Nitrosamine Impurities: Beyond a Compendial Standard - Learnings from USP's Nitrosamines Exchange Community

Naiffer Romero, MSc, MPH
Principal Scientist
USP Science Division
Rockville, MD

Nitrosamine Quick Evolution

Timeline

2018

- 26 Jun — **NDMA in ZH Valsartan** *Rapid Alert Network*
- **Taiwan FDA** — **NDMA in ZT Valsartan**
- **NDEA in ZH Valsartan**
- **OMLC in Germany** — **NDEA in HL Losartan**
- 20 Sep — Article 31 Extend the scope to review all sartans with tetrazole ring
- **NDEA in Irbesartan**
- Dec — **NDIPA in valsartan**
- Jul — Recalls of valsartan
- Oct — Recall expanded to other sartans

2019

- Jan — **NDMA in Pioglitazone**
- 2 May — **NMBA in HL Losartan**; Sartans End Article 31
- July — **NMPA in Valsartan**
- 12 Sep — Ranitidine Article 31 triggered
- Sept — **NDMA** Found in Ranitidine medicines
- Nov — Nitrosamine found in Nizatidine
- Oct19 — FDA issue warning letters due cGMP violations

2020

- Apr — Suspension of ranitidine medicines in the EU
- 24 Jun — Lessons Learnt Nitrosamines in Sartans
- Jul — Release of USP nitrsoamine standards NDMA, NDEA, NDIPA NDBA, NEIPA, NMBA
- 1 Sep — FDA issues guidance "Control of N-Nitrosamine Impurities in Huma Drugs"
- 1 Sep — USP <1469>
- 1 Apr — Ranitidine Market Withdrawal
- 16 Apr — Recalls of Nizatidine
- **NDMA** in metformin products

2021

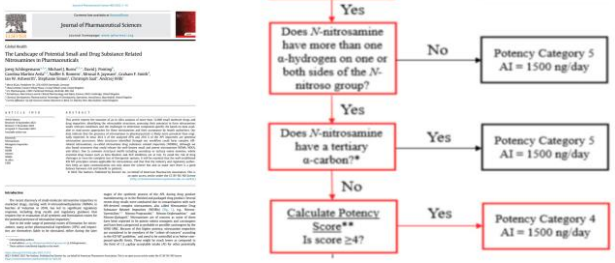
- Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products
- nitrosamine drug substance related impurities (NDSRIs)

2022

- **N-Nitroso-irbesartan**
- **N-Nitroso-Desloratadine**
- **N-Nitroso-Folic Acid**
- **N-Nitroso-Quinapril**
- **N-Nitroso-Orphenadrine**
- **N-Nitroso-Propranolol**

2023

- July — **CPCA**



Nitrosamine Activities

1 Documentary Standard

General Chapter <1469>
Nitrosamine Impurities

2 Reference Standard

- 8 USP Reference Standards (NDMA, NDEA, NDIPA, NDBA, NEIPA, NMBA, NMPA and NDMA-d6)

- Pharmaceutical Analytical Impurities
  34 impurities to be released in 2023
  (e.g., CPNP, MNP, NPYR, NDELA, NDPA, NMOR, **NDSRI** etc)

3 Analytical Procedures

- In-house procedure development and validation
- External Collaborations
- Analytical Hub

