

N-Nitrosamines

Past, Present and
Future (a personal
perspective)

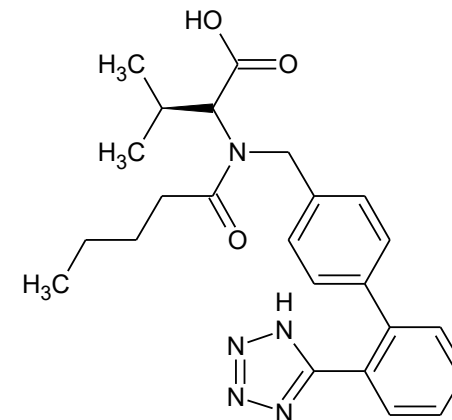


Outline

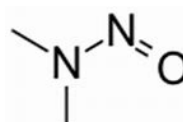
- **Introduction**
 - Background and History
 - Impact
- **Current situation**
 - Risk Assessment outcomes
 - Collaboration
- **Safety Science and Acceptable Intakes**
 - CPCA (Carcinogenic Potency Categorization Approach)
 - EAT (Enhanced Ames Test)
- **What next for Nitrosamines**



Where it all started – Valsartan recall



- On 6 June 2018, Zhejiang Huahai Pharmaceuticals, was [informed by a customer](#) of an unexpected impurity in the manufacturer's valsartan API.
- After an initial investigation, on 20 June 2018 Zhejiang Huahai sent a letter to its customers informing them of the presence of 'a previously unknown impurity that may have genotoxic potential'
 - [requested that they immediately put on hold the use of its valsartan API.](#)
- 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'



The screenshot shows a press release from the European Medicines Agency (EMA) dated 05/07/2018. The title is "EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity". The text states that the EMA is reviewing medicines containing the active substance valsartan supplied by Zhejiang Huahai Pharmaceuticals in Linhai, China, due to the detection of an impurity, *N*-nitrosodimethylamine (NDMA). NDMA is classified as a probable human carcinogen. The release also mentions that national authorities across the EU are recalling medicines containing valsartan supplied by Zhejiang Huahai.



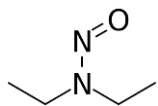
Evolution of the Problem

Nitrosamine Drug Substance Related impurities
(NDSRIs)

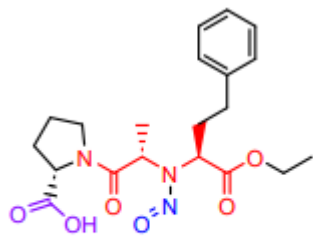


Industry Risk Assessments

Step 1 – a new phase - NDSRIs

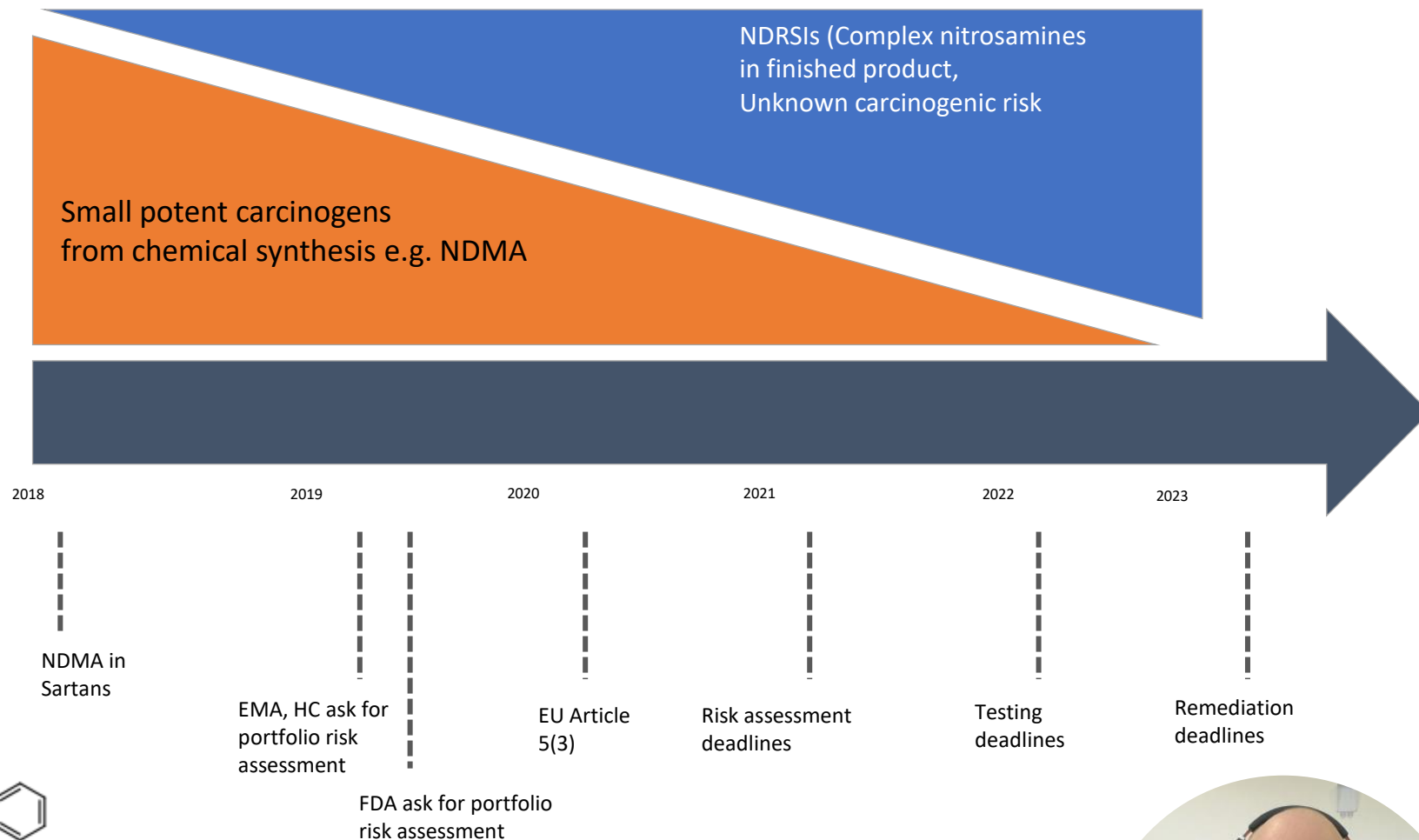


NDEA



Nitroso-Enalapril

NDSRI (Novel Drug Substance Related Impurity)



First issue associated with chemistry – AP
 Second – focused on Drug Product



Nitrosamine Challenge – NDSRIs : the problem statement

The Ames test



The bacterial **Ames test** is used to **assess mutagenic** potential of chemicals and drugs

Initially Negative Ames test for complex nitrosamines, used for some products to justify no risk

Regulatory challenge & Health Authority Differences



Regulators have concerns about validity of Ames tests to determine mutagenicity of nitrosamines*

Control Limit Challenge



Unlike simple dialkyl amines – NDSRIs have limited / no carc. Data

Implications



nanogram limits were enforced
- it essentially impossible to manufacture to these limits



Reflections / Opinion Pieces

- Both industry and regulators have published a lot of material over the 5-6 yr. period, this includes
- [Horne et al.](#) and [Bream et al.](#) Provide a regulatory context.
- The Landscape paper of Schlingemann et al provides a good overview of the extent of the risk - particularly NDSRIs :
<https://doi.org/10.1016/j.xphs.2022.11.013>
- The **saga paper** – provides an overview of progress made since the start of the Nitrosamines crisis <https://doi.org/10.1021/acs.oprd.3c00100>



Overview of industry perspective – narrative



The saga paper.



We showed that even ppm levels of nitrite may be enough to create concerning amounts of N-NO in a drug product,



that limits like 18ng/day are challenging/impossible as they require sensitivity beyond what's currently achievable,



Outstanding Issues and Priorities – pre July 2023

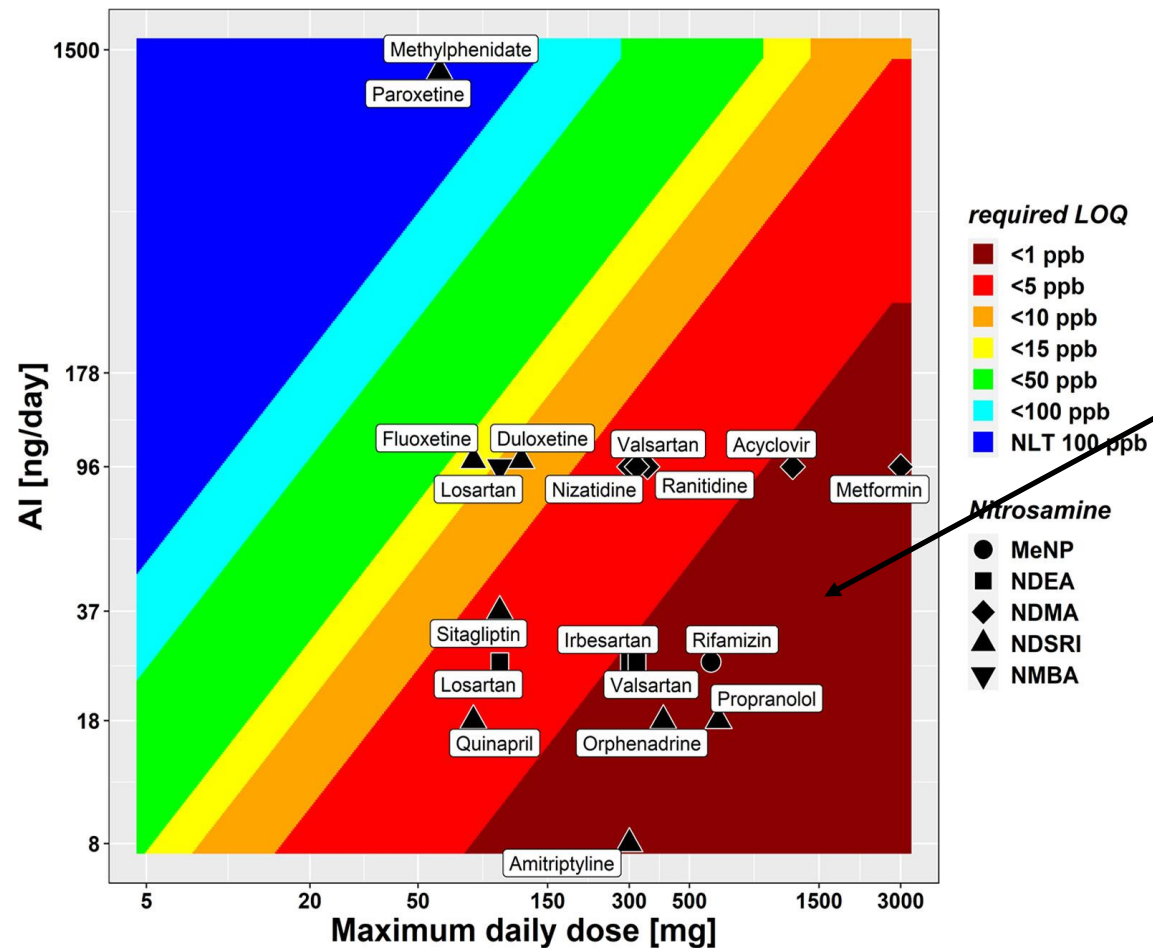
Focussing and prioritising control and remediation resources

