



PHARMACEUTICAL REFERENCE STANDARDS

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Presentation Abstracts

ASSESSORS VIEW POINT: EXPECTATIONS AND FINDINGS IN DOSSIER

Kowid **HO**, PhD

Agence Nationale Sécurité du Médicament, France

Jean-Louis **ROBERT**, Ph.D.

Laboratoire National de Santé, Luxembourg

The presentation will provide a brief overview about the type and use of reference standards and what assessors expect to find as information in an application file for marketing authorizations. It will address both chemical and biological reference standards.

It will also highlight future challenges like standardization of PAT methods (NIRs) or harmonisation of methods and standards in the biological area.

PHARMACEUTICAL REFERENCE STANDARDS AT FDA REVIEW AND CGMP

Mr Jon **CLARK**

Associate Director, Office of Pharmaceutical Science FDA-CDER

A brief review of FDA recommendations on reference standards for both review of applications and CGMP enforcement. The reference standard recommendations at the FDA are found in a number of different documents and tend to be consistent. These recommendations are demonstrated as being consistent with the international harmonized recommendations found at the International Conference on Harmonization.

USE OF REFERENCE STANDARDS AND QUALITY CONTROL: EXPERIENCES AND UNMET NEEDS

Dr Bernhard WOLF

Merckle GmbH, Germany

Reference standards are one of the key factors for consistently good quality of pharmaceutical products. They are used as primary or secondary standards for the quality control of active pharmaceutical ingredients (API), excipients and finished pharmaceutical products.

Quality control in our company is responsible for testing of 300 active pharmaceutical ingredients (API) and 500 other excipients in addition to more than 1400 receipts of pharmaceutical products produced by our self or 3rd party manufacturers. For the analyses of this huge number of different substances and products we are handling more than 2000 different reference substances. Wherever possible we are working with secondary standards which are established using pharmacopoeial primary standards as a reference.

In my presentation I will talk about sources of standard substances, storage conditions, labelling, shelf life, distribution and the establishment of sec. standards.

In addition I will present and discuss problems and unmet needs we are facing in daily work:

- Availability of Pharmacopoeial Reference Standards (CRS)
- Insufficient quantities of CRS
- CRS should be available before a new monograph comes into force to be able to implement the methods in the labs.
- Missing information of the form of APIs and impurities (HCl, Base, Hydrate etc.)
- Plausibility check (old versus new CRS) should be introduced during establishment of new CRS batches.
- Since the allocation of impurities is often problematic peak-identification mixtures in conjunction with sample chromatograms would be preferable.
- Unspecified impurities listed in the transparency list are not available as CRS. Allocation of these impurities in sample chromatograms and/or relative retention times should be published in the knowledge data base.
- Indicate which impurities are degradation - or by products. The latter do not have to be considered in the finished pharmaceutical products.
- Numbering of impurities: Identical impurities are used in different monographs. However, in one case it is Imp. A in another Imp. B. Harmonisation would be helpful and may reduce costs.

MANAGEMENT OF REFERENCE STANDARDS WITHIN SANOFI: EXPERIENCES AND CHALLENGES

Dr Joachim **ERMER**

Sanofi, Germany

Within Sanofi, chemical reference standards (RS) are centrally managed and coordinated by two Reference Standards Logistics (RSL) groups in combination with a decentralised analytical testing by so-called expert laboratories. These are either Quality Control laboratories, where the usual routine analyses of the RS or the related drug substance is performed, or Process Development laboratories in case of special techniques required. The RSL groups are responsible to appropriately store, maintain, coordinate the characterisation or retest and distribute the RS to internal as well as external functions requiring Sanofi-RS.

Linked to their routine use, four types of RS are defined: Primary Standards (PS) and Working Standards (WS) for content and identity determinations, Reference Materials (RM) for identification purposes and system suitability testing, and Official Standards (OS) for both, depending on the use defined by the compendia. Each RS must be traceable to either a compendial standard, or to a structural elucidation (PS) or verification (RM). OS are defined as batches identical to compendial standards.

The declared content of PS is calculated on an as is basis taking all determined components into account. The same procedure is applied for WS (if purity > 98%) in order to minimise the propagation of errors. The calculated result is verified vs. a content determination using a PS or compendial standard, or an absolute content method.

