbiological methods, the <1229> series of general chapters associated with sterilization, and USP efforts related to bioburden control in non-sterile products will be key areas of discussion at a USP workshop on microbiology quality standards scheduled for July 2012 at the USP headquarters in Rockville, Maryland, U.S. (http://www.usp.org/meetings-courses/workshops?).

Impurities in Drug Products

Another key area for the USP's standards modernization activities focuses on impurities in both Over-The-Counter (OTC) medicines and prescription products. The USP has established an Expert Panel in partnership with the FDA and the pharmaceutical industry to identify more modern scientific standards that can help ensure the appropriate control of organic impurities. There is a public and regulatory expectation that OTC products will be of comparable quality to prescription products, whether they are marketed under a USP monograph or one from the FDA. Although the USP monographs exist for all active ingredients covered in the FDA OTC monographs, the USP does not have monographs covering most of the drug combinations (drug products) that can be marketed under the FDA monographs, and the USP is working to acquire those currently missing from the *USP–NF*. Such OTCs are available in a wide variety of dosage forms,

colors, and flavors, which change frequently based on market demand and the large number of manufacturers worldwide that make them. All OTC drugs are subject to existing USP quality standards, and in the context of its overall modernization efforts, the USP has received a list of OTC priorities from the FDA, focusing first on acetaminophen and diphenhydramine as well as several inactive ingredients. Modernization of these monographs addresses quality gaps, such as missing or outdated tests for impurities (including degradation impurities) and the replacement of non-specific identification tests with more specific methods.

In a September 2011 workshop sponsored by the USP and the FDA, attendees explored some key quality challenges posed by OTCs. One critical factor is the large number of dosage forms associated with a single drug substance. For example, currently in the *USP–NF* there are 37 different monographs for acetaminophen dosage forms alone (acetaminophen is not covered by an FDA OTC monograph). The USP is looking at a number of novel approaches to help streamline the development of missing or outdated monographs. Future discussions with the FDA and industry stakeholders will help in establishing the optimal paths forward. General Chapter <1086> *Impurities in Drug Substances and Drug Products* includes key definitions associated with impurities that are aligned with those established by other pharmacopoeias and the International Conference on Harmonization Q3B (ICH Q3B) (the guidance for registration applications for the content and quality of impurities in drug products produced from chemically synthesized drug substances not previously registered in a region or a member state of ICH). Proposed revisions to General Chapter <1086> are being addressed by the USP, and could include general guidelines for the detection and qualification of organic impurities as well as a decision tree for use when needing to address or report impurities associated with manufacturing processes.

Today, some 400 monographs in the *USP–NF* are related to OTC drug products, and changes to General Chapter <1086> will be relevant to those as well as any new OTC monographs yet to be included in the USP's compendia. Additionally, the USP's Monograph Modernization list – accessible at http://www.usp.org/USPNF/submitMonograph/improveMon.html – comprises about 700 small molecule and excipient monographs out of approximately 2,600 eventually needing modernization, and input from stakeholders is strongly encouraged.

Identification Tests

In addition to exploring issues associated with the detection and measurement of impurities, the USP's General Chapter Chemical Analysis Expert Committee has been examining modernization needs related to identification tests in General Chapter <191>, *Identification Tests–General*. Recent adulteration issues with some pharmaceutical products have prompted the FDA to pay special attention to compliance with all identification tests since these are the first barrier against counterfeiting and contamination. Mentioned in hundreds of monographs, General Chapter <191> is one of the "top" most-referenced chapters in the *USP–NF*.

Traditionally, wet chemistry tests (e.g., color-based tests, such as acid-base, precipitation, or complex formation) and classic flame tests (complementary tests for sodium, potassium, calcium, copper, and lithium) have been the methods of choice for pharmaceutical product identification. Because these tests rely on users distinguishing such properties as color, they can be subjective. Among the 44 tests included in <191>, 19 currently include substances that are not suitable because of current environmental legislation or safety concerns (e.g., chloroform in bromide identification or mercurous nitrate in thiosulfate identification). Rather than reviewing the 44 tests one at a time for possible revision, the Expert Committee is taking a holistic approach to all tests included in the chapter and is exploring instrumentation procedures to replace traditional testing for identification.

