Nitrosamine Impurities

PAI

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The United States Pharmacopeia
Sep8, 2023

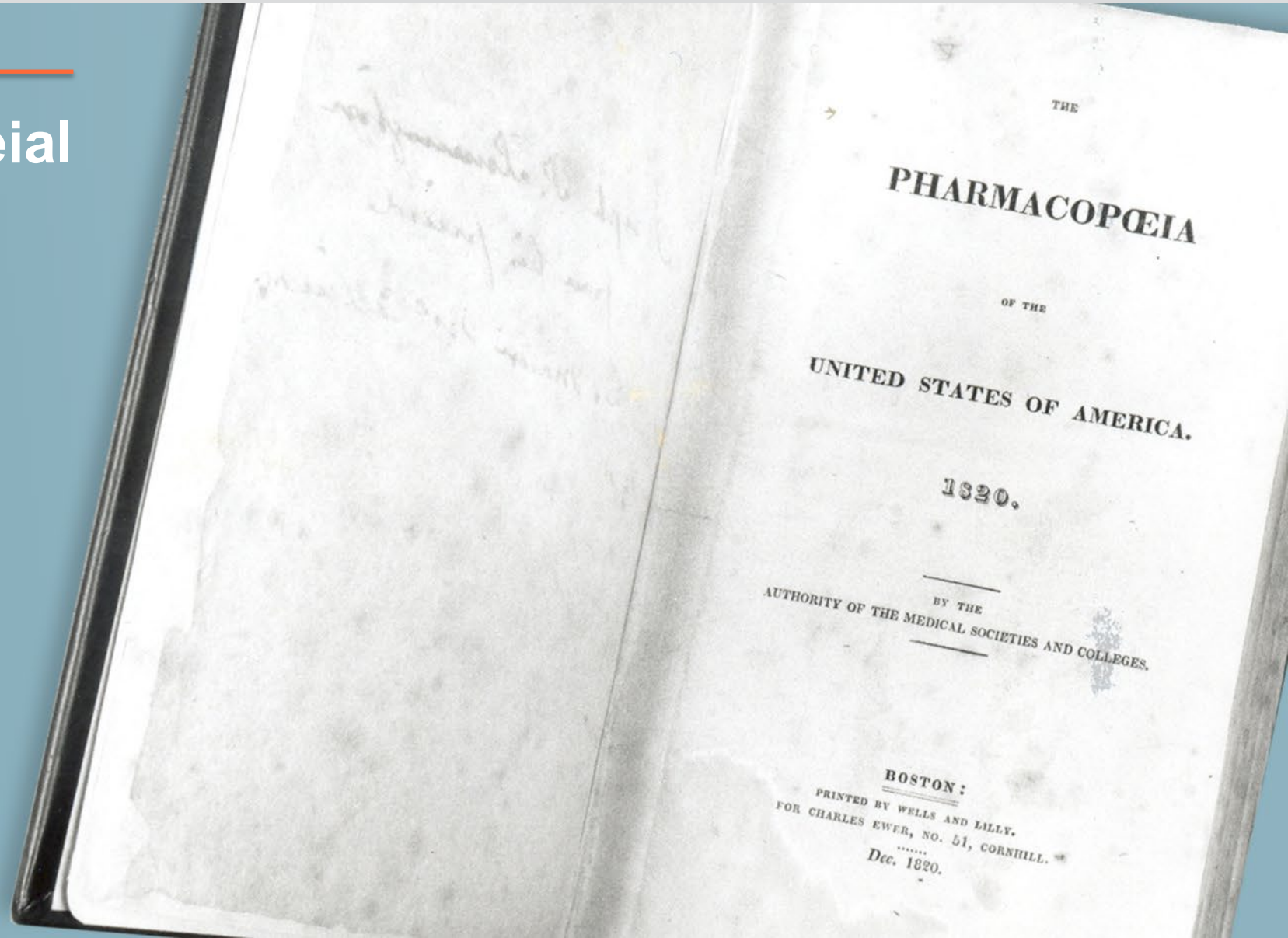
Mission

To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods

Advancing quality for over 200 years

The First Pharmacopeial Convention

- In 1820, 11 physicians gathered in Washington, D.C. to find a solution to the problem of inconsistent preparation of medicines.
- They established a reference book to ensure standardized drug preparation.