Some challenges are discussed, such as use of RS with various methods, for additional applications, and hygroscopic RS.

ESTABLISHMENT OF REFERENCE STANDARDS

CHINA'S POINT OF VIEW

Deputy Director-General, Bo LI

National Institutes for Food and Drug Control (NIFDC), China

In this presentation I would like to present the reference standards related laws and regulations in China, and then focus on the overall information and management of reference standards in China.

In China my institute is responsible for all the activities of national reference standards. I will introduce my institute's experiences and working procedure to the auditions in terms of the reference standards establishment and management.

ESTABLISHMENT OF REFERENCE STANDARDS: POINT OF VIEWS OF INTERNATIONAL AUTHORITIES

Mr Shigeki TSUDA

Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ)

In this rapidly globalizing world, where especially large amounts of drug substance migrate across national borders, how should we consider establishing the national Reference Standards (RSs) of such substances? Traditionally, the Japanese Pharmacopoeia (JP) has concentrated its efforts in developing the JP standards reflecting the whole picture of drug substances approved and used in Japan. The experts and the secretariat have hardly paid attention to the standards of other pharmacopoeias.

However, the world has changed so much in the sense that US FDA made clear in the Commissioner's report that about 80% of drug substances used in US came from abroad and even in Japan, more than half of drug substances are said to be imported. Apart from the large pharmacopoeias of Ph. Eur. and USP, there may be some who question the meaning and significance of setting up its own standards, including Reference Standards.

Although PDG (Pharmacopoeial Discussion Group) has worked hard for harmonisation for a long time, its scope of activity is limited to some general test methods and excipient monographs. In Japan, there is an idea, though only very few try to think, that JP can investigate the monographs of large pharmacopoeias and adopt them when possible. This approach will necessarily lead to the adoption of Reference Standards including Impurity RSs which JP has not yet introduced. Other expert mentioned the possible research on the harmonisation between JP and the pharmacopoeias of large newly industrialising countries.

Under these circumstances, JP, a pharmacopoeia with limited resources, may be facing the challenges different from those of larger pharmacopoeias.

ESTABLISHMENT AND MANAGEMENT OF KFDA REFERENCE STANDARDS

In-Kyu **KIM**, Ph.D.

KFDA, Korea

The Korea Food and Drug Administration(KFDA) is responsible to establish and distribute national reference standards for chemical drugs, biopharmaceuticals, narcotics and herbal medicines to other national agencies, pharmaceutical companies, research institutes and university labs.

Since 2003, 57 chemical reference standards and 54 narcotics reference standards have been established through the collaborative studies with academia. And the end of this year, 17 narcotic reference standards will be established.

As of national biological reference standard, Somatropin was established in 1998 on a trial basis. 1 to 6 items have been established each year and 37 items have been established until now.

In case of herbal medicine, 68 reference standards and 90 reference medicine plant materials (RMPM) have been established.

For the systemic establishment of reference standards, we are trying to set up the Center for the National Reference Standard. And also to promote the quality of reference standard, we plan to get on accreditation of ISO Guide 34(General requirements for the competence of reference materials producers).

INTERNATIONAL BIOLOGICAL STANDARDS: HOW TO FACE THE FUTURE CHALLENGES?

Dr Hye-Na **KANG**
World Health Organization, Switzerland

‘Setting norms and standards and promoting and monitoring their implementation’ are set out one of core functions of World Health Organization in the 11th General Programme of Work adopted by the World Health Assembly in May 2006. WHO has played a key role for over 50 years in developing WHO guidelines and recommendations to assure the quality, safety, and efficacy of biological products as well as establishing the WHO international standards/reference preparations necessary to standardize biological materials. The establishment of these two standards, i.e. written and measurement standards, are accomplished through the endorsement and adoption of each project by the WHO Expert Committee on Biological Standardization and through collaborative works with WHO International Laboratories, WHO Collaborating Centres for Biological Standardization, national regulatory authorities and individual experts.

There continues to be a strong demand for the work and activities undertaken by WHO, but reforms are being initiated by WHO to adjust to a new and constrained global economic reality. This requires WHO to continue to re-evaluate its ability to continue some of its current activities. Although WHO work on norms and standards is very critical to assist WHO Member States in ensuring the quality and safety of biological products, it should be better related to (a) setting more transparent prioritizing the biological products for which written standards should be developed as well as (b) ensuring their implementation into the practice of regions/countries. In addition, in order to reflect the increasing expectation in the development of WHO reference materials in innovative product areas, an increase of the overall capacity of the measurement standards programme will be required.