Cognizant that not all manufacturers will adopt instrumentation approaches for identification, the USP asked manufacturers in 2011 about current user needs and practices. Of approximately 400 responses, the majority (92%) reported using wet chemistry for identification testing, but many of those who do so (64%) also use additional testing methods. For example, there is moderate use of atomic absorption (35%) and spectrophotometric methods (30%). Fewer use ion chromatography (22%) or inductively coupled plasma (19%). When asked to explain ways in which General Chapter <191> can be improved or modernized, nearly seven in ten respondents (68%) provided suggestions. The top suggestion focused on the addition of modern techniques or clarifying procedures. The top reason for favoring wet chemistry replacement was that alternative methods are more quantitative and less subjective, while the top reason for being opposed was instrument cost. Additionally, nearly one in five indicated that other methods should be alternative or optional. These and other results of the survey will help to shape the USP's thinking about future revisions to General Chapter <191>.

Biologics and Biotechnology

Another area of focused activity for the USP general chapters is large molecule products increasingly used to treat complicated disorders and diseases. Collectively referred to as "biologics," these products range from small peptides with simple structures to more complex mixtures such as vaccines. What they have in common is that they are manufactured using living material. The role of biologics in the therapeutic landscape has been rapidly expanding, as are, in consequence, critical issues associated with their quality assessment.

The USP's expanding portfolio of monographs and chapters for biologics increasingly uses a modular approach that involves vertical (product-specific), horizontal (general), and product-class standards. Due to the complexity of and variety among biologics, it is helpful to group these drugs into product classes based on their molecular make-up. Within a single molecule class, the same or at least similar analytical approaches often can be applied across multiple products. This "platform approach" applies to many classes of modern biologics, such as Monoclonal Antibodies (MAbs). Centered on shared quality attributes and testing expectations, these ap-

proaches can be captured in a general chapter. A USP Expert Panel has worked on General Chapter <1260> *Therapeutic Monoclonal Antibodies*, which provides a general overview of antibody therapeutics. In addition, the USP is developing a clearly defined set of quality expectations related to monoclonal antibodies in General Chapter <129> *Quality Attributes of Monoclonal Antibodies*. General Chapter <129> will be linked to other *USP–NF* general chapters that cover relevant analytical procedures as well as quality expectations for ancillary and process materials used in the manufacture of MAbs. It also will contain analytical procedures and acceptance criteria for monoclonal immunoglobulin (IgG) products. The Expert Panel working on the chapter will be conducting a round-robin study with broad industry participation to obtain stakeholder feedback on some of the proposed procedures, as well as collect batch data that will allow the USP to set meaningful specifications in the general chapter.

Clearly, common specifications will not be feasible for all procedures and quality attributes that define a monoclonal antibody product, and defining the analytical "common ground" among products represents a major challenge in this standard-setting effort. Based on the current thinking of the Expert Panel, common methods like Size-Exclusion Chromatography (SEC) for the detection of size variants, as well as Sodium Dodecyl Sulfate (SDS) capillary electrophoresis for purity, are the most promising candidates for platform methods with agreed-upon specifications. Much more challenging is the area of biological potency determination since this is unique to the mechanism of action for each individual antibody. Thus, this area will only lend itself to the development of general recommendations on how potency assays for MAbs should be approached. With this product-uniqueness in mind, class chapters are intended to link to individual product monographs that delineate the specific quality attributes of a given drug. However, given the complexity of biologics, it is critical that a broad foundation of general standards underpin the individual product monograph and set a more level bar for minimum quality expectations across a molecule class. Figure 1 illustrates the linkage between horizontal (general chapters) and vertical (monographs) standards for the example of monoclonal antibodies.