USP's convention organizations power our global engagement and impact

FAST FACTS

460+ Total Members

40+ Countries represented

USP standard setting committees
1000 expert volunteers and 200 FDA liaisons

Biologics

Biologics Monographs 1–Peptides & Oligonucleotides
Michael De Felippis

Biologics Monographs 2–Proteins
Wendy Saffell-Clemmer

Biologics Monographs 3–Complex Biologics & Vaccines
Earl Zablackis

Biologics Monographs 4–Antibiotics
Matthew Borer

Biologics Monographs 5–Advanced Therapies
Mehrshid Alai

Small Molecules

Small Molecules 1
Mary Selbel

Small Molecules 2
Justin Pennington

Small Molecules 3
Eric Kesslen

Small Molecules 4
Kim Huynh-Ba

Small Molecules 5
Amy Karren

Over-the-Counter (OTC) Methods & Approaches
Raphael Omaf

Excipients

Simple Excipients
Eric Munson

Complex Excipients
Otilia Koo

Excipients Test Methods
Chris Moreton

General Chapters

General Chapters–Dosage Forms
Martin Coffey

General Chapters–Chemical Analysis
Nancy Lewen

General Chapters–Microbiology

General Chapters–Packaging & Distribution
Renaud Janssen

General Chapters–Measurement & Data Quality
Jane Weitzel

General Chapters–Statistics
Charles Tan

General Chapters–Physical Analysis
Xiaorong He

Healthcare Quality & Safety

Nomenclature & Labeling
Stephanie Crawford

Healthcare Safety & Quality
Melody Ryan

Compounding
Brenda Jensen

Healthcare Information & Technology
Jeanne Tuttle

Dietary Supplements & Herbal Medicines, Food Ingredients

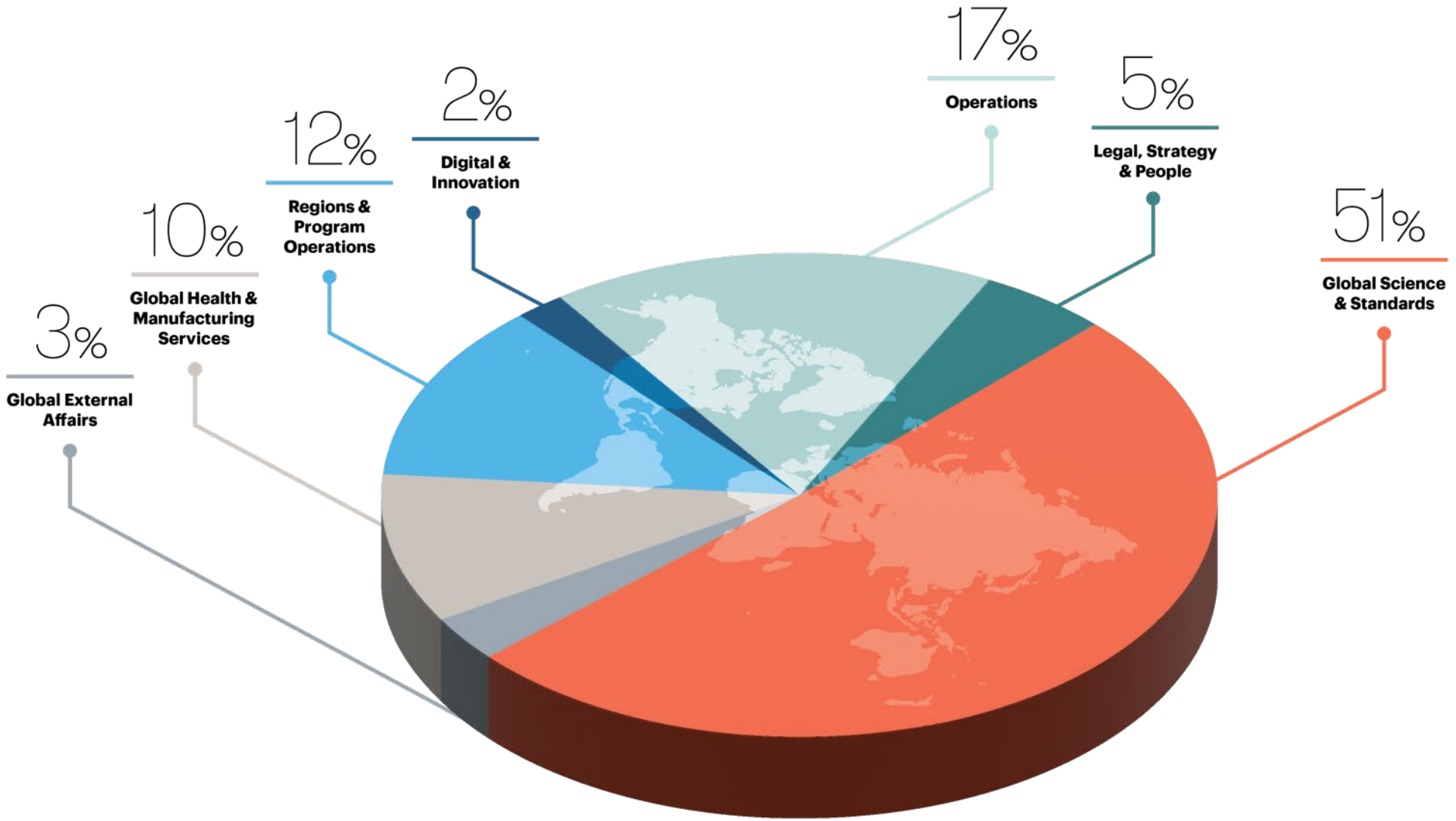
Botanical Dietary Supplements & Herbal Medicines
Robin Marles

Non-botanical Dietary Supplements
Guido F Pauli

Dietary Supplements Admission Evaluation & Labeling
Tieraona Low Dog

Food Ingredients
Jon DeVries

More than 1300 USP staff deliver our global mission



What do USP's people do?

