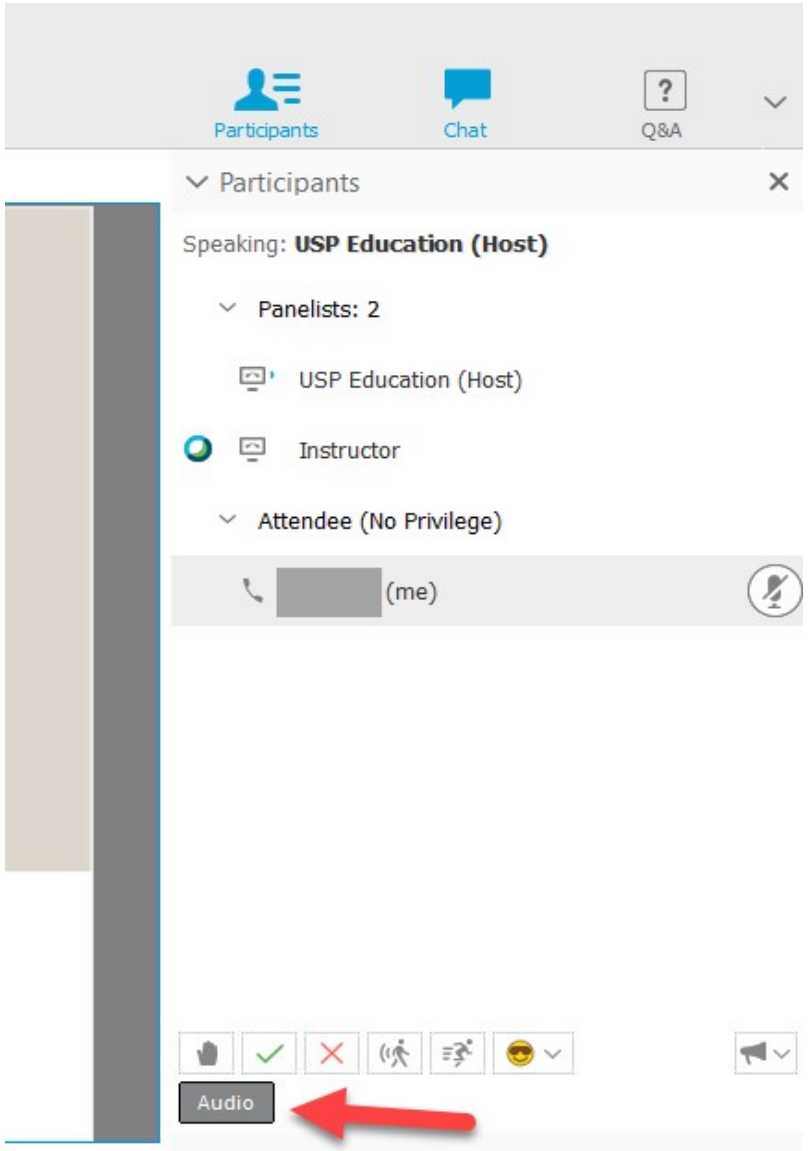
Quality Hour – Dec Edition

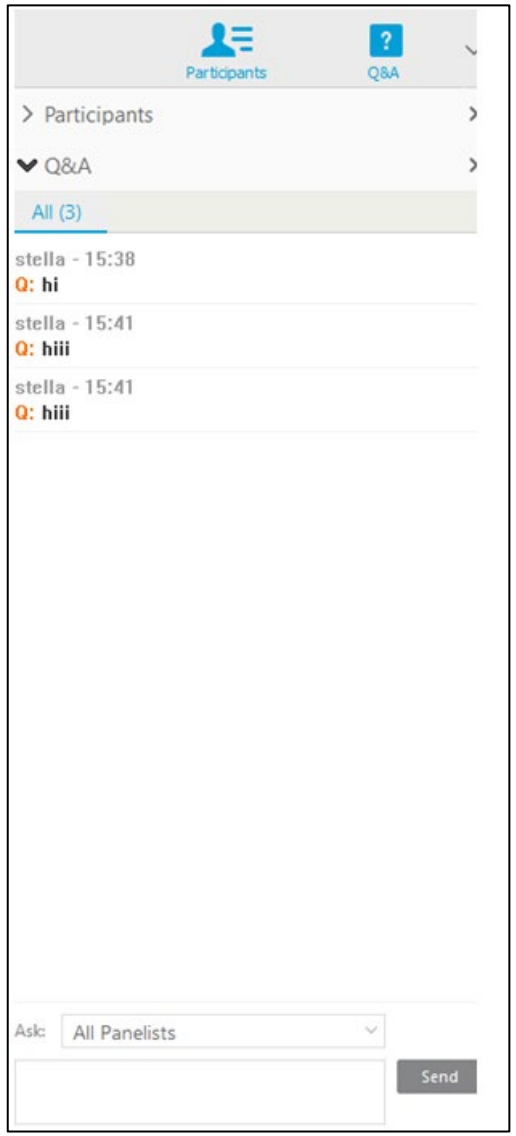
Welcome! The session will start at 3pm Singapore time

You can connect to the **audio** by selecting the tab ‘Audio→ Audio Conference’ on the top of your screen

If you cannot hear us at this time



Question and Answer Session



1. Select the Q&A tab

2. Make sure 'All Panelists is selected

3. Type in your question and click send

Today's Speaker

Christine Zeine, Ph.D.

