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*Meeting Report*

# Enhancing Value of Global Pharmacopoeia Standards: Summary of Joint USP-MHLW/PMDA Workshop

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**USP and MHLW-PMDA held a joint workshop on September 10-11, 2024 in Tokyo, Japan[1]. This workshop was organized by the United States Pharmacopeia (USP) in collaboration with Japan's Ministry of Health, Labour, and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). This workshop aimed to address critical issues in pharmaceutical quality and foster international collaboration between our two organizations and critical stakeholders. The workshop covered a range of topics, including the harmonization of standards with a specific focus on the inaugural pilot between USP and JP on the harmonization of a drug substance monograph and a drug product monograph, as well as on ICH Q2(R2)/Q14. Participants discussed advancements in quality testing, particularly for high-risk excipients like ethylene glycol and diethylene glycol, and shared insights on managing contamination issues. The event also explored the integration of emerging technologies such as quantitative nuclear magnetic resonance (qNMR) and the challenges associated with complex generics. Overall, the USP-MHLW/PMDA joint workshop underscored the commitment of both organizations to advancing public health through the development and harmonization of high-quality standards. By fostering collaboration and innovation, the workshop aimed to enhance the safety, efficacy, and accessibility of medicines globally.**

**Key words** pharmacopoeia, standards, harmonization, USP, PMDA

## OPENING REMARKS

*"USP Overview and Global Impact"* by Ron Piervincenzi, CEO of the United States Pharmacopeia (USP)[2]

Dr. Piervincenzi provided a comprehensive look at the organization's mission, key initiatives, and future directions. USP is an independent, scientific global non-profit organization founded in 1820 that is dedicated to improving global health through public standards and related programs that ensure the quality, safety, and benefit of medicines and foods.

**Mission and Vision** USP's mission is centered on enhancing global health by developing and maintaining public standards for medicines, food ingredients, and dietary supplements. These standards are crucial for ensuring the quality, safety, and efficacy of these products. As a non-profit organization, USP operates with a global perspective, employing over 1,300 staff members globally to support its mission.

**Key Initiatives** One of USP's primary initiatives is to foster greater availability of the world's most relied upon medicines, and to increase access to quality medical products through the development of quality standards for pharmaceuticals, biologics, dietary supplements, and food ingredients. This work is essential to address emerging challenges and incorporate scientific advancements. Fostering local manufacturing, strengthening regulatory and laboratory systems, optimizing resources and financial structures for sustainability, and strengthening medical product quality assurance systems are key drivers for USP's mission. Dr. Piervincenzi also highlighted the activities of the USP Convention Sectors and Chapters. The purpose of these important engagements is to share information, learn from each other, provide insight to USP, collaborate on priority topics, and engage with regional chapter members and shared interests.

**Global Impact** USP's impact is truly global, as it collaborates with international partners and regulatory bodies to harmonize standards and improve global public health. Dr. Piervincenzi highlighted the strong partnership with PMDA and MHLW through our joint activities with the Pharmacopeial Discussion Group, which along with the European Pharmacopeia and Indian Pharmacopeial Commission works on the harmonization of excipient monographs and general chapters. Bilateral cooperation through executive exchange partnership and a prospective harmonization project was also discussed.

**Future Directions** Looking to the future, USP is exploring the integration of emerging technologies such as artificial

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intelligence. These technologies have the potential to revolutionize pharmaceutical manufacturing and regulation, making processes more efficient and reliable. USP is also focusing on environmental sustainability, ensuring that the development and implementation of standards contribute to social well-being. This includes efforts to reduce the environmental impact of pharmaceutical production and promote sustainable practices within the industry.

**Conclusion** In conclusion, the 2025-2030 strategic priorities for USP focus on increasing the availability of quality-assured medicines, strengthening the resilience of the global pharmaceutical supply chain, expanding access to biologics, accelerating the adoption of digital tools for quality assurance, and enabling more environmental sustainability across the pharmaceutical lifecycle.

## OPENING REMARKS

*"PMDA Updates and Recent Cooperation with USP"* by Hiroshi Suzuki, Executive director, Pharmaceuticals and Medical Devices Agency (PMDA)[3)]

This presentation provided a comprehensive overview of the PMDA, international initiatives and collaboration with the USP. PMDA is a Japanese regulatory agency established in 2004. Their obligation is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices. PMDA conducts scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety. PMDA is also responsible for providing relief compensation for sufferers from adverse drug reactions and infections by pharmaceuticals or biological products.

**Purpose** The PMDA established a purpose for the 20th anniversary as a "New Start of the PMDA." The purpose is as follows. We, PMDA continue to create "Tomorrow's Normal" together, as a "life platform" that supports everyday life, where everyone can feel peaceful and can lead vibrant and healthy lives, by PMDA's "Safety Triangle" of review, safety and relief, with "intelligence" weaved through science and information, and with "human resourcefulness" accompanying and bringing the world and the future into harmony.

**Key Initiatives** The PMDA launched its fifth mid-term plan this year. The first of the PMDA's mid-term plans is to further improve and upgrade the quality of each operation through regulatory science. This includes the consultation and review for the innovative products, appropriate follow-up of safety measures, and the development of emergency response systems for pandemics, etc. The second is to strengthen international activities and contributions. Specifically, Regulatory support and disseminate regulatory information are provided to overseas companies to development of innovative products in Japan. The third is strengthening PMDA governance and professional personnel.

**International Initiatives** The PMDA participates in ICH, ICMRA, PIC/S and PDG as major international cooperation and coordination frameworks. These frameworks are considered critical to ensure fast and stable access to products that are quality-assured, effective and safe. In addition, PMDA has established overseas offices contributing to innovative medicines access in close collaboration with PMDA Tokyo Headquarters. In July 2024, it established an Asia office in Bangkok, Thailand. The office is also scheduled to be opened in Washington, D.C., U.S.A.

**Collaboration with USP** In addition to the PDG cooperative relationship, USP and MHLW/PMDA signed Memorandum of Cooperation (MOC) and Confidentiality Arrangement in September 2016 and June 2017, respectively, with the aim of further strengthening relations and promoting cooperation. As part of this MOC activity, USP and MHLW/PMDA strengthened their collaboration. First, a prospective harmonization pilot of pharmacopoeial standards for drug substances and drug products is launched. In the future, the possibilities and challenges of expanding the international harmonization of pharmacopoeial standards for drug substances and drug products will be discussed, and based on the lessons learned, further contributions will be made to the harmonization of pharmacopoeia and international cooperation with the pharmacopoeia in each region. Finally, the USP and PMDA jointly hold workshops. PMDA intends to continue to cooperate with the USP, focusing on harmonization with the pharmacopoeia.

**Conclusion** In conclusion, the presentation highlighted the 20th anniversary of the PMDA as the "New Start of the PMDA" and the enacted purpose, "Making everyone's lives brighter together" PMDA has directed to further improve and upgrade the quality of each operation through regulatory science, and to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices in order to provide citizens and healthcare professionals with rapid access to safer, more effective medical products, and to ensure their safe use. Since the signing of the MOC with the USP in 2016, PMDA and USP have been cooperating in the field of pharmacopoeia, and it was stressed that the cooperation based on the MOC would be expected to further develop the cooperative relationship with the USP in the future.

## SESSION 1: ADVANCING HARMONIZATION OF STANDARDS

### Topic A: ICH-Q14 and ICH-Q2

"*Q2(R2)/Q14:Summary and JP perspective*" by Hiroko Shibata (National Institute of Health Sciences (NIHS))[4)]

In this presentation, the background and overview of ICH Q2(R2)/Q14 were explained, and the perspective on the incorporation of ICH Q2(R2)/Q14 into JP was presented. Q2 did not cover recent analytical procedures such as Near Infrared spectroscopy and Raman spectroscopy, so the lack of common understanding between applicants and reviewers regarding adequate validation data for submission brought repetitive information requests and responses resulting in the delay of application approval. In Q2, the purpose of the revision was to provide information on validation using multivariate analysis and to guide various analytical procedures during the life cycle. In addition, there have been no guidelines for analytical procedure development in ICH guideline. Loss of opportunities for applicants to present scientific basis for a flexible approach to changing analytical methods after approval or when non-conventional analytical procedures were employed. Thus, Q14 aimed to provide a guide to risk-based approaches for developing and maintaining analytical procedures including multivariate analytical procedure and real time release testing (RTRT), and how the tools presented by Q12 can be applied to post-approval change management of analytical

procedures.