Region	Location	Laboratory & Standard Setting	Engagement (Scientific, Customer, & Stakeholder)	Strategic Support
North America	Frederick, MD	●	●	
	Richmond, VA	●	●	
	Rockville, MD	●	●	●
	Washington, DC		●	
Latin America	Brazil		●	
	Chile		●	
	Columbia		●	
	Mexico		●	
Central America	Guatemala		●	
Asia	China		●	
	Japan		●	
	Knowledge Park, Hyderabad, India	●	●	●
	HITEC City, Hyderabad, India		●	●
	Singapore		●	
	South Korea		●	
Middle East and Africa	Ghana	●	●	
	Jordan		●	
Europe	Basel, Switzerland		●	
Donor funded work (e.g., PQM+, World Bank, etc.)	Bangladesh, Ethiopia, Ghana, Indonesia, Kenya, Nepal, Nigeria, Pakistan, Uzbekistan		●	
	Rockville, MD	●	●	●

Engaging with regulators to ensure quality of medicines

- USP standards are tools that regulators utilize to ensure quality
- USP frequently comments on proposed regulations and guidance
- Regulatory agencies are involved in standard setting committees
- In the US, regular engagement with FDA, CMS, NIOSH

We partner with regulatory bodies worldwide

World Health Organization

Official Relations Framework for Engagement of Non-State Actors (FENSA)

ECOSOC United Nations

NGO Consultative Status
United Nations Economic & Social Council

ICH harmonisation for better health

Observer Status
International Council for Harmonisation

APEC Asia-Pacific Economic Cooperation

APEC Board Member; Center of Regulatory Excellence

NEPAD TRANSFORMING AFRICA

African Medicines Quality Forum
Reference Center of Regulatory Excellence (RefCORE)

Pan American Health Organization
World Health Organization Regional Office for the Americas

Official Observer Status
Non-State Actor

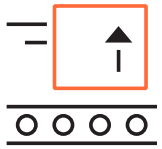
Advocate for medicines quality issues in global policies
Consultations at different levels of governments

More than 7,500 USP standards support medicine quality across the supply chain

Manufacturing

- Standards
  - Drug and API monographs
  - Compounding monographs
  - General chapters
  - Characterized reference materials
- Manufacturer capability building
  - Advanced Manufacturing, incl. Pharmaceutical Continuous Manufacturing
  - USAID-funded PQM+ program
  - API and excipient verification

Distribution



- Standards
  - Good Distribution Practices
  - Packaging and distribution

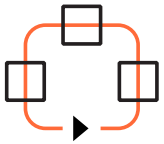
Administration

- Standards
  - Labeling
  - Nomenclature
- COVID-19 Vaccine Handling Toolkit

Collaborations

- USAID-funded PQM+ program for regulatory capability building in low- and middle- income countries
- APEC Center of Excellence on product and supply chain quality
- Co-hosted summits with WHO to advocate for medicines quality around the world
- Collaboration towards pharmacopeial convergence within the Pharmacopeial Discussion Group (PDG)

Supply chain diagnosis and monitoring



- Medicine Supply Map – identifying, characterizing and quantifying risk in the upstream supply chain

USP Compendia

U.S. Pharmacopeia and the National Formulary with the Pharmacopeial Forum (USP-NF/PF)

- 7,500+ Official Documentary Standards for APIs, Excipients, Drug Products, and more for FDA-approved drugs.

USP-NF Compounding Compendia

- 300+ Official Document Standards from the USP-NF for pharmacists and healthcare practitioners including compounding methods, preparations, and more.

USP Dictionary of United States Adopted Names (USAN) and International Drug Names

- Contains 44,000+ substances with International Nonproprietary Names (INNs), British Approved Names, Japanese Accepted Names, brand names, Unique Ingredient Identifier (UNII) codes, manufacturers, official USP–NF names, molecular weights, graphic formulas, pharmacologic and/or therapeutic categories, and pronunciations.

Food Chemicals Codex (FCC/FCCF)

- 1,300+ Document Standards for the food industry to verify the identity, quality, and purity of the food ingredients

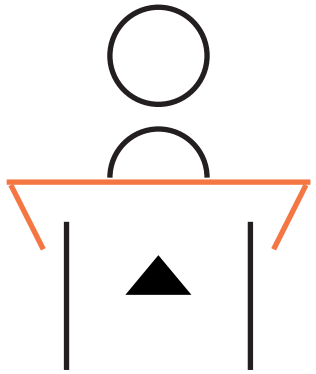
Dietary Supplements Compendium (DSC)

- 4,000+ Document Standards for the dietary supplement industry to verify the identity, strength, quality, purity, packaging and labeling.