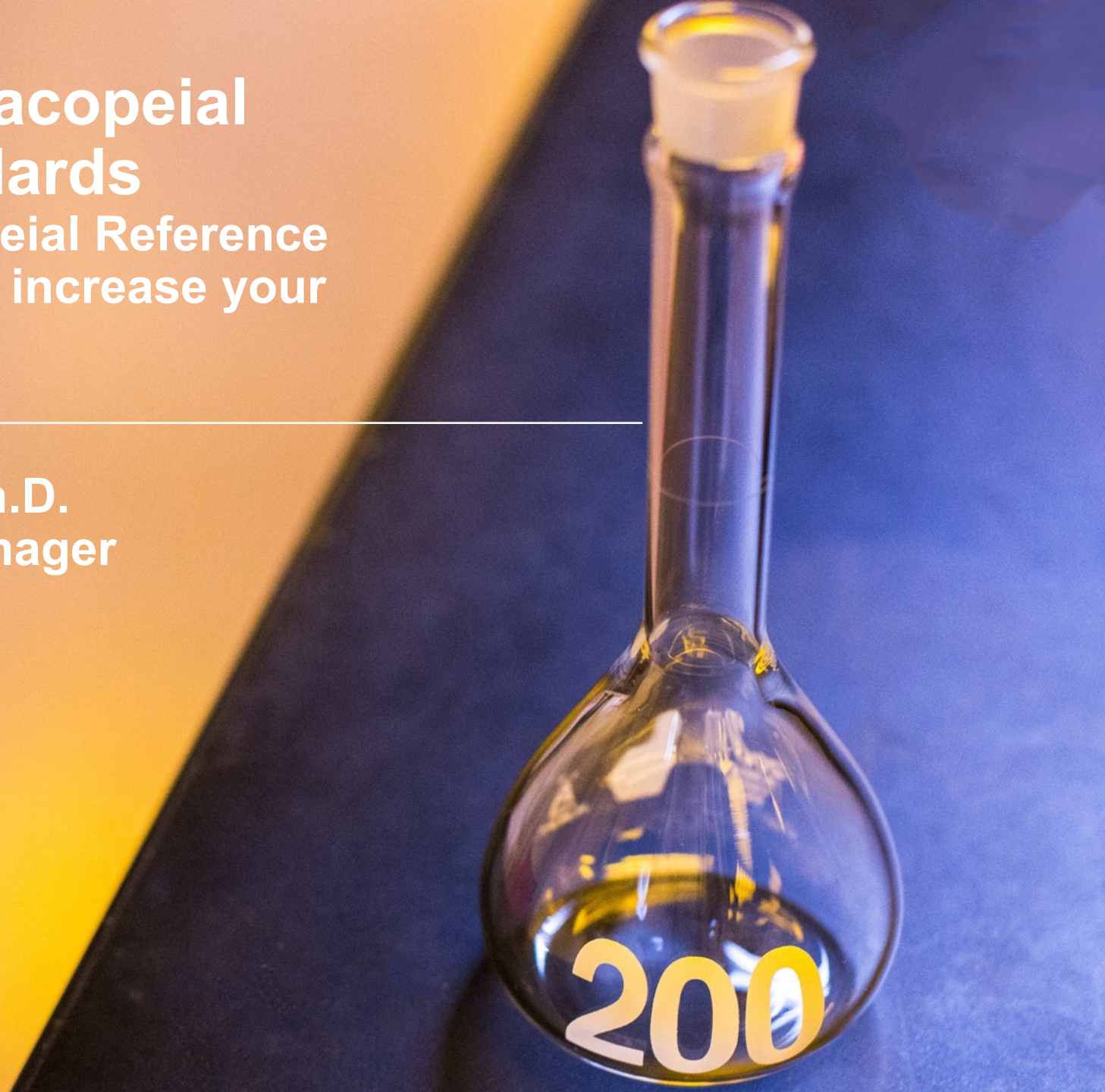
Title: Senior Manager Scientific Affairs, EMEA
Company: The United States Pharmacopeia
Education: Ph.D. in Silicon-Organic Chemistry, Westphalian Wilhelms University Muenster, DE

Dr. Christian Zeine is Senior Manager in the Scientific Affairs Group for the EMEA region, with a focus on Small Molecules, USP's General Chapters and Biologics. Dr. Zeine collaborates with scientific experts and stakeholders and is responsible to protect and grow USP's scientific reputation in the region and globally. Before joining USP, Dr. Zeine worked for seventeen years in the field of pharmaceutical reference standards with a focus on impurities, and before that in the IVD (In Vitro Diagnostic) industry. His scientific expertise includes impurity testing, reference standards characterization and adjacent fields. Dr. Zeine has published several articles and white papers on topics such as impurities, overview about (certified) reference materials, and the use of reference standards in method development and validation.

The Value of Pharmacopeial Reference Standards

Do you know how Pharmacopeial Reference Standards save you work and increase your efficiency?