The revision of Q2 added the following new items: general considerations for analytical procedure validation, validation during the life cycle of analytical procedures, demonstration of stability-indicating properties, considerations for multivariate analytical procedures, appendix 1: selection of validation tests, and appendix 2: illustrative examples for analytical techniques. The Q14 provided a minimal approach and enhanced approach to the development of analytical procedures. All for lifecycle management and post-approval changes, a diagram of the risk-based approach for identification of ECs and the reporting categories for associated changes in the enhanced approach was also provided.

The incorporation of Q2 and Q14 into the JP was discussed from various perspectives in the presentation. JP has been actively incorporating ICH guidelines as indicated in the basic principles for the preparation of JP19 that includes the introducing the latest science and the further promotion of internationalization. General test 2.00 chromatography listed in JP18-1 shows the extent to which the various parameters of a chromatography procedure may be adjusted without fundamentally modifying the pharmacopoeial test procedures in the monograph, which corresponds to the prior knowledge in Q14. When considering the life cycle of an analytical method, the knowledge accumulated at each stage differs, so it is important to conduct appropriate experiments and evaluations according to each stage of the life cycle. Shibata emphasized that the JP general information chapter <G1-5-181> summarizes the points to be considered at each stage.

In conclusion, Shibata's presentations showed that ICH Q2 (R2) and Q14 describe the development and validation activities during the life cycle of analytical procedures, and that the concepts or elements described in Q14 have already been partially incorporated in JP. The JP general chapter for validation of analytical procedures may not necessarily match ICH Q2 (R2) for each objective, but some new items could be incorporated into JP. As future challenges, when analytical procedures developed using the enhanced approach described in ICH Q14 are incorporated into JP, it is necessary to consider whether information on the performance of analytical procedures should be indicated in the monographs of the Pharmacopoeia. Shibata finally gave the expectation that JP becomes a pharmacopoeia that can incorporate the latest technologies and present ways to utilize those new technologies, given the differences in the nature and role of the JP and ICH guidelines.

"*ICHQ14 and USP Chapter <1220>: Historical perspective and the path forward in Analytical QbD*" by Horacio Pappa from the United States Pharmacopeia (USP)[5]

In this presentation, Pappa compared ICHQ14 with USP <1220> and introduced the historical perspective and the path forward in AQbD in detail. The AQbD is "framework of analytical procedures that holistically incorporates all the events that take place over the procedure life cycle that are designed to demonstrate that a procedure is and remains, fit for the intended purpose.". AQbD is "systematic approach that begins with predefined objective (ATP) and emphasizes analytical procedure understanding and control based on sound science and quality risk management.".

**USP GC <1220> and ICH Q14** Pappa explained that analytical procedure development has shifted from broader development to analytical target profile and knowledge management, and emphasized the importance of what profiles are managed, whether they fit the intended approach, and whether they are applicable to existing ones. The analytical target profile (ATP) in USP general chapter (GC) <1220>: *Analytical Procedure LifeCycle* is a prospective description of the desired performance for an analytical procedure that is used to measure a quality attribute. ICH Q14: An ATP consists of a description of the intended purpose, appropriate details on the product attributes to be measured and relevant performance characteristics with associated performance criteria. Pappa highlighted that the ATP is the driving force behind the selection of analytical procedures.

Relevant prior knowledge can assist with the selection of technology and development activities. This includes the following. Physical and chemical properties of the analytes, information in the scientific literature, existing procedures for the analysis of the similar material attributes, the availability of any relevant analytical technology and platform analytical procedures, and other relevant operational requirements such as instrumentation setup and sample preparation. Additional knowledge should be actively managed throughout the product lifecycle.

For Quality Risk Management (QRM), in ICH Q14, risk assessment is typically performed early in analytical procedure development by a risk assessment tool described in ICH Q9, is repeated when more information is available, and can be used to establish a procedure control strategy. In USP GC <1220>, QRM activities can be applied to assess the proposed procedure conditions and identify appropriate control on the analytical procedure parameters. QRM activities can also identify, reduce or eliminate the major sources of bias and variability.

This presentation introduced that the Analytical Procedure Performance Qualification (USP GC <1220>) evaluate the procedure to determine if it can consistently generate reportable values that occur in the stage 2 of the life cycle and meet the defined ATP and if it can consistently generate reportable values that meet the defined ATP. Analytical Procedures Validation (ICH Q14) explains that the goal of development is to obtain an analytical procedure fit for its intended purpose. The attribute of the analyzed material over the reportable range with the required specificity/selectivity, accuracy and/or precision should be measured. Generally, data from the development phase can be used as validation data for the related analytical procedure performance characteristics and does not need to be repeated.

Monitoring analytical procedures during use and confirming that ATP criteria are still being met is involved. Effective monitoring of analytical procedure provides ongoing confidence that the reportable values generated are fit for purpose. Risks should be assessed for the impact of changes in analytical procedures to determine the appropriate activities required. In addition, appropriate change management approaches and documentation should be used when changing procedures.

In summary, Pappa's presentation provided that analytical procedure development is sifted from wide-ranging to analytical target profiles and knowledge management, explaining the importance of what profiles are managed and fitted to the intended approach and what is applicable to existing procedure. Pappa stressed that the concepts of ICH Q14 and USP GC <1220> are the same and that they should be actively managed throughout the product life cycle.

Two presentations on ICH Q14 highlighted the critical importance of life-cycle management. Shibata's presentation stresses the importance of reflecting the latest science in pharmacopoeias and appropriate control strategies at each stage of the product life cycle. Pappa's presentation detailed the importance of ATP management and the comprehensive USP approach, including QRM activities. These efforts demonstrate the importance of incorporating new quality standards into the pharmacopoeia.

**Topic B: USP-JP Prospective Harmonization**

"*Overview of Pharmacopeial Convergence and Harmonization: Pilot for USP- JP Prospective Harmonization Project*" by Kevin Moore from USP[6]

This presentation outlined the significance of the pharmacopoeial harmonization, USP-JP prospective harmonization pilot project, and the outlook for the future. Stressing the value of effective pharmacopoeial collaboration by promoting access to quality medicines, increasing the value of quality standards, facilitating global access to industrial technologies, prioritizing the balance between current paradigms and future trends, and enabling global pharmaceutical trade.

With the globalization of the supply chain, the importance of pharmacopoeial harmonization is increasing today. Country/region have its own regulations thus, when pharmaceutical products approved in one country/region and sold in other country they must meet the quality standards recognized in those countries/regions and must conduct similar tests in each country/region, which may be redundant. Pharmacopoeia harmonization can align test methods and specifications to common quality standards, eliminating the need to duplicate tests.

**Overview of USP-JP Prospective Harmonization** A memorandum of Cooperation was signed in September 2016. In May 2023, JP and USP identified potential candidates. In June 2023, Dapagliflozin Tablets monograph was selected as a pilot product. The USP API monograph was already harmonized with EP, and JP considered adopting it. The JP, USP and innovator held a meeting in August 2023 and the press release for the pilot was released in October 2023. After three touch points, the proposal monograph was published for public consultation on PF50 (5) on September 3, 2024.

The goal of the pilot is alignment of test methods and limits, but texts do not have to be identical. The monograph preparation process for the pilot is followed by respective internal processes for monograph elaboration and its work is initiated by collaboration with the innovator. Moore emphasizes that the advantages of prospective harmonization include sharing experience and knowledge among the innovator, JP and USP, saving cost and time for manufacturers, and elaborating similar standards by working together based on the same documents and samples.

The next step is to identify future eligible products. Further harmonization of monographs of the JP and USP will have a positive impact on public health improvements. The challenge is that most formal harmonization efforts are conducted exclusively by the pharmacopoeia, and early engagement of industry and regulators is important to publish more harmonized standards. In conclusion, Moore's presentation provided the value of pharmacopoeial harmonization and the importance of bilateral harmonization pilot projects. It aims to promote global integration of pharmaceutical quality standards by leveraging its own resources and capabilities through collaboration to increase patient access to quality medicines, considering changing the stakeholder landscape and implications.

