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CMC Considerations and Bridging Bioequivalence Studies of Reformulated Products Impacted by Nitrosamines

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Outline

Nitrosamines and CMC Considerations

- Nitrosamines analysis and method performance criteria
- Nitrosation precursors in drug products

Bridging Bioequivalence Considerations

- Context: SUPAC requirements for drug product changes
- The case of nitrosation inhibitor additives (e.g., antioxidants) as nitrosamine remediation formulation changes
- Proposals for streamlined bioequivalence

Guidance Update since the last GDSR Workshop

On 8/4/2023, FDA issued a final guidance on *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023) (NDSRI Guidance)

- August 2023 issuance of the NDSRIs guidance including the CPCA was a significant enhancement to efficient and independent nitrosamines risk assessment by pharmaceutical manufacturers

NDSRI Method Performance Criteria

- NDSRI analyses predominantly based on LCMS methods with sensitive mass spectrometric detectors (e.g., triple quad and orbitrap)
- CPCA now resulting in AIs up to 1,500 ng/day
- In low MDD drugs this can result in “high” NDSRI specifications:
  - E.g., a 1 mg/day drug with an NDSRI AI of 1,500 ng would result a specification of **NMT 1,500 ppm**

What challenge does this create?

NDSRI Method Performance Criteria

Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

SEPTEMBER 2020

- This guidance requires all nitrosamine analytical methods to have a LOQ of **NMT 0.03 ppm** (this was relevant to sartan products when the guidance was drafted in the "early days" of nitrosamines)

- Achieving linear response in methods between 0.03 ppm – 1,500 ppm is challenging to impossible depending on the product

- Method recovery at the 0.03 ppm LOQ can also be challenging in method development due to high ratios of excipients present

LOQs proportionate to specifications (e.g. 10% of limit) should be adopted

Analysis of Nitrites in Excipients

Current state of analytical methodology

- Mostly chromatography-based
- Parts-per-billion sensitivity

Table 5
Figure of merit of some published methods for nitrite determination.

Method	Category	Sample Prep	Linearity Range (ng/g or ng/mL)	RSD %	LOQ (ng/g or ng/mL)	Sample Matrix	Ref
IC-MS	Direct	liquid extraction	20–7500	3.4 at 400 ng/g, 9.5 at 30 ng/g	16	MCC	this study
IC-CD	Direct	liquid extraction	30–300000	1.2–2.6	50	saliva	12
LC-UV	Indirect	liquid extraction, Griess derivatization	6–400	< 2.5	2.0–6.0	vegetable, blood, urine	16
LC-MS	Indirect	liquid extraction, 2,3-diaminonaphthlalene derivatization	200–10000	1.5 – 3.3	200	excipients	11
GC-MS	Indirect	liquid extraction, PFB bromide alkylation	250–2000	3.8	10	urine, plasma	10

LOQ for MCC

*Zhu K., Kerry M.,Serr B., Mintert M., J. Pharm. Biomed. Anal. 235 (2023) 115648

Nitrite as a proxy for nitrosating species in excipients

- The techniques listed convert the nitrosating species present to nitrite **"NO_2^-"** or an organic derivative like DAT

- However, the nitrosating species present in a given excipient may differ
  - **NO_2^-** as salt with counterions, e.g., Na^+, K^+, Ca^+
  - **N_2O_3** a gas at room temperature
  - **Nitrosyl halides** and pseudohalides, e.g., NOCl, NOBr, NOSCN
  - **Alkyl nitrites** – R-ONO
  - **NO+**, e.g. $NO(HOSO_3)$
  - **Surface adsorbed NOx** – NO_2, NO
- And their microspatial distribution within excipients (same excipient different manufacturer) can differ, affecting nitrosation kinetics