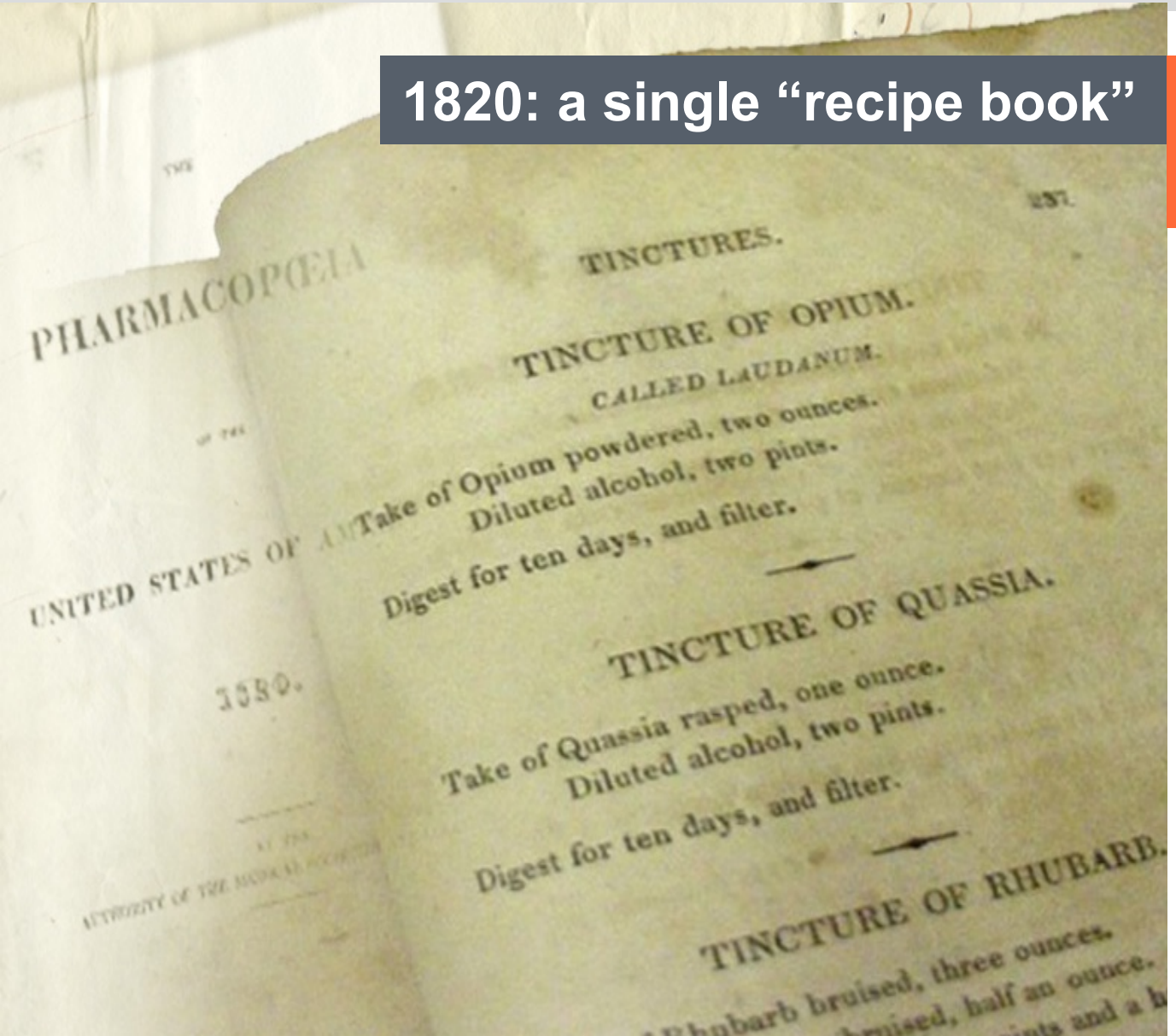
Christian Zeine, Ph.D.
Scientific Affairs Manager



Agenda

- About USP
- Conclusive results
- Understanding uncertainty and risk
- Conclusions

About USP: 200+ years of building trust



1820: a single "recipe book"

2021: Procedures and acceptance criteria to support medicinal articles in the marketplace

Heparin Sodium

DEFINITION
Heparin Sodium is the sodium salt of sulfated glycosaminoglycans present as a mixture of heterogeneous molecules varying in molecular weights that retains a combination of activities against different factors of the blood clotting cascade.

IDENTIFICATION
- **A. ^{1}H NMR Spectrum**
- **B. Chromatographic Identity**
- **C. Anti-Factor Xa to Anti-Factor IIa Ratio**
- **D. Molecular Weight Determinations**
- **E.** A solution of Heparin Sodium imparts an intense yellow color to a nonluminous flame.

Filgrastim

DEFINITION
Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor.

IDENTIFICATION
- **A.** It meets the requirements in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained as directed in the test for *Organic Impurities, Related Compounds*.
- **C. Peptide Mapping**
  (See *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩.)

USP's role in United States law: Standards for drugs

Naming and Identity

Drug deemed *misbranded* unless its label bears the established USP name

FD&C Act section 502(e)

Strength, Purity, and Quality

Drug deemed *adulterated* if strength or quality or purity falls below standards set forth in compendium [USP], ***unless*** differences are plainly stated

FD&C Act section 501(b)

Packaging and Labeling

Drug deemed *misbranded*, with certain exceptions, unless it is packaged and labeled as prescribed in official compendium [USP]

FD&C Act section 502(g)

Compounding

Compounded drugs exempted from specific FD&C Act requirements for labeling, manufacturing, and new drugs, if certain USP chapters are followed

FD&C Act section 503A

Note: USP is an independent, scientific nonprofit organization, that has no role in enforcement.

Compendial standards: Data driven and grounded in science

- Transparent setup process
- Used by manufacturers and regulatory bodies to help ensure the quality of pharmaceutical products, and to facilitate access to affordable medicines*
- Compendial standards are of high value to the pharmaceutical industry because they decrease the development effort of pharmaceutical articles**

PLOS ONE

RESEARCH ARTICLE

Association between US Pharmacopeia (USP) monograph standards, generic entry and prescription drug costs

Irene B. Murimi-Worstell[1,2*], Jeromie M. Ballreich[2,3], Marissa J. Seamans[2,4], G. Caleb Alexander[1,2,5*]

1 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 2 Center for Drug Safety and Effectiveness, Johns Hopkins University, Baltimore, Maryland, United States of America, 3 Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 4 Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 5 Division of General Internal Medicine, Department of Medicine, Johns Hopkins Medicine, Baltimore, Maryland, United States of America

Abstract

Introduction

Journal of Pharmaceutical Sciences 109 (2020) 944-949

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Special Topic Commentary

Commentary on the Benefits of US Pharmacopeial Standards: A Generic Pharmaceutical Industry Survey