- **General remediation of NDSRIs to 18ng/day not technically feasible**
- Implementation of CAPAs / remediation, when possible, will likely take several years.
- **Analytical capacity** for NDSRI testing under real strain especially where there is a need for low level routine testing.



Sensitivity

Analytical Procedure – What should be the sensitivity?



With increasing MDD, the LOQ (<1ppb) requirement exceeds the capability of the instrument.



What was needed

- Maintain benefit / risk-based and science-based regulatory oversight
 - Many of the medicines are vital.

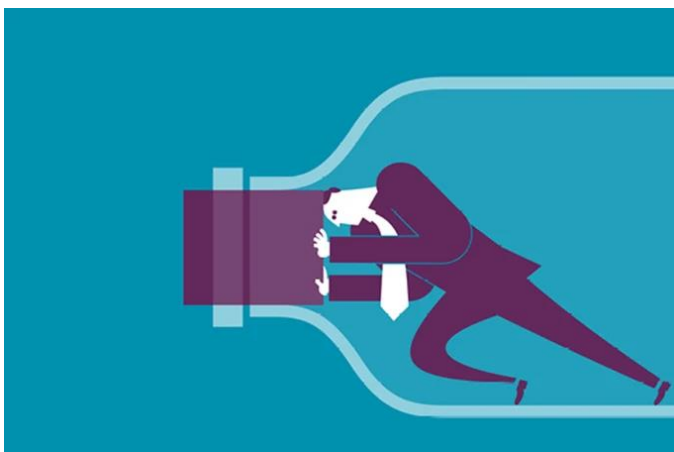
➤ GLOBAL ALIGNMENT

- **Without some changes we faced a crisis and an inability to maintain supply of products potentially containing structurally-complex nitrosamines**



Agency Acceptable Intakes

- Agreeing Acceptable Intakes (AI) for NDSRI's was a significant bottle neck
 - FDA/HESI/trade associations meeting (May 31/Jun 1)
Backlog of ~60 NDSRI's requiring assessment
- Led directly to the introduction of the **Carcinogenic Potency Categorisation Approach (CPCA)** intended to address this
 - Allows SAR to be used to define an AI for a given structure



Agency Acceptable Intakes

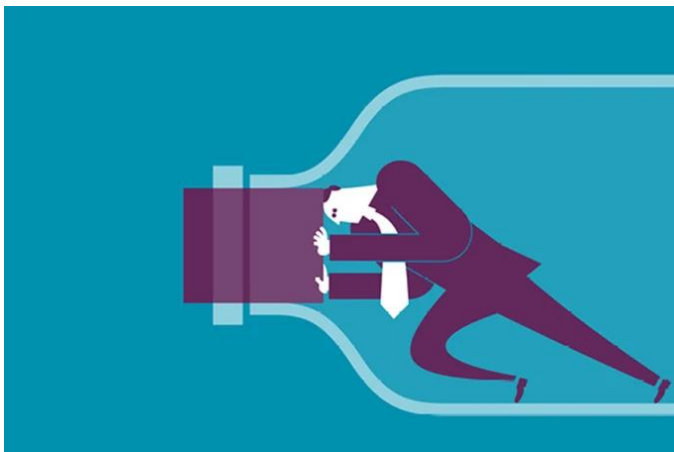


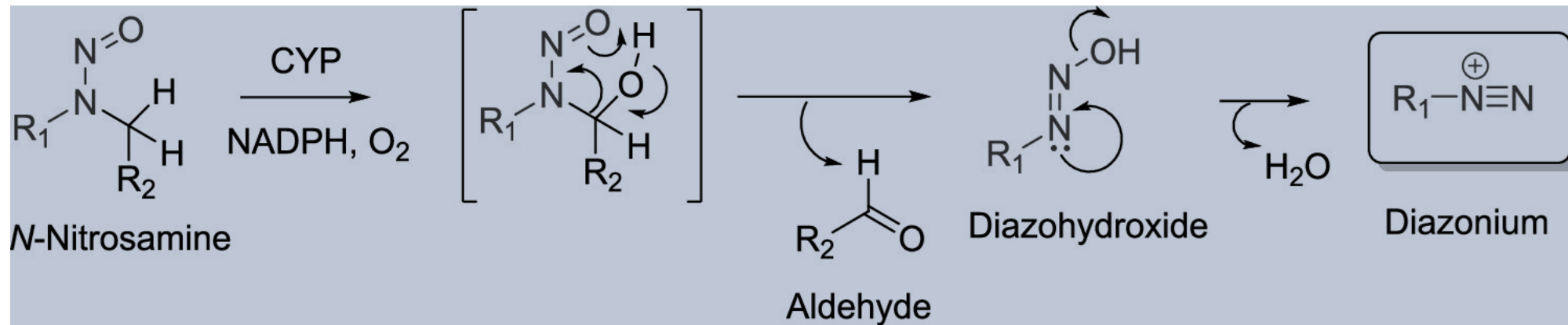
Table 1. The Five Predicted Potency Categories and Associated AI Limits for *N*-Nitrosamines

| Potency Category | Recommended AI Limit (ng/day) | Comments |
|------------------|-------------------------------|--|
| 1 | 18 | The recommended AI limit of 18 ng/day is equal to the class-specific TTC for <i>N</i> -nitrosamine impurities.* <i>N</i> -nitrosamines assigned to Category 1 are predicted to have high carcinogenic potency; however, the class-specific TTC for <i>N</i> -nitrosamine impurities is considered sufficiently protective to patients. |
| 2 | 100 | The recommended AI limit of 100 ng/day is representative of two potent, robustly tested <i>N</i> -nitrosamines, <i>N</i> -nitrosodimethylamine (NDMA) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK), which have recommended AI limits of 96 ng/day and 100 ng/day, respectively. <i>N</i> -nitrosamines assigned to Category 2 are predicted to have carcinogenic potency no higher than NDMA and NNK. |
| 3 | 400 | Compared to Potency Category 2, <i>N</i> -nitrosamines in this category have lower carcinogenic potency due to, for example, the presence of a weakly deactivating structural feature. The recommended AI limit was set to reflect a 4-fold decrease in carcinogenic potency from Category 2. |
| 4 | 1500 | <i>N</i> -Nitrosamines assigned to Category 4 may be metabolically activated through an α -hydroxylation pathway but are predicted to be of low carcinogenic potency, for example, because the pathway is disfavored due to steric or electronic influences, or because clearance pathways are favored. The recommended AI limit of 1500 ng/day is set at the TTC per ICH M7.** |
| 5 | 1500 | <i>N</i> -Nitrosamines assigned to Category 5 are not predicted to be metabolically activated through an α -hydroxylation pathway due to steric hindrance or the absence of α -hydroxylation. They are predicted to form unstable species that will not react with DNA. The recommended AI limit is set at the TTC per ICH M7.** |



Mechanism – Activation

Nitrosamines require metabolic activation



R₁, R₂ = alkyl or aromatic
R₁ = alkyl, R₂ = aromatic
R₁ = aromatic, R₂ = alkyl
R₁ & R₂ - part of cycloalkyl motif

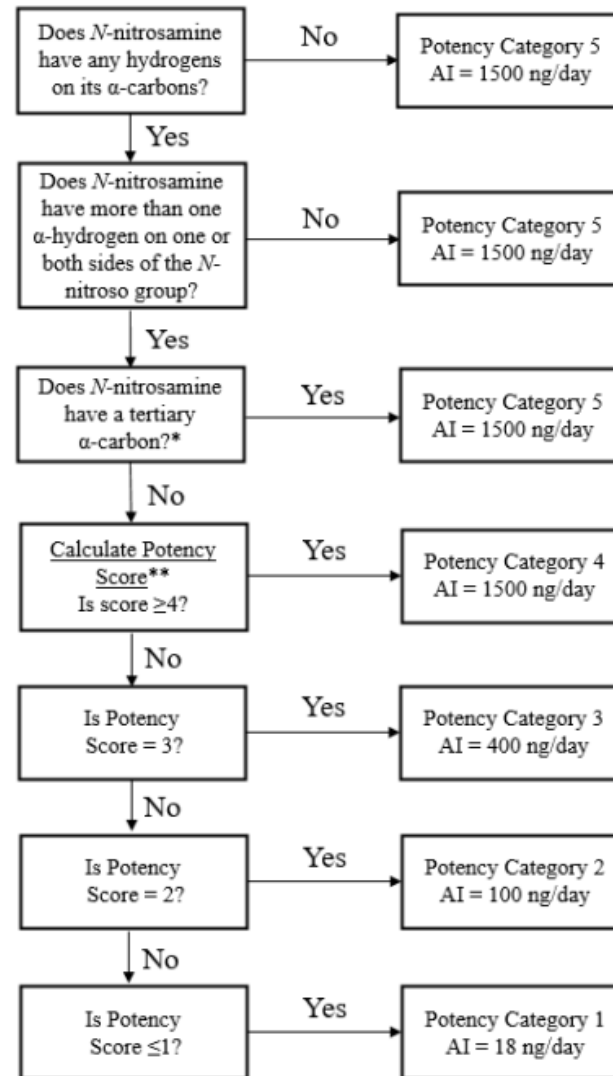
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CPCA