Nitrite as a proxy for nitrosating species in excipients

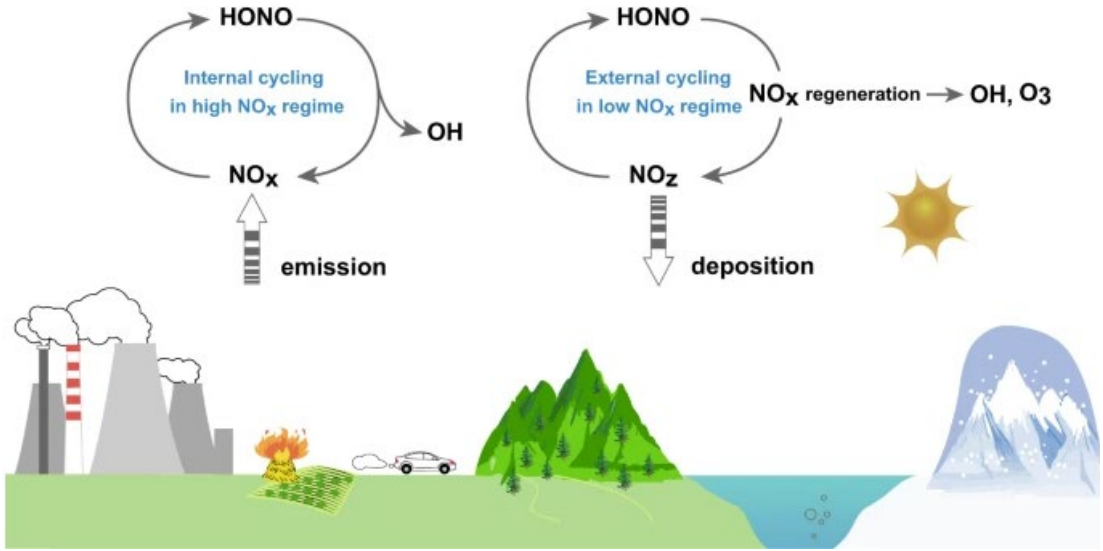
The same nominal **"NO_2^-"** content between two different suppliers could show differing nitrosation kinetics in a given drug product

- Regulatory challenge – spiking studies requested by agency to establish "nitrite" specifications for specific excipients for specific formulations

Research Opportunity

- Design/conduct studies on widely used excipients to either:
  - Speciate nitrosating agents in materials from different manufacturers, *or*
  - Develop a protocol to differentiate nitrosation kinetics "nitrosating potential" of different excipient grades or from different manufacturers if speciation is not possible

Challenges with NOx

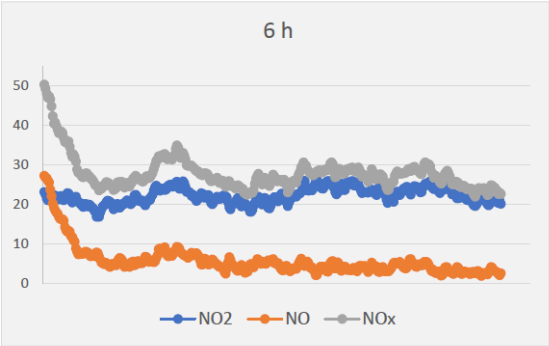


Ye C., Zhou X., Zhang Y., et al., Nat. Commun. 2023 14, 7995

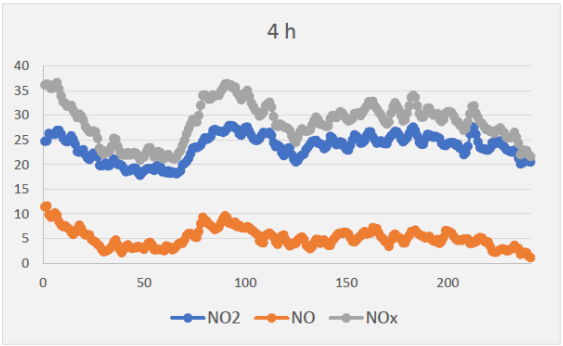
- Atmospheric HONO concentrations can range from 100's of pptv in rural areas to 10's of ppbv in urban areas and have a diurnal variation (highest at night)
- Apotex observed a 2° amine API sample increase in NDSRI content from ~50 ppb to ~100 ppb in only 4 hours sitting open on lab bench

