



Message from the **Vice President—International, India**

## USP-IPC Annual Scientific Meeting Addresses Adulteration of Drugs, Quality Control in the Global Environment



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I am pleased to share with you the latest edition of the *USP-India Quarterly Update*. In this column, I will share recent developments as well as upcoming events and activities for the USP-India facility.

This quarter was an especially exciting one for USP-India as we hosted approximately 250 people for the USP-Indian Pharmacopoeial Commission (IPC) Joint Annual Scientific Meeting (ASM) in mid-February in Hyderabad. This was the third year USP sponsored this meeting with the IPC, and the eighth year in which USP has worked closely with Indian manufacturers and their trade associations to advance important and timely topics related to standards setting via this event. One item of note is that this year's ASM occurred almost on the third-year anniversary of the establishment of the USP-India facility (February 9, 2006). It is hard to believe that it has already been three years since USP-India's inception. On a personal note, I can say that it has been a real honor to work with all of you.

This year's ASM commenced with a keynote address by Dr. Valerio Reggi, executive secretary of the World Health Organization's International Medical Products Anti-Counterfeiting Taskforce (IMPACT), on "Globalization—Opportunities and Challenges." His presentation fed into a running theme of this year's meeting—how to assure high-quality medicines and foods in a global manufacturing environment. The ASM featured three tracks, the first of which was "Drug Substances—Adulterants,

Impurities." Throughout multiple sessions, presenters from USP, IMPACT, the U.S. Food and Drug Administration, and Indian pharmaceutical companies addressed recent episodes of commercial adulteration, including those of the blood thinner heparin and binding agent and sweetener glycerin, which have resulted in severe morbidity and mortality throughout the world. These events challenge our confidence in the safety nets that are supposed to protect us from substandard medicines and foods and reinforce the important role of quality standards, set by pharmacopeias, to prevent such occurrences.

Presenters and attendees discussed these incidents and their implications, including the unique roles of pharmacopeias, regulatory bodies, manufacturers, and forensics in assuring the drug supply; other articles that are at risk for adulterations; and key questions including how to find something you're not looking for, when to start looking for adulterants/contaminants, and where to look. These are obviously crucial issues that will shape all of our work in the future, and USP will continue to advance efforts with its collaborators in India and throughout the world to curb the risk substandard drugs and foods pose. One key takeaway from the meeting was that such efforts must include use of cutting-edge science

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Dr. Valerio Reggi of the WHO discusses the challenges and opportunities of globalization at the ASM.



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From the **CEO**

## Annual Scientific Meetings Offer a Home for Important and High-Caliber Scientific Deliberations

Roger L. Williams, M.D.

USP hosted its fifth Annual Scientific Meeting (ASM) this past September in Kansas City, Mo. The first North American ASM was held in Iselin, New Jersey, at the close of the 2000–2005 cycle and continued in San Diego (2005), Denver (2006), Tampa (2007), and recently in Kansas City (2008). The last in the cycle is planned for Toronto, September 23–25, 2009. These are remarkable events for USP, and in this CEO Column I'd like to give you some background and insight into how they come about. I also want to show how the North American ASMs lead into an equally remarkable series of ASMs around the world.

Over the years I have been especially delighted at the caliber of the scientific deliberations of our ASMs, not only in the United States but around the world. These are proceeding at the highest level, with strong input from our manufacturer stakeholders and many others.

most urgent science and policy priorities are and, of course, to gain input, just as did the open conferences of the past.

Let's look first at the recent Kansas City ASM. Planning for such a meeting occurs far in advance of the meeting itself, as meeting planners well know. The hotel was booked in August of 2006, and a planning committee composed of USP Council of Experts members, industry stakeholders, and USP staff began to discuss proposed meeting content. This is an arduous process, with many iterations before the agenda begins to settle down. USP works carefully to build multiple tracks into the ASM, so more topics can be covered, yet repeats some of these tracks so attendees won't miss key sessions. The big days finally do arrive and, from my perspective, they are a joyous time, when hundreds of members of the USP family—volunteers, staff, stakeholders, national and international visitors, and the press—arrive to engage in deliberations on compendial science. And the sidebar and impromptu meetings at an ASM can be as important as the sessions themselves. USP sponsors many outings and special events at ASMs for family and friends, and this year in Kansas City was no exception.

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and technology aimed at staying *ahead* of counterfeiters rather than chasing whatever the next contaminant will be—which is very difficult to predict. I will be providing more details about progress in this area through this newsletter and meetings in India.

The second track focused on “Drug Product Manufacturing and Control,” examining manufacturing



Attendees listened to international experts discuss key standards-setting topics.

standards such as Good Manufacturing Practices (GMPs) that have been put in place in many countries and regions over the last decade or longer to assure that a medicine maintains the same quality and performance characteristics as the clinical trial material on which safety and efficacy are based (includes initiatives such

as Quality by Design, GMPs

for the 21st century, and life cycle management), as well as modern measurement strategies that have occurred at the same time based on advances in the science of metrology. As presenters noted, these two approaches can work in tandem, but in practice have sometimes been working against each other. I have written about Quality by Design in this newsletter in the past, and will continue to keep readers up-to-date about future developments in this important discussion. Finally, the third ASM track was “Biologics and Biotechnology,” and featured several topics highly relevant to Indian manufacturers on biomolecules and mixtures. These included an update on current regulatory approaches to biosimilars in the United States as well as in Canada and Europe, updates on USP standards for bioassays, and new technological advances in the areas of product characterization, novel vaccines, and liposomal drug delivery systems.