REFERENCE STANDARDS FOR RECOMBINANT BIOPHARMACEUTICALS: EXPECTATIONS AND LIMITATIONS

Adrian **BRISTOW**

National Institute for Biological Standards and Control, United Kingdom

The requirement for reference materials in the field of biopharmaceuticals has, until the present, been met by a combined approach of WHO international standards (IS) and local, regional and Pharmacopoeial Reference Materials (RM). Typically, with few exceptions, WHO IS's serve to support biological assays, and are essentially primary, defining the activity unit. Pharmacopoeial RM's, in contrast, support both physico-chemical analyses, and biological assays (with traceability to the WHO IS). Current developments however require a re-evaluation of the expectations and limitations of RM's available.

The increasingly global concept of Bio-similarity is essentially one based on comparison against a RM, which for regulatory purposes is usually considered to be a reference product. There have been calls for the bio-similarity concept to be supported by appropriate RM's, and appropriate activity is the subject of debate. RM's to define the quality of bio-similar products seem incompatible with regulatory requirements, and unlikely to be supported by the availability of materials. On the other hand, RM,so to define the performance of key physico-chemical tests such as size-exclusion chromatography and peptide mapping are not generally available, and may represent an opportunity for productive activity in this field.

Development in biopharmaceuticals also raise issues with respect to the provision of appropriate RM's. Monoclonal antibodies and derivative (eg pegylated) products will soon move into follow-on products phase, and approaches to the standardization of products with qualitatively similar but quantitatively varying activities need to be elaborated. In standardization, the "like against like" principle has tended to dictate standardization of products rather than tests, leading to the usual approach of separate RM's for separate molecules (eg separate RM's for Interferon alpha 2a and alpha 2b). The examples discussed above (biosimilarity, monoclonal antibodies, derivative products) are all areas where, for different reason, alternative or supplementary positions could be considered.

REFERENCE STANDARDS FOR CELL AND GENE-THERAPY PRODUCTS

- REGULATOR'S EXPECTATIONS

Paula SALMIKANGAS

Finnish Medicines Agency (Fimea), Finland

The rapidly evolved scientific knowledge has led to development of new innovative therapies especially for diseases and tissue / organ defects for which traditional therapies and medicinal products have not provided satisfactory outcome. The most recent paradigm was the introduction of a new class of medicinal products - the Advanced Therapy Medicinal Products (ATMPs = cell and gene therapy medicinal products, tissue engineered products) targeting, not only the metabolic, pharmacologic and/or immunological action but also the more complex interaction for regeneration, repair, replacement of human tissues.

The new regulatory environment (regulation 1394/2007/EEC, Annex I of Directive 2001/83/EEC, EMA guidelines) is slowly beginning to support the industry in issues related to ATMPs, but still the boundaries for regulatory requirements are under discussion. Manufacturing and quality control for ATMPs are not as straight forward as they might be for other pharmaceuticals. The use of reference materials is foreseen for all medicinal products in Directive 2001/83/EC and specifically mentioned for cell-based medicinal products in Directive 2009/120/EC (implementing Directive of Regulation 1394/2007/EC). In the corresponding guidance for gene and cell-based therapeutics, necessity of having a reference preparation especially for potency testing is recognised. However, due to various challenges and limitations, industry considers reference preparations for ATMPs difficult to establish or even useless (autologous cell-based products). Considering the risks related to ATMPs and the challenges of testing these complexed products, identification and characterisation of a suitable reference material is of utmost importance for all ATMPs. The possibility of having international reference standards for ATMPs may be a more challenging task, but should be considered and discussed.