"*Challenges on USP-JP harmonization from Pilot Project on drug substances and drug products monographs*" by Tatsuo Koide from the National Institute of Health Sciences (NIHS)[7]

This presentation provided a detailed overview of USP-JP harmonization, challenges in harmonization, and differences between USP and JP monographs. Of the JP expert committee, the review of chemical medicines monographs is examined by the Expert Committee on Chemicals. In the pilot project for bilateral harmonization, WG of Monograph Harmonization was established under the Expert Committee on Chemicals.

**Overview of the Pilot Project** Dapagliflozin propylene glycolate hydrate and its tablets were selected for the project. The adaptation of USP API monographs has been investigated. The monograph of the drug product was developed through information exchange with USP. The reference standard monographs were excluded in the pilot. After the committee's examinations, the draft of the monograph has been under public consultation since September 2024.

**Challenges on USP-JP Harmonization** Major issues in the USP-JP harmonization included (1) differences in the description of operations, (2) application of 2.00 chromatography, and (3) identification tests.

(1) For the procedure for preparing solutions, the USP describes the concentration, but the JP generally specifies the amount of the substance and the volume of the solvent. JP accepts the description of concentration like USP and adds the remarks "Operate the tests accurately and precisely if required.".
(2) As this was the first case that the JP "2.00 chromatography" was introduced in the monograph, the WG discussed what and how to review the validation data for acceptance. In addition, notification regarding validation for some changes to chromatographic conditions will be published in the future.
(3) In the monograph preparation, UV spectroscopy has been conventionally included as identification in the JP, but in this project, the retention time of the major peak and IR spectroscopy were added instead of UV spectroscopy.

**Differences between USP and JP Monographs** In the drug substance, the system suitability for assay and purity test is different between USP and JP. In the case of drug products, the content volume, IR test method, disintegration test and system suitability for assay and purity test are different.

In conclusion, Koide's presentation outlined the harmonization of USP-JP and the challenges in the harmonization project in detail. Although several challenges in the pilot have been identified, they have been resolved one by one, with monographs harmonized, and highlighted their achievements in reaching public consultation. By addressing these challenges, USP and JP aim to harmonize more APIs and drug products monographs and ultimately contribute to reducing stakeholder burdens and improving global public health.

"*AstraZeneca's Perspective on the Prospective Harmonisation pilot*" by Ryo Kondo (AstraZeneca), Edward Bush (AstraZeneca)[8]

The presentation highlighted the benefits and challenges of a bilateral harmonization pilot project from a stakeholder perspective. A bilateral project was approached in May 2023, and a kick-off meeting was held in August 2023. After that, a team that was exclusively responsible for compilation of the data package to support the development of the drug substance and drug product monographs was established in AZ. The JP Expert Committee on Chemicals, Working Group was established in September 2023, and a press release was posted on PMDA website in October 2023. This enabled AZ to accelerate preparations for the submission of documents, and in conjunction with the request for documents in October 2023, documents for review were submitted in December 2023 and January 2024.

Pharmacopoeia lists essential pharmaceuticals and provides quality information and explanatory guidance. Pharmacopoeia also demonstrates official standards for appropriate pharmaceutical quality, support innovation, and emphasize consistency in global pharmaceutical quality assurance. The harmonized monographs also explained the importance of leading the development of a global pharmacopoeia standards that reduces the burden on their adoption, simplifies the review process, disperses risks and ensures a more stable supply of products.

Regarding the effect of monographs on drug product release, it was explained that compliance with pharmacopoeial quality standards is legally mandated, the burden of change documentation and implementation is adjusted, and resource allocation for monograph development throughout the product life cycle is essential.

Major challenges include differences in UV identification, IR identification, chromatography <2.00> adoption, system suitability, and dissolution testing between JP and USP. It was also pointed out that translation is time-consuming and cannot be prepared in a timely manner.

Advantages of prospective harmonization were stressed for JP and USP to share the same documents and data, to facilitate harmonization of technical requirements and facilitate direct communication with regulators, to encourage early monograph adaptation, to reduce the burden of compendial tests, to expand the convergence of pharmacopoeial standards for API and drug products contributing to global harmonization.

In conclusion, the necessity and importance of pharmacopoeial harmonization were emphasized. It was explained that addressing these issues is expected not only to reduce the burden on stakeholders but also to contribute to ensuring the quality of pharmaceuticals worldwide.

The three presentations on harmonization of drug substances and drug product monographs in the pharmacopoeia showed the advantages and challenges of harmonization. Moore's presentation emphasized that harmonization reduces the burden on manufacturers and contributes to access to quality pharmaceuticals, and Koide's presentation details the differences between USP and JP monographs and the challenges of harmonization. Presentations by Kondo and Bush explained the significance of the pharmacopoeia, the need for harmonization, and industry challenges. These efforts demonstrate the importance of harmonization of pharmacopoeial standards for drug substances and drug products.

**Panel Discussion** Panelists: Hiroko Shibata (NIHS), Horacio Pappa (USP), Kevin Moore (USP), Tatsuo Koide (NIHS), Ryo Kondo (AstraZeneca), Edward Bush (AstraZeneca); Moderator: Hikoichiro Maegawa (PMDA).

The discussion started with a question about the issues of international harmonization in ICH harmonization activities and bilateral monograph harmonization activities. Panelists noted differences in regulatory requirements, particularly post-approval change and pharmacopoeial regulatory requirements; the importance of understanding the scope of ICH and PDG because of its different objectives; differences in operations, data submission methods, and communication among regulators; and different harmonization processes.

The session then shifted to the solutions for the issues raised. The panelists noted not losing sight of the essentially important points; not losing sight of the particularly important scientific points; understanding the background and exploring concerns for harmonization; considering a more efficient harmonization process; using platforms and sharing data in real time.

The panelists were asked what initiatives would be expected. Panelists noted increasing the items for the harmonization project.

A participant at venue asked panelists if there could be harmonization in the three areas (EU, US and Japan) by adding EP to this framework. Panelists commented that the benefits need to be discussed because of the complexity of the harmonization process.

In summary, the discussion provided it has been important to promote international harmonization, to understand the differences in regulations among themselves, and to seek the most effective harmonization process.

## SESSION 2: EXCIPIENT QUALITY

"*Testing of Ethylene Glycol and Diethylene Glycol in High-risk Excipients*" by Catherine Sheehan (USP), Jenny Liu (USP)[9]

In this presentation, Sheehan and Liu explained the importance of excipients quality, the issues and responses to DEG/EG poisoning, USP perspective and activity and PDG harmonization. Excipients can make up to about 90% of the total mass of drug products and are important ingredients of the drug products, such as enhancing therapeutic properties, bulking up solid formulations and ensuring stability. In recent years, however, there have been serious issues due to the quality of excipients. As part of these measures, USP has established five general chapters as supplier qualifications excipients monographs, excipients reference standards and ingredient verification program.

The issue of DEG/EG contamination has occurred since 1937 in the USA, and recent responses are that the WHO Alert and FDA guidance were published in 2023. FDA issued more than ten warning letters between May 2023 and April 2024. In response, USP explained that it developed the DEG/EG tool kit in 2023 and is working with FDA to include DEG/EG tests in the Identification section for different polyethylene glycol (PEG) types.[10]

Major challenges of methodology in the current USP-NF PEG monograph include difficulties in purchasing packed gas chromatography (GC) columns for PEG with MW up to 450, problems of test accuracy for PEG MW 450-1000, and problems of EG/DEG testing for PEG above MW1000 as no tests

have been established. A GC method is developed for PEG up to MW1000, and a gel permeation chromatography (GPC) method is developed for PEG MW above 1000. In the current USP-NF PEG monograph, the NMT of the combined EG and DEG is 0.25%, but in the FDA 2023 guidance, the acceptance criteria are NMT 0.10% for each of DEG and EG respectively. PEG is manufactured by polymerizing ethylene oxide to ethylene glycol or diethylene glycol under elevated pressure in the presence of an alkaline catalyst. If the manufacturing process is not complete, more unreacted EG could be detected. As PEG molecular weight increased, the amount of EG and DEG decreased, so USP has engaged stakeholders to provide batch data of EG and DEG levels in different PEGs.

USP published the PEG monograph revision proposal in PF 50(3). MW ≤ 1000 of PEG includes the validated GC method in the Identification section and MW > 1000 of PEG includes the validated GPC method in the Impurities section. Acceptance criteria were also established for each MW category. A new proposed general chapter <470> *Determination of Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Polyethylene Glycol* was published in PF 50(5) for public consultation. In addition to the existing GC-FID method in GC <469>, four test procedures were proposed by utilizing backflush, derivatization, shorter run-time, and lower temperature of column and detector. Stakeholders can evaluate the equivalency and interchangeability of these methods and use them as alternative methods as necessary.