Herbal Medicine Compendium (HMC)

- 59 Published Documentary Standards of herbal ingredients used in herbal medicines.

USP Education
Connecting You to Quality



People around the world rely on USP's world-class standards for the supply of safe, quality medicines.

Who better to provide education and training for these standards than experts from the organization involved in creating them?

25,000
students per year

150,000
since 2000

Nitrosamines Course	Formats
USP <1469> Nitrosamines Impurities with Laboratory Demonstration	Classroom/Lab
USP <1469> Nitrosamines Impurities On-Demand Video Tutorials	On-demand
Risk Assessment for a Nitrosamine Contamination of Peptide APIs Manufactured by Solid-Phase Peptide Synthesis (SPPS)	On-demand
USP 1469 Nitrosamines Impurities Q&A Session	On-demand Live Webcast
USP <1469> Nitrosamines Impurities	On-demand Classroom Live Webcast
USP <1469> Nitrosamines Impurities with Laboratory Demonstration	Classroom/Lab
USP <1469> Nitrosamines Impurities On-Demand Video Tutorials	On-demand

Visit USP Education on the Web or Contact Us

USP Verification Programs

USP Dietary Supplement Verification

Launched 2002

USP Dietary Ingredient Verification

Launched 2004

Dietary Ingredients, Traditional Chinese Medicine Ingredients, Ayurvedic Medicine Ingredients

USP Active Pharmaceutical Ingredient Verification

Launched 2006

USP Excipient Verification

Launched 2006

USP Products
Comprehensive solution for your analytical needs

Official USP Reference Standards

- 4,000+ Highly characterized materials when used with USP Documentary Standards provide conclusive results to ensure quality.

Analytical Reference Materials†

Well characterized substances appropriate for a range of analytical applications, when USP RS is unavailable or not applicable

- Biological Analytical Reference Materials
  - A growing catalog of materials for analytical research and testing of peptides, cell lines, r-proteins and antibodies.
- Pharmaceutical Analytical Impurities
  - 350+ (and growing) readily-available impurities supported with detailed documentation for the pharmaceutical industry.
- FCC Analytical Materials
  - Fit-for-purpose materials designed specifically for the food industry.

†Analytical Reference Materials are different from official USP Reference Standards. Analytical Reference Materials are not required for compendial compliance.

USP Nitrosamines Solutions

Sections

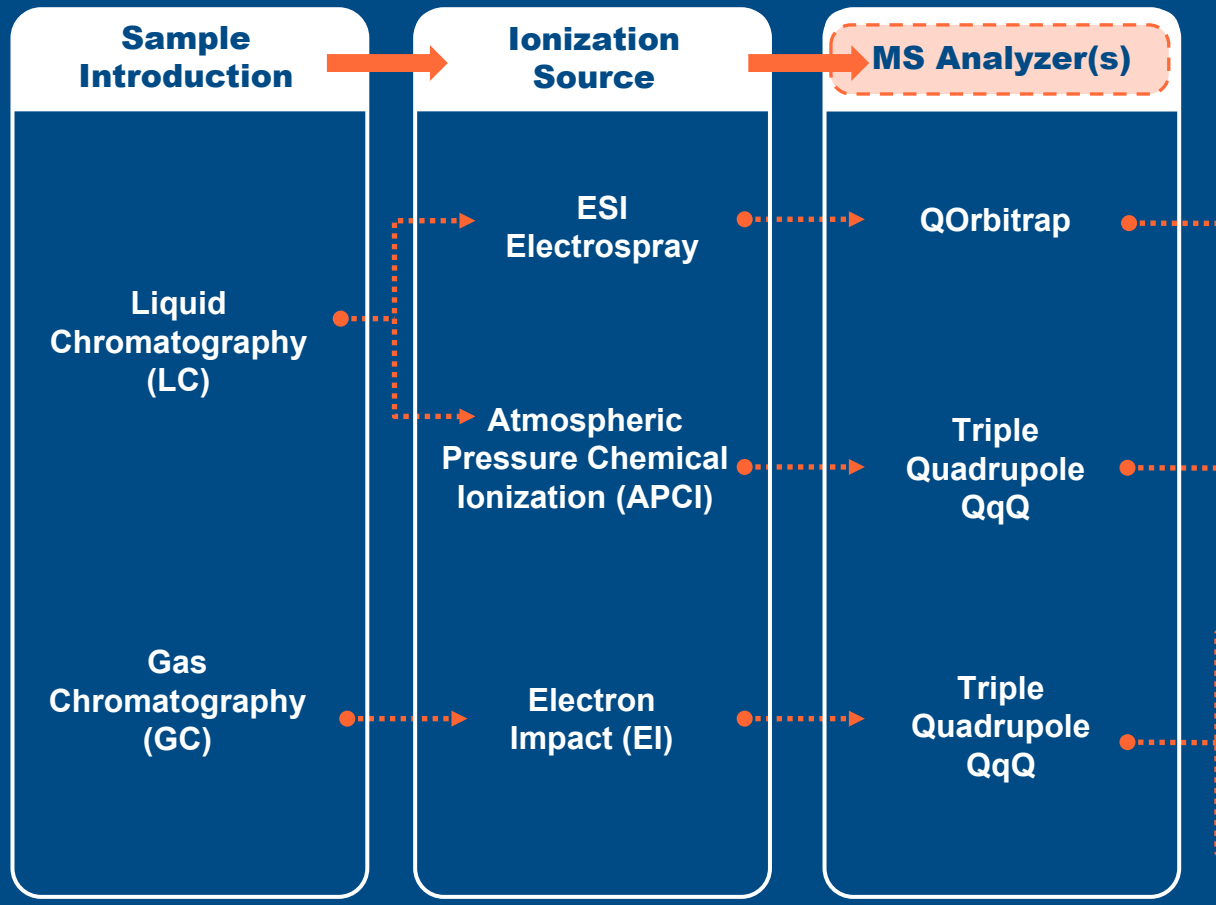
1. **USP-NF General Chapter <1469>--** *Nitrosamine Impurities* & **Reference Standards**
2. **Nitrosamines Exchange**
   - Online community
   - **Analytical Hub**
3. **Pharmaceutical Analytical Impurities** (PAIs) - simple nitrosamines & NDSRIs
4. Additional Resources: USP **publications, events & activities**