Other USP initiatives related to biologics include general chapters related to protein structure and post-translational modifications. General Chapter <1084> *Glycoprotein and Glycan Analysis–General Considerations* addresses modifications that result from the process of glycosylation, which adds to the complexity of characterizing biologic products. The general chapter is an analytical strategy document that uses decision tree diagrams to guide users through the analytical choices available to design product analysis in the spirit of ICH Q6B and based on molecule type. The ICH Q6B guidance document provides general principles for the setting and justification of specifications for biotechnological and biological products to support new marketing applications. Figure 2 shows one of these decision trees.

In addition to <1084> as an informational general chapter, the USP is working on two general chapters that contain procedures for oligosaccharide and monosaccharide analysis. These general chapters will be associated with physical refer-

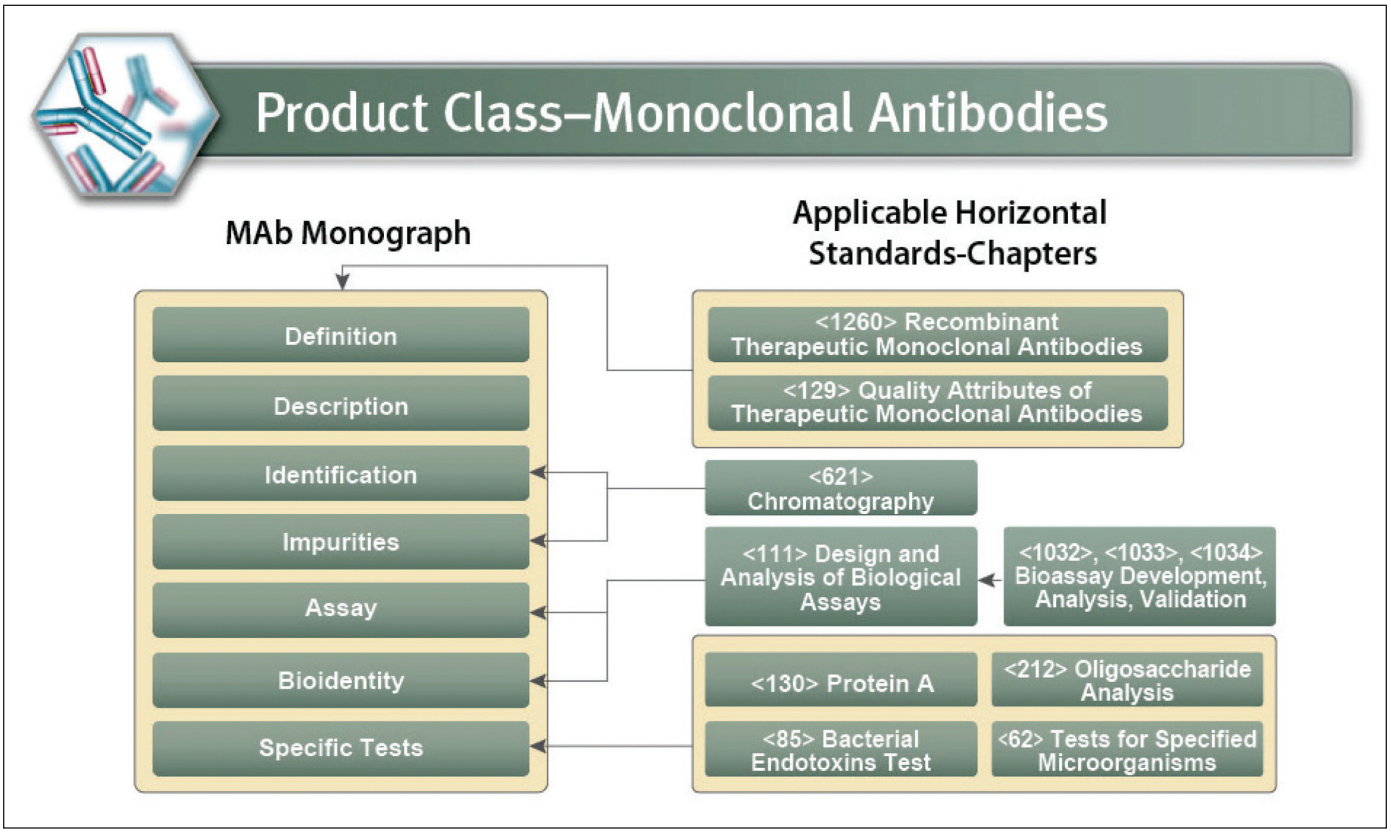

Figure 1. Linkage between horizontal (general chapters) and vertical (monographs) standards for the example of monoclonal antibodies. (Source: U.S. Pharmacopeia)

ence materials designed to aid in establishing and verifying system suitability during method development, qualification, and validation.