REFERENCE MATERIALS FOR CELL-BASED MEDICINAL PRODUCTS: AN INDUSTRY PERSPECTIVE

Dr Christopher **BRAVERY**

Consulting on Advanced Biologicals Ltd, UK

The standard approach of developing a product reference material (RM) poses significant issues for cell-based medicinal products (CBMP). While in general terms it should be possible to prepare product RM for off-the shelf (allogeneic) products, it can be almost impossible where the product is patient-specific (autologous). Issues of concern to industry include (particularly for patient-specific products) difficulties obtaining suitable starting material to produce batches of RM, capacity of available clean rooms and the high unit cost of manufacture of cell products. While other RM's may provide a solution for physicochemical methods, the lack of a product RM is particularly problematic for bioassays, in particular potency assays. These issues will be explored through a hypothetical immunotherapy case study, focussing on the issue of identifying suitable RM's for its potency assay.

Selected recent publications

The Delivery of Regenerative Medicines and Their Impact on Healthcare (2010)

Chapter 19: A Catalyst for Change. Regulating Regenerative Medicines in Europe

CRC Press Editor(s): Catherine Prescott; Dame Julia Polak.

Regulating interface science Healthcare products: myths and uncertainties

J. R. Soc. Interface December 6, 2010 7 Suppl 6 S789-S795

PAS 83:2012 (BSI), Developing human cells for clinical applications in the European Union and the United States of America. Guide.

Free Download

CHARACTERIZATION OF PHARMACEUTICAL REFERENCE STANDARDS BY NMR

Dr Ian MCEWEN

Medical Products Agency, Sweden

When establishing a reference standard, its identity and purity has to be ascertained.

There are different techniques for both identity and purity tests. One of them is NMR spectroscopy which has since decades been an excellent technique for the identification of new substances.

Quantitative NMR (qNMR) is gaining acceptance as a method per se or as an orthogonal method. A major advantage of qNMR is that there is no need for a reference standard.

The concepts of qNMR will be presented. Three cases, a pentasaccharide and two peptides will be presented, showing among other things examples of how to determine the sequence of the units in the chain.

CHARACTERIZATION OF SECONDARY STANDARDS: KEY CHALLENGES ADDRESSED

Dr Matthew **BORER**

Eli Lilly and Company, USA

Pharmaceutical companies often establish Secondary Reference Standards for routine testing, as described in the International Conference on Harmonization Q7 document. Establishing Secondary Reference Standards results in a variety of benefits for manufacturers, including the ability to demonstrate global equivalency with one reference standard, control of the material supply, and the potential for reduced cost. However, there are many challenges associated with establishing Secondary Reference Standards that must be considered to assure that the desired benefits can be achieved and to prevent compliance gaps. This presentation will describe the key challenges such as the design of a sufficient characterization protocol, how to demonstrate equivalency to Official (Primary) Reference Standards, and problems that can result when there are differences between Official Reference Standards. These and other considerations will be combined to share a viable approach for managing an in-house Secondary Reference Standard Program.

ROLE OF WHO INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES (ICRS)

Dr Herbert SCHMIDT

World Health Organization, Switzerland

The International Pharmacopoeia, issued by the World Health Organization, is a global medicines compendium that focuses on priority medicines listed in the Model List of Essential Medicines and recommended by WHO specific disease programmes, for instance malaria, tuberculosis, HIV/AIDs and reproductive health. It is ready for implementation and is free for use by WHO Member States.

International Chemical References Substances (ICRS) are intended to serve as a benchmark for physical and chemical tests and assays described in *The International Pharmacopoeia*. Furthermore, they can be used for establishing secondary reference substances that are supplied as official, e.g. regional/national standards, to satisfy all local needs (also in hard-to-reach areas) and to reduce cost and delay in receiving reference material.

The International Pharmacopoeia aims to keep at a minimum the number of ICRS needed to perform analytical tests to promote the global applicability of its specifications and methods and to facilitate post-marketing surveillance testing of medicines globally, and in particular in low- and middle-income countries. Several examples of this concept are given in the presentation.

MATRIX REFERENCE MATERIALS

Professor Dr Hendrik **EMONS**

Institute for Reference Materials and Measurements (IRMM), Joint Research Centre, European
Commission

The characterisation of the composition of complex materials, derived mostly from naturally occurring matter, is an analytical challenge even if only a few components are of interest. This challenge is enhanced for the analysis of parameters, may they be structurally or functionally oriented, for matrix materials intended to be used as Reference Materials (RMs). In such cases the quantities of interest (the so-called 'measurands') have to be known at an appropriate level of accuracy for making the RMs useful in quality assurance measures of analytical laboratories.