The mission of the PDG is to harmonize pharmacopoeial standards while maintaining a constant level of science with the shared goal of protecting public health. The PDG Pharmacopoeia presently differs in DEG/EG test methods and criteria, highlighting the potential for harmonization in the future.

Sheehan and Liu concluded that global efforts, regulatory review, pharmacopoeial up-to-date standards, and compliance with cGMP by industry are important in ensuring the quality of excipients. The USP is amending pharmacopoeial standards, general chapters, and excipients monographs, as appropriate, with the ultimate goal of contributing to improved global health outcomes.

"*Current Regulatory Landscape of Pharmaceutical Excipients in Japan*" by Yasuhiro Abe (NIHS)[11]

In this presentation, an overview of the regulations for excipients in the Japanese Pharmacopoeia (JP) and the risk of adulteration of diethylene glycol (DEG) and ethylene glycol (EG) adulteration was discussed. Excipients are defined as substances other than active pharmaceutical ingredients (APIs) contained in preparations in the General Notices for Preparations (6) of the JP18. Excipients must be pharmacologically inactive and harmless in the administered amount and must not interfere with the therapeutic efficacy of the formulation. Excipients are essential for enhancing the manufacturability, stability, and bioavailability of APIs. In Japan, not all excipients are listed in JP and some excipients are listed in the Japanese Pharmaceutical Excipients.

The JP is notified by the Minister of Health, Labour and Welfare (MHLW) under the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The first edition of JP was published in 1886, and the latest edition is the 2nd Supplement to JP18, published in 2024. The JP is revised every five years, and two supplements are published between each revision. An English version of JP is freely available on the PMDA website. JP excipient monographs are reviewed by the Expert Committee on Excipients. In addition, the JP is developed in accordance with the basic principles for preparation of JP.

Abe explains the potential risks and regulatory challenges as follows. The globalized supply chains for excipients increases the risks of quality control failures, adulteration, mis-labelling and supply instability. Most excipients manufacturers produce primarily for industrial and food applications, with pharmaceutical applications comprising a small part of their business. Many small Japanese excipients manufacturers face budget constraints, making it difficult to install the latest analytical equipment.

EG and DEG are widely used in industry, and they are highly toxic to kidneys. Due to their sweet and viscous nature, they can be easily used as adulterants in glycerin and syrup. EG/DEG adulteration has resulted in fatal outcomes worldwide. DEG tests were added to the monographs of glycerin and concentrated glycerin in JP15, and the DEG tests were updated and added to the monographs of glycerin, concentrated glycerin, and propylene glycol in JP16-2. In Japan, there have been no cases of EG and DEG adulteration in pharmaceutical products, emphasizing the role and importance of the pharmacopoeia in public health.

In conclusion, as a challenge of supply chain globalization, complex networks increase the risk of quality control failures. Abe stressed that rigorous inspection of incoming excipients is critical to prevent adulteration and contamination, and that supporting developing countries in strengthening their regulations is also important. In promoting global collaboration, Abe emphasized how harmonization of both test procedures and criteria can help to reduce duplication of testing, save resources and time for both industry and regulators, and encourage global standards for supplier qualifications and audits.

"*Detecting and Managing Excipient Quality Issues: Singapore's Experience*" by Tan-Koi Wei Chuen (Duke-NUS Centre of Regulatory Excellence, Singapore)[12]

This presentation addressed the issue of DEG, EG poisoning, Singapore's post-marketing framework, and the importance of risk communication and regulatory guidance for excipient quality issues. First reported in 1937 in the sulfanilamide incident, the problem of DEG and EG poisoning remains a challenge to global health. Between 2022 and 2023, multiple DEG, EG poisoning was reported across different WHO regions. Post-marketing surveillance and communication consisting of signal detection, signal evaluation, communication, and engagement are pivotal for early detection and mitigation of excipient quality issues including that of DEG and EG.

The purpose of environmental scans in signal detection is to pay attention to global quality and safety issues in the global supply chain. Asst. Prof Tan-Koi shared the innovative approach of using automated web crawler adopted by the Health Sciences Authority, Singapore to support active surveillance of global quality and safety issues. In the increasingly digitalized world, it is necessary to explore a machine learning approach to supplement the existing signal detection tools that could facilitate faster detection of quality and safe-

ty issues.

Another surveillance method is the Product Quality Surveillance programme (PQS). PQS is a risk-based pre-emptive sampling approach to monitor the quality of health products available in the market based on the provisions provided by the Regulation 65 of the Health Products Regulations. When PQS detect adulterated and substandard products, regulators are able to take prompt and appropriate regulatory action to address potential risks.

In PQS, depending on the purpose of testing, identification, assay, disintegration/dissolution, related substance/chromatographic purity tests and other relevant tests will be performed at the Health Sciences' Authority Pharmaceutical Laboratory and other accredited laboratories. For reporting of product defects, regulatory oversight in ensuring completion of recall process and communication to stakeholders is critical. Clear guidance on product defect assessment and recall types are essential to facilitate early withdrawal of products with excipient quality issues from the market.

Sharing of product recall information and risk communication raises awareness of adverse events, causality and evidence to-date, contamination, contaminants and names of affected products. Communication audiences include the public, healthcare professionals, industry and communication channels include letters to health professionals, press releases, hotlines, service touchpoints, industry stakeholder dialogue, and websites. Using the case study of nitrosamine impurities in health products, Asst Prof Tan-Koi emphasized sharing information on the background, actions taken by the national and international agencies, list of affected medicines, guidance for product registrants, and test methods are important information for stakeholders. She also added that there was significant public interest in the nitrosamine impurities issues with, congressional questions raised on the rigor of the health product regulatory system, international best practices on medicine testing and management of excipient quality issues.

In conclusion, excipient quality issues can have serious consequences for global health and erode trust in the regulatory system. Pharmacopoeial harmonization, regulation, and post-marketing surveillance facilitate the exchange of information and actions on excipient quality issues. Continuing regulatory systems strengthening and capacity building in quality management systems, post-marketing surveillance and risk communication is essential to detect and communicate excipient quality issues in a timely manner. Asst-Prof Tan-Koi stressed that collaboration among regulators, industry, health care systems, and pharmacies are critical to managing excipient quality issues.

"*The Problem of Ethylene Glycol and Diethylene Glycol Contamination*" by Paul Huleatt (Therapeutic Goods Administration, Australia)

This presentation addressed quality issues, issues of ethylene glycol and diethylene glycol contamination, the generation of syrups contaminated with DEG and EG, and what the regulation should be.

There were problems with DEG/EG contamination from both medications produced domestically and imported medications. Historic incidents have common characteristics: the victims are often young children. The lack of deterrence, such as few arrests, lack of verification by manufacturers, suppliers and regulators, lack of transparency, lack of accountability, and difficulties in performing root cause analysis and documenting are key observations.

In regulation, it is important to consider 'theory' versus 'reality' and whether the introduction of new regulations will solve the DEG and EG contamination problem in practice. Additional, industry-wide regulatory burden must have positive cost-benefit and needs to be weighed against the risk of over-regulation.

In Haiti (1995-96) and Panama (2006), contaminated excipients were derived from chemical companies that were not certified to produce pharmaceutical ingredients. Exporters shipped toxic syrups from Asia through European traders who resold it without identifying the previous owner to keep buyers from bypassing them on future orders. This was done intentionally, and it is a practice referred to as neutralization. Huleatt explained that neutralization was common and may still present a challenge.

WHO has issued a Medication Product Alert for counterfeit USP/EP propylene glycol, which is the first ever alert for an excipient. The article from *Pharmaceutical Technology* by Agnes Shanley in 2018[13] discloses details of numerous case studies in which FDA inspections revealed extraordinary violations in the use or production of COAs. The paper also argues that an appropriate approach to managing and evaluating CoA is also key to maintaining data integrity and that many pharmaceutical companies' compliance strategies remain inadequate. Huleatt stresses that in the case of PG and other at-risk excipients, the certificate of analysis should be verified through testing of the raw material without reliance on the CoA.