Prior to the ASM, USP organized meetings of the USP-India Advisory Group, USP-India Stakeholder Forum, and USP Advisory Panel on Monographs and Reference Materials. These groups are all important to USP—comprising experts from the country that can offer valuable guidance, feedback, and expertise to the organization. Each group focused on items of immediate interest in their respective areas, as well as next steps.

The advisory group in India helps increase awareness of the importance of public standards through work with the Indian government, pharmaceutical companies, and manufacturing associations. The group, chaired by Dr. Roger L. Williams, USP chief executive officer, discussed progress on USP-IPC joint working group activities and opportunities and challenges that lie ahead. The USP-India Stakeholder Forum focused on what Indian stakeholders need and the role of the USP, followed by updates on USP Council of Experts' 2010–2015 workplan, which guides the standards-setting work of the organization, along with nominations for Council membership. Finally, the Monograph and Reference Standards Advisory Panel focused on its continuing work in monitoring and considering the scientific, technical, and policy issues associated with acquisition of monograph and candidate reference standard materials

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# Introducing USP's Certified Reference Materials Program

Next Generation of Quality Standards to Provide a Higher Degree of Confidence in Measurements

In September 2008, USP released its first Certified Reference Material (CRM), Dextromethorphan Hydrobromide. That was about a month after becoming the first global pharmacopeia to receive International Organization for Standardization (ISO) accreditation as a producer of chemical CRMs. The release represented the next generation of exceptional, quality reference standards from USP that pharmaceutical manufacturers could begin utilizing to help ensure improved information for measurements of their products when meeting requirements set forth in the *United States Pharmacopeia–National Formulary (USP–NF)*. Each CRM comes with a Certificate of Analysis containing data on certified property value, uncertainty value, and for the first time an expiration date (period of validity), all of which aim to produce a higher level of trueness and traceability in measurement.

Additional CRM features and applications include:

- Metrologically based testing and statistical analysis;
- Traceability to an accurate realization of the unit in which the property value is expressed;
- Trueness and traceability of CRM measurement system helps with consistency and comparability of measurement data among labs and over time;
- Data for calibration, validating processes, comparison and value assignment;
- Values meet ISO 17025 documentation requirement for testing labs; and



- CRM program meets the requirements of ISO 17025 and ISO Guide 34 for Reference Materials Producers (RMPs).

To learn more about this program, USP Chief Metrology Officer William Koch, Ph.D., explains some of the key aspects of CRMs:

## When did the CRM initiative at USP begin?

Planning for the CRM program started in 2005. Analytical testing using collaborating laboratories began in 2006. Since then, I'm proud to say USP has become the first global pharmacopeia to produce CRMs, and in doing so, is meeting the demanding measurement needs of the industry, which are always increasing.

## Why is USP pursuing the production of CRMs?

Recognizing the need to advance state-of-the-art pharmaceutical testing to be consistent with ISO guidelines used by nearly all industries, CRMs seemed to be a necessity. USP has always produced quality reference materials and the CRMs are a further improvement in the final product by advancing the metrological science of our reference standards; the purpose of the CRMs is to provide a higher degree of confidence in the analytical measurement. This increased level of confidence then leads to more accurate decisions regarding product specification and acceptance limits.

## Why is a stated level of uncertainty so important?

All measurements are comparisons, and there is always some uncertainty when making such comparisons. Knowledge of this uncertainty (or variability) helps one decide if the measurement is adequate to meet the needs. With the stated level of uncertainty, the user has the ability to propagate uncertainty to the final result, and is able to make meaningful comparisons of measurement results. If

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Moving beyond the Kansas City meeting, USP's ASMs are designed to springboard into other science meetings in different regions of the world. The remaining scientific meetings in 2008 were in China, then in Jordan and Cairo. In 2009, the first meeting took place in India, to be followed by Europe and Central America before starting the cycle again in September 2009 in Toronto. ASMs held outside North America are adjusted carefully to meet national and regional needs. USP always tries to work with a hosting organization to make the meeting a success. Each meeting is a little different—and that, of course, is what makes the follow-on meetings as exciting as the primary one in North America.

Next year, we hope to make the final ASM of the 2005–2010 cycle a huge success by partnering with our friends to the North. Canada is not just a neighbor—it is a close partner in USP's standards-setting activities, with 23 representatives participating as Expert Committee or Advisory Panel members. Canadian scientists and other stakeholders help USP in many other ways as well, so I'm

especially delighted that we will leave the United States for the beautiful city of Toronto.