Ian K. Warthin*, Julia Berik, Doug Podolsky, Vimala Raghavendran, Ravi Reddy, Judy Chang, Noah Porter, Nicholas Garito

USP, Rockville, Maryland 20852

ARTICLE INFO

ABSTRACT

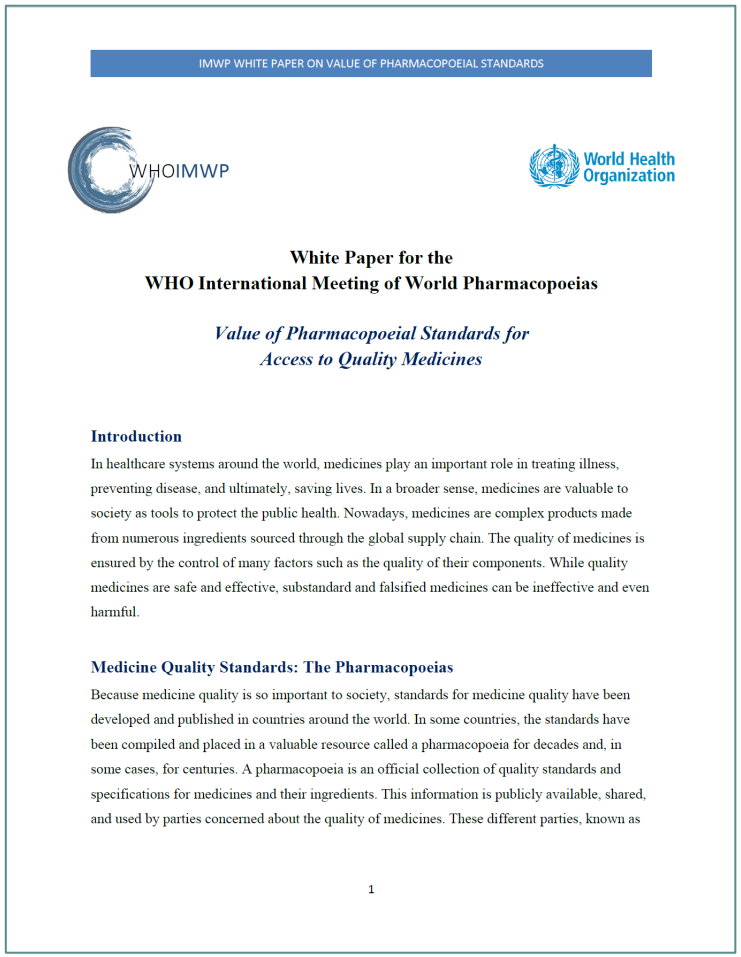
Introduction

Compendial standards such as those developed by USP—the acronym for the independent, scientific, nonprofit organization also known as the United States Pharmacopeial Convention—include documentary standards and physical reference standards (RSs) as well as related programs for medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide. Documentary standards provide users with the name of the ingredient or preparation; the definition; packaging, storage, and labeling requirements; and the specification. The specification consists of a series of tests, procedures for the tests, and acceptance criteria. These tests and procedures require the use of compendial RS materials. Medicinal ingredients and products will have the stipulated identity, strength, quality, and purity if they conform to the requirements of the *United States Pharmacopeia–National Formulary* monograph and relevant general chapters.

During a 5-week period in the fall of 2018, the authors in collaboration with BioInformatics Inc. (Arlington, VA) conducted a blinded online survey of finished-dosage generic drug manufacturing organizations to gain a better understanding of (1) the perceived value of pharmacopeial documentary standards and physical RSs to generic pharmaceutical manufacturers seeking US Food and Drug Administration (FDA) approval for the manufacturing and sale of their products in the US and (2) to

*I.B. Murimi-Worstell et al., PLoS ONE 14 (11) (2019).
**I.K. Warthin et al., J. Pharm. Sci. 109 (2) 944–949 (2020).

Compendial standards in general



IMWP WHITE PAPER ON VALUE OF PHARMACOPOEIAL STANDARDS

WHOIMWP

World Health Organization

White Paper for the
WHO International Meeting of World Pharmacopoeias

Value of Pharmacopoeial Standards for Access to Quality Medicines

Introduction

In healthcare systems around the world, medicines play an important role in treating illness, preventing disease, and ultimately, saving lives. In a broader sense, medicines are valuable to society as tools to protect the public health. Nowadays, medicines are complex products made from numerous ingredients sourced through the global supply chain. The quality of medicines is ensured by the control of many factors such as the quality of their components. While quality medicines are safe and effective, substandard and falsified medicines can be ineffective and even harmful.

Medicine Quality Standards: The Pharmacopoeias

Because medicine quality is so important to society, standards for medicine quality have been developed and published in countries around the world. In some countries, the standards have been compiled and placed in a valuable resource called a pharmacopoeia for decades and, in some cases, for centuries. A pharmacopoeia is an official collection of quality standards and specifications for medicines and their ingredients. This information is publicly available, shared, and used by parties concerned about the quality of medicines. These different parties, known as

1

- White Paper “Value of Pharmacopoeial Standards” by the World Health Organization International Meeting of World Pharmacopoeias:

  Pharmacop(o)eial standards …

  - Facilitate the preparation and assessment of regulatory submission
  - Provide a public mechanism for an independent verification of the quality of a product at any time during its shelf life