The US FDA also issued guidance on DEG/EG. Regarding the pathways to crisis and the points of intervention, preventing manufacture of contaminated syrup medications should be the aim. Prevention is possible through the excipient supply chain but is most practical and effective through testing by the manufacturers prior to use. WHO also has the Member State Mechanism on SF Medical Products. The goal of the WHO member state mechanism is to protect public health and promote access to affordable, safe, efficacious and quality medical products, and to promote through effective collaboration among member states and secretariat the prevention and control of substandard and falsified medicinal products and associated activity.

In conclusion, Huleatt stressed the importance of regulation on ethylene glycol and diethylene glycol contamination issues. However, because excessive regulation is a risk, it is necessary to carefully consider the establishment of new regulations while balancing with the tightening of existing regulations.

"*Ethylene Glycol and Diethylene Glycol Contamination Cases Learnings and Regulatory Challenges*" by Tri Asti Isnariani (Badan POM, Indonesia)[14]

This presentation described regulatory oversight of pharmaceuticals in Indonesia, cases of ethylene glycol and diethylene glycol contamination, and the response of the Indonesian FDA. For post-marketing surveillance of pharmaceuticals in Indonesia, manufacturing, distribution, and pharmaceutical service facilities are inspected. Risk-based sampling and test-

ing, advertising, label management, import and export control, and information activities are carried out in the central secretariat, regional offices, and laboratories.

The purpose of risk-based sampling and testing is to protect the public from substandard and falsified products, to ensure the quality of marketed products, to detect illegal, defective, and expired products, to ensure compliance with the requirements for packaging and labeling information for marketed products, and to ensure compliance with the regulations for nicotine and tar content in tobacco products.

These activities are conducted by the Central Office and 76 Technical Implementation Units/Offices respectively. More than 17,000 samples are collected and tested every year. More than 96% of samples meet the specification. Both sampling and testing are conducted by the Regional Office based on sampling and testing guidelines. A risk-based sampling plan must be developed in advance by each regional office. Samples are collected from manufacturers, wholesalers, provincial and district warehouses, health facilities, pharmacies and drug stores.

EG/DEG as a contaminant may exist in excipient propylene glycol, polyethylene glycol, sorbitol, and glycerin solvents. Isnariani reported there are substandard pediatric medicines identified in Indonesia and other countries in 2022-2024.

With respect to the Indonesian FDA's response, distributors are required to take administrative action against investigations and tracking of drugs used by patients, investigations of the pharmaceutical industry and raw material distributors, development of analytical methods for EG-DEG contamination testing on drug products, strengthening of product quality surveillance through risk-based sampling and testing, and imposing administrative sanctions to industry for non-compliance with standards and regulations. Pharmacovigilance systems are being strengthened, publication/press releases are being issued, quality assurance procedures are being strengthened for drug manufacturers and distributors, standards and regulations are being reviewed to tighten requirements and compensate affected patients are provided.

In conclusion, the Indonesia FDA continuously strives to improve access to safe, efficacious, and quality-assured medicines. Ensuring the quality of excipients is a top priority for protecting public health. The Indonesia FDA took prompt and decisive action to overcome the EG-DEG crisis and to raise awareness of how to identify and avoid contaminated products while maintaining access to essential medicines for the public. Isnariani stressed that cooperation with relevant domestic stakeholders, other national regulators and WHO was essential to managing the crisis and preventing similar incidents in the future. Isnariani argued for a secure and reliable supply chain that can protect patients worldwide from the dangers of substandard and contaminated drugs.

The five presentations on excipients demonstrated the importance of pharmacopoeial standards and regulations. Sheehan and Liu's presentation stressed the importance of pharmacopoeial standards in ensuring the quality of excipients, and Abe's presentation highlighted the importance of harmonizing pharmacopoeial standards in response to globalization of the supply chain. Chuen's presentation highlights the importance of product quality monitoring and the need for collaboration with other countries. Hulaitt stressed the importance of balanced regulatory arrangements. Isnariani explained that protection of the public from contaminated medicines by risk-based sampling and testing can be achievable. These efforts demonstrate the contribution of pharmacopoeial standards and regulatory requirements to public health in ensuring the quality of excipients.

**Panel Discussion** Panelists: Yasuhiro Abe (NIHS), Nguyen Thi Hong Hanh (Institute of Drug Quality Control, Vietnam), Tan-Koi Wei Chuen (Duke-NUS Centre of Regulatory Excellence, Singapore), Paul Huleatt (Therapeutic Goods Administration, Australia), Tri Asti Isnariani (Badan POM, Indonesia); Moderator: Hikoichiro Maegawa (PMDA).

The discussion began with the question about how pharmacopoeias or standards could contribute to strengthening global pharmaceutical quality and supply chains and resolving excipient problems. The panelists noted the importance of standards for high-level quality control; harmonization of standards; strengthening of regulatory authorities; traceability; and international cooperation in tackling challenges.

The panelists were asked what options such as recognition, reliance, pharmacopoeial reference, work-sharing or normal/standard processes would be preferable if administrative resources were inadequate for response to DEG and EG issues. The panelists noted the importance of combining work sharing and normal processes; the risk-based approach of recognition and GMP; reliance and information sharing; and the importance of international cooperation.

In summary, the discussion provided findings that international collaboration is important for tackling global issues of excipients such as DEG and EG poisoning and to ensure the quality of excipients under globalization of the supply chain for excipients.

## SESSION 3: FUTURE SEGMENT – WHAT LIES AHEAD

### Topic A: Complex Generics

"*Japanese Perspectives on the Complexity of Complex Generics*" by Kumiko Sakai-Kato from Kitasato University [15]

Sakai-Kato delved into the intricate challenges and regulatory considerations surrounding complex generics in Japan. Complex generics are generic drugs that have complex active substances, formulations, routes of administration, or combinations with devices. These include products like low-molecular-weight heparin, microcapsules, lipid microspheres, and nanotechnology-based drug products such as liposomes and polymeric nanoparticles.

One of the primary challenges highlighted is the lack of a specific regulatory definition for complex generics in Japan. This absence necessitates a case-by-case evaluation to ensure quality and efficacy. The presentation emphasizes the importance of developing consensus-based standard test methods, which are produced by the Japanese Pharmacopoeia. These methods are crucial for the quality assurance of complex generics, ensuring they meet the necessary specifications and criteria.

Sakai-Kato also discussed the regulatory framework for nanomedicines, which are a significant category within complex generics. Nanomedicines are developed using innovative materials and nanotechnology to control the biodistribution

of active substances. The quality attributes of these products, such as particle size, morphology, and surface charge, are critical for their efficacy and safety. The Japanese Pharmacopoeia lists various analytical techniques for measuring these attributes, including dynamic light scattering, laser diffraction, and atomic force microscopy.

Sakai-Kato highlighted the need for standardized methods for the physicochemical properties of nanomedicines. These methods are essential for ensuring consistent quality and facilitating the global acceptance of complex generics. The presentation outlines the efforts of the Japanese Pharmacopoeia and the Ministry of Health, Labour, and Welfare (MHLW) in developing guidelines and reflection papers for the evaluation of liposome drug products and other nanotechnology-based medicines.

Sakai-Kato also touched on the importance of international collaboration in the development and regulation of complex generics. Harmonization of standards and test methods with international counterparts, including the USP, is crucial for ensuring that these products can be effectively evaluated and approved across different regions. This collaboration helps in addressing the unique challenges posed by complex generics and promotes the global availability of high-quality medicines.

In conclusion, the presentation by Kumiko Sakai-Kato provided a comprehensive overview of the complexities involved in the development and regulation of complex generics in Japan. It underscored the need for robust analytical methods, standardized test procedures, and international cooperation to ensure the quality and safety of these advanced pharmaceutical products. By addressing these challenges, MHLW and JP aim to enhance the accessibility and reliability of complex generics, ultimately contributing to better health outcomes globally.

"*USP Initiatives for Complex Generics – Documentary and Physical Standards*" by Prabhakar Reddy, Ph.D., from the United States Pharmacopeia (USP)[16]

Dr. Reddy provided an in-depth look at USP's efforts to support the development of quality standards for complex generics. Complex generics are generic drugs that have intricate active substances, formulations, routes of administration, or are combined with devices. These include products like peptides, oligonucleotides, liposomes, microspheres, and drug-device combination products.