4 Education

- USP Education Course
- Tutorial Videos

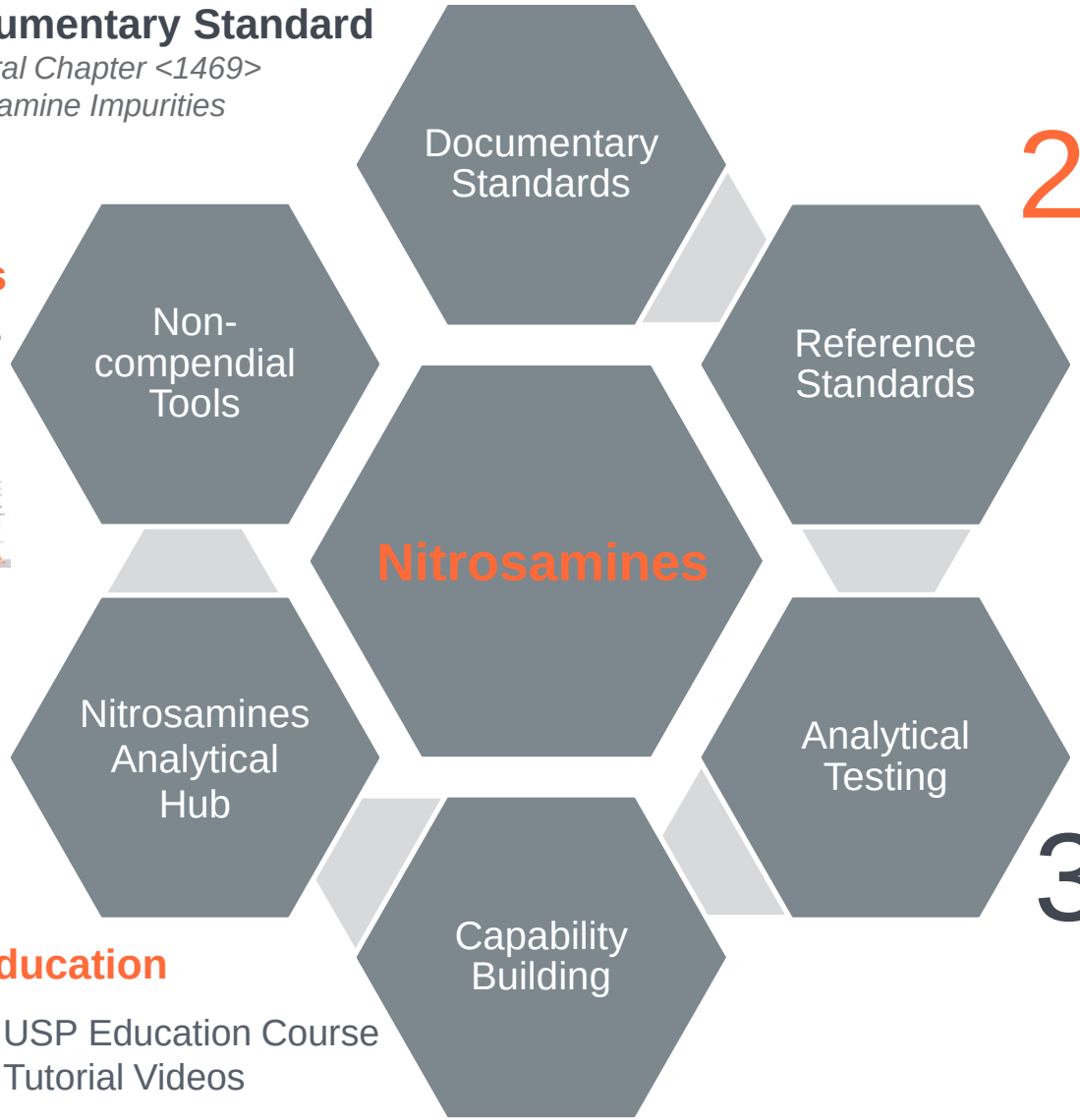
5 Capability Building

6 Stakeholder Engagement

- Support regulators and industry
- Collaborations

7 Non-compendial tools

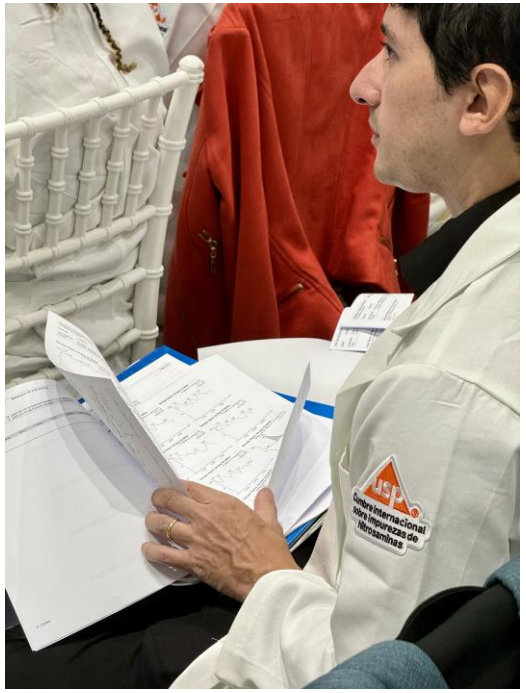
- Nitrosamines Exchange Community
- Analytical Hub
- Publications



Collaboration and Training

"The training course was especially helpful to those doing research in quality control of Nitrosamine impurities in pharmaceutical products circulated in [the] Vietnamese market ... [because] challenges in drug quality are a concern for not only Vietnam but [for] all countries."

