

Promoting the
Quality of
Medicines Plus

Nitrosamines Exchange: A Global Knowledge Hub

Frederick Meadows, Ph.D.

Senior Technical Advisor – Supply Chain Management/CMC

November 30, 2023



Shared vision

PQM+ is a cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low-and middle-income countries.



USAID
FROM THE AMERICAN PEOPLE

+



USP's global mission

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



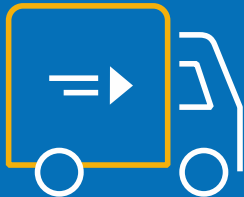
PQM+ Objectives

1



Improve **governance** for medical product quality assurance systems

2



Improve country and regional **regulatory systems** to assure the quality of medical products in the public and private sectors

3



Optimize and increase **financial resources** for medical product quality assurance

4



Increase **supply** of quality-assured essential medical products of public health importance

5



Advance global medical products quality assurance learning and operational agenda

PQM+ is building GMP capacity for decentralized manufacturing in Africa and Asia

Africa: Supporting 16 manufacturers of 12 different products in 5 countries.

Asia: Supporting 18 manufacturers of 10 different products in 6 countries.



Essential Medicines Approvals in 2023

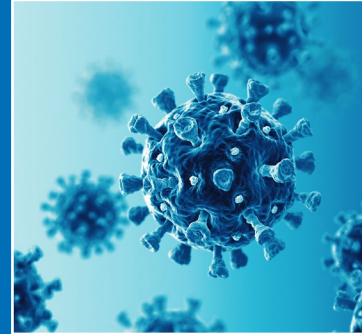
PQM+ supported the WHO PQ of the following essential medicines:

- Zinc sulphate in Pakistan (1st WHO PQ syrup in-country)
- Zinc sulphate in Nigeria (1st WHO PQ in West Africa)
- Albendazole in India (facility approved by WHO)

Antivirals for the treatment of COVID-19

In Pakistan:

- PQM+ supported the technology transfer of remdesivir to a manufacturer
- PQM+ is supporting a Pfizer-MPP sublicensee toward local manufacture of Paxlovid



Advanced Manufacturing Technology

- PQM+ and collaborators developed an efficient rifapentine API synthesis process.

Nitrosamines Pose Health Risks Across the Pharmaceutical Industry

Carcinogenic Genotoxic

Form by nitrosating agents in the presence of secondary or tertiary amines in APIs, impurities, solvents, catalysts...

Nitrosating agents can form from low levels of present nitrites and other impurities

Achieving acceptable intake (AI) level is a challenge:

- Difficult to control in manufacturing
- Difficult to analyze

Exposure is greater in foods than pharmaceuticals

Lack of nitrosamine drug-substance-related impurities (NDSRIs) data impacts:

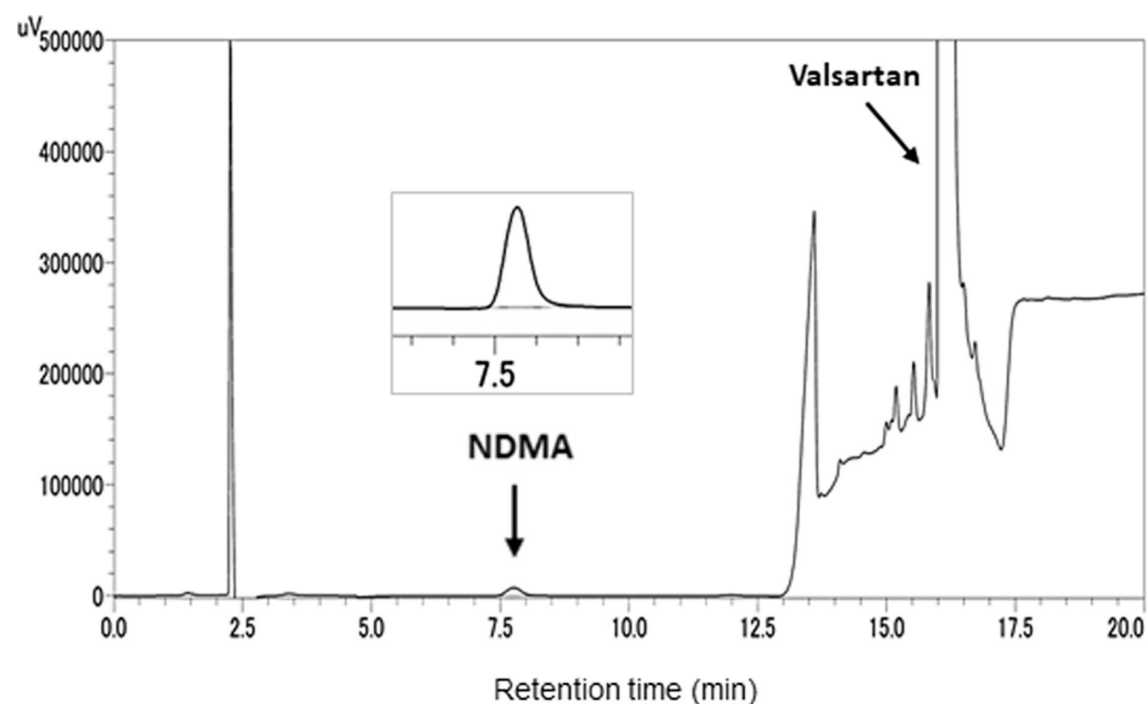
- Toxicity knowledge
- Development of test methods
- Ability to make AI calculations