**Current Standards and Initiatives** USP has developed a comprehensive set of documentary standards to support complex generics. These include over 250 official monographs and numerous general chapters that provide detailed guidelines for various categories of complex generics. For instance, there are specific standards for inhalation, mucosal, ophthalmic, topical, transdermal, and injectable products. Additionally, USP has created general chapters addressing complex active pharmaceutical ingredients (APIs), complex routes of delivery, complex dosage forms, and drug-device combination products.

To address the unique challenges posed by complex generics, USP has established a Complex Generics Program Unit (PUT). This unit engages with stakeholders through qualitative and quantitative surveys, open forums, and industry visits to identify gaps and prioritize areas for standard development. One significant initiative is the development of physical reference standards for complex excipients, such as PLGA polymers for microspheres and phospholipids for liposomes and lipid nanoparticles. These standards are crucial for ensuring the quality and consistency of complex generics.

**Challenges and Solutions** Dr. Reddy highlighted several challenges in developing complex generics, including the lack of reverse characterization data, *in vivo*/in vitro correlation tools, and standard compendial methods for *in vitro* release testing. Additionally, the proprietary nature of technologies and methods, manufacturing complexities, and the need for dedicated sterile facilities pose significant hurdles. To address these challenges, USP is developing new general chapters and physical standards. For example, new chapters on iron colloidal formulations, microspheres, and drug-device combination products are in progress.

USP is also focusing on extractables and leachables (E&L) for complex generics, which have a higher risk of contamination. They are developing system suitability standards for various analytical methods, including GC-MS and LC-MS, to ensure consistent and reliable data across multiple laboratories. These standards will help in the identification and quantification of unknown compounds, enhancing the safety and efficacy of complex generics.

**Stakeholder Engagement and Future Directions** Stakeholder feedback is a critical component of USP's approach to developing standards for complex generics. Through surveys and open forums, USP gathers input from industry experts, regulators, and other stakeholders to refine and improve their standards. This collaborative approach ensures that the standards meet the needs of the industry and regulatory bodies.

Looking ahead, USP is committed to continuing its efforts to support the complex generics industry. This includes ongoing development of new standards, addressing gaps in current methodologies, and fostering international collaboration to harmonize standards globally. By staying at the forefront of scientific and technological advancements, USP aims to ensure the quality, safety, and accessibility of complex generics.

In summary, Dr. Reddy underscored USP's dedication to advancing the field of complex generics through rigorous standards development, stakeholder engagement, and innovative solutions to industry challenges. These efforts are essential for ensuring that complex generics can be developed, approved, and brought to market efficiently and safely.

The two presentations on Complex Generics underscored the critical importance of developing robust standards and methodologies to ensure the quality and efficacy of complex generics. Kumiko Sakai-Kato's presentation highlighted PMDA's regulatory challenges and the need for standardized test methods for complex generics, while Prabhakar Reddy's presentation detailed USP's comprehensive initiatives, including the development of documentary and physical standards, to support the industry. Together, these efforts emphasized the necessity of international collaboration, continuous innovation, and rigorous analytical methods to enhance the accessibility and reliability of complex generics, ultimately contributing to improved global health outcomes.

## Topic B: Quantitative Nuclear Magnetic Resonance (qNMR)

"*Updates and Future Vision of qNMR at U.S. Pharmacopeia*" by Yang Liu, Senior Scientist from USP[17]

**Historical Context and Current Status** qNMR is a powerful analytical technique used for the precise quantification of compounds, and its application is expanding within the pharmaceutical industry. The presentation begins with a brief history of spectroscopy in the USP-NF (United States Pharmacopeia-National Formulary), highlighting the inclusion of NMR spectroscopy in the 1980 edition. Over the years, qNMR has evolved from a proof-of-principle stage to a fully operational technique within USP's framework. This evolution aligns with USP's 2020-2025 top-level priorities, which include revising general chapters to update qNMR content and incorporating benchtop NMR and solid-state NMR chapters.

**Key Initiatives and Developments** One of the significant initiatives discussed is the revision of general chapters to include updated qNMR content. This includes the development of new chapters for benchtop NMR and solid-state NMR, which are crucial for expanding the technique's applicability. USP is also leading discussions on the validation of qNMR methods, emphasizing a life cycle approach to ensure robust and reliable analytical procedures.

The presentation highlighted the expanded use of qNMR for reference standard evaluation. This involves the development of standardized procedures for sample preparation, data acquisition, and analysis. A digital platform is being developed to support these activities, featuring a spectral library and quantum mechanics-based software for data analysis (QMSA). This platform aims to enhance the accuracy and reproducibility of qNMR measurements.

**Applications and Case Studies** Several case studies are presented to illustrate the practical applications of qNMR. For example, the analysis of ascorbic acid demonstrates the technique's repeatability and linearity. The results show that qNMR provides highly accurate and consistent data, which is essential for quality control in pharmaceutical manufacturing. Another case study involves the detection of diethylene glycol in syrup samples, showcasing qNMR's capability to identify and quantify contaminants.

**Future Vision and Goals** Looking ahead, USP aims to further integrate qNMR into its operations and expand its applications. This includes continued development of digital solutions to support qNMR activities and the creation of new reference standards. USP is also focusing on enhancing the education and engagement of the scientific community through workshops, summits, and collaborative projects.

Dr. Liu underscored the importance of international collaboration in advancing qNMR technology. By working with global partners, USP aims to harmonize standards and promote the widespread adoption of qNMR. This collaborative approach is vital for addressing the complex challenges in pharmaceutical analysis and ensuring the quality and safety of medicines worldwide.

"*qNMR in the Japanese Pharmacopoeia (JP), Now and Future*" by Yukihiro Goda from the National Institute of Health Sciences (NIHS)[18]

**Historical Context and Adoption** qNMR is an absolute quantification method that utilizes internal standards to determine the purity or concentration of low molecular organic compounds with SI traceability.

Dr. Goda outlined the historical context of qNMR's adoption in the Japanese Pharmacopoeia. Since 2008, a joint research group comprising NIHS, the National Institute of Advanced Industrial Science and Technology (AIST), Fujifilm-Wako Pure Chemical Industries, and JEOL Ltd. has been working on integrating qNMR into the JP. The method was officially adopted in 2014 for the absolute quantification of marker compounds in herbal medicines and impurities in chemical drugs. This adoption was driven by the high cost and complexity of preparing these compounds using traditional methods.

**Advantages of qNMR** qNMR offers several advantages over conventional methods. It eliminates the need for extensive purification steps, as the purity of a compound can be determined directly from its NMR peak if it is well-separated. This reduces costs and simplifies the process compared to the mass-balance method, which requires multiple purification steps and the determination of impurity values. The presentation highlights the proliferation of SI-traceable reference compounds using qNMR, which has led to the preparation of certified reference standards (CRS) with high accuracy.

**Current Applications and Validation** Dr. Goda detailed the current applications of qNMR in the JP, particularly in the assay of crude drugs and Kampo formula extracts. Several reagents, including geniposide, paeonol, magnolol, and rosmarinic acid, have been evaluated using qNMR and listed as reference standards. The validation studies conducted in multiple laboratories have demonstrated that qNMR can determine the purity of these compounds with high accuracy, making it a reliable method for quality control.

**Future Directions** Looking ahead, Dr. Goda outlined several future directions for qNMR in the JP. One key area is the expansion of qNMR utilization to the field of chemical drugs. The JP has allowed the use of impurity standards for the quantification of organic impurities in chemical drugs, and the expert committee has prepared guidelines for drafting quality standards that include qNMR. This expansion aims to enhance the accuracy and reliability of impurity quantification in chemical drugs.

Another future direction is the development of new analytical techniques and methodologies. The presentation mentions the use of $^{1}$H iterative Full Spin Analysis (HiFSA) for obtaining precise spin information from NMR spectra. This technique allows for the accurate determination of spin information, which can be used for detailed confirmation tests and the identification of diastereomers.

The two presentations on qNMR highlighted the significant advancements and future potential of quantitative Nuclear Magnetic Resonance (qNMR) in pharmaceutical analysis. Yang Liu's presentation emphasized USP's efforts to integrate qNMR into its standards and operations, focusing on digital transformation and international collaboration to enhance accuracy and reliability. Yukihiro Goda's presentation underscored the adoption and expansion of qNMR in the Japanese Pharmacopoeia, showcasing its application in quality control for herbal medicines and chemical drugs. Together, these efforts demonstrate the critical role of qNMR in ensuring the quality and safety of pharmaceuticals, driven by continuous innovation and global cooperation.