Challenges with NOx –Sandoz Study on Excipients

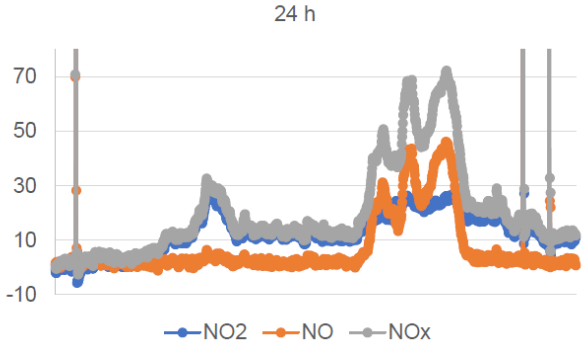
NOx in Lab: 6h, avg: NO_2: 22 ppb; NO: 6 ppb; NO_X: 28



NOx in Lab: 4 h; avg NO_2: 24 ppb; NO: 5 ppb; NO_X: 29



24 h avg: NO_2: 17 ppb; NO: 10 ppb; NO_X: 28



Excipient	Nitrite ppb t=0	Nitrite ppb t=6h
Lactose	< 50	< 50
Starch	< 50	320

Excipient	ppb t=0	ppb t=4h
Kollidon CL	918	2686
Povidone K30	901	1431

Excipient	ppb t=0	ppb t=24h
Croscarmellose	< 50	138
Lactose Batch A	< 50	< 50
Lactose Batch B	< 50	< 50
Lactose Batch C	< 50	< 50
Starch Batch A	< 50	658
Starch Batch B	< 50	147
Starch Batch C	< 50	507

From CRCG workshop, June 15, 2023

Determination of nitrite in pharmaceutical excipients; air as source for higher nitrite levels.

Rok Grahek

June 15, 2023

SANDOZ A Novartis Division

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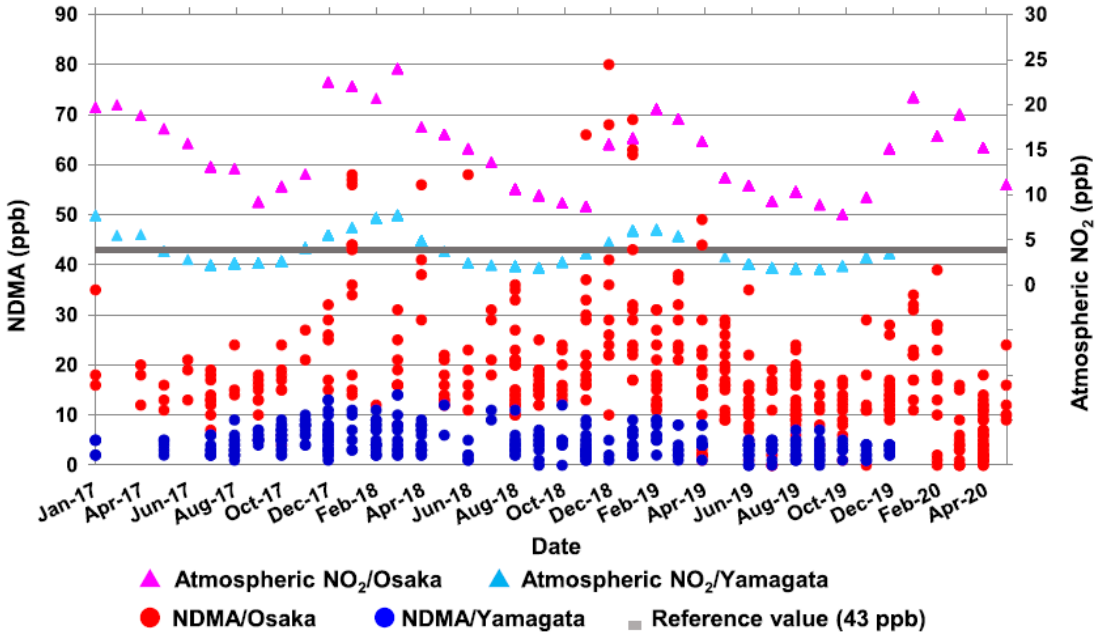
Challenges with Nox – Towa Study on Metformin