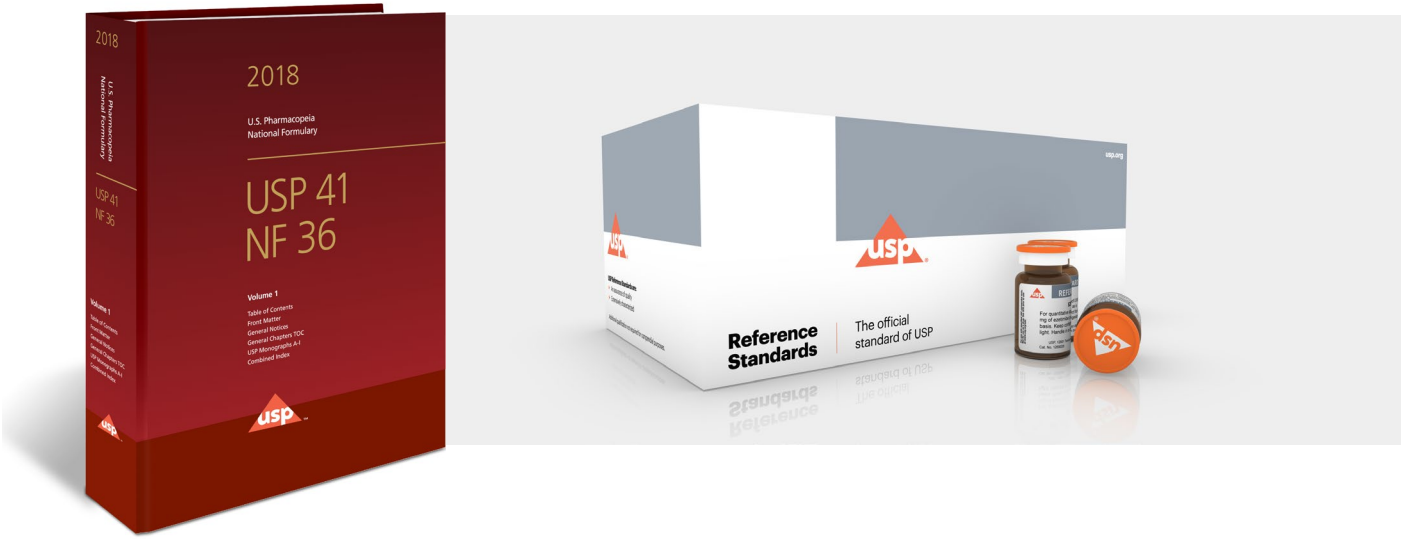
WHO International Meeting of World Pharmacopoeias (IMWP), Value of Pharmacopoeial Standards for Access to Quality Medicines (Oct. 2020). https://www.who.int/docs/default-source/medicines/norms-and-standards/value-of-pharm-stds-updated-final-oct-2020.pdf?sfvrsn=2d4e5052_4

What are conclusive results?

The starting point

Pharmacopoeias establish public compendial standards

- Compendial standards developed in a transparent process
  - Two types of standards
    - Documentary standards (DS, e.g. general chapters, monographs)
    - Physical reference standards (RS)
  - Pharmacopeial RS
    - Almost always primary RS
    - Established by robust collaborative approach
    - Official status when connected to DS
      - As outlined in USP GC <11>



What is a conclusive result?

- When assessing <u>compliance with monographs</u>: Only combination of DS/RS is conclusive/authoritative
  - Ph.Eur., General Text 5.12.
    - Where a European Pharmacopoeia reference standard is referred to in a monograph or general chapter, it represents the official standard that is alone authoritative in case of doubt or dispute.
  - USP General Notices 5.80.
    - Where USP or NF tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.

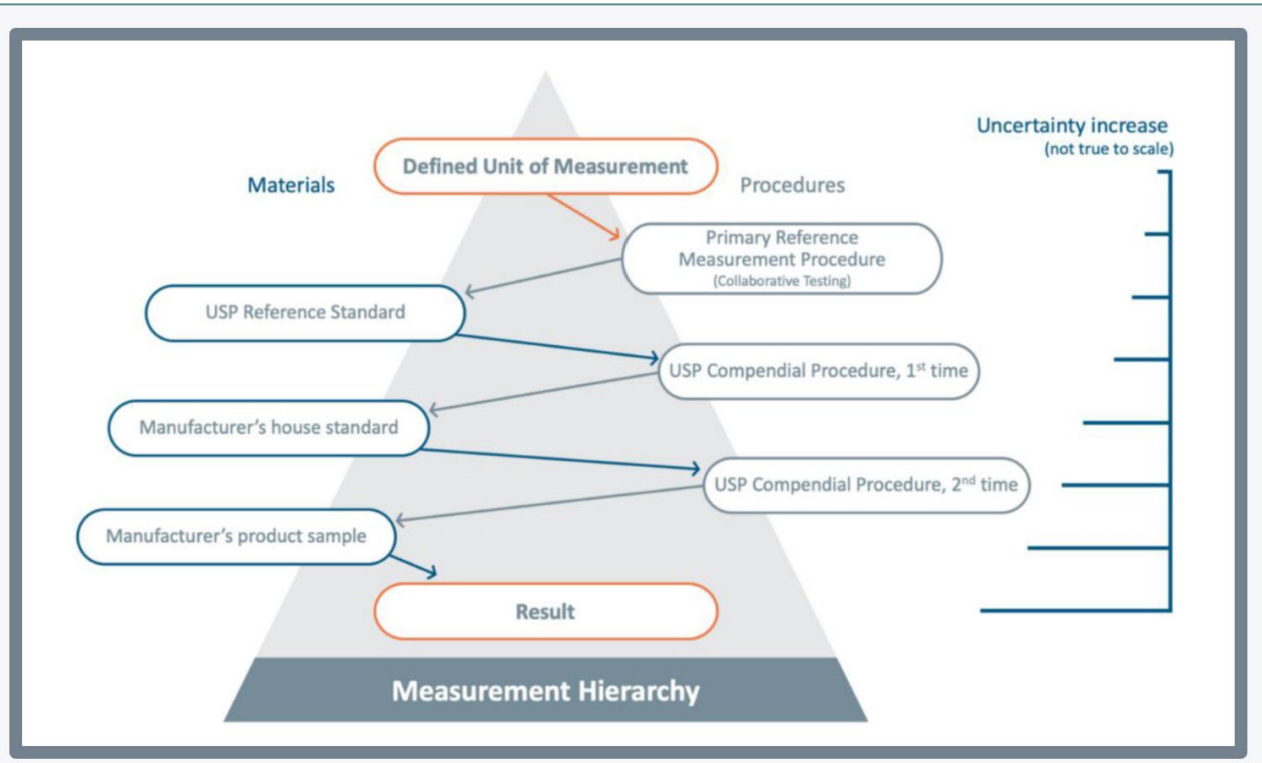
Consequently, other combinations of DS/RS are **NOT** conclusive and may potentially **increase RISK.**