Carcinogenic Potency Categorisation Approach

Figure 2. Flowchart to Predict the Potency Category of an N-nitrosamine

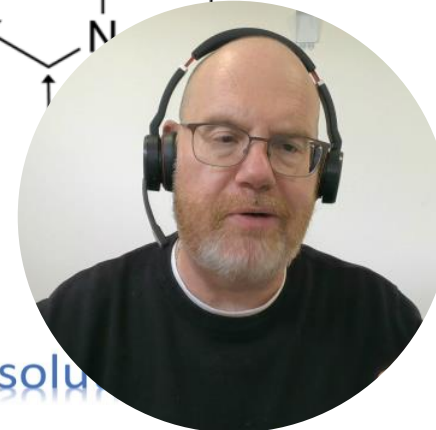
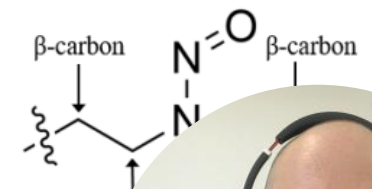


* A tertiary α -carbon is defined as an α -carbon atom in an sp^3 hybridisation state, bonded to three other carbon atoms.

** To calculate Potency Score, see Annex A.

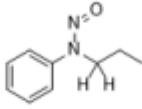
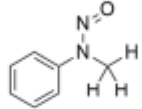
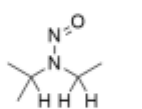
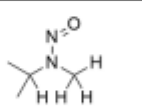
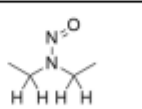
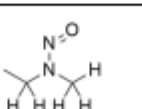
In basic terms this is an empirical model that relates to the mechanism of action of N-Nitrosamines –this is tied the number of protons on the alpha carbon.

Figure 1. Structural Representation of α - and β -carbons on an N-nitrosamine



CPCA Potency 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 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.

The more protons the higher the potency and the lower the score

- Start here then adjust for Activating and Deactivating



CPCA Activating and Deactivating Features

Table 3. List of deactivating features and associated scores. To calculate Deactivating Feature Score, sum the individual scores for all listed features present in the N-nitrosamine structure. Each deactivating feature row in the table may only be counted once. For N-nitrosamines where the N-nitroso group is within more than one ring, the feature score for only the smallest matching ring should be applied. Examples are intended to be illustrative only and are not intended to be exhaustive.

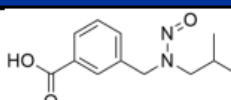
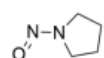
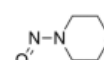
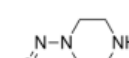
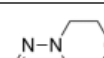
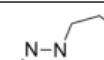
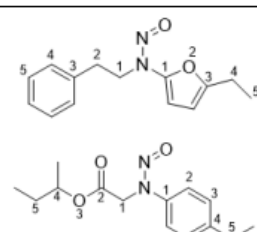
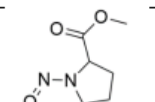
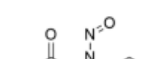
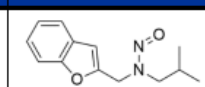
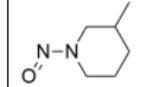
| Deactivating Feature | Example | Individual Deactivating Feature Score |
|---|---|---------------------------------------|
| Carboxylic acid group anywhere on molecule |  | +3 |
| N-nitroso group in a pyrrolidine ring |  | +3 |
| N-nitroso group in a 6-membered ring containing at least one sulfur atom |  | +3 |
| N-nitroso group in a 5- or 6-membered ring* |  | +2 |
| N-nitroso group in a morpholine ring |  | +1 |
| N-nitroso group in a 7-membered ring |  | +1 |
| 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. |  | +1 |
| Electron-withdrawing group** bonded to α -carbon on <u>only one</u> side of N-nitroso group (cyclic or acyclic) |  | +1 |
| Electron-withdrawing groups** bonded to α -carbons on both sides of N-nitroso group |  | +2 |

Table 4. List of activating features and associated scores. To calculate Activating Feature Score, sum the individual scores for all listed features present in the N-nitrosamine structure. Each activating feature row in the table may only be counted once. Examples are intended to be illustrative only and are not intended to be exhaustive.

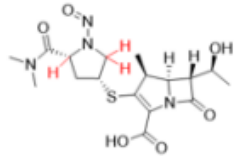
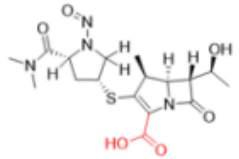
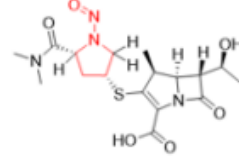
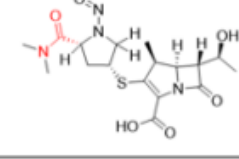
| Activating Feature | Example | Individual Activating Feature Score |
|--|---|-------------------------------------|
| Aryl group bonded to α -carbon (i.e., benzylic or pseudo-benzylic substituent on N-nitroso group) |  | -1 |
| Methyl group bonded to β -carbon (cyclic or acyclic) |  | -1 |



CPCA Examples from EMA Appendix 2

Example 5 – N-Nitroso-meropenem

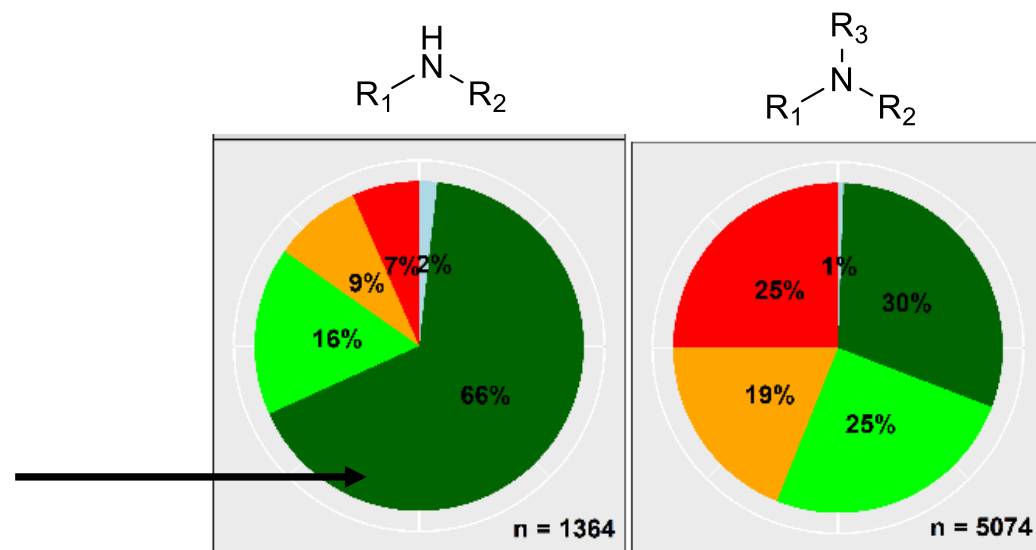
Example 5 shows how the potency categorisation approach flow chart (Figure 2) can be applied to the *N*-nitrosamine, *N*-nitroso-meropenem. A Potency Score of 4 is calculated for *N*-nitroso-meropenem, resulting in its placement in Potency Category 4 with an associated AI limit of 1500 ng/day.

| Count of α -Hydrogens | Score | Feature Highlighted in Red |
|--|---------------------------|---|
| 1,2 | 3 |  |
| Deactivating Features | Score | Feature Highlighted in Red |
| Carboxylic acid group anywhere on molecule | +3 |  |
| <i>N</i> -nitroso group in a pyrrolidine ring | +3 |  |
| Electron-withdrawing group bonded to α -carbon on <u>only one</u> side of <i>N</i> -nitroso group (cyclic or acyclic) | +1 |  |
| No Activating Features Present | | |
| Potency Score = 3 + 3 + 3 + 1 = 10 | Potency Category 4 | AI = 1500 ng |



How widespread is the issue?

- Up to 40% of APIs and 30% registered impurities may be susceptible!
- Significant improvement following introduction of CPCA. 66% of secondary amines result in a 1500 ng/day limit.