- NDMA in metformin drug products at Towa Pharmaceutical Co. and NOx levels at their Osaka and Yamagata mfg. sites
- Model study provided strong evidence that atmospheric NOx and total air exposure correlated with NDMA formation

*Fukada S., Kondo K., Fukumoto S., et al., Org. Process Res. Dev. 2023 27(11), 2123-2133

Bridging BE studies – *current state*

- Reformulations may include:
  - Adding stabilizer to existing formulation
  - Change to multiple excipients - levels and/or type
- SUPAC Level 3
  - additional excipient requires full BE study
  - BE can be waived with appropriate IVIVC

→ SUPAC Level 3 Change

What are the options for bridging the BE studies when it comes to nitrosamines control related changes?

Bridging BE studies – *adding nitrosation inhibitors*

FDA funded research studies on antioxidants

- Impact on permeability – four antioxidants
  - alpha tocopherol,
  - ascorbic acid,
  - cysteine HCl ,
  - propyl gallate
- Four BCS3 model drug substances
  - acyclovir
  - atenolol
  - cimetidine
  - ranitidine

2023- caco-2 cells

Bode, C., **CRCG Conference Presentation,** June 15, 2023

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

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

Yu Y., Lu D., Rege B., Polli J., **J. Pharm. Sci.** preprint (2024)

- acyclovir
- pirenzepine
- cimetidine
- ranitidine

- 10 inhibitors

2024- MDCK-II cells

Study findings:
Tested antioxidants had no impact on permeability

Bridging BE studies – *adding nitrosation inhibitors*

FDA funded research studies on antioxidants

- Impact on intestinal transporters –
  - 30 antioxidants studied
  - 3 transporters
    - P-gp
    - BCRP
    - OATP2B1

2023

Study finding:
Tested antioxidants had no impact on transporters

Yee S., **Generic Drugs Science and Research Workshop Presentation,** May 11, 2023

Bridging BE studies – *considerations*

- PBPK modeling for Biopharmaceutics Risk Assessment (BRA) of potential nitrosation inhibitor effect
  - Parameter Sensitivity Analysis (PSA) to assess sensitivity for a specific drug
  - Virtual BE for selected %change in Papp (based on PSA)

BRA should be utilized to critically assess the potential risk/effect of changes to formulation on:

- Dissolution - in vitro tests (pre- and post-change formulation)
- Permeability – utilize research database

Research Opportunity

Industry would benefit from extending the research for impact on Papp on nitrosation inhibitors to BCS IV actives and, possibly, more cross-check across model cell types

Bridging BE studies – *considerations*

- For IR products, BRA approach can be used for drugs of different BCS class

BCS class (IR)	Risk/Complexity	Option
BCS1 (HS,HP)	Unlikely to impact	BCS1 biowaiver
BCS3 (HS,LP)	Permeability is a limiting factor for absorption	BRA approach considering DS absorption mechanism (active or passive) vs excipient change
BCS2 (LS,HP)	Unlikely to impact	Excipient/nitrosation inhibitor unlikely to impact solubility, permeability is high (significant impact in unlikely)
BCS4 (LS,LP)	Complex as both solubility and permeability are low	BRA approach considering DS absorption mechanism vs excipient change, provided dissolution is comparable

However, when it comes to nitrosation inhibitor additions for nitrosamines control, this approach should be considered acceptable for MR products also

Acknowledgement

Thanks to Dr. Emilija Fredro-Kumbaradzi of Apotex Inc. for her valuable input on bridging bioequivalence study considerations

Thank you.