Nitrosamines Discovered in Pharmaceuticals

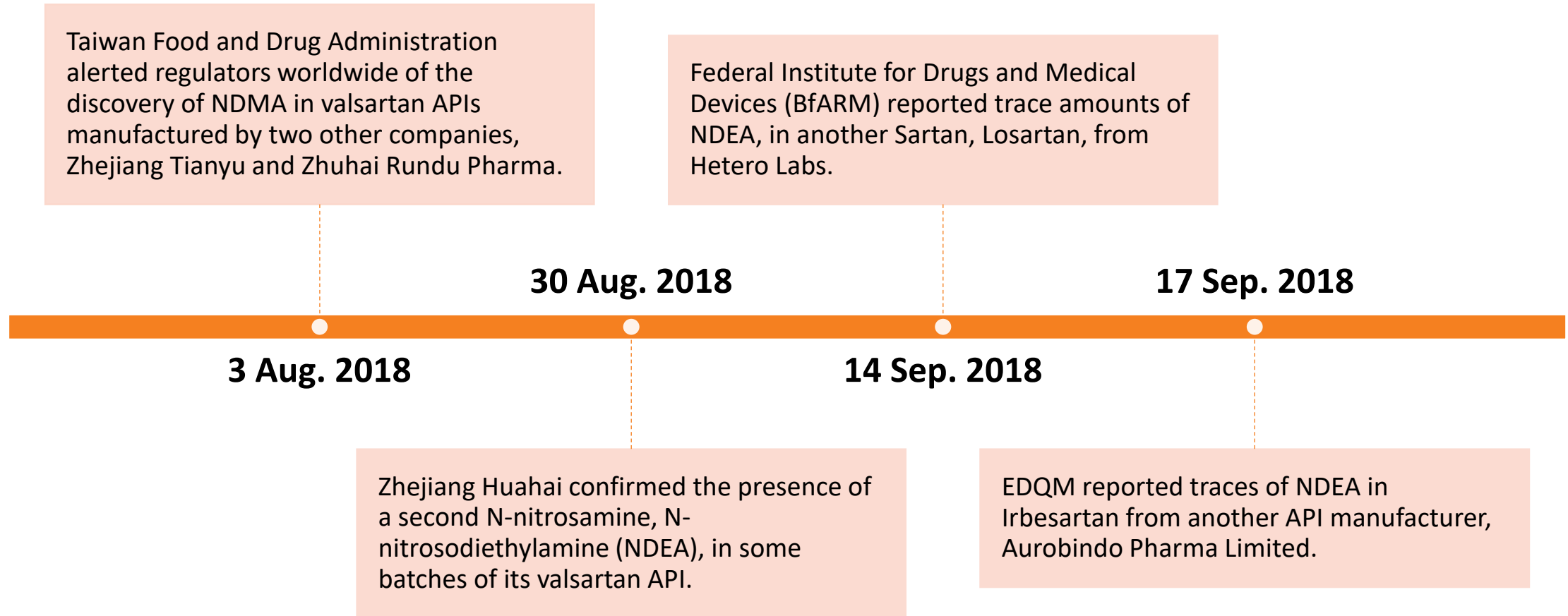
Timeline

- **6 June 2018:** Zhejiang Huahai Pharmaceuticals was informed by a customer of an unexpected impurity in the manufacturer's valsartan API
- **20 June 2018:** After an initial investigation, Zhejiang Huahai sent a letter to its customers informing them of the presence of “a previously unknown impurity that may have genotoxic potential”
- Zhejiang Huahai contacted its customers again, stating that the impurity in question was *n*-nitrosodimethylamine (**NDMA**) and that this was likely to be process related
- **July to August 2018:** FDA and EMA inspected drug manufacturing facility