EAT

Enhanced Ames Test

- **Enhanced Ames Test** Introduced at same time as CPCA
- Essentially “Enhanced” OECD 471 conditions
 - Use of Rat S9 and Hamster S9
 - Many companies already using both Rat and Hamster
 - However, recommended at 30%
Most companies had been using 10%
 - Two N-nitrosamines that are known to be mutagenic in the presence of S9 should also be included as positive controls.



| Content | EMA position (HC) | FDA position | Comment |
|---|--|--|--|
| Carcinogenicity Potency Characterisation Assessment (CPCA) | Fully adopted | Fully adopted | Identical text - only difference - less examples used in FDA guidance |
| Enhanced Ames Test (EAT) | Based on 30% rat / hamster, 2 positive controls, preincubation, use of water (preferred vehicle). EMA position - if negative AI = 1500ng | Based on 30% rat / hamster, 2 positive controls, preincubation, use of water (preferred vehicle). Negative position - less clear | FDA: A negative result in a valid enhanced Ames assay <u>may</u> be used to support a higher limit for an NDSRI; however, manufacturers and applicants should note that FDA may request <u>additional safety data</u> , beyond the enhanced Ames assay to support alternative AI limits. |
| In vivo data | Negative TGR = Q3A/B limits | In-vivo mutagenicity: No mention of what to do with a negative in vivo study. | FDA concern over correlation between in vivo mutagenicity data and carcinogenicity |

Comparison between Guidelines

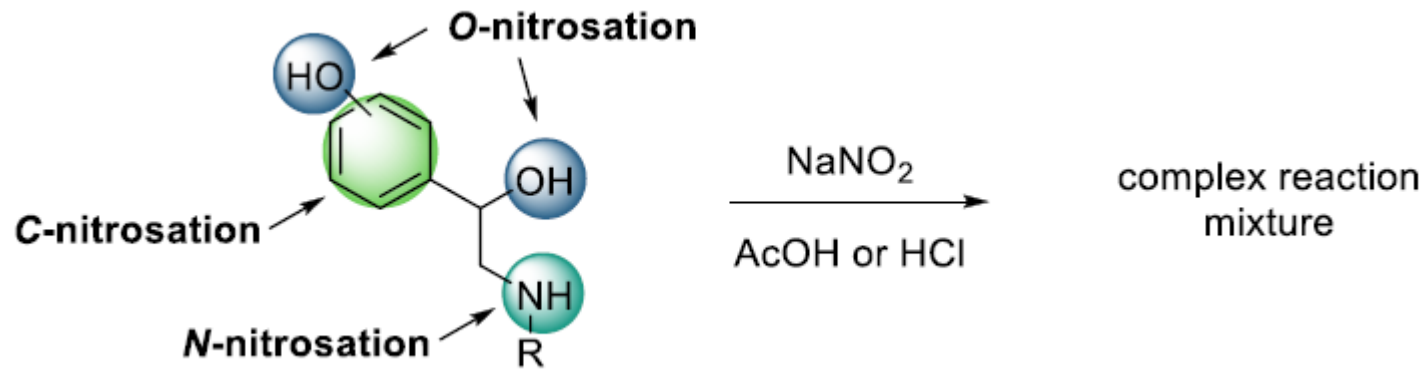


Nitrosamines

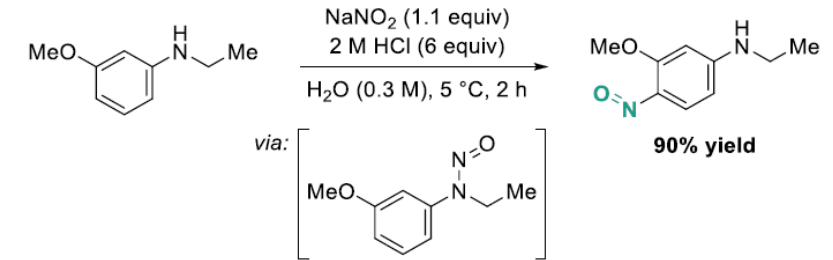
Risk Assessment



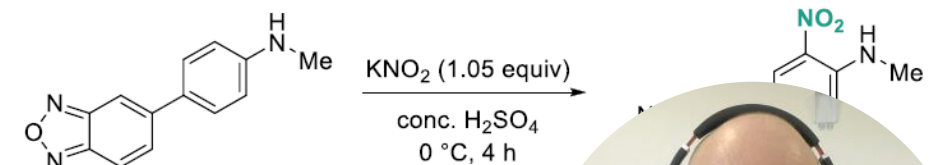
Not all Amines can lead to a Nitrosamine



B) Fischer-Hepp Rearrangement



Scheme 3. C-Nitration Facilitated by Reaction with Potassium Nitrite and Sulfuric Acid



Approaches and Considerations for the Investigation and Synthesis of N-Nitrosamine Drug Substance-Related Impurities (NDSRIs)

Ian W. Ashworth, Alexander Blanz,^{*} Jonathan J. Byrne, Olivier Dirat, Jared W. Fennell, Nadine Kuhl, Stuart L. Wells, and Matthew P. Whiting



Cite This: *Org. Process Res. Dev.* 2023, 27, 1784–1791



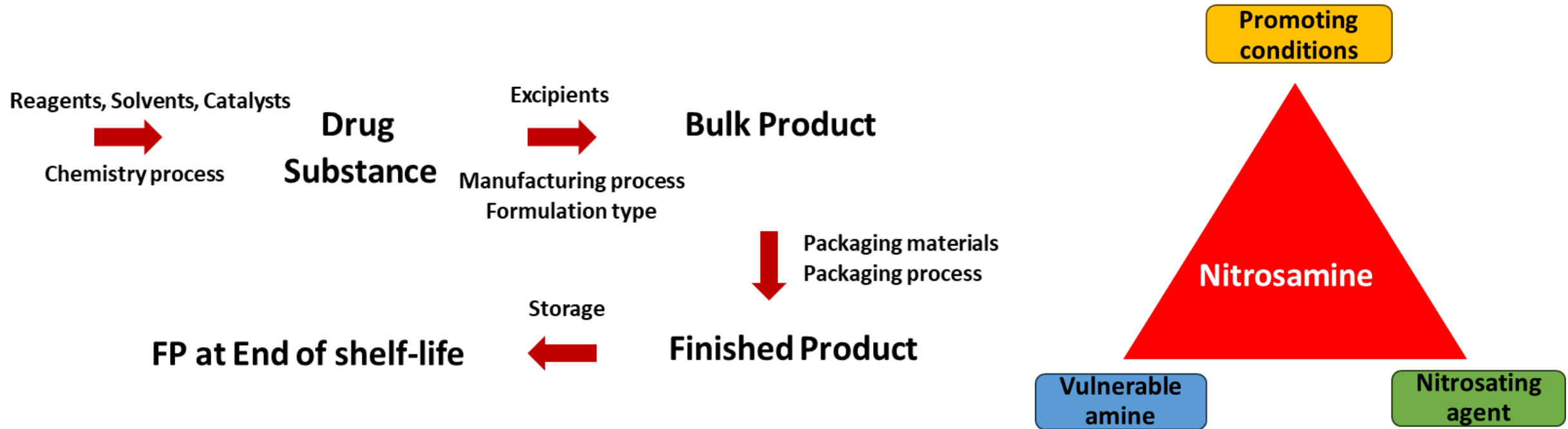
Read Online



ATCMC solutions



Basics behind the EFPIA Drug Substance and Product Risk Assessment workflows



- Workflows and comprehensive guidance notes are compiled from:
 - risk factors reported by health authorities,
 - experiences from industry following root cause investigations and
 - scientific studies



Drug Substance Risk Assessment Workflow

<https://www.efpia.eu/media/tkbnsicy/efpia-nitrosamines-risk-management-workflows-jun-24-udpate.pdf>

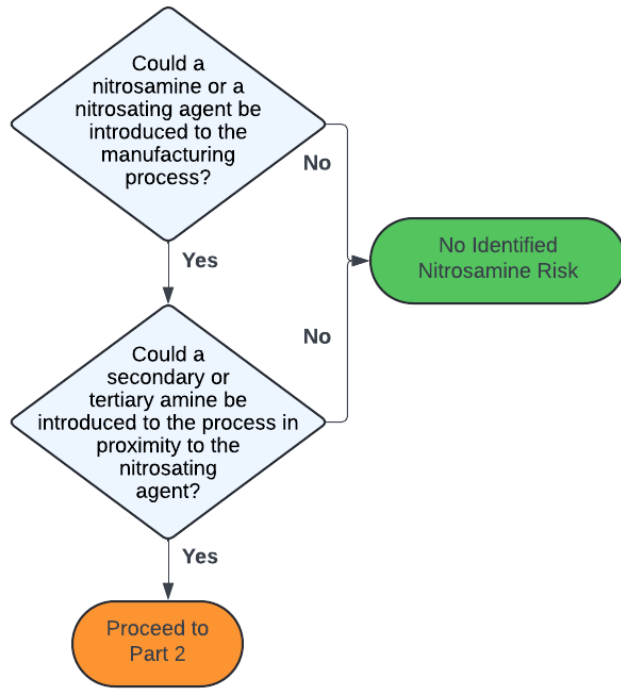
Drug Substance Manufacturing Process Risk Assessment
Part 1 - Risk Identification

Assess all stages of the drug substance manufacturing route after the registered starting materials. The synthesis routes for registered starting materials also need to be assessed, particularly when they contain amine, nitro functionalities, use nitrosating agents or are introduced late in the synthesis.