-Assoc. Prof. Doan Cao Son, PhD
Dir., National Institute of Drug Quality Control of Vietnam



- Nitrosamines Regulatory Summit (12 countries LATAM)
- Nitrosamines Impurities Testing Hands-on Training (Brazil)
- Regulatory Training Vietnam NIDQC (USP India)

USP Knowledge Hub

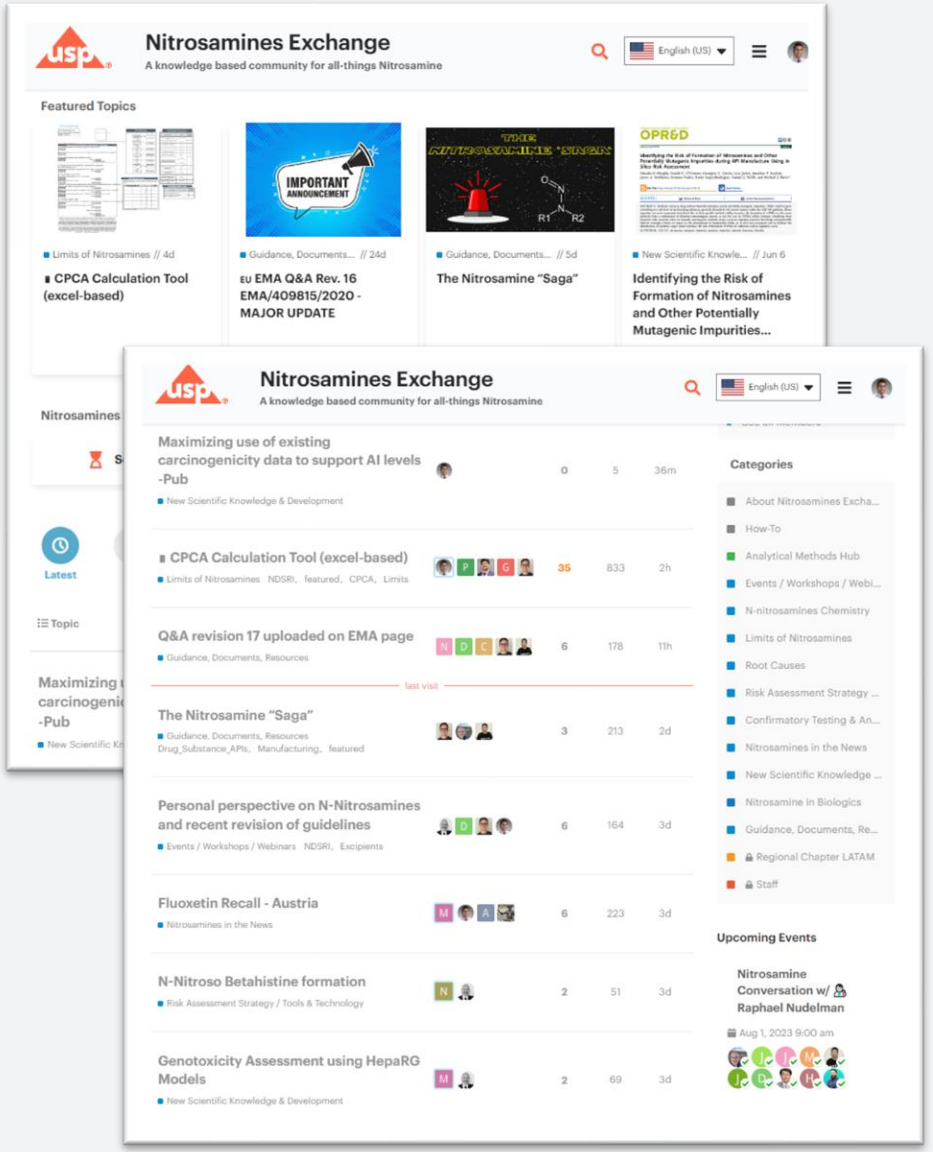
- Unleashing the **power of online communities**
- Increase and **accelerate early scientific knowledge** exchange in select topics
- Peer-to-peer collaboration and **best practice sharing**
- Strong **sense of community and belonging**, despite not operating in physical space
- *Democratization and inclusion of knowledge*
- A new tool in USP's ecosystem of engagement approaches