General Chapter <1469>

Content

1. Introduction
2. Nitrosamine impurities
3. Sources of nitrosamines
4. Nitrosamine risk assessments – development of a control strategy
5. Limits of nitrosamine
6. Testing for the presence of nitrosamines
7. Test method performance characteristics of nitrosamine methods
8. Analytical procedures
9. Additional sources of information

General Chapter <1469> Test Procedures



Use of internal standard:
- Account for possible losses during workup or due to the thermal instability inherent to several N-nitrosamines
- Minimize repeatability issues

Methods

1

HPLC-HRMS (QOrbitrap)
Procedure 1: Quantitation of NDMA, NDEA, NDIPA, NEIPA, NMBA, NDBA, and NMPA in selected sartans by HPLC–HRMS
LC Column: L43 - PFP

2

HPLC-APCI-QqQ
Procedure 3: Quantitation of NDMA, NDEA, NDIPA, NEIPA, NMBA, and NDBA in selected sartans by HPLC–MS/MS (Using Internal standards NDMA-d6, NMBA-d3, NDEA-D10, NDBA-D18
LC Column: L1 – C18

3

GC-MS/MS (Headspace) GC-EI-QqQ
Procedure 2: Quantitation of NDMA, NDEA, NDIPA, and NEIPA in selected sartans by GC–MS (using Internal Standard NDMA-d6)

4

GC-MS/MS (Direct injection) GC-EI-QqQ
Procedure 4: Quantitation of NDMA, NDEA, NDIPA, NEIPA, NMPA, and NDBA in selected sartans by GC– MS/MS (triple-quad) – (Using internal standards NDMA-13C-d6)