Risks associated with the drug substance and associated impurities / degradants containing vulnerable amines in the drug product are addressed in the Drug Product Workflow

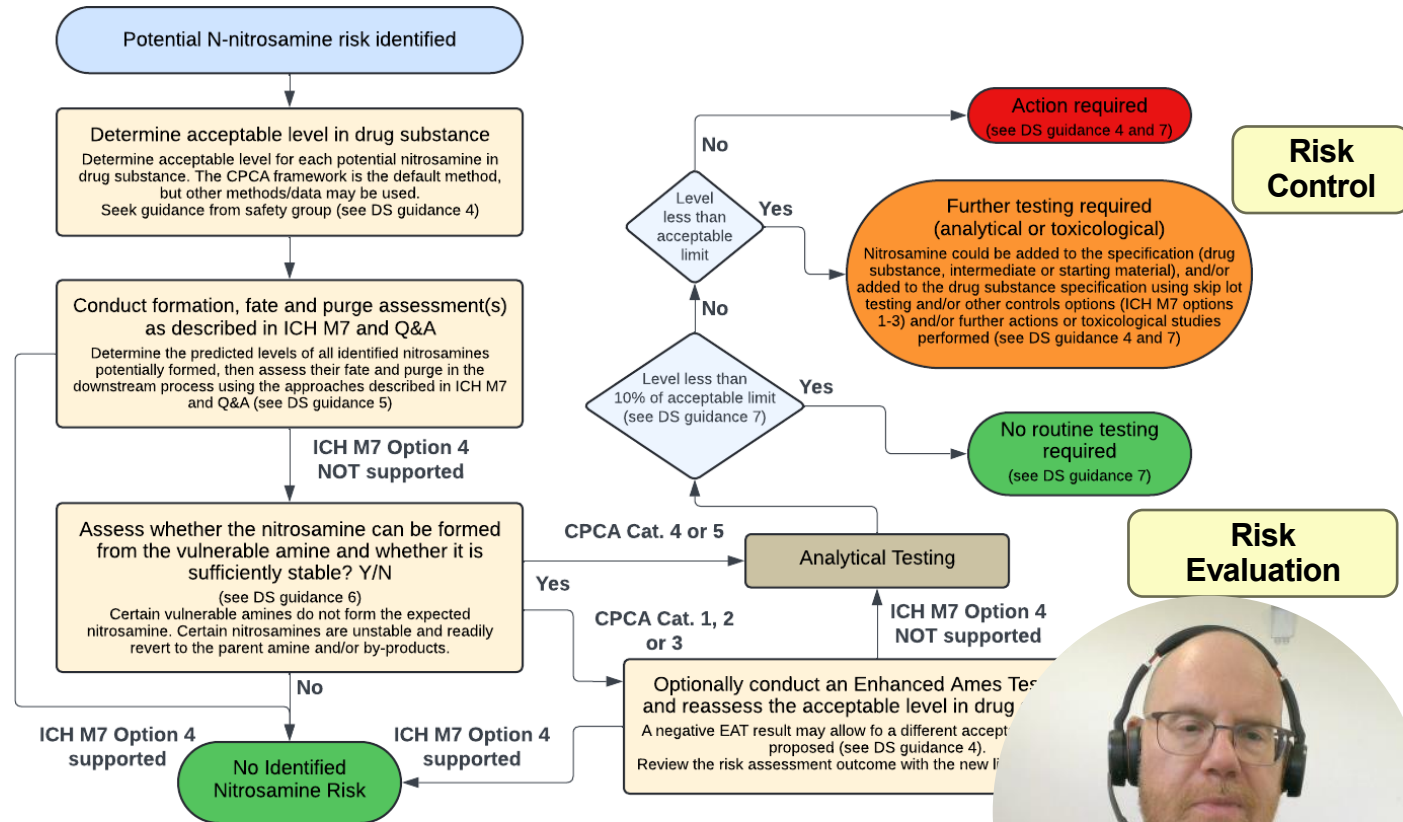
Nitrosating agents can be used in the process during a reaction or work-up, introduced as impurities in input materials or processing environment or generated during the process (see DS Guidance 1). Other root causes included in regulatory guidance should also be considered (see DS References 1, 2, 16 and 17).

Certain secondary and tertiary amines are vulnerable towards reaction with nitrosating agents to form nitrosamines. They can be part of the core structures, used in the process as reagents or solvents, introduced as impurities in input materials or generated during the process as impurities. In rare instances, other functional groups may directly lead to a nitrosamine (see DS guidance 3). Other root causes included in regulatory guidance should also be considered (see DS DS References 1, 2, 16 and 17).



Hazard Identification

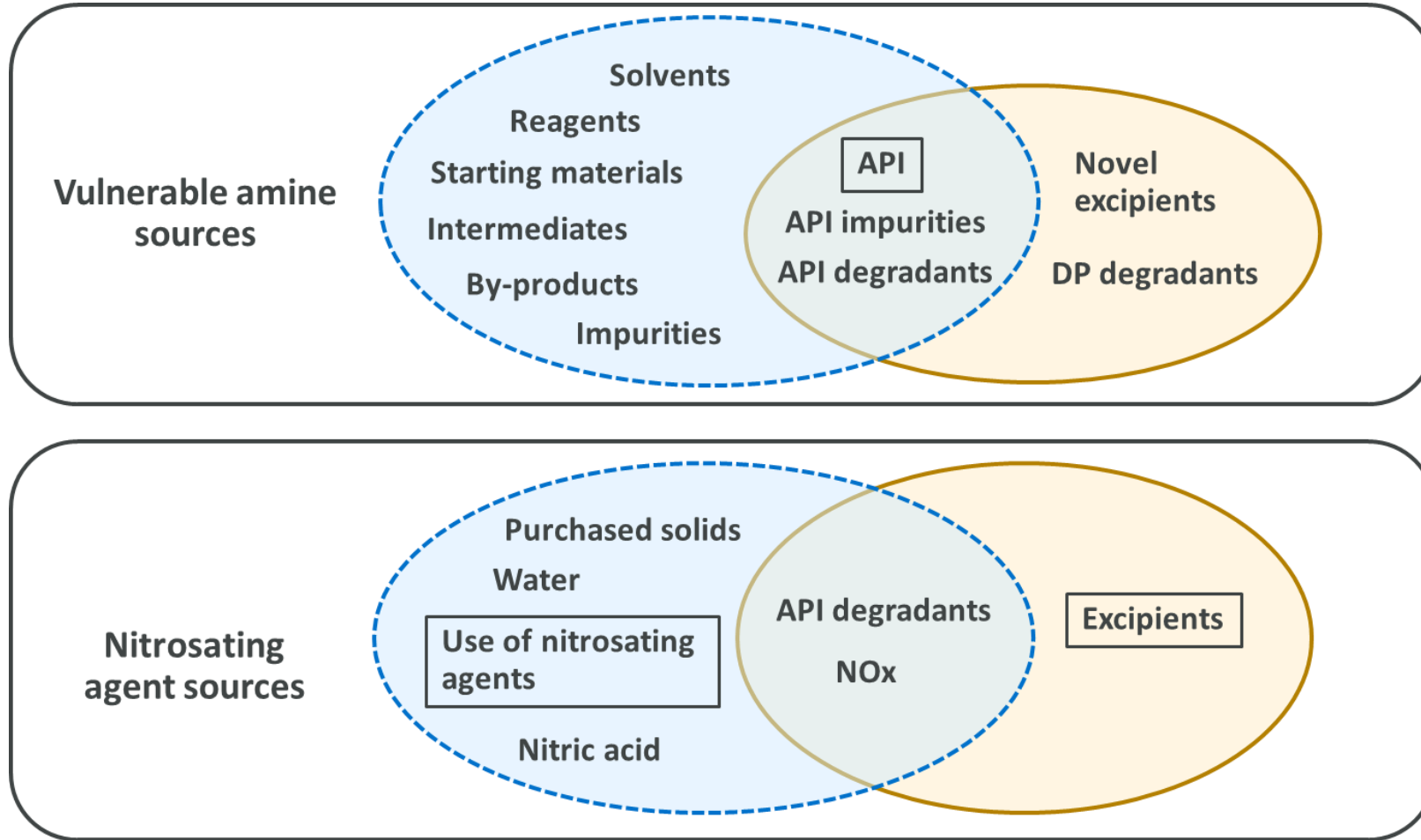
Drug Substance Manufacturing Process Risk Assessment
Part 2 - Characterisation and Confirmatory Testing



Risk Analysis



Vulnerable Amines and Nitrosating Agents



Very common

- Vulnerable amines
- Trace nitrosating agents (e.g. in reagents/inorganics and water)

Less common

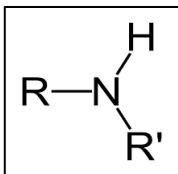
- Deliberate use of nitrosating agents
- NO_x (DS processing operations mostly performed under inert atmosphere)



Potential sources for vulnerable amines and nitrosating agents

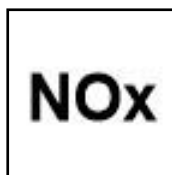
N-Nitrosamine formation in drug product

3 risk factors – ALL required



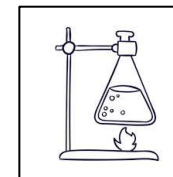
Secondary Amine

- Secondary amine
- Tertiary amine
 - Aliphatic/aromatic
- Free base/salt
- API/degradant/contaminant from:
 - Solvents
 - Intermediates
 - Reagents
 - Catalysts



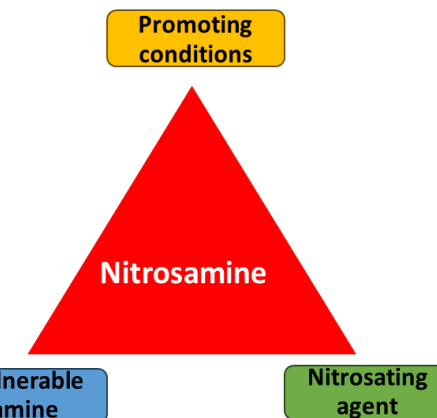
Nitrosating Agents

- Reagents:
 - Nitrites, Nitric acid
 - Nitrosyl ion
- Nitrite in excipients
- Nitrite in water
- (API) degradation to NOx

