Promoting the Quality of Medicines Plus

Nitrosamines Exchange: A Global Knowledge Hub

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USAID FROM THE AMERICAN PEOPLE

usp®

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

USP's global mission

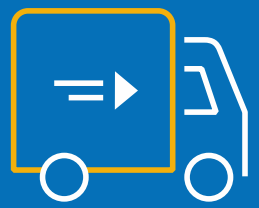
To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

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

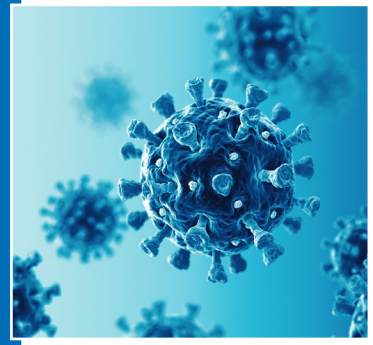
PQM+ supported the WHO PQ of the following essential medicines:

- 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:

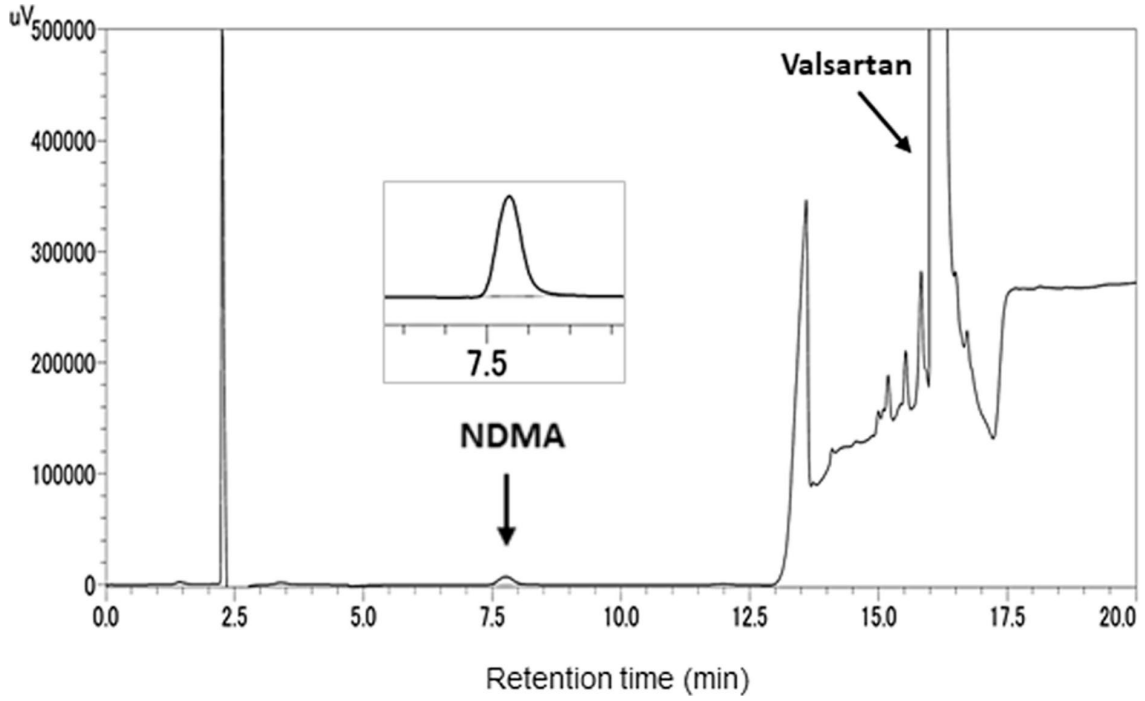
- Toxicity knowledge
- Development of test methods
- Ability to make AI calculations