Nitrosamines Exchange

An online knowledge-based community on all-things nitrosamines

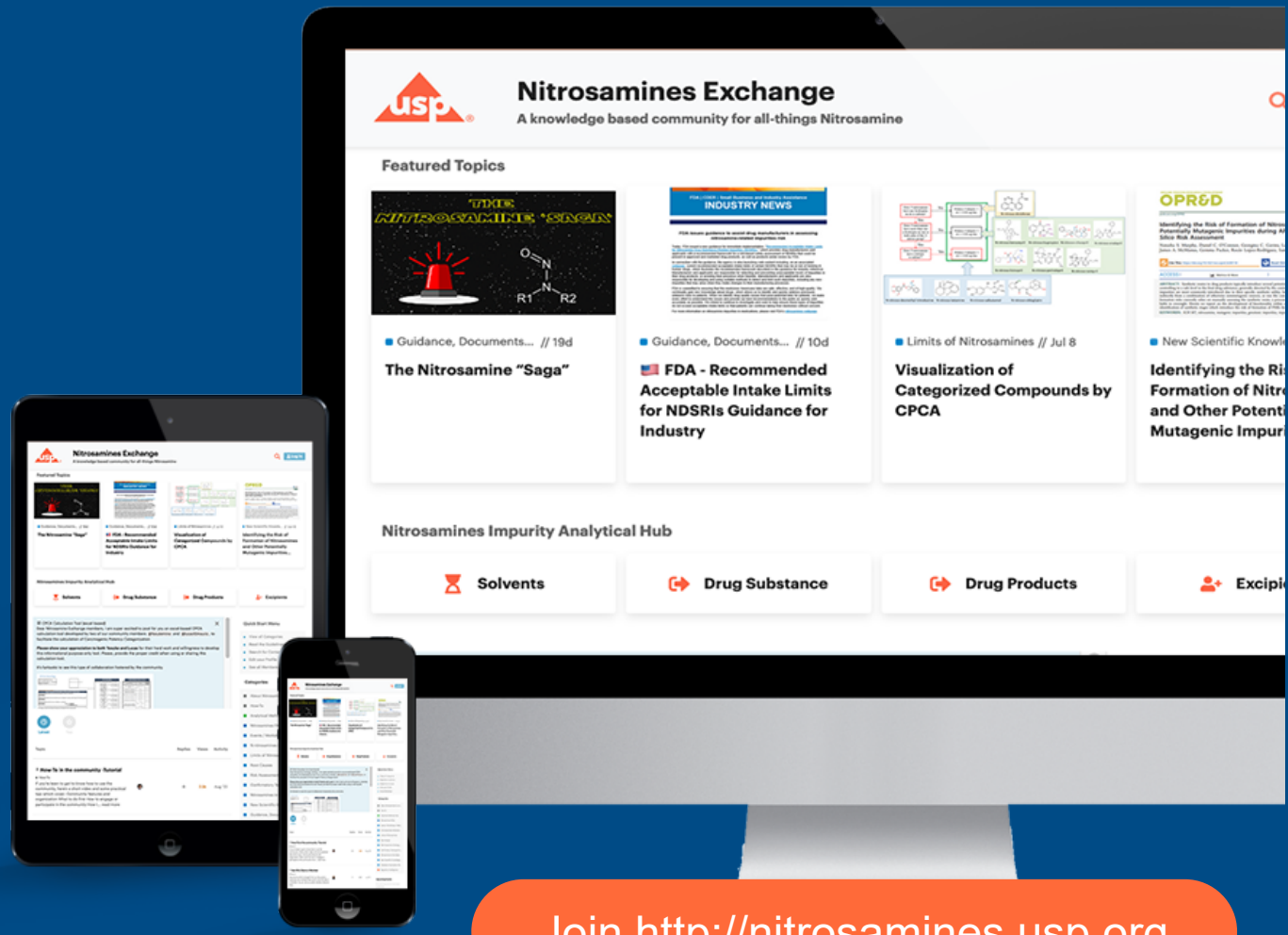
2800+
Members

90
Countries

Ability to translate text between

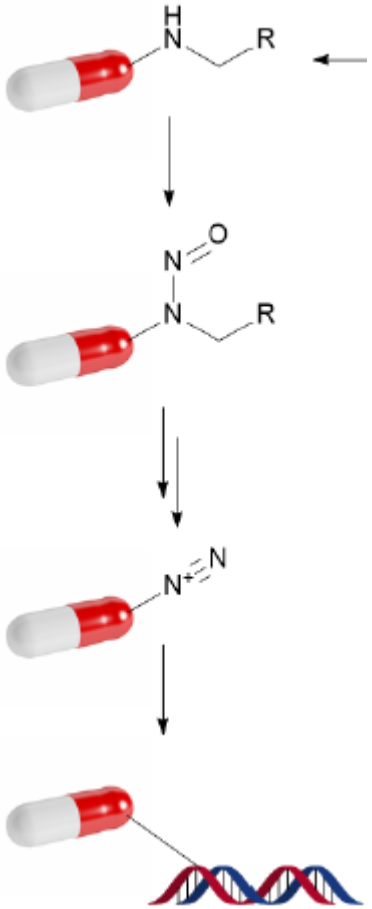
22
Languages

Analytical-Hub



Join http://nitrosamines.usp.org

Next Challenge… NDSRIs



12,000+ USP DB

4,848 APIs (40.4%)

3,552 Impurities (29.6%)

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Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Global Health

The Landscape of Potential Small and Drug Substance Related Nitrosamines in Pharmaceuticals

Joerg Schlingemann[a,1,*], Michael J. Burns[b,1,*], David J. Ponting[b], Carolina Martins Avila[b,f], Naiffer E. Romero[c], Mrunal A. Jaywant[c], Graham F. Smith[d], Ian W. Ashworth[e], Stephanie Simon[a], Christoph Saal[a], Andrzej Wilk[c]

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GSRS

ABSTRACT

This article reports the outcome of an *in silico* analysis of more than 12,000 small molecule drugs and drug impurities, identifying the nitrosatable structures, assessing their potential to form nitrosamines under relevant conditions and the challenges to determine compound-specific AIs based on data available or read-across approaches for these nitrosamines and their acceptance by health authorities. Our data indicate that the presence of nitrosamines in pharmaceuticals is likely more prevalent than originally expected. In total, 40.4 % of the analyzed APIs and 29.6 % of the API impurities are potential nitrosamine precursors. Most structures identified through our workflow could form complex API-related nitrosamines, so-called nitrosamine drug substance related impurities (NDSRIs), although we also found structures that could release the well-known small and potent nitrosamines NDMA, NDEA, and others. Due to common structural motifs including secondary or tertiary amine moieties, whole essential drug classes such as beta blockers and ACE inhibitors are at risk. To avoid the risk of drug shortages or even the complete loss of therapeutic options, it will be essential that the well-established ICH M7 principles remain applicable for nitrosamines and that that the industry and regulatory authorities keep an open communication not only about the science but also to make sure there is a good balance between risk and benefit to patients.