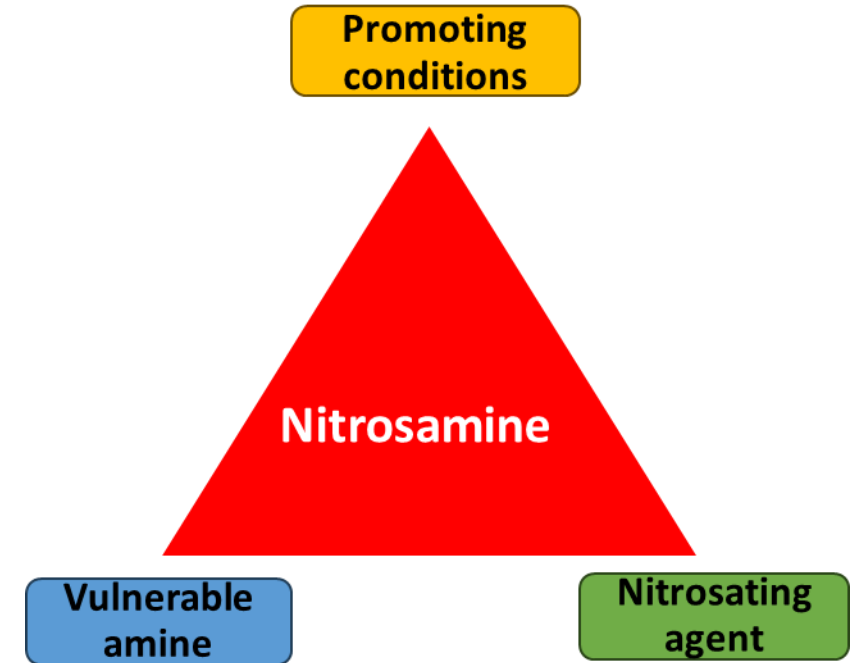
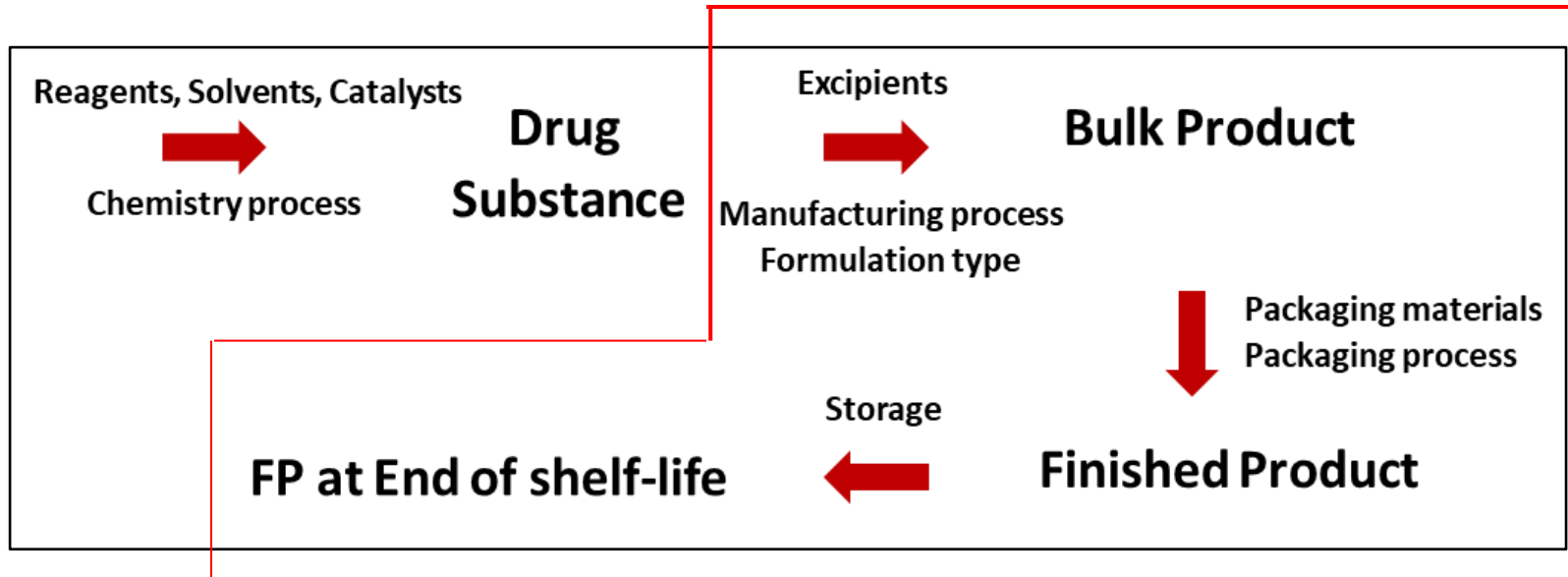


Conditions

- pH
- Temperature
- Nitrosation catalysts
- Water presence
- Drying process
- Equipment cleaning process





Basics behind the Drug Product Risk Assessment Workflows



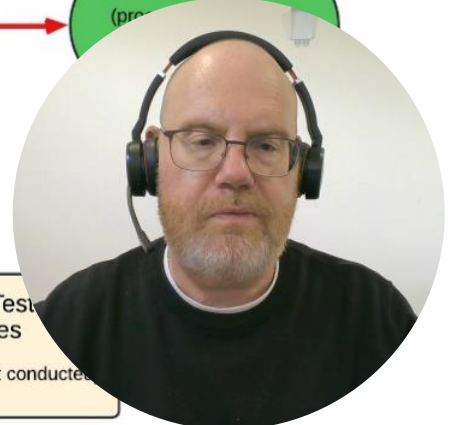
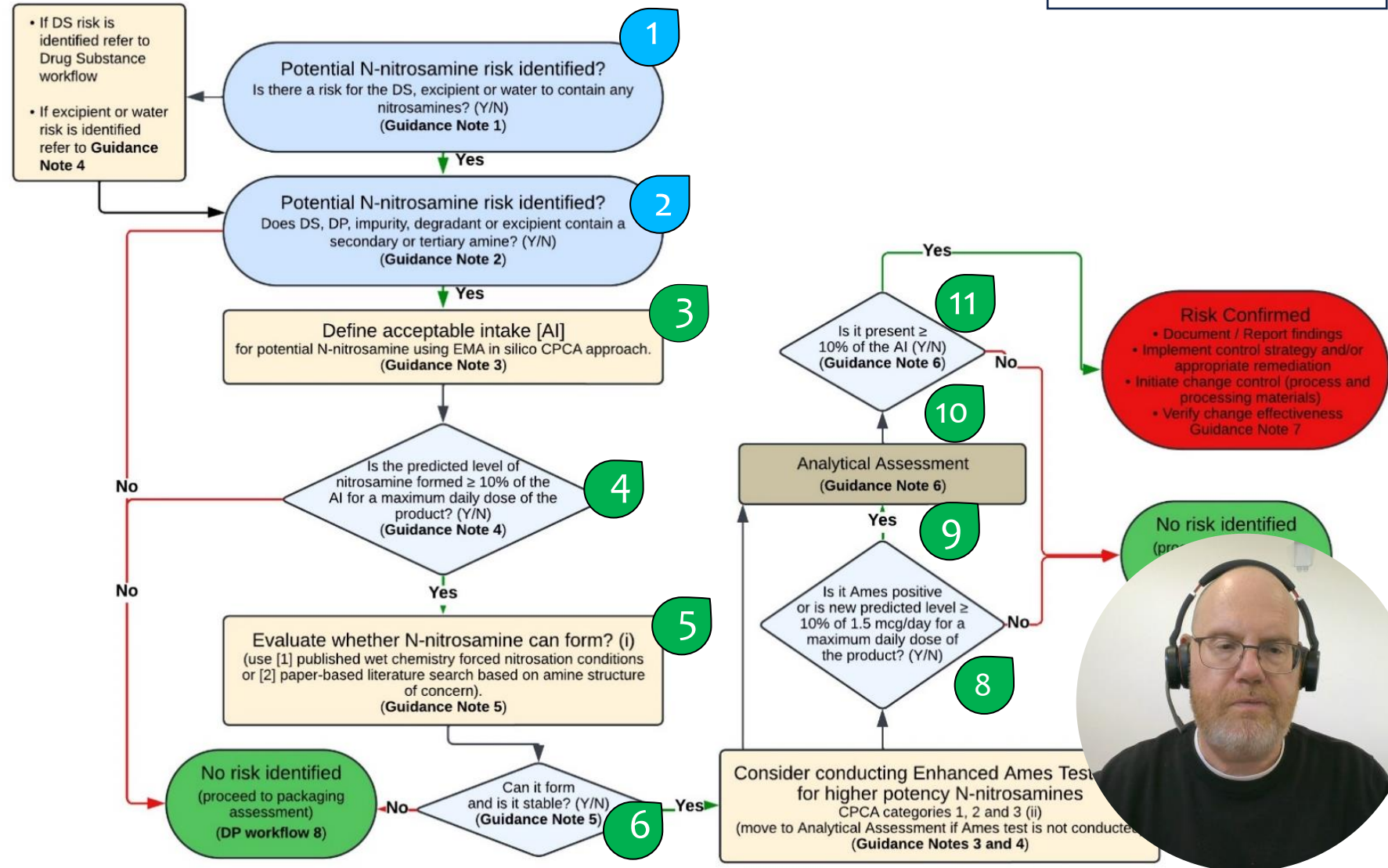
- Focus on workflows for formulation process, finished products, and subsequent packaging and shelf-life evaluation – this can be based on
 - Review of some published works on formulation and packaging
 - Importance of predictive models for formulation
 - Wet chemistry can be used to predict solid chemistry
 - Enhanced Ames Test
 - Packaging
 - Analytical Testing



Drug Product (DP) Workflow: Risk ID

-  No more info
-  More detail to come

- 1) Evaluate for NA
- 2) Evaluate for vulnerable amine
- 3) Evaluate nitrosamine (CPCA)
- 4) **Is the predicted level < 10% of AI – no risk**
- 5) Obtain experimental data
- 6) If formed, is the NA stable? If cannot form or if NA is not stable - **no risk**
- 7) Perform Toxicity study (EAT Ames)
- 8) If negative, and predicted level $\leq 10\%$ of 1.5 mcg/day (for cat 4,5) based on dosing regimen- **no risk**; consider packaging
- 9) If positive EAT Ames or predicted level $\geq 10\%$ of 1.5 mcg/day (for cat 4,5), then you have identified a risk and move into Analytical Assessment. (session 2)
- 10) **Is the level $\leq 10\%$ of AI? No risk; consider packaging**
- 11) **Is the level $\geq 10\%$ of AI?**



What if levels of a Nitrosamine are predicted to be above AI?