NDMA Discovery

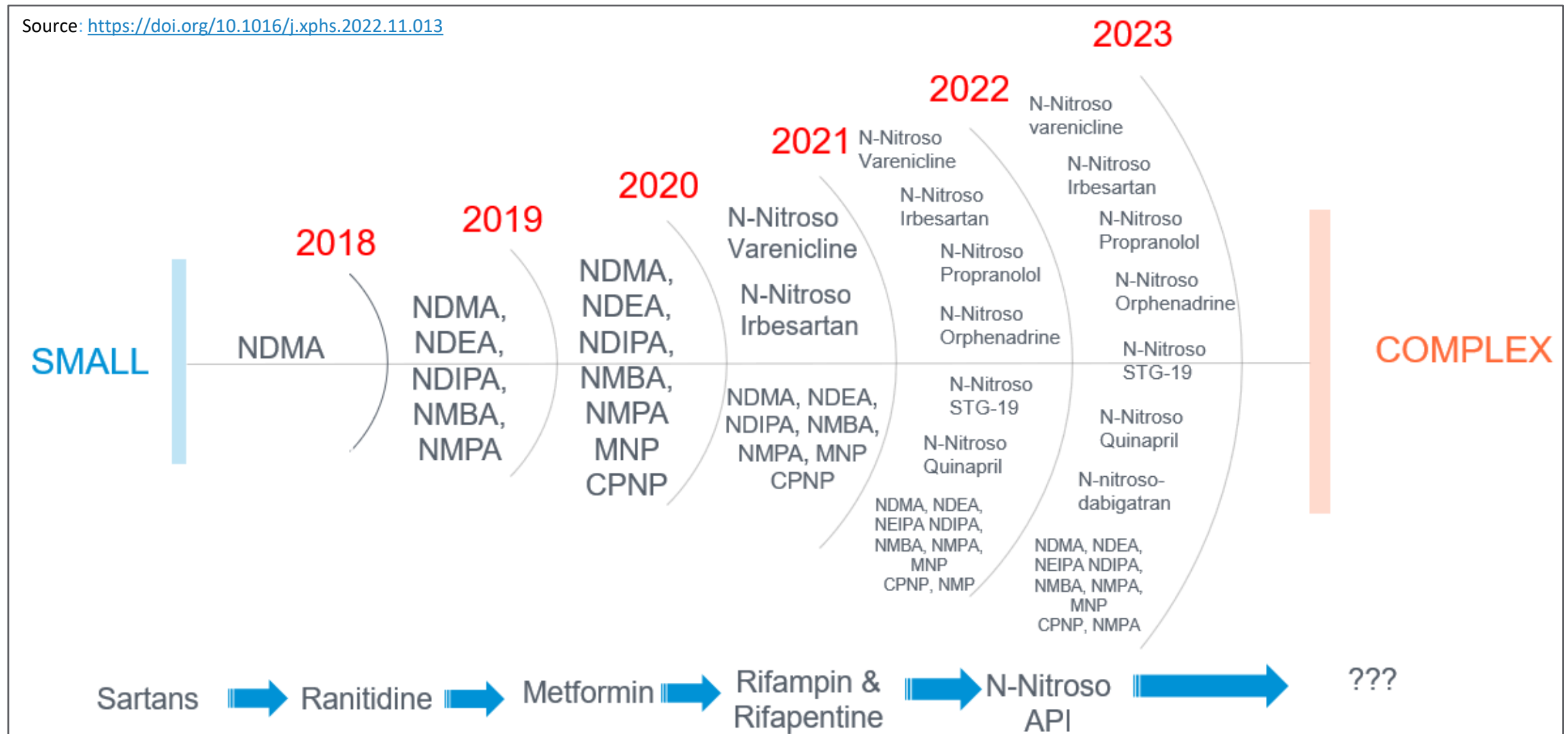


Regulatory Concerns and Awareness



Knowledge about Nitrosamines Is Evolving

Source: <https://doi.org/10.1016/j.xphs.2022.11.013>



Next Challenge...NDSRIs



Contents lists available at ScienceDirect

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

^a Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany

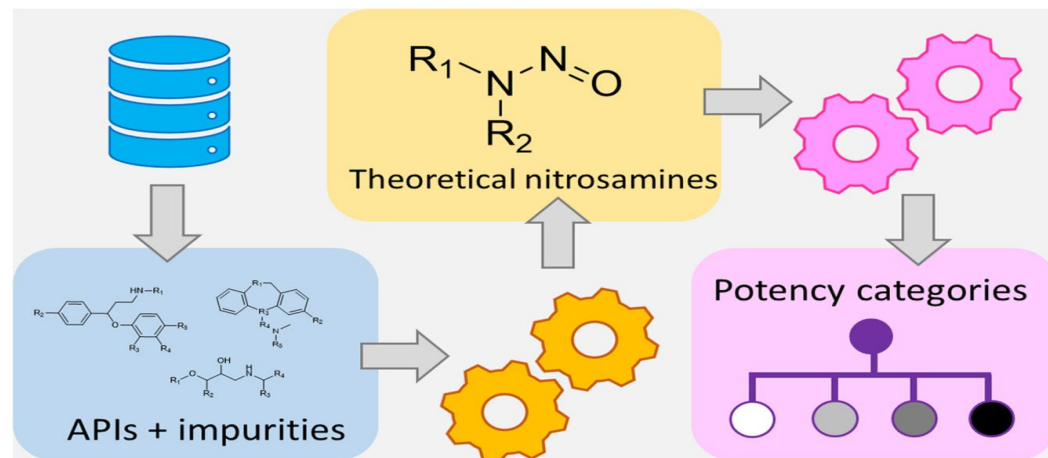
^b Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, United Kingdom

^c U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD, USA

^d AstraZeneca, Data Science and AI, Clinical Pharmacology and Safety Sciences, R&D, Cambridge, United Kingdom

^e Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, United Kingdom

^f Current affiliation: Sai Life Sciences Limited, Basement A, Block 33, Alderley Park, Macclesfield, United Kingdom



12,000 USP-NF

4,848 APIs (40.4%)

3,552 Impurities (29.6%)



Journal of Pharmaceutical Science Nov'23 - <https://doi.org/10.1016/j.xphs.2022.11.013>

Promoting the
QUALITY OF MEDICINES Plus

USP's Nitrosamines Exchange

An online knowledge-based community on all things nitrosamines

- 2800+ members, 90 countries
- Ability to translate text between 22 languages



Join <http://nitrosamines.usp.org>

Two screenshots of the Nitrosamines Exchange website. The top screenshot shows the homepage with featured topics like 'Limits of Nitrosamines', 'Guidance, Documents...', 'EMA Q&A Rev. 16', and 'The Nitrosamine "Saga"'. The bottom screenshot shows a detailed view of a topic, 'Maximizing use of existing carcinogenicity data to support AI levels', with a list of categories and upcoming events.