The Landscape of Potential Small and Drug Substance Related Nitrosamines in Pharmaceutical. Journal of Pharmaceutical Science Nov'23 - https://doi.org/10.1016/j.xphs.2022.11.013

Pharmaceutical Analytical Impurities (PAIs)

Nitrosamine PAIs available at the USP Store

Simple nitrosamines & NDSRIs (and more to come...)

Item Number	Item Description	Associated API	Status
1A03930	N-Nitrosodipropylamine Solution		Available
1A04020	1-Methyl-4-nitrosopiperazine (MNP) Solution	Rifampicin	Available
1A04060	N-Nitrosopyrrolidine (NPYR) Solution	NA/54 APIs	Available
1A04190	1-Cyclopentyl-4-nitrosopiperazine (CPNP) Solution	Rifapentine	Available
1A04080	1-(2-Methoxyphenyl)-4-nitrosopiperazine Solution		Available
1A04100	4-Nitrosopiperazine-1-ethanol solution Solution		Available
1A04140	4-Nitroso-1-(4-fluorobenzoyl)piperazine Solution		Available
1A04380	N-Nitroso Dabigatran Etexilate		Available
1A04400	N-Nitrosoiminodiacetic acid		Available
1A04410	4-Nitrosopiperazine-1-ethanol		Available
1A04420	1-Benzhydryl-4-nitrosopiperazine		Available
1A04440	2-(4-Nitrosopiperazin-1-yl)pyrimidine		Available
1A04130	1-Benzhydryl-4-nitrosopiperazine Solution (1-benzhydryl-4-nitrosopiperazine)		Available
1A04200	N-Nitroso Metoprolol Solution (N-(2-hydroxy-3-(4-(2-methoxyethyl)phenoxy)propyl)-N-isopropylnitrous amide)	Metoprolol	Available
1A04230	N-Nitroso Propranolol Solution (1-[(1-Methylethyl)nitrosoamino]-3-(1-naphthalenyloxy)-2-propanol)	Propranolol	Available
1A03950	N-Nitrosopiperidine Solution (1-Nitrosopiperidine)		Available
1A04220	N-Nitroso Atenolol Solution	Atenolol	Coming Soon
1A04250	N-Nitroso Bisoprolol Solution	Bisoprolol	Coming Soon
1A04000	N-Nitroso Duloxetine Solution		Coming Soon
1A04240	N-Nitroso Labetalol Solution	Labetalol	Coming Soon
1A03980	N-Nitroso Nortriptyline Solution		Coming Soon
1A04030	N-Nitroso Rasagiline Solution		Coming Soon

Additional Resources

Published Papers


Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

Pharmaceutical Biotechnology

A GC-MS/MS method for trace level quantification of six nitrosamine impurities (NDMA, NDEA, NEIPA, NDIPA, NDPA, and NDBA) in commercially used organic solvents: Dichloromethane, ethyl acetate, toluene, and o-xylene

Eswara Raju Kosuri[a,*], Mayank Bhanti[a], Mrunal A Jaywant[a], Mark Han[b], Xiaochun Wang[b], Marcus Obeng[b]

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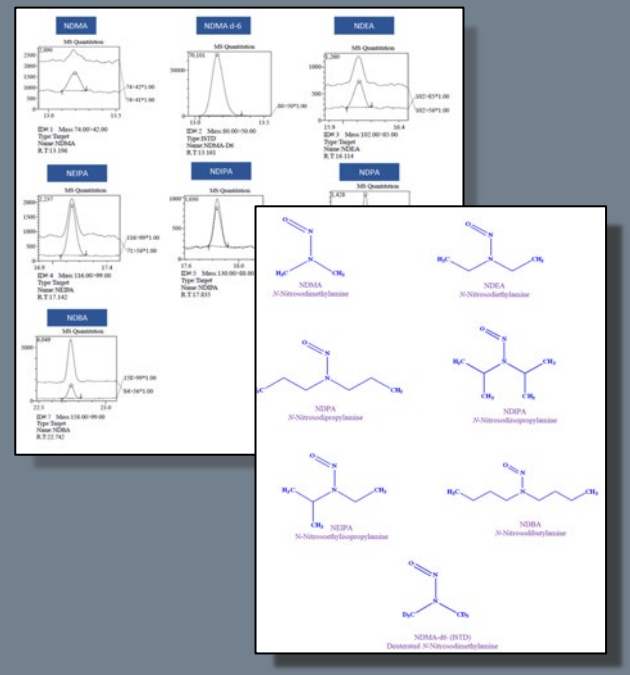