Nitrosamines Discovered in Pharmaceuticals

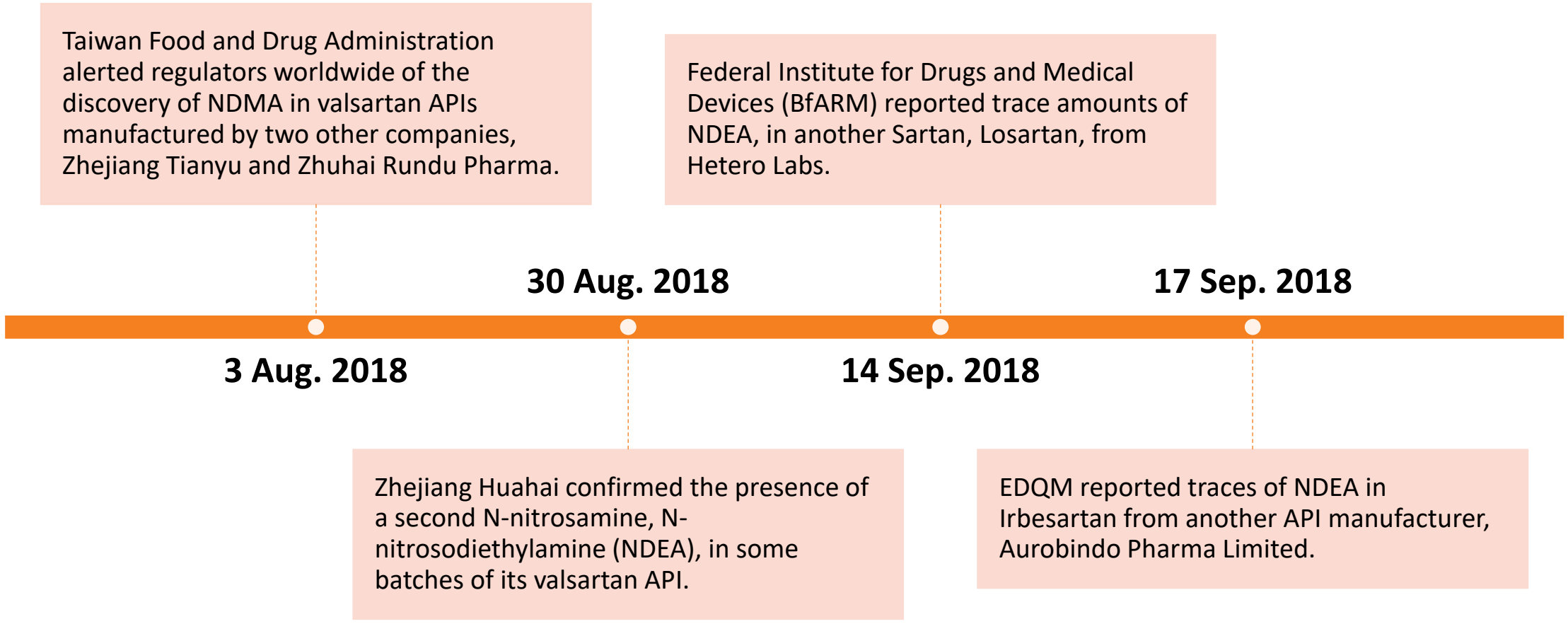
Timeline

- **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

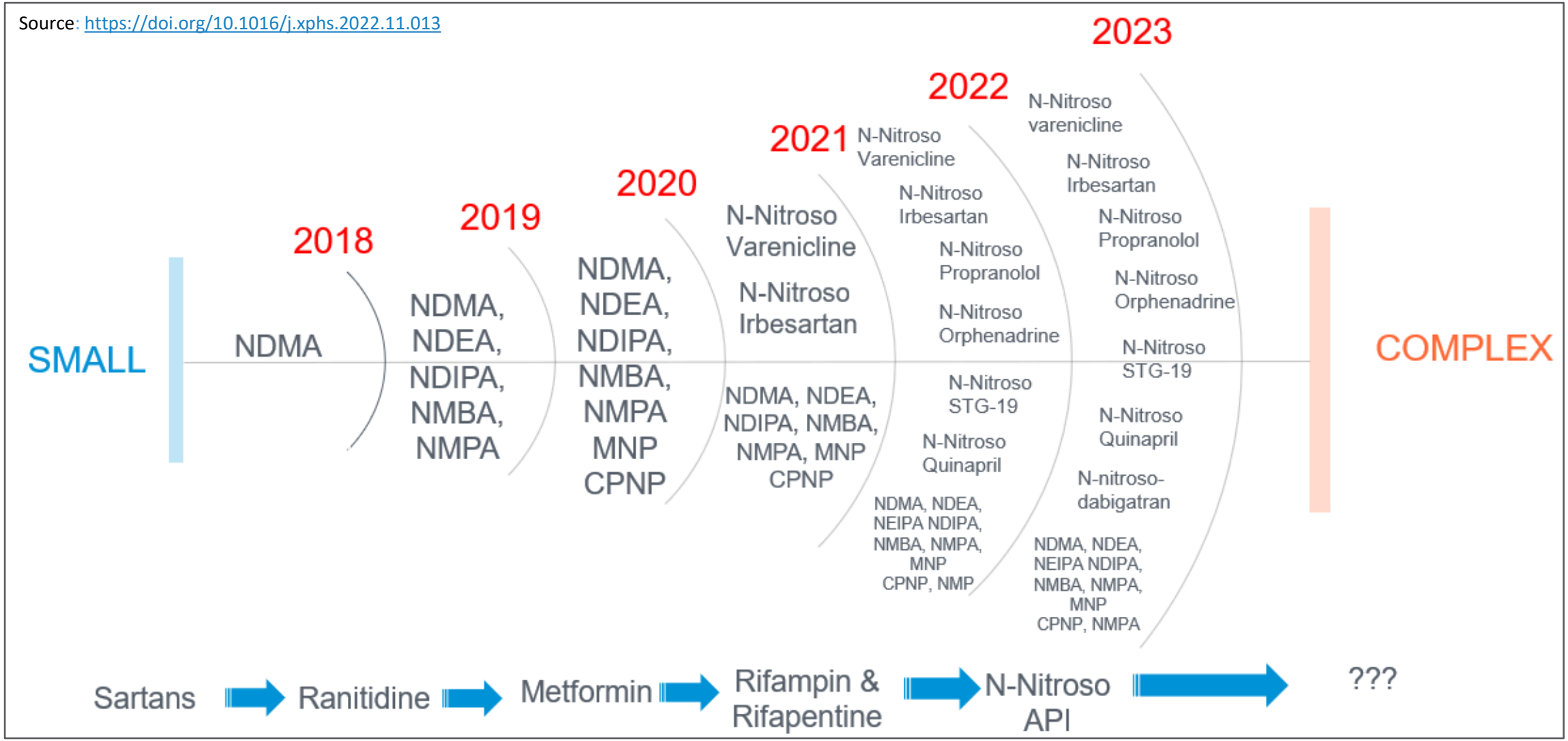


Regulatory Concerns and Awareness



Knowledge about Nitrosamines Is Evolving