Join http://nitrosamines.usp.org

Nitrosamines Exchange

An online knowledge-based community on all-things nitrosamines

- 4800+ members, 80+ countries
- Ability to translate text between 22 languages



Join http://nitrosamines.usp.org

Regulatory guidelines (revisions)

www.nitrosamines.usp.org

Most active posts in the community

After the publication of Regulatory guidelines updates, community members are using the community to discuss the changes, considerations, impact and clarify cases where the framework can be challenging

EMA Q&A Rev. 16 EMA/409815/2020 - MAJOR UPDATE

Guidance, Documents, Resources
Drug_Substance_APIs, NDSRI, featured

FDA - Recommended Acceptable Intake Limits for NDSRIs Guidance for Industry

Guidance, Documents, Resources

Health Canada updated the guidance and Appendix 1(March 15, 2024)

Limits of Nitrosamines NDSRI

TGA (Australia) Updates Published Acceptable Intakes

Limits of Nitrosamines

Medicines: MAH' submission of Nitrosamine risk evaluation, risk assessment and confirmatory testing

Guidance, Documents, Resources Regulation

Korea Drug Review Briefing session on Nitrosamines

Guidance, Documents, Resources

Swiss Medic Guidelines

Guidance, Documents, Resources NDSRI

Addressing Analytical Challenges

"Analytical procedure development and proposed established conditions- A case study of a mass spectrometry based NDSRI analytical procedure" Jinhui Zhang et al.

Identify Emerging Challenges

A new root cause? NOx

New Scientific Knowledge & Development

[redacted] 1 Nov '23

To be honest, I had never considered the geographical location of the factory as a root cause, but I'll let you all read...

N-Nitrosodimethylamine Formation in Metformin Drug Products by the Reaction of Dimethylamine and Atmospheric NO2 | Organic Process Research & Development (acs.org) 118

4 Reply

Nitrosamines evaluation in transdermal patches

Risk Assessment Strategy / Tools & Technology featured

A [redacted] 4 27d

Hi all,

Recently, it got to our attention that several NDSRIs indicated in EMA Appendix 1 theoretically could be in transdermal formulations (i.e., Rotigotine, Lidocaine, Methylphenidate etc.). with NDSRIs in Category 1, 2, 3 or more. Under EMA/409815/2020 there is no difference between route of administration unless you provide data.

Nitrosamines from polybags to finished product

Root Causes Packaging

H [redacted] 27d

HI,

I want to discuss about nitrosamines from Polybags. Can Nitrates/amines will be available in poly bags and transfer to API/Finished product during the storage. I have asked couple of vendors for the declaration, but they cannot arrange for it.
So, do we need to consider the risk from polybags also?

Thank you...

Duplex Sequencing - Future of mutagenicity assessment

Risk Assessment Strategy / Tools & Technology

Naiffer_Host Community Host Jul '23

With so much discussion around Limits and AI calculations, I want to debate for a moment to share information about 'Duplex Sequencing'. After the recent safety discussion at the Hesi/FDA meeting, I went down a rabbit hole to understand some of the proposed assays and testing that can be used to evaluate the safety or mutagenicity potential in Nitrosamines Impurities.