Promoting the
QUALITY OF MEDICINES Plus

USP's Nitrosamines Exchange

An online knowledge-based community on all things nitrosamines



No cost to join - <http://nitrosamines.usp.org>



Members include manufacturers, regulatory authorities, researchers, subject matter experts ...



Source for latest information, articles, data, NDSRIs, test methods, discussions, tools, networking...



Any member may ask questions/pose challenges

Methods Are Shared in the Nitrosamine Analytical Hub

The image shows a screenshot of the Nitrosamines Exchange website and a poster for the USP Analytical Hub. The website header includes the USP logo, the title "Nitrosamines Exchange", and the tagline "A knowledge based community for all-things Nitrosamine". It features a search bar, a language dropdown set to "English (US)", and a user profile icon. The "Featured Topics" section displays four articles: "Limits of Nitrosamines // 20d", "New Scientific Knowledge... // Jun 6", "Guidance, Documents... // 21d", and "Limits of Nitrosamines // Jul 8". Below this is the "Nitrosamines Impurity Analytical Hub" with four categories: Solvents, Drug Substance, Drug Products, and Excipients. The poster at the bottom is titled "USP Analytical Hub Nitrosamines analysis in Solvents by GC-MS/MS" and describes the quantitation of NDMA, NDEA, NDIPA, NEIPA, NDPA, and NDBA in various solvents.