As I close, I have to emphasize something very important to USP and to its Board of Trustees. The new Board of Trustees' Strategic Plan, recently finalized, was presented to attendees at the Kansas City ASM by Dr. Duane Kirking, speaking on behalf of the Board. That Strategic Plan emphasizes that USP is a science-based standards-setting organization, and it is the compendial science undergirding our standards in USP's five compendia that is the core of our ASMs. Over the years I have been especially delighted at the caliber of the scientific deliberations of our ASMs, not only in the United States but around the world. These are proceeding at the highest level, with strong input from our manufacturer stakeholders and many others. It is a true joy to listen to these discussions and to see thorny scientific issues move from debate to resolution. For this, I express my deep thanks and appreciation to all involved—those who plan, those who speak, and those who attend. 🧪

## USP Hosts International Food Ingredients Issues Workshop

USP's first International Food Ingredients Issues Workshop was held on October 15, 2008, at USP headquarters in Rockville, Md. About 120 attendees from around the world had the chance to listen, discuss, and present the pressing issues regarding food ingredient standards and practices at this workshop.

The sessions covered country/region-specific presentations from the United States, Canada, Europe, South America, Mexico, the Middle East, China, Australia and Japan. Scientific topics that were discussed over multiple presentations included biotechnology, genetically modified organisms (GMOs), allergens, supplements, and active packaging.



Attendees heard experts speak on food ingredient standards and practices.

The food-related issues found in current international headlines, such as contamination and adulteration, were also frequently addressed throughout the workshop.

“Melamine is an issue of adulteration, not an illegal use,” said Junshi Chen, M.D., from the National Institute of Nutrition and Food Safety with the Chinese

Center for Disease Control and Prevention. He spoke on food ingredient regulations in China, saying that current practices in general are acceptable and in compliance with international practices. Chen did say there was a lack of specification for almost half of the food additives approved for use and that few specifications for flavors and a list for packaging materials have not been updated in about 10 years. He ended by saying that there are food safety problems in China because of the rapid development of China's economy.

Vincent Hegarty, founding director of Michigan State University's Institute for Food Laws and Regulations and an expert in setting up food standards and agencies in the Middle East, summed up the meeting by noting that, “A majority of countries still have overly fragmented, less developed, or outdated systems for food control.”

USP will host another Food Ingredients Issues Workshop in 2009. Presentations from the 2008 meeting are available at [www.usp.org/meetings/agendas/foodIngredientsWorkshop2008-10-15.html](http://www.usp.org/meetings/agendas/foodIngredientsWorkshop2008-10-15.html).

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it is assumed that the variability of a standard is zero, this assumption will underestimate the total measurement uncertainty and could lead to a wrong decision. A CRM becomes very helpful here because it includes an uncertainty value, as well as a statement of traceability (that is, a declaration of how the measurement was made and which standards were used to support the measurement). Hence, the three components inherent in a CRM and provided either explicitly or implicitly in a Certificate of Analysis for a CRM are: 1) the property value, tested and certified to be true, 2) the uncertainty of this property

## upcoming courses

### VALIDATION OF COMPENDIAL PROCEDURES

Mumbai: March 17, 2009

Bangalore: March 18, 2009

### GOOD MANUFACTURING PRACTICES IN PHARMA

April 2009 (Exact date and location to be determined)

### EFFECTIVELY USING USP-NF

April 2009 (Exact date and location to be determined)

Dates and location are subject to change. Please call customer service in India at +91-40-2348-0088 for updated information.

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(drug substances, active pharmaceutical ingredients, and/or impurities) for entry into official status of the *United States Pharmacopeia* compendium. Suggestions and contributions from the industry are welcomed in this area.

Following the ASM, experts from various biotechnology companies gathered for the Biotech Conclave and the Biologics and Biotechnology Advisory Panel meeting, during which USP's Dr. Williams presented his vision of the proposed interaction between Britain, China, and India to elaborate standards and harmonize units for biological products. The panel has made progress in the submission of the insulin cell-based assay. Further, the panel has decided to recommend two products, erythropoietin (EPO) and granulocyte-colony stimulating factor (GCSF), to develop bioassay methods, specifications, and collaborative testing.

The month of February also included two pharmacopeial education courses—“Microbiological Testing and Bacterial Endotoxin Testing” and “Effectively Using Reference Standards.” The courses were taught by USP staff Drs. Radhakrishna Tirumalai and Shawn Dressman, respectively. USP is committed to conducting education programs in India, which are designed to be interactive learning experiences to help participants understand and apply USP standards and achieve conformances. Upcoming courses are listed in this newsletter.

As you can see, this was an eventful quarter full of international collaboration. I am happy to share more information on any topics discussed in this column. Please feel free to email me at [kvs@usp.org](mailto:kvs@usp.org).

value, and 3) the path of metrological traceability. These three components, taken together, add confidence in and assurance to the subsequent measurements using the CRM.

### Are there plans for additional CRMs to be released?

USP is committed to producing CRMs, and you can expect to find more available to purchase each year. USP has developed criteria for the selection of future CRMs, and is working to identify a list of candidates.

For additional information about USP Reference Standards and CRMs, visit: [www.usp.org/referenceStandards](http://www.usp.org/referenceStandards).