**Panel Discussion** Panelists: Kumiko Sakai-Kato (Kitasato

University), Prabhakar Reddy (USP), Yang Liu (USP), Yukihiro Goda (NIHS); Moderator: Kevin Moore (USP).

The discussion began with a question about the scarcity of generic complex injectable products in the market despite patent expirations. The response highlighted the inherent complexity and differing pharmacodynamics of these products as primary challenges. In Japan, there are specific guidelines for complex generic formulations, particularly for liposome products, which are already included in the Japanese Pharmacopoeia.

The role of the United States Pharmacopeia (USP) in aiding the generic industry was also addressed. It was noted that USP can help by incorporating feedback from stakeholders and focusing on developing missing chapters, such as those for microspheres.

The session then shifted to the analytical advantages of quantitative Nuclear Magnetic Resonance (qNMR) over other techniques. The key benefits, summarized as ESR, include **Efficiency** (no need for identical reference substances), **Speed** (no calibration curve required), and **Reliability** (SI traceable analysis). There was also a discussion on the potential for developing a qNMR-based digital reference standard, which is feasible if comprehensive QMSA data is available and high magnetic field NMR is used.

Finally, the identification of free chemical drug substances using high-resolution qNMR spectra compared to QMSA data was considered generally sufficient, though future advancements will require integrating all available technologies.

## SESSION 4: NITROSAMINES – PAST, PRESENT, AND FUTURE

"*Nitrosamine Impurities: Beyond a Compendial Standard – Learnings from USP's Nitrosamines Exchange Community*" by Naiffer Romero and Mrunal Jaywant (USP) [19]

Romero and Jaywant explored the challenges and advancements in managing nitrosamine impurities in pharmaceuticals. Nitrosamines are a class of chemical compounds that can form in drug products and are potentially carcinogenic, making their control and mitigation a critical issue for the pharmaceutical industry.

**Background and Evolution** Romero and Jaywant began by outlining the timeline of nitrosamine contamination issues, starting with the discovery of nitrosamines in angiotensin II receptor blockers (ARBs) in 2018. This led to widespread recalls and regulatory actions globally. The USP responded by developing General Chapter <1469> on nitrosamine impurities, which provides guidelines for detecting and controlling these impurities in drug products.

**Key Learnings and Initiatives** One of the significant initiatives discussed is the establishment of the Nitrosamines Exchange Community, an online platform that facilitates knowledge sharing and collaboration among industry professionals, regulators, and scientists. This community has over 4,800 members from more than 80 countries, enabling a global exchange of information and best practices[20].

Romero and Jaywant highlighted the development of documentary standards and reference standards for various nitrosamine impurities, including NDMA, NDEA, and NMBA. These standards are essential for ensuring consistent and reliable detection of nitrosamines in pharmaceuticals. USP has also created non-compendial tools, such as the Nitrosamines Analytical Hub, which provides resources and support for analytical testing.

**Analytical Challenges and Solutions** Addressing the analytical challenges associated with nitrosamine detection, Romero and Jaywant emphasized the need for robust and reliable methods. USP has developed standardized approaches and reference standards to support the industry in implementing effective control strategies. The presentation also discusses the importance of understanding nitrosamine reactivity and formation mechanisms to develop better risk assessment and mitigation strategies.

**Stakeholder Engagement and Education** Stakeholder engagement is a critical component of USP's approach to managing nitrosamine impurities. Various educational initiatives, including USP courses, tutorial videos, and hands-on training sessions were discussed. These efforts aim to enhance the industry's understanding of nitrosamine risks and the implementation of control measures.

**Future Directions** Looking ahead, Romero and Jaywant outline several future directions for managing nitrosamine impurities. These include expanding the scope of nitrosamine testing to cover more drug products and excipients, developing new analytical methods, and enhancing international collaboration. USP is also focusing on building mechanistic knowledge of scavenger agents, which can help prevent nitrosamine formation during drug manufacturing.

"*Approaches and Considerations for N-nitrosamine Issues from a Quality Perspective*" by Yusuke Nagato from FUJIFILM Toyama Chemical[21]

**Background and Regulatory Context** Nagato provided an overview of nitrosamine contamination, which gained widespread attention following the discovery of nitrosamines in angiotensin II receptor blockers (ARBs) in 2018. This led to numerous recalls and heightened regulatory scrutiny worldwide. Nitrosamines are classified as a "cohort of concern" under the ICH M7 (R2) guideline due to their high carcinogenic potential, necessitating stringent control measures to keep their levels significantly below acceptable intake limits.

**Sources and Formation of Nitrosamines** Nagato explained that nitrosamines can form through various pathways during the manufacturing process of active pharmaceutical ingredients (APIs) and drug products. Key factors contributing to their formation include the presence of secondary or tertiary amines, nitrosating agents, and specific reaction conditions. For example, nitrosamines can form when amine moieties in APIs or their impurities react with nitrites in excipients or when hydrazine moieties are oxidized.

**Risk Assessment and Mitigation Strategies** Nagato outlined a comprehensive risk assessment framework for identifying and controlling nitrosamine impurities. This involves evaluating the manufacturing processes of APIs and drug products, assessing potential cross-contamination from raw materials and manufacturing facilities, and conducting stability studies to understand degradation pathways. A flowchart is provided to guide the risk assessment process, which includes steps such as investigating the API manufacturing process, evaluating the drug product manufacturing process, and conducting confirmatory testing.

To mitigate the risk of nitrosamine formation, Nagato emphasized the importance of removing one of the three key factors: the nitrosating agent, the amine source, or the conditions conducive to nitrosamine formation. Practical strategies include changing reagents or solvents, modifying manufacturing conditions, and using alternative packaging materials. Additionally, implementing robust control strategies and timely reporting to regulatory authorities are crucial for managing nitrosamine risks.

**Challenges and Future Directions** Nagato highlighted several challenges in managing nitrosamine impurities, including the lack of comprehensive toxicity data for many nitrosamine drug substance-related impurities (NDSRIs) and the need for new acceptable intake limits. Nagato calls for ongoing research to fill these data gaps and improve risk assessment methodologies. Furthermore, Nagato stressed the importance of international collaboration to harmonize regulatory approaches and share best practices for controlling nitrosamine impurities.

"*Past, Present (& Future) Regulation on Nitrosamines in Japan*" by Tomoyuki Miyasaka from the Ministry of Health, Labour, and Welfare (MHLW) [21]

**Historical Context and Initial Response** Mr. Miyasaka began his presentation by detailing the discovery of nitrosamine impurities in angiotensin II receptor blockers (ARBs) in 2018, which triggered global recalls and regulatory actions. In response, Japan's MHLW issued guidelines and memos to address the contamination. The initial focus was on sartan drugs, where nitrosamines like N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) were found. The MHLW mandated risk assessments and testing for these impurities, leading to the establishment of acceptable intake limits and testing protocols.

**Current Regulatory Framework** Miyasaka outlined the current regulatory framework, which includes stringent guidelines for the detection and control of nitrosamine impurities. The MHLW has implemented a comprehensive risk assessment approach that requires pharmaceutical companies to evaluate their manufacturing processes, raw materials, and packaging for potential nitrosamine contamination. This includes detailed investigations into the sources of nitrosamines, such as secondary and tertiary amines reacting with nitrosating agents under specific conditions.

The presentation emphasized the importance of robust analytical methods for detecting nitrosamines. Techniques such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) are highlighted as essential tools for accurate detection and quantification. The MHLW has also developed guidelines for the validation of these methods to ensure their reliability and reproducibility.

**Challenges and Industry Collaboration** One of the significant challenges discussed is the complexity of nitrosamine formation pathways, which can vary depending on the drug formulation and manufacturing process. This complexity necessitates a tailored approach for each product, making the regulatory process more demanding. Miyasaka stresses the need for continuous collaboration between regulatory bodies, industry stakeholders, and academic institutions to address these challenges effectively.

The presentation also highlighted the role of international collaboration in harmonizing standards and sharing best practices. Japan has been actively participating in global forums and working with international regulatory agencies to develop unified guidelines and strategies for managing nitrosamine impurities. This collaborative effort is crucial for ensuring the safety and efficacy of pharmaceuticals worldwide.