The potency assessment of a biologic is also a central quality consideration. Over the last several years, the USP has developed a comprehensive set of informational general chapters dedicated to bioassays. In addition to General Chapter <111> *Design and Analysis of Biological Assays*, which provides direction on creating appropriate strategies for biologic potency, the USP has completed a new suite of general chapters that includes guidance and information on the development, analysis, and validation of biologic assays. General Chapters <1032>, <1033>, and <1034> are scheduled to become official with the *First Supplement* to the *USP 35–NF 30* in August 2012.

Another key component of biologics manufacturing is the use of ancillary materials, such as growth factors and process enzymes, in the production of vaccines and cell- or tissue-based therapies. In general, these materials must be removed from the final product once the manufacturing process is complete. General Chapter <1024> *Bovine Serum* looks at quality issues related to the production, sourcing, and characterization of this group of ancillary materials along with risk-assessment and -mitigation measures associated with their use. In addition, General Chapter <90> *Fetal Bovine Serum–Quality Attributes and Functionality Tests* became official in the *USP–NF* in 2011. General Chapter <90> includes tests that determine the functionality of specific Fetal Bovine Serum (FBS) lots and aid in optimizing growth conditions of mammalian cell cultures in the presence of FBS.

Internationally Harmonized Chapters

As the discovery and manufacture of pharmaceutical products have become global endeavors, the pharmaceutical enterprise has looked for ways to minimize redundancies that impact regulatory and/or legal requirements for companies around the world and ultimately help to expedite delivery of medicines to patients. One activity that aids in overcoming such redundancies is the harmonization of standards by the Pharmacopoeial Discussion Group (PDG) – which consists of representation from the European Pharmacopoeia (EP), the Japanese Pharmacopoeia (JP), and the USP (the World Health Organization is an observer). Since its formation in 1989, the PDG has worked to eliminate or minimize industry's need to perform multiple tests and procedures and to comply with different countries' acceptance criteria for the same pharmaceutical article. Because excipients and general chapters affect a broad range of pharmaceutical articles, PDG's workplan has targeted 63