The presentation will provide a brief overview on modern concepts for the reliable characterisation of candidate matrix RMs regarding defined elemental or organic components as well as operationally defined parameters. Aspects such as the definition of the relevant measurands, requirements on the performance characteristics of applied analytical procedures, establishing metrological traceability for the measurement results and assigning values for the target properties of the materials will be outlined with examples from IRMM's reference material activities.

HOW TO MONITOR REFERENCE SUBSTANCES FOR CONTINUOUS FITNESS FOR PURPOSE: NOVEL APPROACHES OR SOLUTIONS TO CHALLENGES?

Jane **WEITZEL**

Quality Analysis Consultants

USP Expert Committee Member

One component of USP's strategic plan is to develop and maintain the quality and availability of reference materials that support new and revised documentary standards based on advances in measurement science. This is supported by producing cutting-edge USP Reference Standards, including Certified Reference Materials (CRM), based on sound, scientific, metrological principles. It includes the use of metrological concepts such as Measurement Uncertainty (MU).

These metrological concepts are being applied to the Continued Suitability for Use (CSU) program. The USP Expert committee on Reference Standards has reviewed the CSU program and is making recommendations on the application of measurement uncertainty to the program. Some of the challenges and novel approaches being recommended will be presented. These include using the Test Accuracy Ratio (TAR) to assess initial fitness-for-purpose of a CRM and using uncertainty to define "small" and "insignificant" when assessing results obtained during CSU monitoring. As well, a data simulation program that has been developed to illustrate the use of TAR and uncertainty to CSU testing will be presented.

MANAGING THIRD PARTIES FOR THE PREPARATION AND MAINTENANCE OF REFERENCE STANDARDS

Mr Vaughn R. **STULTZ**

Eli Lilly and Company, USA

The appropriate implementation and maintenance of pharmaceutical reference standards is of critical importance in pharmaceutical analysis. In the current global environment, reference standard manufacturing and testing operations occur more frequently in third party labs or other facilities. There are often unique requirements for manufacturing and testing of reference standards, which can be different than drug product/drug substance manufacturing and testing. As the use of third-party manufacturers and testing laboratories increases, the need for a comprehensive plan to manage and support these potentially complex relationships must be developed and maintained. This presentation will describe a strategy for managing third party relationships associated with reference standard activities with focus on the benefits and detriments of the approach. These and other considerations will be combined to share a viable approach for managing an externally leveraged reference standard program.

Selection of Material for Reference Standard

Anu Bansal

Genentech, A Member of Roche Group, USA

The quality of reference standards used in the Quality Control Laboratories of Pharmaceutical industry is critical in ensuring that the product being released to the market has the similar quality attributes as those used in clinical setting and registered in the original product license. Hence, it is essential to have the reference standard that provides consistent and desired quality attribute during analytical testing. This assurance is achieved through careful selection, qualification and characterization and on-going stability of the reference standards used in QC analytical testing. While a lot of attention is paid to the qualification and characterization of reference standard as well as to its on-going stability, at times not enough attention is paid to the selection of material to be used for reference standard establishment. Reference standard lacking quality, purity or strength can lead to inaccurate analytical test results. Therefore, it is essential to carefully select material of desired quality, purity and strength for a reference standard manufacturing.

In this presentation I would like to discuss possible sources and desired quality for reference standards. Similarities and differences in reference standard requirements between chemical based pharmaceuticals and biotech drugs will be explored. Special emphasis will be given to the biologic or biotech pharmaceutical reference standards as the knowledge in this area is still evolving.

COMPENDIAL REFERENCE STANDARDS MANUFACTURING

Deputy Director-General, Bo LI

National Institutes for Food and Drug Control (NIFDC), China

In this presentation I would like to introduce two points: China reference standards evaluation and manufacturing.

Regarding with the reference standards evaluation, details of the whole process of reference standards establishment in China, for instance, candidate materials sourcing, value assigning, traceability, packaging, stability evaluation and monitoring, etc will be presented.

I also will introduce the manufacturing process of reference standards in my institute. The facilities, operation procedures, management guidelines, supply chain etc. will be majorly introduced and discussed.

STORAGE AND DISTRIBUTION OF PHARMACEUTICAL REFERENCE STANDARDS

Dr Robert **WATTERS**, Jr.