The role uncertainty plays in understanding risk

Uncertainty and risk

Measurement hierarchy

- Each step adds measurement uncertainty (MU)
- Secondary RS (or manufacturer's (in)house standard):
  - Often compared to pharmacopeial RS
  - Comparison inevitably leaves secondary RS with a higher MU than pharmacopeial RS
  - Higher MU also for the testing result (reportable value)
- Guard band principle can visualize uncertainties and the implications

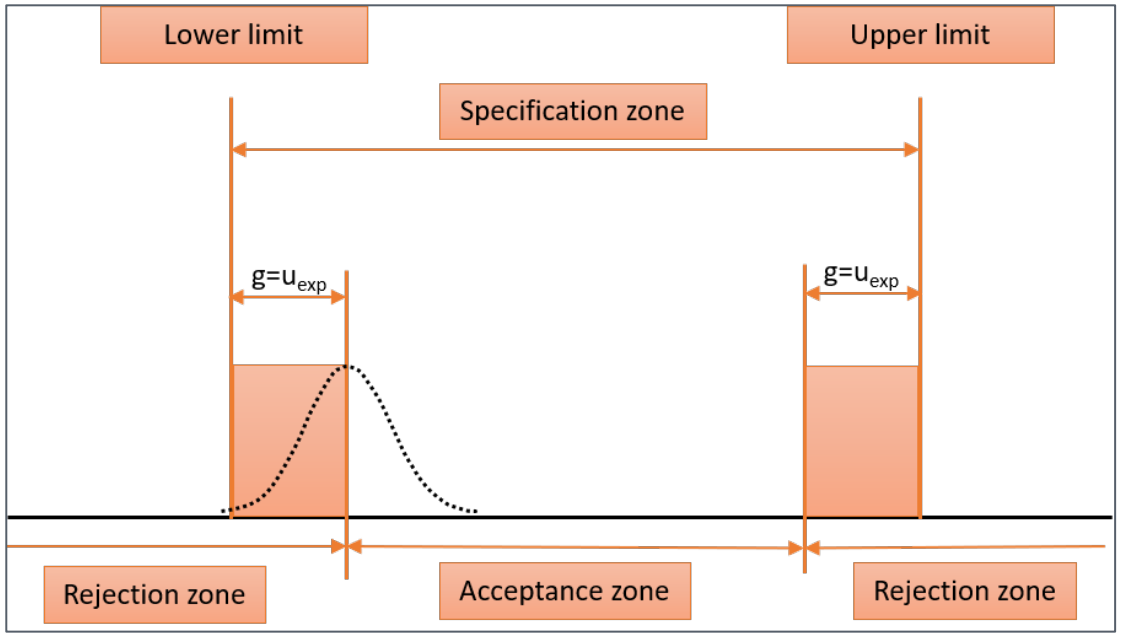


Source:
- Principle adopted from ISO 17511, 2013
- Not all standards are created equal. USP website. https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/not-all-standards-are-created-equal.pdf.

Uncertainty and risk

Guard bands*

- Commonly used
- Consider expanded uncertainties
- Should be as wide as expanded uncertainties
- Have also been suggested for pharmaceutical quality control**



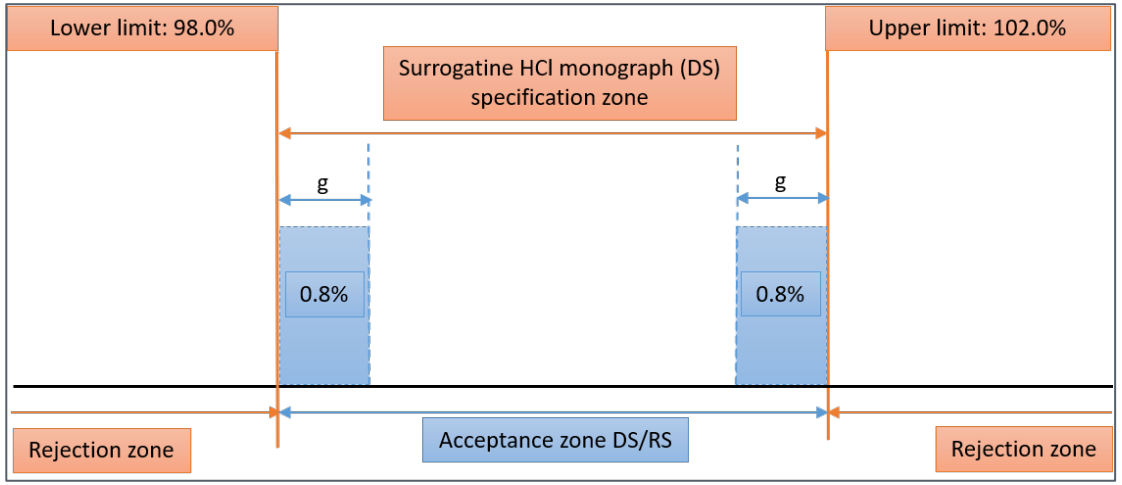
*Eurachem, "Use of Uncertainty Information in Compliance Assessment," 2007

**C. Burgess, Pharm. Tech. 38 (10) 52–58 (2014)
**C. Burgess, et al., "Fitness for Use: Decision Rules and Target Measurement Uncertainty," Pharmacopeial Forum 42 (2) (2016).