**Future Directions** Looking ahead, Miyasaka outlines several future directions for the regulation of nitrosamines in Japan. These include expanding the scope of nitrosamine testing to cover more drug products and excipients, developing new analytical methods, and enhancing the mechanistic understanding of nitrosamine formation. The MHLW is also focusing on improving the risk assessment framework by incorporating more comprehensive data on nitrosamine toxicity and exposure levels.

The presentation concluded by emphasizing the importance of proactive risk management and continuous improvement in regulatory practices. By staying at the forefront of scientific and technological advancements, Japan aims to ensure the highest standards of pharmaceutical safety and quality.

The presentations collectively emphasized the critical need for comprehensive strategies to manage nitrosamine impurities in pharmaceuticals. Naiffer Romero and Mrunal Jaywant highlighted the collaborative efforts and knowledge sharing within USP's Nitrosamines Exchange Community to develop robust standards and analytical tools. Yusuke Nagato discussed practical approaches and risk mitigation strategies from a quality perspective, focusing on the complexities of nitrosamine formation and control. Tomoyuki Miyasaka provided an overview of Japan's regulatory evolution and future directions, underscoring the importance of stringent guidelines and international cooperation. Together, these presentations underscore the necessity of proactive risk management, continuous innovation, and global collaboration to ensure the safety and quality of pharmaceuticals.

**Panel Discussion** Panelists: Mrunal Jaywant (USP), Naiffer Romero (USP), Yusuke Nagato (FUJIFILM Toyama Chemical), Tomoyuki Miyasaka (MHLW); Moderator: Kevin Moore (USP).

The discussion covered several key topics related to the regulation and management of Nitrosamine Drug Substance-Related Impurities (NDSRIs). The panel addressed the opportunities presented by the new CPCA approach for calculating NDSRI limits, which all leading regulatory agencies have adopted. The panelists discussed how this approach could help better address the challenges posed by NDSRIs.

For the United States Pharmacopeia (USP), the focus was on the importance of risk assessment as part of the three-step mitigation strategy recommended by regulators. USP acknowledged that many medium and small-scale manufacturers are still learning and emphasized its role in supporting these stakeholders through guidance and resources to meet the requirements.

The representative of MHLW was asked about setting standard values for nitrosamines detected below the published Acceptable Intake (AI) levels in Japan. The discussion highlighted whether the AI should be considered a recall limit or if stricter standards based on actual measurements should be set.

MHLW's stance and advice on this matter were sought.

The actions required when changing the manufacturing method of a formulation to reduce nitrosamine risk were discussed. The panel also explored the potential of in-silico tools to predict the toxicity of newly discovered NDSRIs, given the increasing number of these impurities being identified.

Finally, the panel discussed the evolving regulatory requirements and limits for nitrosamines, noting the differences in approaches and limits recommended by various authorities. The contributions of USP and MHLW in this area were highlighted, emphasizing their roles in providing clarity and guidance to ensure compliance and safety.

"*USP Future Perspectives*" by Jaap Venema, Chief Science Officer (USP)[22], outlined the organization's strategic vision and key initiatives aimed at advancing global public health.

**Strategic Vision and Mission** USP's mission is to improve global health through public standards and related programs that ensure the quality, safety, and benefit of medicines and foods. Venema highlighted the organization's commitment to this mission by continuously evolving its standards to meet scientific advancements. This involves a proactive approach to responding to today's public health challenges through coordinated standards, advocacy, and capacity building.

**Key Initiatives and Innovations** One of the primary initiatives discussed is to be a definitive source of quality standards. USP is focusing on employing new scientific approaches, providing knowledge on complicated and emerging modalities, and facilitating equivalence for evolving analytical technologies, updating standards and processes to remain relevant and impact supply of quality medicine, and lowering adoption barriers to new technologies. USP supports innovation through the development of standards that support new products and modalities, including complex generics, cell therapies, and digital toolkits.

Venema also emphasized the importance of digital transformation at USP. This includes the creation of digital tools and platforms that make standards more accessible. This digital shift is crucial for keeping pace with the rapid advancements in technology and ensuring that standards remain relevant and fit for use, including the use of digital reference standards.

**Global Collaboration and Impact** USP has over 9000 standards which span across the entire global supply chain. USP recognizes the critical importance of collaboration and work collectively with expert volunteers, regulators, and industry experts. Venema also underscored USP's commitment to global collaboration. By working with international partners and regulatory bodies, USP aims to harmonize standards and improve global public health. This collaborative approach is essential for addressing the complex challenges posed by globalization and ensuring that quality standards are consistent and effective across different regions in the world.

**Future Directions and Sustainability** Looking to the future, USP scientific priorities are grounded in our Science Quality Framework, which defines how we work in all the areas that we work, including evolving standards, product performance, emerging modalities, novel technologies, and working in a quality environment. USP is committed to exploring new frontiers in science and technology to enhance its standards. This includes ongoing research into enabling greater availability of the world's most relied upon medicines, solving persuasive quality challenges that impact medicines, expanding global availability of quality assured biologics products, and advancing quality through the increased use of digital technologies. Venema also emphasized the importance of environmental sustainability in USP's future initiatives. This involves reducing our own environmental footprint, as well as facilitating the development of standards that allow industry to be more environmentally sustainable.

In conclusion, Dr. Venema's presentation on USP's future perspectives highlighted the organization's strategic vision and key initiatives aimed at advancing public health. Through innovation, digital transformation, and global collaboration, USP is committed to solving persuasive quality challenges that impact medicines, supplements, and foods for the benefit of patients around the globe.

"*JP Future Perspectives*" by Yoshiro Saito, NIHS[23], outlined the direction of future revisions to the Japanese Pharmacopoeia and possible collaboration with USP. Saito stressed the importance of the five pillars of the JP Basic Policy, the enhancement of the listed items, incorporation of science and technology, and internationalization.

**Recent Revisions Based on the Basic Policy For Preparation** Based on the basic policy of JP19, the revision for JP19 is under consideration. In recent years, the 2nd Supplement to the JP18 was issued in June 2024 and contains 13 new monographs, one new general test method, 6 references, and 13 new monographs. The general monograph of monoclonal antibodies has been investigated for enrichment of the JP contents. JP have made public consultations on transparency and have received stakeholder opinions.

**Key Initiatives for Reflecting the Current Science** Inclusion in general chapter of near infrared spectrum and CD spectrum in JP18-1 and in new reference information of chromatography and shear cell method. In the second supplement, inclusion in new reference information such as AFM. JP19 is expected to be included in new reference information such as HifSa. Saito also explains the management of nitrosamine. The Ministry of Health, Labour and Welfare has issued a notification that takes the approach of risk assessment, measurement of nitrosamine levels, and risk reduction by industries, and it is necessary to take measures by August 2025. The working group of JP is considering the incorporation of ICHM7 in JP.

**Internationalization of JP** This presentation emphasized the prompt publication of an English version of JP as part of the JP internationalization. On September 5, the JP released a provisional English version of the guidelines for drafting. In order to ensure a stable supply of pharmaceuticals, the MHLW issued a notification to promptly consider harmonization with other major pharmacopoeias.

Saito highlighted several successful cooperative relationships with USP or EP on the harmonization of drug substance and drug product monographs of pilot activities. These cooperations has led to the development of harmonized standards to facilitate the global trade of safe and effective pharmaceuticals. In addition, a framework was established for NIHS to conduct the necessary tests for international harmonization. Saito stressed that this would ensure a stable supply through

international harmonization of pharmacopoeia.

**Future Directions** In anticipation of the revision of the draft standards by JP20, each committee of the JP has begun examining the basic principle for JP20. Saito stressed that JP would be more internationalized in the future. The present edition of the Guidelines for Preparation of Draft Documents was also a product of experience and knowledge, but he suggested that it could be revised with greater internationalization and flexibility in mind. Saito highlighted collaboration with USP, particularly on new technologies, environmental footprints, and collaboration on biopharmaceuticals and new modalities.

In conclusion, Saito's presentation on JP's future prospects highlighted JP's strategic vision and key initiatives aimed at improving public health. JP is committed to ensuring the quality of pharmaceuticals through the incorporation of state-of-the-art technologies and global cooperation. By remaining at the forefront of scientific and technological progress, the JP aims to address current and future health challenges and to have a significant impact on global health outcomes.

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