National Institute of Standards and Technology, USA

As research and regulations expand into human, environmental, and ecological systems, reference standards (RSs) that address these challenges have progressed from simple surrogates to more complex real samples of these systems. Accordingly, requirements for maintaining the stability of relevant RSs have transformed the reference material warehouse from simple controlled environments with shelves to a building filled with specialized refrigerators and freezers maintained at various temperatures. Controlled access, especially for bio-hazardous RSs, and environmental alarm systems are now standard features.

The technical complexity of RS development is well-recognized. As systems of measurement and requirements for traceability have expanded beyond national borders, the distribution of RSs has become a worldwide enterprise with its own regulatory complexity. Most regulations are driven by concern for safety and environmental sustainability goals. Successful transport while maintaining the integrity of an RS involves navigating a maze of local carrier, national, and regional requirements that often change without notice. Individual importers may have their own licensing requirements that require specialized documentation.

Many regulations are designed to address the transport of bulk chemicals and materials without regard to exemptions for very small quantities. Labelling requirements for small RS packages can be difficult to fulfil. A multi-agency effort to harmonize hazard analysis and labelling into a universally accepted standard has resulted in the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals. Although harmonization is the goal, implementation of GHS in different regions is resulting in some variances.

I will present the approaches used by the National Institute of Standards and Technology (NIST) and the United States Pharmacopoeia (USP) in dealing with these challenges, including looking ahead to OSHA's implementation of GHS.

GUIDES FROM THE ISO COMMITTEE ON REFERENCE MATERIALS (ISO/REMCO)

Professor Dr Hendrik **EMONS**

Institute for Reference Materials and Measurements (IRMM), Joint Research Centre, European
Commission

The main task of ISO/REMCO is preparing guides for the preparation, characterization, certification and use of reference materials (RMs) and the competence assessment of reference material producers. Therefore a system of ISO Guides was designed for providing RM producers, users and their assessors internationally agreed harmonisation documents. For instance, the Committee has issued ISO Guide 34 which describes the requirements for the quality management system and the technical competence of reference material producers (RMP) and is in its latest edition aligned with ISO/IEC 17025:2005 “General requirements for the competence of testing and calibration laboratories” to such an extent that it can be used as a stand-alone document for RMP accreditation.

As ISO/REMCO work items are very horizontal by nature and are covering a broad range of scientific disciplines and application sectors, networking and cooperation with other experts and organisations is a vital characteristic of REMCO's way of working. In that respect the official liaisons, such as with the Pharmacopeia Discussion Group, are very important. It is aimed to avoid duplication of efforts and, where possible, to share resources namely the limited number of experts. The presentation will outline the system of guidance documents and other deliverables and activities of ISO/REMCO as well as opportunities for further collaboration.

CHALLENGES ASSOCIATED WITH IMPORT AND EXPORT OF REFERENCE SUBSTANCES

Dr Steve **WOOD**

LGC, UK

Reference substances are used in the identification, purity assessment and assay of pharmaceuticals and considerable time and effort is expended in their preparation to ensure they are fit for their intended purpose. Part of the preparation process is to ensure the property values of the reference substances are stable for the period of validity stated by the producer. This period necessarily covers the transportation of the substance from the producer to the end user. Delays in the import and/or export of reference substances not only inconvenience the end user, but can also affect the integrity of the property value(s).

An earlier UK review identified 33 international regulations applicable to reference materials of which

12 can severely impact the import and export of reference substances. These regulations include chemical supply regulations, CITES, preferential trade, Re-Export USA, Dangerous goods transport and REACH. In this presentation I will give an overview of the key regulations, providing examples of their impact and suggesting ways to minimise that impact.

The presentation will draw heavily from LGC's experience of reference substance distribution and on the work of the International Organization for Standardization Reference Materials Committee (ISO REMCO) working group on reference material transportation.

FREQUENTLY ASKED QUESTIONS TO COMPENDIAL ORGANIZATIONS

Dr Shawn **DRESSMAN**, Vice President
United States Pharmacopeia, United States

USP receives over a thousand inquiries annually about USP Reference Standards. This brief presentation will highlight a few of the common questions from USP customers, and USP's answers for them. In addition, notable results from a recent USP Reference Standard user survey will be summarized.