Firstly – check – *can the nitrosamine form?*

Next – model it

Control it – reduce levels of Nitrite

Consider scavengers

Additional Safety testing



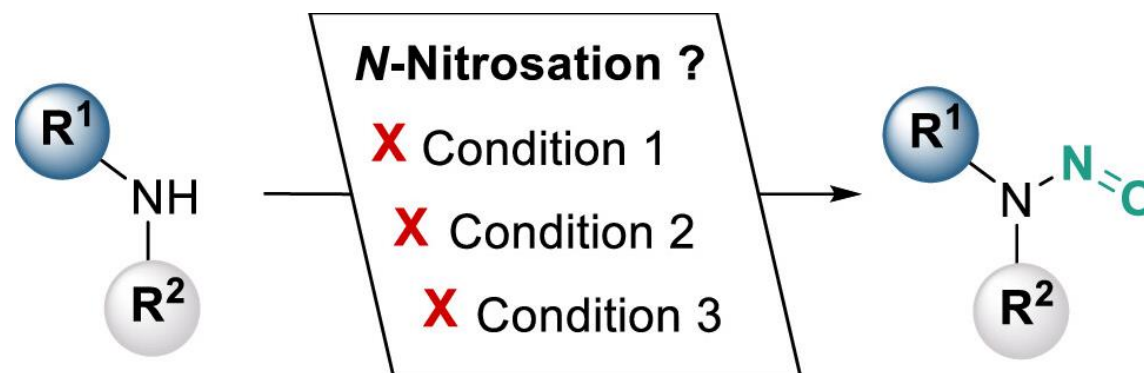
How to determine if a nitrosamine can be formed?

Approaches and Considerations for the Investigation and Synthesis of *N*-Nitrosamine Drug Substance-Related Impurities (NDSRIs)

Ian W. Ashworth, Alexander Blanz,^{*} Jonathan J. Byrne, Olivier Dirat, Jared W. Fennell, Nadine Kuhl, Stuart L. Wells, and Matthew P. Whiting

 Cite This: *Org. Process Res. Dev.* 2023, 27, 1784–1791

 [Read Online](#)



A negative outcome for all 3 **conditions** leads to a **no** risk conclusion (nitrosamine cannot be formed)

Optimal nitrosating conditions

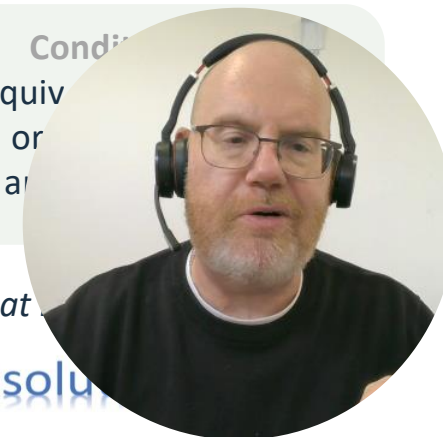
Nitrite 10^6 times higher than at ppm levels

Conditions 1
1.5 equiv. NaNO_2
 $\text{AcOH}/\text{H}_2\text{O}$ 1/2 (v/v)
amine free base or salt

Conditions 2
1.5 equiv. NaNO_2
aqueous. HCl (pH 3-4)
amine free base or salt

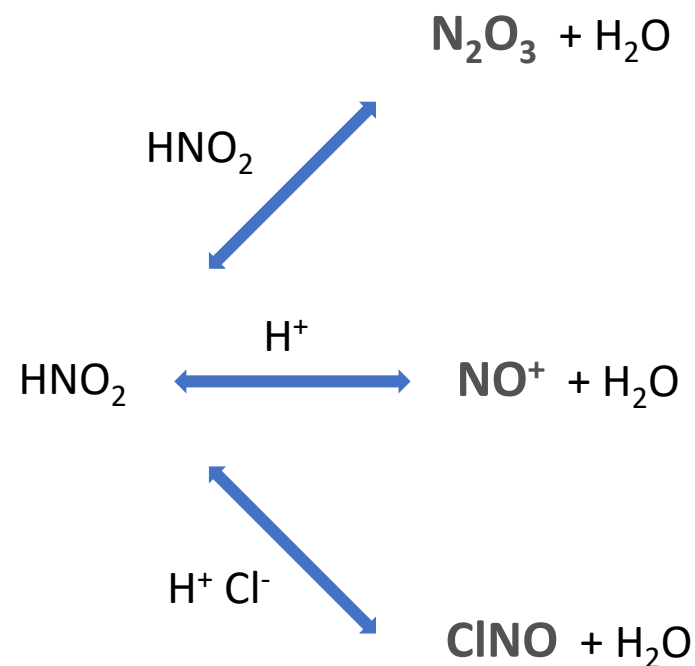
Conditions 3
1.5 equiv. NaNO_2
or NaNO
aqueous. HCl (pH 3-4)
amine free base or salt

Reactions are performed at room temperature and analyzed by LCMS down to at least 1 ppm



Aqueous Nitrite / Nitrous Acid Based Nitrosation

- Nitrous acid is not a nitrosating agent. It needs to react with at least one other reactant to form a nitrosating agent
 - Reaction with itself generates dinitrogen trioxide (N_2O_3)
 - Reaction with HX generates nitrosyl nucleophile adducts such as nitrosyl chloride (ClNO)
 - Reaction in the presence of H^+ can generate NO^+



All react rapidly with the free secondary amine to produce



Nitrite in Process Water

- Nitrite is known to be present in potable water – But how much is actually present?
 - WHO established a safety based limit of 3 ppm
 - Typical data from local water companies indicates levels below 0.01 ppm
 - Pfizer has developed an ultra sensitive method for trace nitrite in water and found that **potable water is typically below 0.001 ppm nitrite (method LOQ)** (highest data point being 0.003 ppm) and **purified water is typically below 0.0001 ppm (method LOQ)** from 42 samples in 9 locations

Nitrite in Pharmaceutical Manufacturing Water: Development of an Ultra-Sensitive Analytical Method, Typical Data, and Discussion of Potential Nitrosamine Formation in Drug Substance and Drug Product from Water

A. B. Suresh Kumar, Debasis Dey, T. S. Balaji, Haridoss Karthik, K. Sathishkumar, Paul McDaid,*
Brian Fitzpatrick, Atul Awasthi, Simon Davies, and Olivier Dirat



Cite This: <https://doi.org/10.1021/acs.oprd.4c00037>

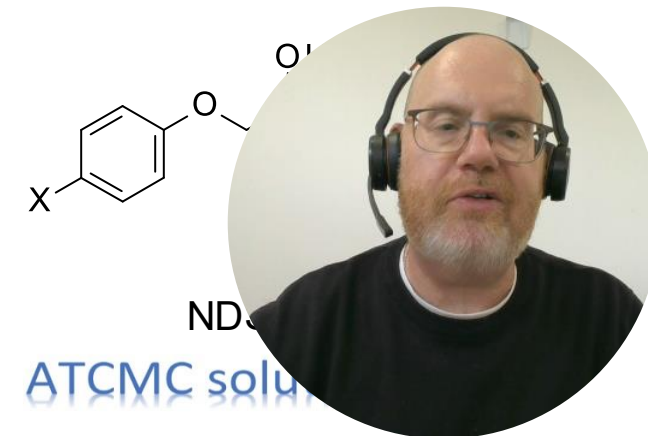
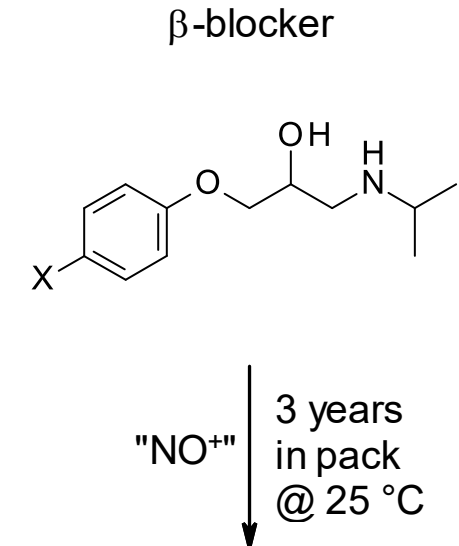


Read Online



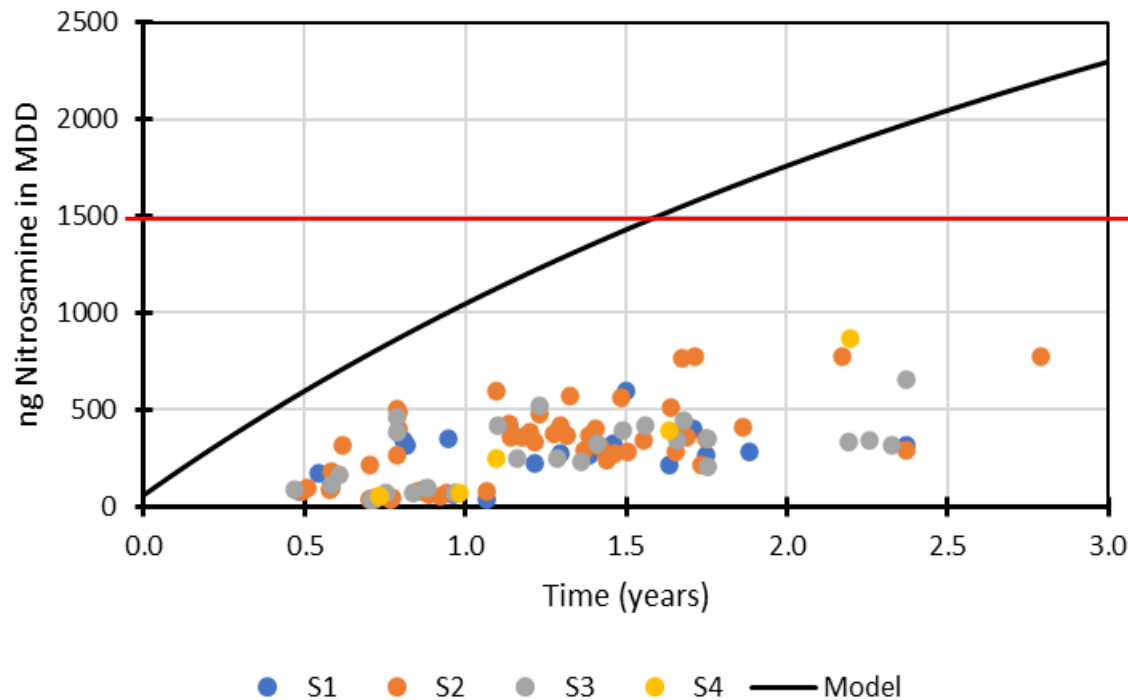
Validation example : Beta blocker NDSRI formation model predictions