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



Next Challenge…NDSRIs

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Global Health

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

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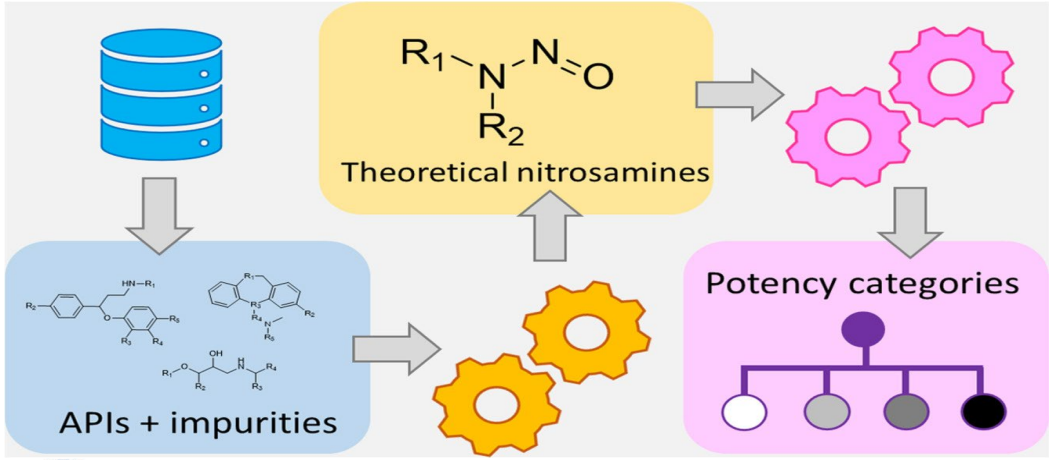