Nitrosamines Exchange
A knowledge based community for all-things Nitrosamine

Featured Topics

- Limits of Nitrosamines // 20d
■ CPCA Calculation Tool (excel-based) -Updated
- New Scientific Knowledge... // Jun 6
Identifying the Risk of Formation of Nitrosamines and Other Potentially Mutagenic Impurities...
- Guidance, Documents... // 21d
The Nitrosamine "Saga"
- Limits of Nitrosamines // Jul 8
Visualization of Categorized Compounds by CPCA

Nitrosamines Impurity Analytical Hub

- Solvents
- Drug Substance
- Drug Products
- Excipients

USP Analytical Hub
Nitrosamines analysis in Solvents by GC-MS/MS
Quantitation of NDMA, NDEA, NDIPA, NEIPA, NDPA, and NDBA in Solvents (Dichloromethane, Ethylacetate, Toluene and o-Xylene) by GC-MS/MS

- Public **online repository** containing **non-compendial** analytical procedures (analytical notes) for the testing of nitrosamine impurities and related substances.
- USP's scientists curate analytical procedures through **internal development/validation** or through scientific review of non-compendial donations. These are **NOT** compendial standards.
- The **procedures** contained in the analytical notes should be **validated** by the user. USP is **not** and will not be responsible for the use or implementation of the procedures.
- Hosted in **The Nitrosamine Exchange**, the Analytical Hub allows keyword searches and the view of key analytical procedure parameters and chromatograms.

<https://nitrosamines.usp.org/t/nitrosamines-analysis-in-solvents-by-gc-ms-ms/4556>

<https://nitrosamines.usp.org/t/quantitation-of-ndma-in-ranitidine-ds-by-lc-ms-ms/6352>

Collaborations in Progress to Develop a Risk Assessment ‘Practical Tool’

Scope:

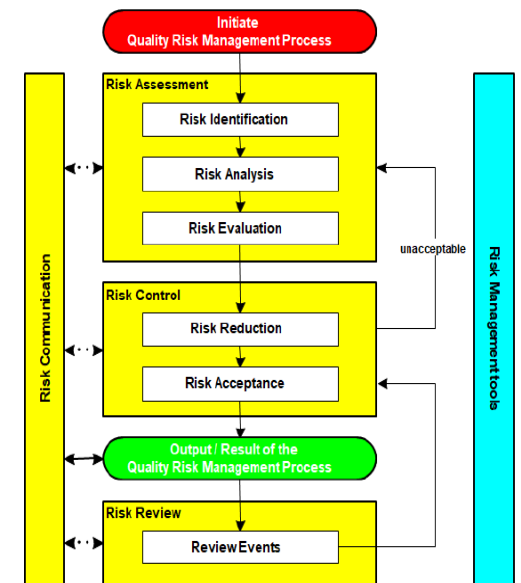
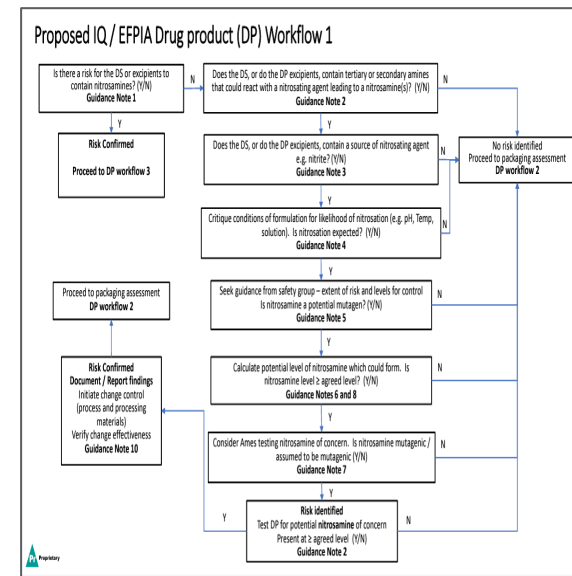
To develop a tool for conducting Risk Assessment
[What ← → How]