Additional Resources

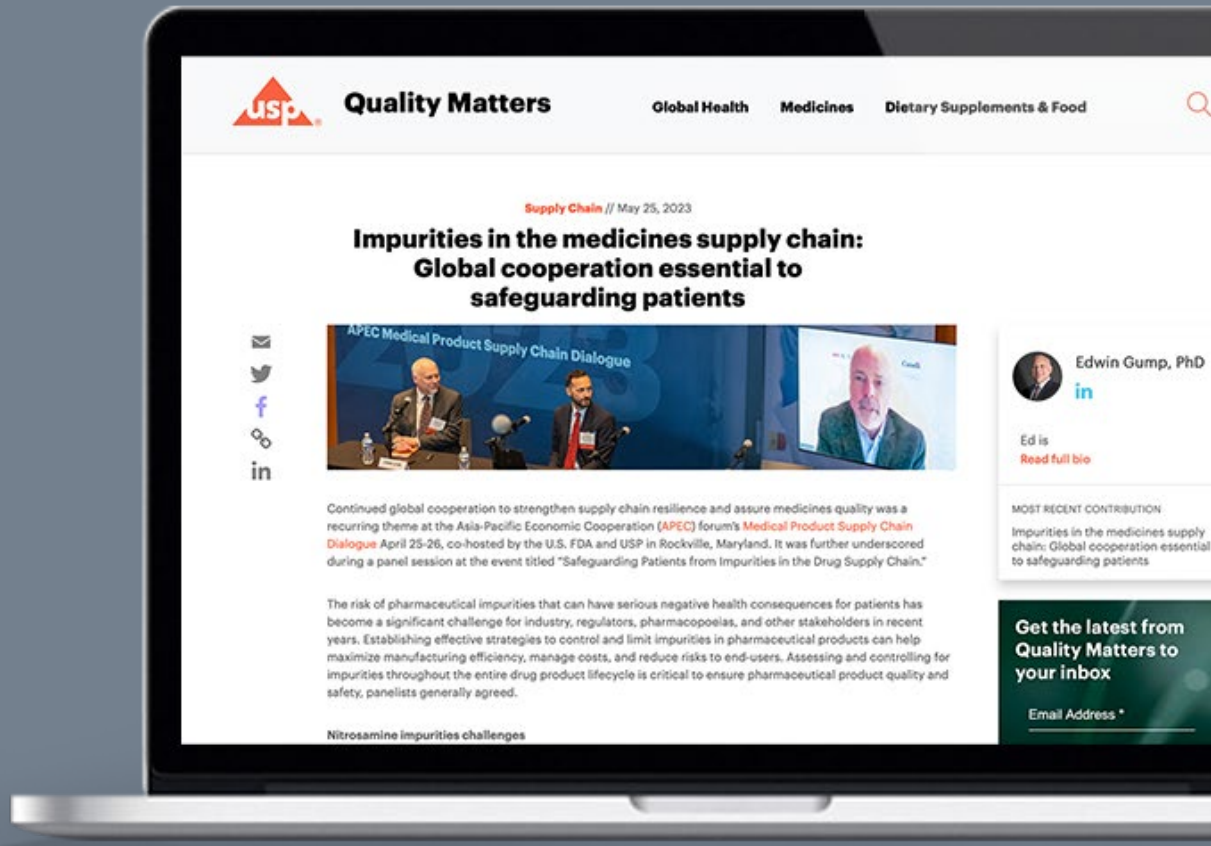
Planned Activities

- Method for NDSRIs
- Nitrite & Nitrates in Excipients
- Risk Assessment Tool
- Laboratory Demonstration Videos
- Webinars
- App Notes

Additional Resources: Planned activities

USP Blogs & Interviews

- **Impurities in the medicines supply chain: Global cooperation essential to safeguarding patients**
  - USP Quality Matters blog by Ed Gump, PhD, USP, VP of Small Molecules
- **Insights from India: Q&A with USP nitrosamines expert**
  - USP Quality Matters blog by Mrunal Jaywant, PhD, USP India, VP of Research & Development
- **Understanding the Impact Nitrosamine Impurities Can Have in the Work of Pharmacy Professionals**
  - *Pharmacy Times* interview with Naiffer Romero, MSc, MPH, USP, Principal Scientist - Scientific Affairs & Community Manager, USP Nitrosamines Exchange



Post Survey for Nitrosamines Impurities workshop- (Japan) 8 September 23

- Your input will be used to plan and improve future USP event. Please help us by providing your feedback. Your help is greatly appreciated!

Questions

The standard of trust