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12,000 USP-NF

4,848 APIs (40.4%)

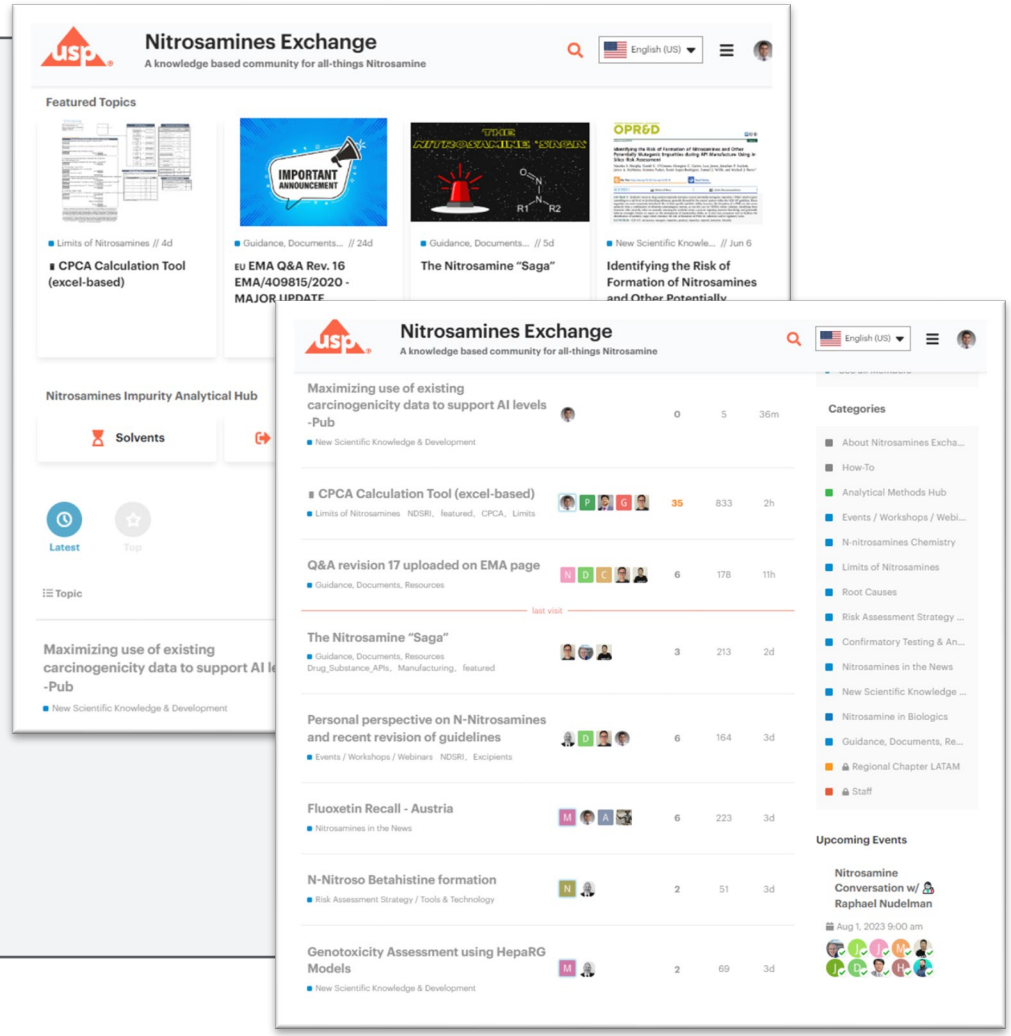
3,552 Impurities (29.6%)