New paper - Use of molar, instead of weight-based, safety limits

New Scientific Knowledge & Development

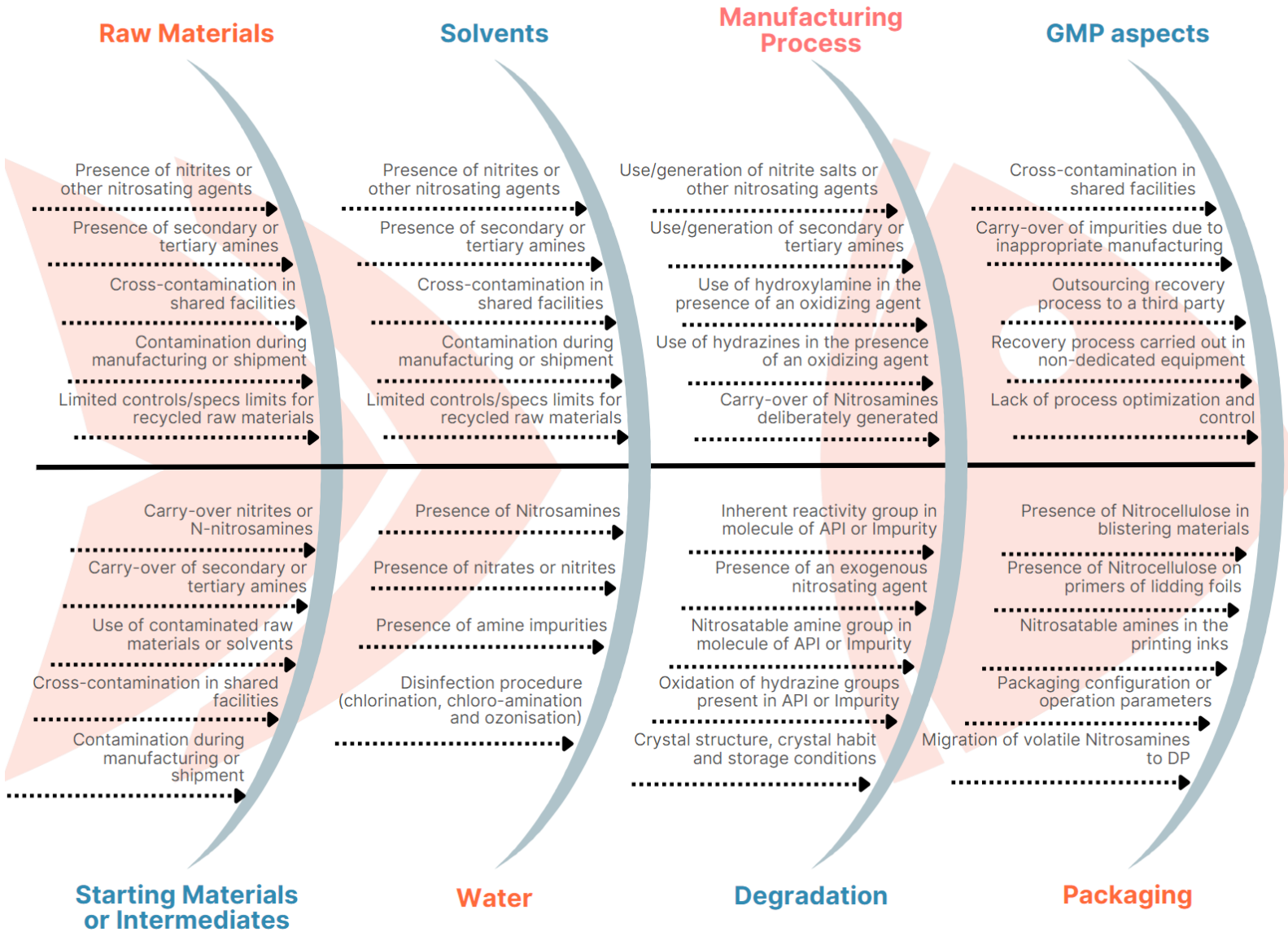
[redacted] Nitrosamine Exchange Ambassador Oct '23

I've said a few times on here and in talks "watch this space" for more evidence for the use of molar limits for nitrosamines - the paper is now out!

https://doi.org/10.1016/j.yrtph.2023.105505 297

This should be particularly relevant for scaling read-across analogues, often far larger molecules than the compounds they are read-across from...