Uncertainty and risk: Surrogatine HCl

Monograph situation

- Combination of documentary standard and pharmacopeial reference standard
- Uncertainties not needed for compendial purpose
- Acceptance zone identical with monograph limits

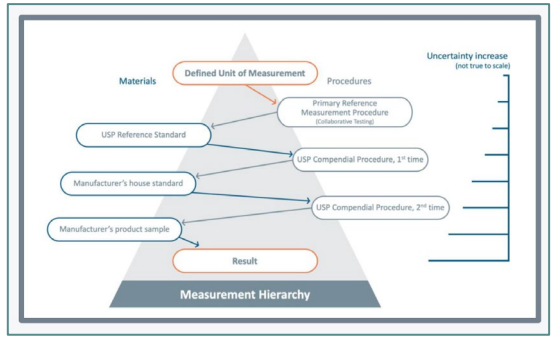


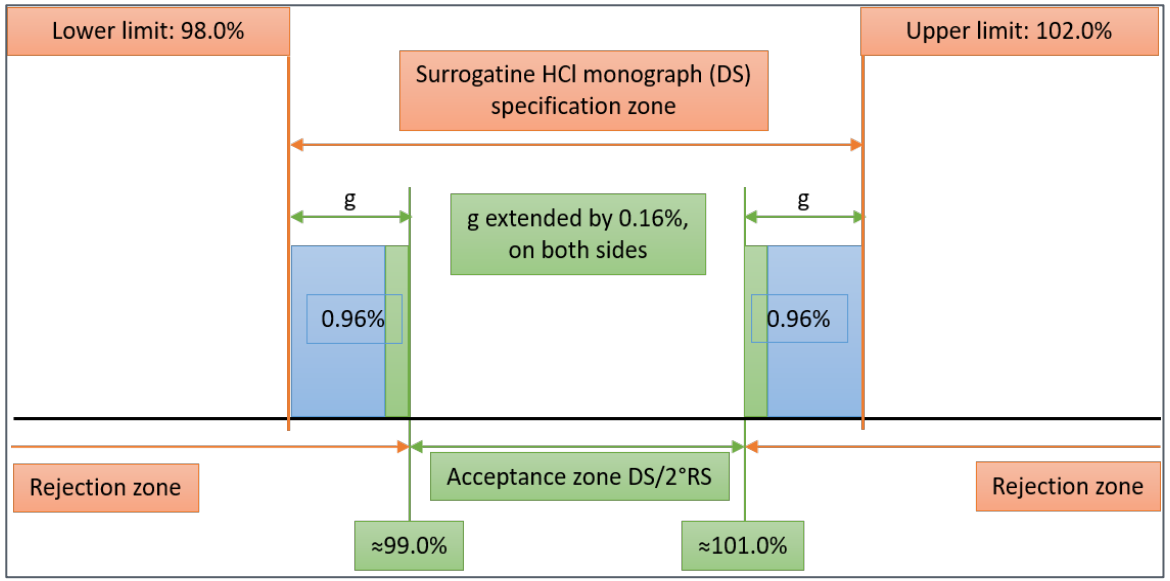
C. Zeine et al., Pharm. Tech. 45 (2) 52–58 (2021).
https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards

Uncertainty and risk: Surrogatine HCl

Using secondary RS

- Additional measurement step – additional uncertainty
- Means extension of guard band – narrowing down acceptance zone to avoid risk of unknown OOS
- In theory, the "full" uncertainty of 0.96% would apply as guard band
- Not really possible for users to estimate adequate narrowing of acceptance zone





C. Zeine et al., Pharm. Tech. 45 (2) 52–58 (2021).
https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards

Uncertainty and risk: Surrogatine HCl

The risk may be compounded, depending on method precision

Expanded uncertainties for reportable values of Surrogatine Hydrochloride, depending on reference standard used and measurement relative standard deviation (RSD) assumed, in %(w/w)	RSD 0.2%	RSD 0.3%	RSD 0.4%	RSD 0.5%
Pharmacopeial reference standard	0.80	1.00	1.23	1.48
Secondary reference standard	0.96	1.29	1.65	2.01

- Depending on precision (relative standard deviation, RSD) of the chromatographic methods used for comparison
- An RSD of 0.2% is realistic, but larger RSD (and lower) are also possible

Inevitably, guard bands widen with transition from pharmacopeial to secondary RS; they also widen with increasing measurement RSD

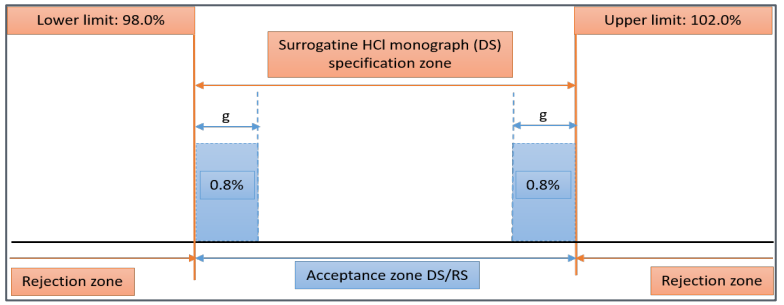
C. Zeine et al., Pharm. Tech. 45 (2) 52–58 (2021). https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards

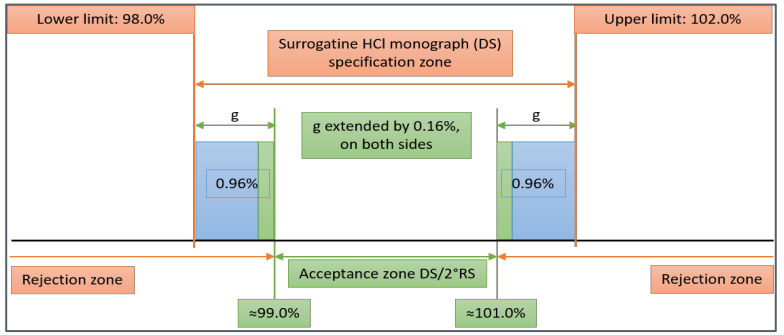
Conclusions

Conclusions

Setup and use of secondary inhouse RS is of challenging complexity

- Using pharmacopeial RS directly wherever possible saves time and energy related to:
  - Inherently larger MU of assigned values of secondary RS, compared to primary (pharmacopeial) reference standards
  - Consequently, larger MU of measurements obtained with those secondary reference standards
  - The difficulty of and effort related to correctly adapting the range of acceptance/rejection zones, compared with the range associated with pharmacopeial reference standards
    - Inappropriate to work with unchanged zones





- Establishing secondary standard always leads to more risk*
- **Remember: Only pharmacopeial RS in combination with documentary standards deliver conclusive results** (e.g. USP General Notices 5.80)

* C. Zeine et al., Pharm. Tech. 45 (2) 52–58 (2021). https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards
T. Hadad-Avadyayev, "Pharmacopeia Standards—Global Teva R&D Perspective," presentation at the 13th International Symposium on Pharmaceutical Reference Standards (Strasbourg, France, March 13–14, 2019)

Final remarks and acknowledgements

- Co-authors (paper published in February 2021 in Pharmaceutical Technology)
  - Steven Walfish, Ravi Reddy, Doug Podolsky (all USP Staff)
  - Jane Weitzel (USP Volunteer, Chair of EC Data Quality and Measurement)
  - https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards

Useful links

- www.usp.org
- www.usp.org/reference-standards
- EMEA Webinar series playlist (USP YouTube Channel)

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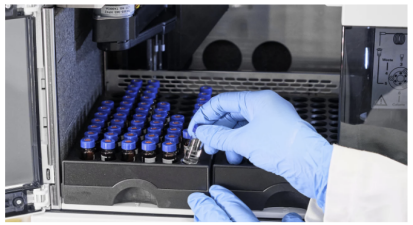
The Value of Pharmacopeial Reference Standards

February 3, 2021
Christian Zeine, Doug Podolsky, Jane Weitzel, Ravi Reddy, Steven L. Walfish
Pharmaceutical Technology, Pharmaceutical Technology-02-02-2021, Volume 45, Issue 2
Pages: 36-42

This article provides an overview of the key risks that can be associated with the use of secondary reference standards (RS) and illustrates scientific challenges associated with transitioning from pharmacopeial RS to secondary RS.



vladim_ka - Stock.adobe.com

Peer-Reviewed

Submitted: Aug. 25, 2020. Accepted: Sept. 8, 2020

Abstract

The US Pharmacopeia and other major pharmacopoeias have established that only the combination of documentary standards and pharmacopeial reference standards (RS) is conclusive and determines compliance to their official quality requirements. Therefore, the use of non-pharmacopeial RS with pharmacopeial methods is inconclusive, and the user takes responsibility at their own risk. Secondary RS are often used for qualitative and quantitative purposes This article provides an overview of the key risks that can be associated with the use of secondary RS based on the measurement uncertainties that are intrinsically connected to the approach, and information that might help mitigate these risks to some extent. Case study examples are included to illustrate scientific challenges associated when

Thank You

Empowering a healthy tomorrow

Stay Connected

christian.zeine@usp.org

Empowering a healthy tomorrow

USP-NF Compendial Update (Nov 2021)

Nov 2021

New Revision Bulletins

- Baclofen Injection Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2021)
- Dextrose Injection Notice and Monograph (posted 19–Nov–2021; official 01–Jun–2022)
- Magnesia Tablets Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Magnesium Carbonate Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Magnesium Hydroxide Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Magnesium Hydroxide Paste Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Magnesium Oxide Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Magnesium Trisilicate Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)
- Milk of Magnesia Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2022)

Nov 2021

New Revision Bulletins

- Metformin Hydrochloride Extended-Release Tablets Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2021)
- Quetiapine Extended-Release Tablets Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2021)
- Starch TS Notice and Monograph (posted 19–Nov–2021; official 01–Dec–2021)
- Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules Notice and Monograph (posted 04–Nov–2021; official 05–Nov–2021) *Previously published as a Pending Notice of Intent to Revise*
- Dexamethasone Tablets Notice and Monograph (posted 02–Nov–2021; official 03–Nov–2021) *Previously published as a Pending Notice of Intent to Revise*

Your APAC representatives

Rocky Qiu
Senior Manager – APAC Strategic Customer Development
Email: rocky.qiu@usp.org
Mobile: +65 8826 6799

Stella Lau
Strategic Customer Development Manager –Southeast Asia
Email: Stella.Lau@usp.org
Mobile: +65 9879 6799

Shin Kim (김신환)
Strategic Customer Development Manager – Korea & Japan
Contact: Shin.Kim@usp.org
Mobile: +82 10 4083 0715

Upcoming Activities in APAC

APAC activities in Jan 2022

1. USP-APEC Center of Excellence for Advanced Therapies Virtual Training Workshop on “Development and Validation of Bioassays for Advanced Therapies”– 20th- 21st Jan (*only for Regulators*)
2. Quality Hour (Live Webinar) – Jan

Questions?

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2. This webinar has been recorded and will be made available free of charge within 2–4 weeks to all attendees who participated in today's webinar.

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The standard of trust