Work Plan:

- ▶ Development through crowdsourcing with Nitrosamine Exchange community members
- ▶ Inputs from Expert Committee
- ▶ Convergence (Ex: PDG, IMWP)
- ▶ Publication of guidance document (white paper, peer-review article)

Status:

- ▶ Draft on internal work



Two active community members (motivated by recent EMA updates) developed an Excel-based calculation tool to calculate NDSRIs limits using the Carcinogenic Potency Categorization Approach (**CPCA**) framework



Lucas Maciel Mauriz Marques
Nitrosaminas LATAM



Yosuke Mino
Nitrosamine Exchange Ambass...

CPCA Classification ver.
Name of the product: XXXXXXXX
Writer: YYYYYY

Paste the structure of the compound

* For chemical information and draw structure (<https://pubchem.ncbi.nlm.nih.gov>)

Credit: Yosuke Mino & Lucas Mauriz

Please input the information of the product in the boxes.

1. Does N-Nitrosamine have any hydrogens on its α -carbons?

2. Does N-Nitrosamine have more than one α -hydrogen on one or both sides of N-nitroso group?

3. Does N-Nitrosamine have a tertiary α -carbon?

Category: mg/kg/day

4. Please check the following features included in the compounds.

4-1. **Alfa-Hydrogen Score**
What count of Hydrogen Atoms on Each alfa-carbon, Lowest First?
[] Score: []

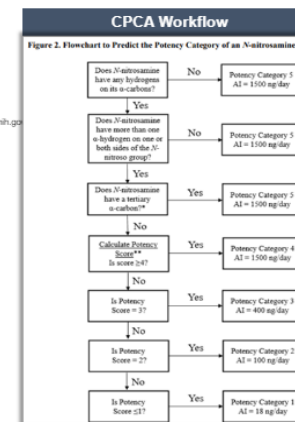
4-2. **Deactivating Feature Score**
Carboxylic acid group anywhere on molecule?
[] Score: []
What ring system is included?
[] Score: []
Chains of ≥ 5 consecutive non-hydrogen atoms (cyclic or acyclic) on both side of acyclic N-nitroso group?
Not more than 4 atoms in each chain may be in the same ring?
[] Score: []
Electron-withdrawing group** bonded to α -carbon of N-nitroso group (cyclic or acyclic)?
[] Score: []
Hydroxyl group bonded to β -carbon*** of N-nitroso group (cyclic or acyclic)?
[] Score: []

4-3. **Activating Feature Score**
Aryl group bonded to α -carbon (i.e., benzylic or pseudo-benzylic substituent on N-nitroso group)
[] Score: []
Methyl group bonded to β -carbon (cyclic or acyclic)?
[] Score: []

Potency Score: []

Category: []
_AI = [] no/day

Disclaimer: This Calculation Tool, including all of its features and content is made available and may be used solely under the following terms and conditions. All this Calculation Tool is not for commercial exploitation. You may not decompile, reverse engineer, modify, create derivative works, or otherwise alter the Calculation Tool. You may not copy, distribute, sell, rent, lease, loan, or otherwise transfer the Calculation Tool. You may not copy, modify, reproduce, republish, distribute, display, or transmit for any commercial, non-profit or public purposes all or any portion of this Calculation Tool. Any unauthorized use of this Calculation Tool is prohibited. All the Calculation Tool is provided "as is" without any warranty, express or implied. The Calculation Tool is provided on an "as is" basis. The Calculation Tool is not warranted or guaranteed. Your use of this Calculation Tool or materials linked from this Calculation Tool is at your own risk. You agree to defend, indemnify, and hold the provider of this Calculation Tool harmless from and against all claims, damages, losses, and expenses, including reasonable attorneys' fees, incurred by the provider of this Calculation Tool due to or arising out of any license or right, by implication, estoppel or otherwise, under copyright or other intellectual property rights, that you agree that the Calculation Tool is protected by copyrights, trademarks, service marks, patents or other proprietary rights and laws. You agree to use this Calculation Tool in accordance with these Terms of Use. The Calculation Tool is protected by copyright law and all other applicable laws. All rights reserved.



alpha-Hydrogen Score

Table 2. Count of hydrogen atoms on each α -carbon (lowest count first) and corresponding α -Hydrogen Score. Examples are intended to be illustrative only and are not intended to be exhaustive.