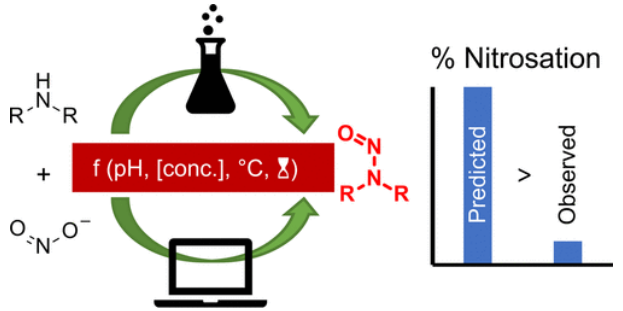
Assessing Nitrosamines Risk

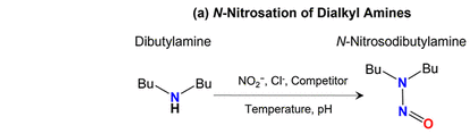


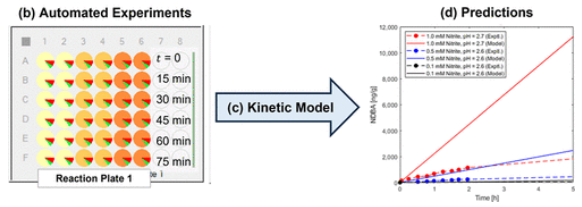
Understanding Nitrosamine Reactivity

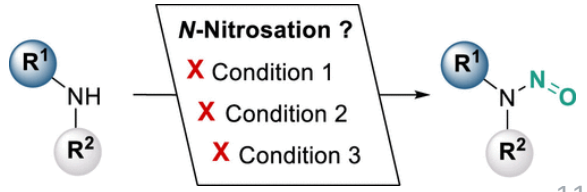
Increase understanding and adoption of theoretical or invitro tools to understand the reactivity of Nitrosamines Formation

- Modeling the Impact of Excipients Selection on Nitrosamine Formation towards Risk Mitigation
- Formation of N-Nitrosamines by Reaction of Secondary Dialkylamines with Trace Levels of Nitrite in Aqueous Solution: An Automated Experimental and Kinetic Modeling Study Using Di-n-butylamine
- Formation of Dialkyl-N-nitrosamines in Aqueous Solution: An Experimental Validation of a Conservative Predictive Model and a Comparison of the Rates of Dialkyl and Trialkylamine Nitrosation
- Approaches and Considerations for the Investigation and Synthesis of N-Nitrosamine Drug Substance-Related Impurities (NDSRIs)



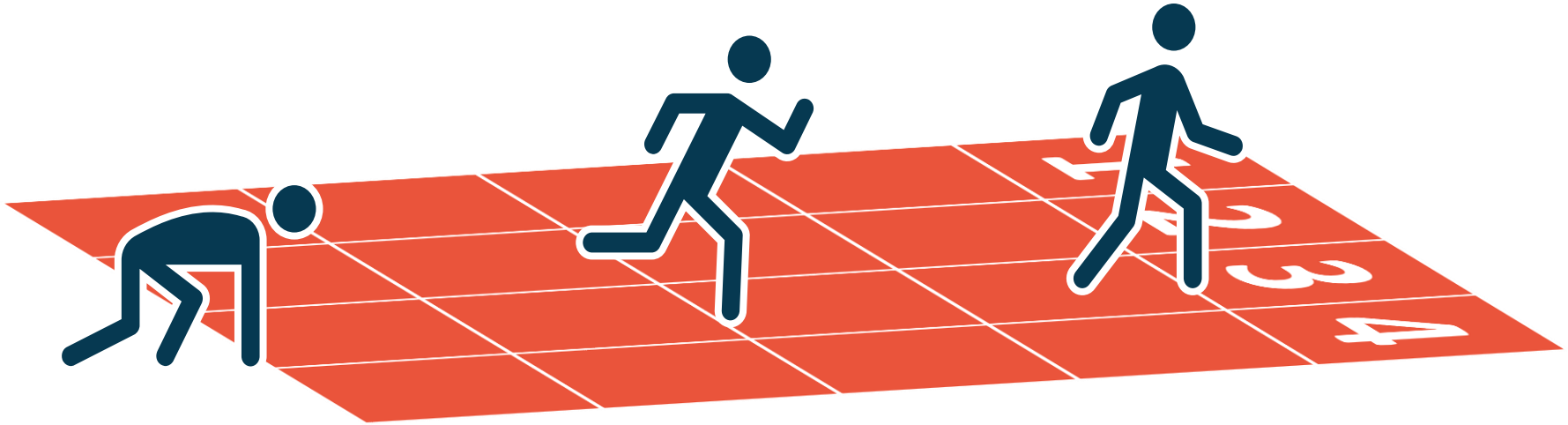






Understanding Future Challenges

- Gather Knowledge on Nitrosation beyond ‘Nitrites in Excipients’
- Understanding and awareness of Nitroso-X beyond Nitrosamines
- Role of compendial tools to facilitate nitrosamines impurities control and/or mitigation