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



USP's Nitrosamines Exchange

An online knowledge-based community on all things nitrosamines

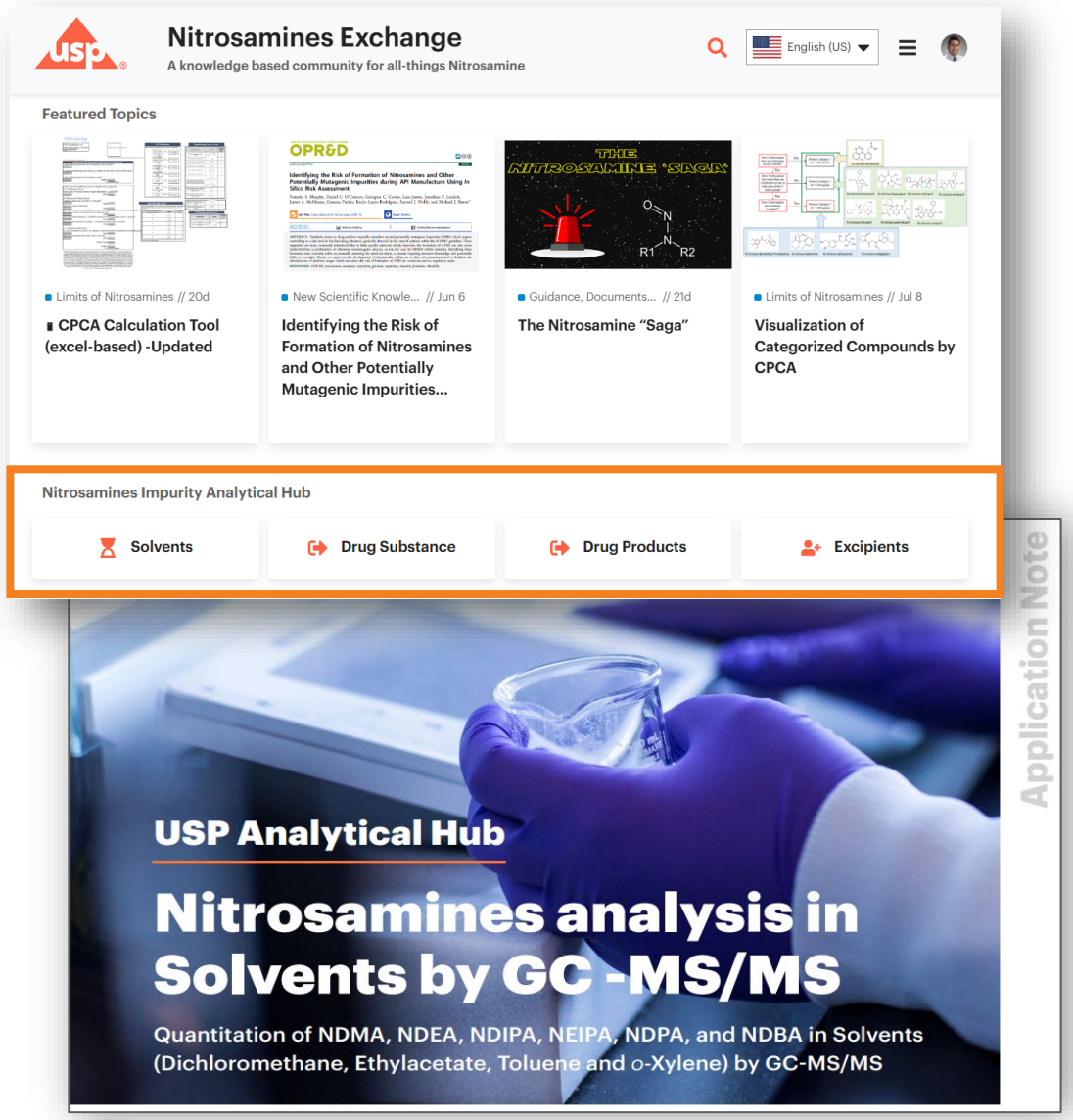
No cost to join - http://nitrosamines.usp.org

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



- 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:

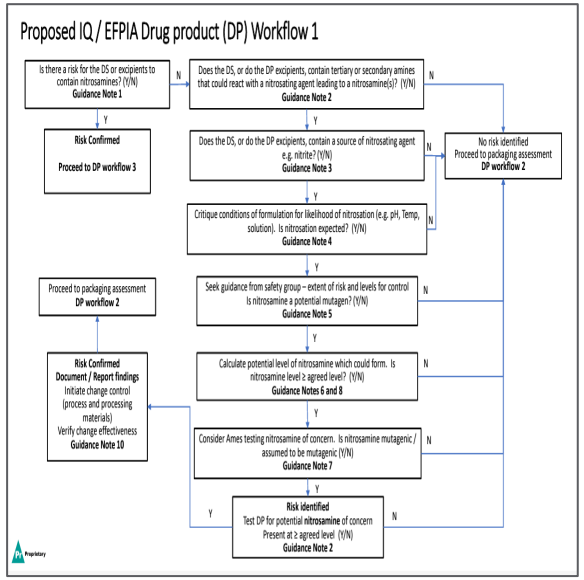
To develop a tool for conducting Risk Assessment [What ← → How]

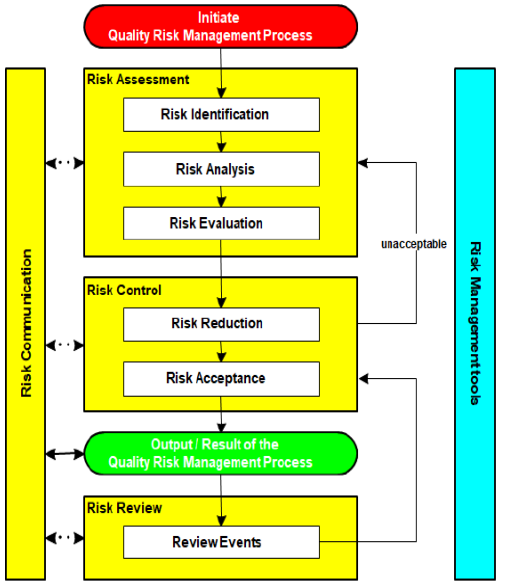
Work Plan:

- 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





Members Have Developed Tools

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

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Yosukemino
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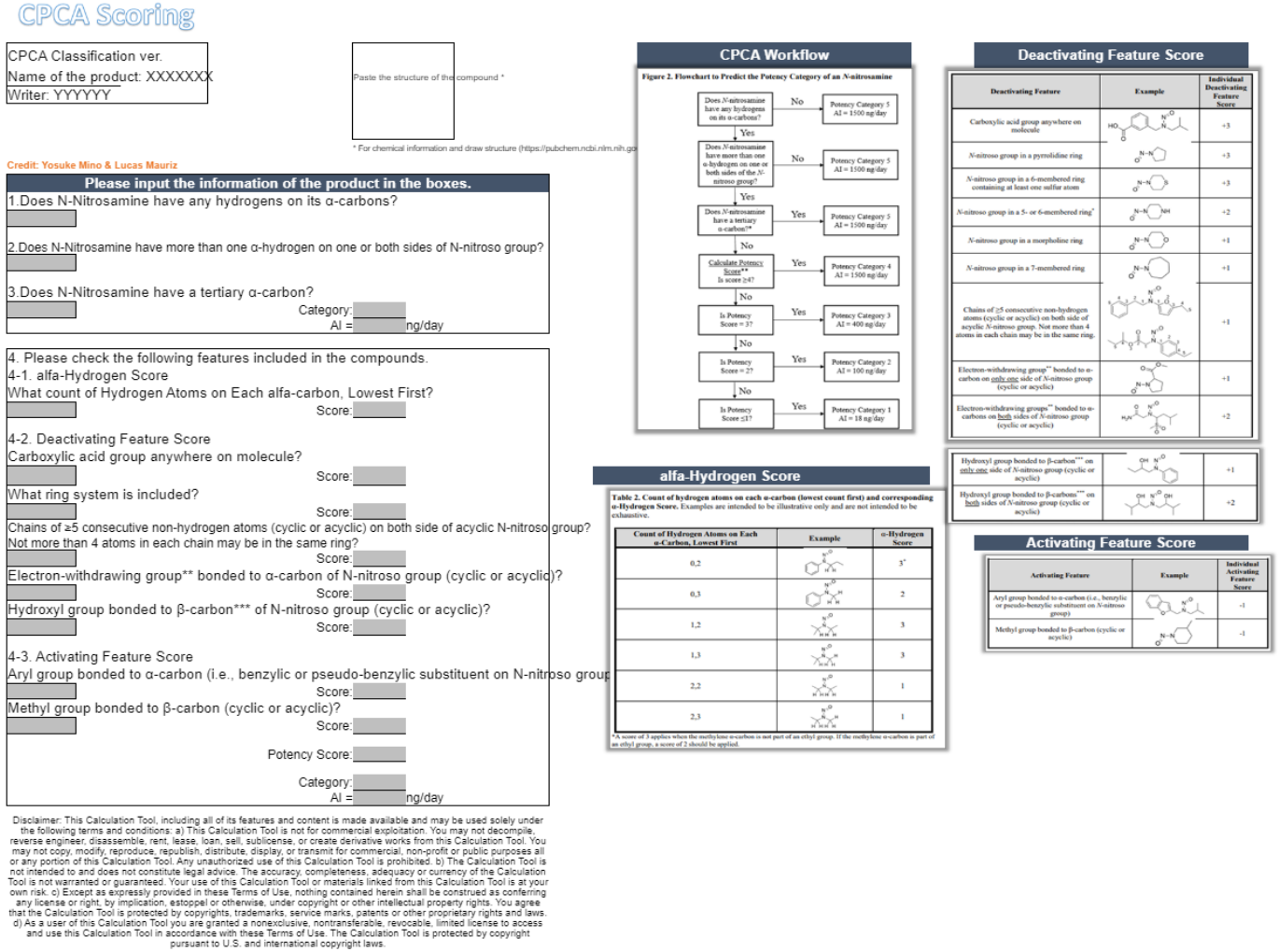
Nitrosamine Exchange Ambass...