Count of Hydrogen Atoms on Each α -Carbon, Lowest First	Example	α -Hydrogen Score
0,2		3*
0,3		2
1,2		3
1,3		3
2,2		1
2,3		1

*A score of 3 applies when the methyl-line α -carbon is not part of an ethyl group. If the methyl-line α -carbon is part of an ethyl group, a score of 2 should be applied.

*A score of 3 applies when the methylene α -carbon is not part of an ethyl group. If the methylene α -carbon is part of an ethyl group, a score of 2 should be applied.

Deactivating Feature Score		
Deactivating Feature	Example	Individual Deactivating Feature Score
Carboxylic acid group anywhere on molecule		+3
Nitroazone group in a pyrazoline ring		+3
Nitroazone group in a 6-membered ring containing at least one sulfur atom		+3
Nitroazone group in a 5- or 6-membered ring ^a		+2
Nitroazone group in a morpholine ring		+1
Nitroazone group in a 7-membered ring		+1
Chains of ≥5 consecutive non-hydrogen atoms (cyclic or acyclic) on both side of acyclic N-azone group. Not more than 4 atoms in each chain may be in the same ring.		+1
Electron-withdrawing group ^b bonded to α-carbon on <u>only</u> one side of N-azone group (cyclic or acyclic)		+1
Electron-withdrawing group ^b bonded to α-carbon on <u>both</u> sides of N-azone group (cyclic or acyclic)		+2

Hydroxyl group bonded to β -carbon*** on <u>only one</u> side of <i>N</i> -nitroso group (cyclic or acyclic)		+1
Hydroxyl group bonded to β -carbon*** on <u>both</u> sides of <i>N</i> -nitroso group (cyclic or acyclic)		+2


Activating Feature Score		
Activating Feature	Example	Individual Activation Feature Score
Aryl group bonded to α -carbon (i.e., benzyl or pseudo-benzyl substituent on a β -carbon group)		+1
Methyl group bonded to β -carbon (cyclic or acyclic)		+1

Combating TB: Transfer of Efficient Rifapentine API Manufacturing Technology to Africa














GLOBAL ACCELERATOR TO END TB *PLUS*

















TB Preventive Treatment (TPT) program:

- To advance the prevention of TB globally, USAID and PEPFAR, in collaboration with the Stop TB Partnership's Global Drug Facility, worked to secure a 30 percent price reduction for a shortened TB prevention regimen, which will procure \$25 million in treatments to treat more than 2.5 million individuals. As part of this effort, USAID will launch a donation program for its TB priority countries to apply for the drugs. [Learn more here](#) .
- USAID is also initiating a **technology transfer** of a more efficient way to produce the active pharmaceutical ingredient (API) for rifapentine to a local pharmaceutical manufacturer in Africa.

Challenges Can Be Posed to the Community e.g. “Understand Factors in CPNP Formation by Rifapentine”

 Nitrosamines Exchange A knowledge based community for all-things Nitrosamine					
Nitrosamines in PMs & Excipients Questions			4	389	5d
 Excipients Excipients					
Low nitrile crosscarmellose sodium			0	80	5d
 Excipients Excipients					
Nitrite content in hydroxypropyl methylcellulose			5	151	9d
 Excipients					
What factors impact the formation of 1-cyclopentyl-4-nitrosopiperazine (CPNP) by rifapentine			0	73	11d
 Root Causes					
Theoretical estimation of the conversion of a tertiary amine to nitrosamine			0	226	12d
 Root Causes					
Low nitrite excipients			2	168	18d
 Excipients Excipients					

Categories	
	About Nitrosamines Excha...
	How-To
	Analytical Methods Hub
	Nitrosamines FAQs
	Events / Workshops / Webi...
	N-nitrosamines Chemistry
	Limits of Nitrosamines
	Root Causes
	Risk Assessment Strategy ...
	Confirmatory Testing & An...
	Nitrosamines in the News
	New Scientific Knowledge...
	Guidance, Documents, Re...
	Regulatory Intelligence

Thank You!



Join <http://nitrosamines.usp.org>