Scavenger as mitigation strategy

- Building mechanistic knowledge of scavenger agents (Mitigation & Prevention)
- Bridging Scavengers Permeability & Absorption

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Bumetanide as a Model NDSRI Substrate: *N*-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets

Diaa Shakleya[a,*], Bethel Asmelash[b], Alaadin Alayoubi[a], Nicolas Abrigo[a], Adil Mohammad[a], Jiang Wang[a], Jinhui Zhang[a], Jingyue Yang[a], Tim Andres Marzan[a], David Li[a], Maha Shaklah[a], Fahd M. Alsharif[a], Saaniya Desai[a], Patrick J. Faustino[a], Muhammad Ashraf[a], Thomas O'Connor[a], Matthew Vera[b], Andre Raw[b], Vilayat A. Sayeed[b], David Keire[a]

[a] *Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Testing and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*
[b] *Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of lifecycle Drug product, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*

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ABSTRACT

Nitrosamine compounds are classified as potential human carcinogens, the origin of these impurities can be broadly classified in two categories, nitrosamine impurity found in drug products that are not associated with the Active Pharmaceutical Ingredient (API), such as N-nitrosodimethylamine (NDMA) or nitrosamine impurities associated with the API, such as nitrosamine drug substance-related impurities (NDSRIs). The mechanistic pathway for the formation of these two classes of impurities can be different and the approach to mitigate the risk should be tailored to address the specific concern. In the last couple of years number of NDSRIs have been reported for different drug products. Though, not the only contributing factor for the formation of NDSIRs, it is widely accepted that the presence of residual a nitrites/nitrates in the components used in the manufacturing of the drug products can be the primary contributor to the formation of NDSRIs. Approaches to mitigate the formation of NDSRIs in drug products include the use of antioxidants or pH modifiers in the formulation. The primary objective of this work was to evaluate the role of different inhibitors (antioxidants) and pH modifiers in tablet formulations prepared in-house using bumetanide (BMT) as a model drug to mitigate the formation of *N*-nitrosobumetanide (NBMT). A multi-factor study design was created, and several bumetanide formulations were prepared by wet granulation with and without sodium nitrite spike (100 ppm) and different antioxidants (ascorbic acid, ferulic acid or caffeic acid) at three concentrations (0.1%, 0.5% or 1% of the total tablet weight). Formulations with acidic and basic pH were also prepared using 0.1 N hydrochloric acid and 0.1 N sodium bicarbonate, respectively. The formulations were subjected to different storage (temperature and humidity) conditions over 6 months and stability data was collected. The rank order of *N*-nitrosobumetanide inhibition was highest with alkaline pH formulations, followed by formulations with ascorbic acid, caffeic acid or ferulic acid present. In summary, we hypothesize that maintaining a basic pH or the addition of an antioxidant in the drug product can mitigate the conversion of nitrite to nitrosating agent and thus reduce the formation of bumetanide nitrosamines.

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Lack of Effect of Antioxidants on Biopharmaceutics Classification System (BCS) Class III Drug Permeability

Yuly Chiang Yu[a], Dongmei Lu[b], Bhagwant Rege[b], James E. Polli[a,*]

[a] *Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, MD, 21201, USA*
[b] *Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, 20993, USA*