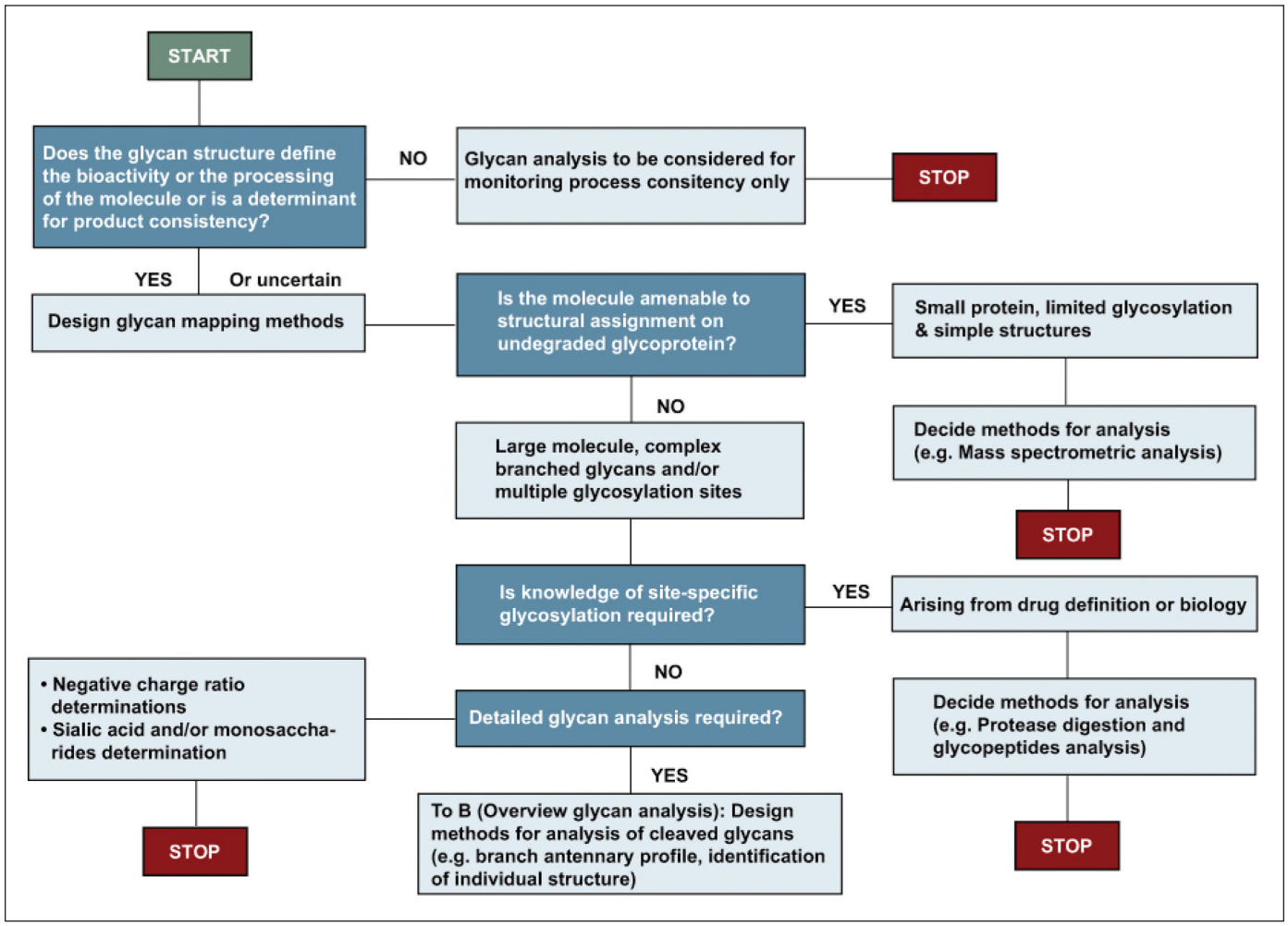

Figure 2. Decision tree diagram. (Source: U.S. Pharmacopeia)

excipients and 34 general chapters. Forty-one excipients and 27 general chapters have been harmonized to date.

Proposals for articles to be harmonized go through a public process similar to that in which the USP sets all standards, involving Expert Committee review and an open comment process. Overall, harmonization is a seven-stage process with PDG items being published at two stages – Stage 4 for "Official Inquiry" and Stage 6 for "Adoption." A coordinating pharmacopoeia takes the lead in drafting a proposal for an article to be harmonized and then shepherds it through the PDG process.

In the area of biotechnology products and biologics, six USP general chapters have been harmonized through PDG's collaborative efforts. Of those six, three are currently undergoing revisions: <1055> *Biotechnology-Derived Articles–Peptide Mapping*; <1056> *Biotechnology-Derived Articles–Polyacrylamide Gel Electrophoresis*; and <1057> *Biotechnology-Derived Articles–Total Protein Assay*. These three general chapters are at Stage 3, 3, and 2, respectively, in the PDG process. Among the general chapters mentioned in this article, portions of General Chapter <71> have been harmonized with the corresponding texts of the European and/or Japanese pharmacopoeias. Harmonized and non-harmonized (regionally-specific) texts are marked accordingly within the chapter for specificity.

Protecting Public Health – A Collaborative Effort

Keeping pace with the many changes in the pharmaceutical, regulatory, compendial, and technological sciences is no small effort. The USP relies on keeping its standards current through collaboration with industry, the FDA, and other regulators. As the manufacture, sourcing, distribution, and registration of pharmaceutical products are ever more global, collaboratively-created quality standards for medicines will continue to play a major role in the overall safety net designed to protect public health.

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