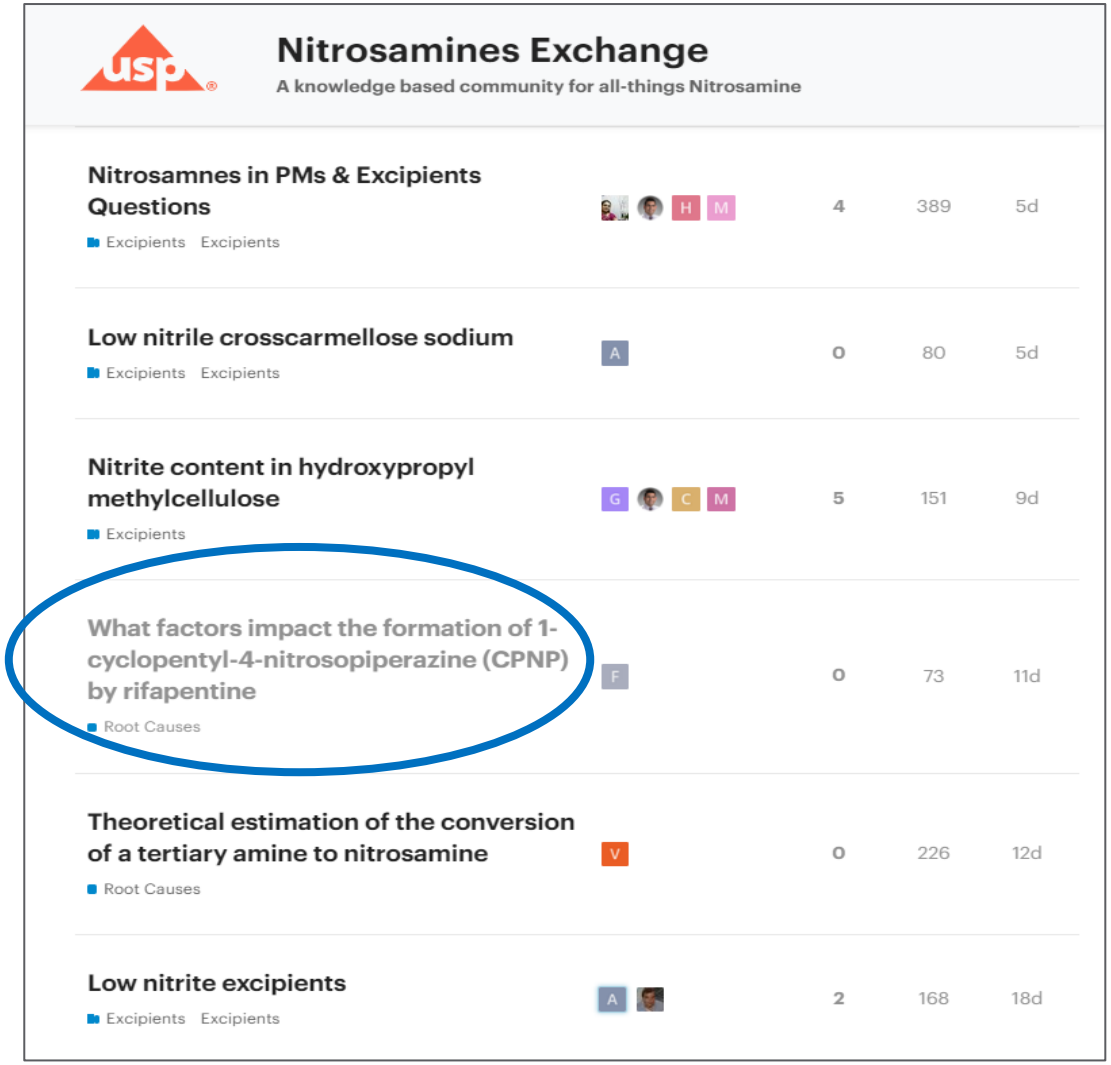
Combatting TB: Transfer of Efficient Rifapentine API Manufacturing Technology to Africa

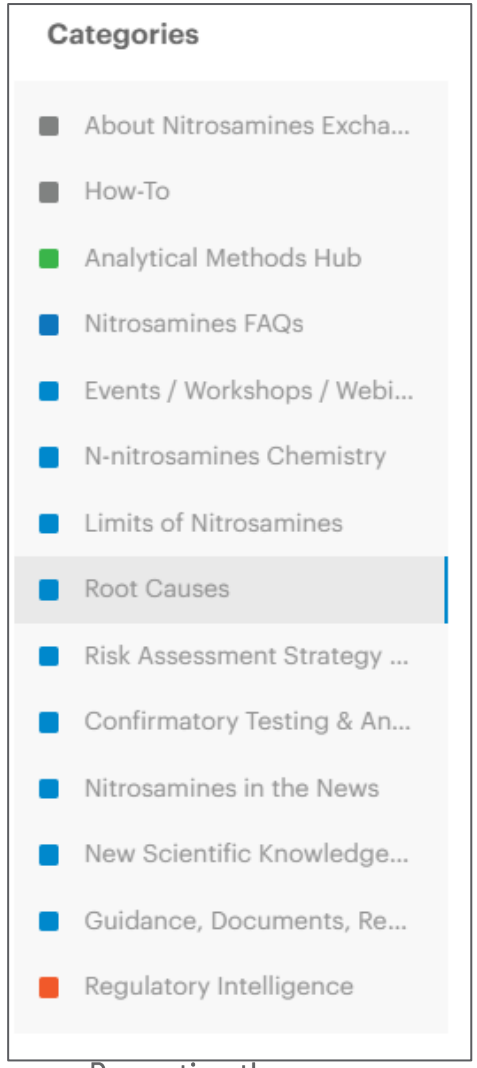
GLOBAL ACCELERATOR TO END TB *PLUS*

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"





Thank You!

Join http://nitrosamines.usp.org