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Excipients

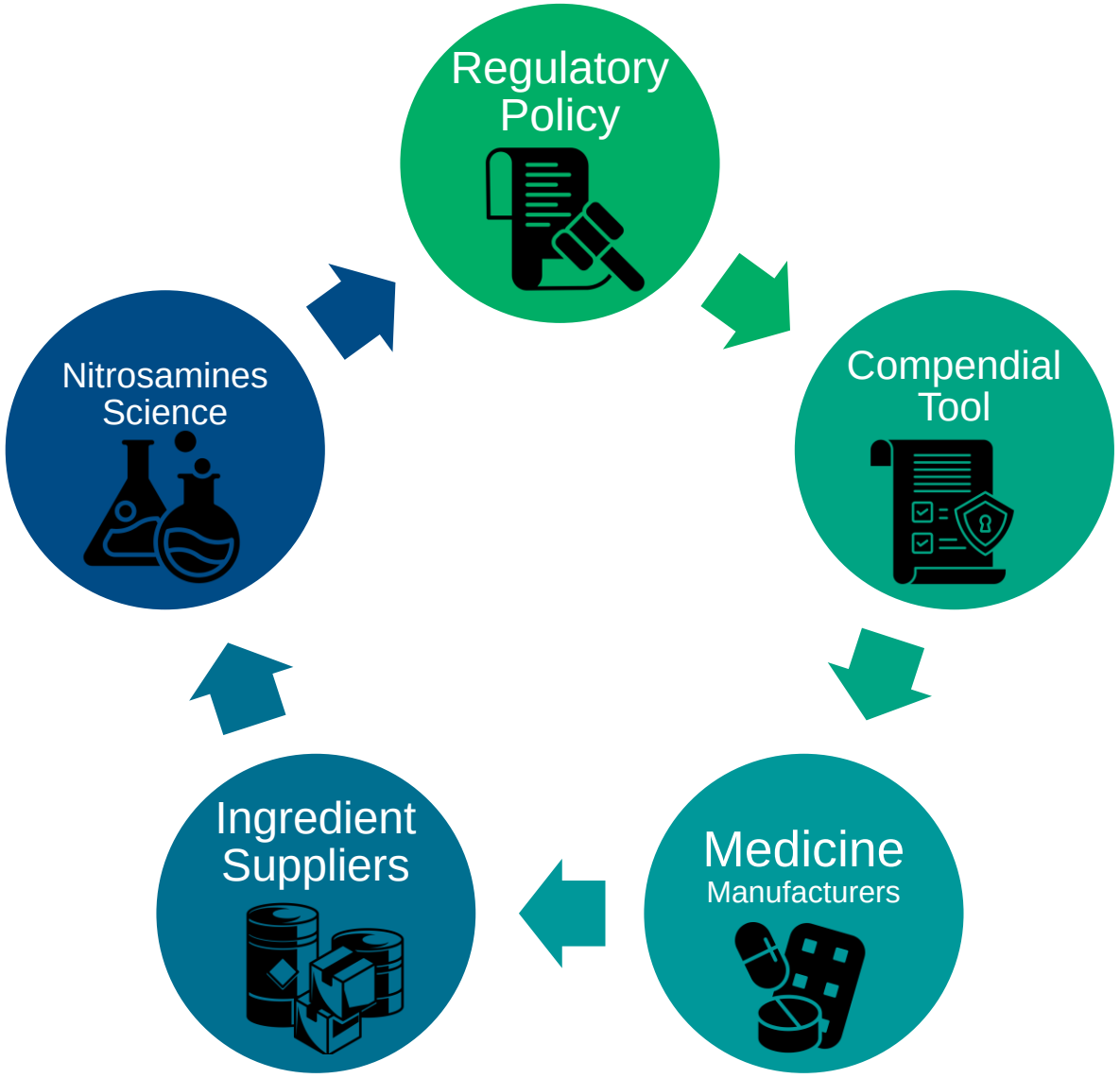
ABSTRACT

The addition of antioxidants to pharmaceutical products is a potential approach to inhibit nitrosamine formation, particularly in solid oral dosage forms like tablets and capsules. The objective was to assess the effect of ten antioxidants on the permeability of four Biopharmaceutics Classification System (BCS) Class III drugs. Bi-directional drug permeability studies in the absence and presence of antioxidants were performed *in vitro* across MDCK-II monolayers. No antioxidant increased drug permeability, while the positive control sodium lauryl sulfate always increased drug permeability. Results support that any of the ten antioxidants, up to at least 10 mg, can be added to a solid oral dosage form without modulating passive drug intestinal permeability. Additional considerations are also discussed.

J Pharm Sci. 2024 Mar 12; https://doi.org/10.1016/j.xphs.2024.03.005

Passive Permeability

Everybody has an important role to play



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Naiffer Romero

NER@usp.org

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