- Simulating NDSRI formation over the shelf life led to the prediction that ~2300 ng would be present in the MDD
 - Less than the theoretical maximum yield but **> than the AI of 1500 ng/day**
 - Proceeded to develop an analytical method and test for the NDSRI



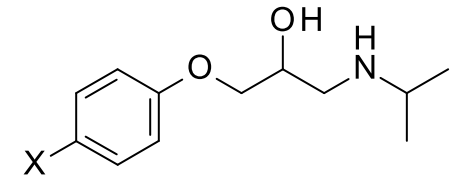
Validation example : Beta blocker NDSRI product testing data

- Product testing showed level of NDSRI to be less than the AI and to increase over time in the packed product

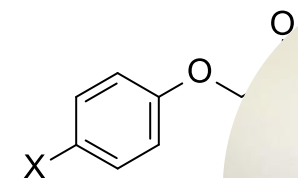


Model
overpredicts
versus
observed

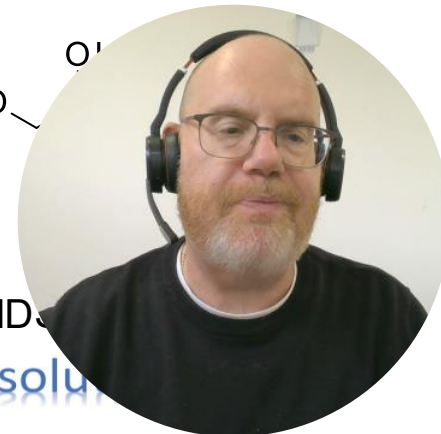
β -blocker



"NO"
3 years
in pack
@ 25 °C

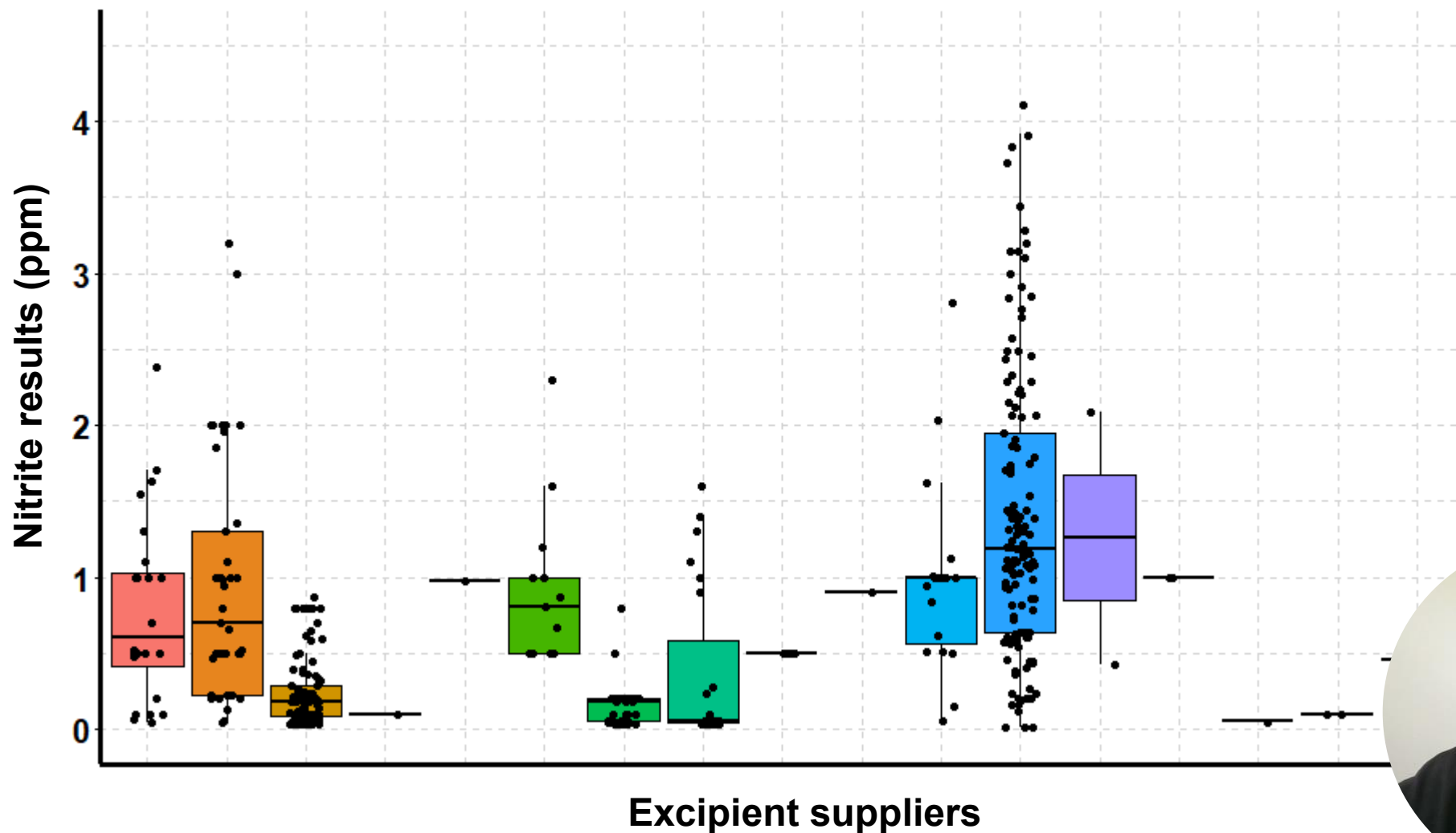


NDS



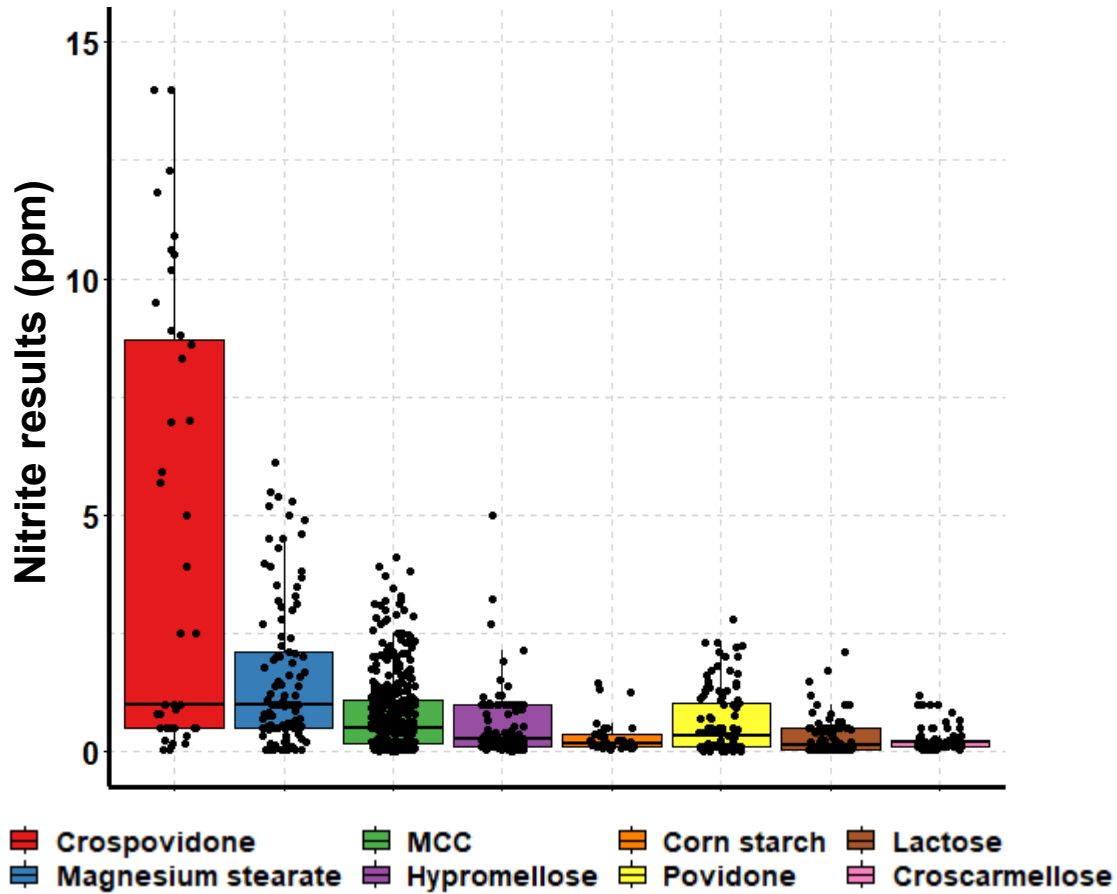
Substantial differences in average nitrite content from **different excipient suppliers**

Microcrystalline cellulose nitrite results divided by excipient supplier

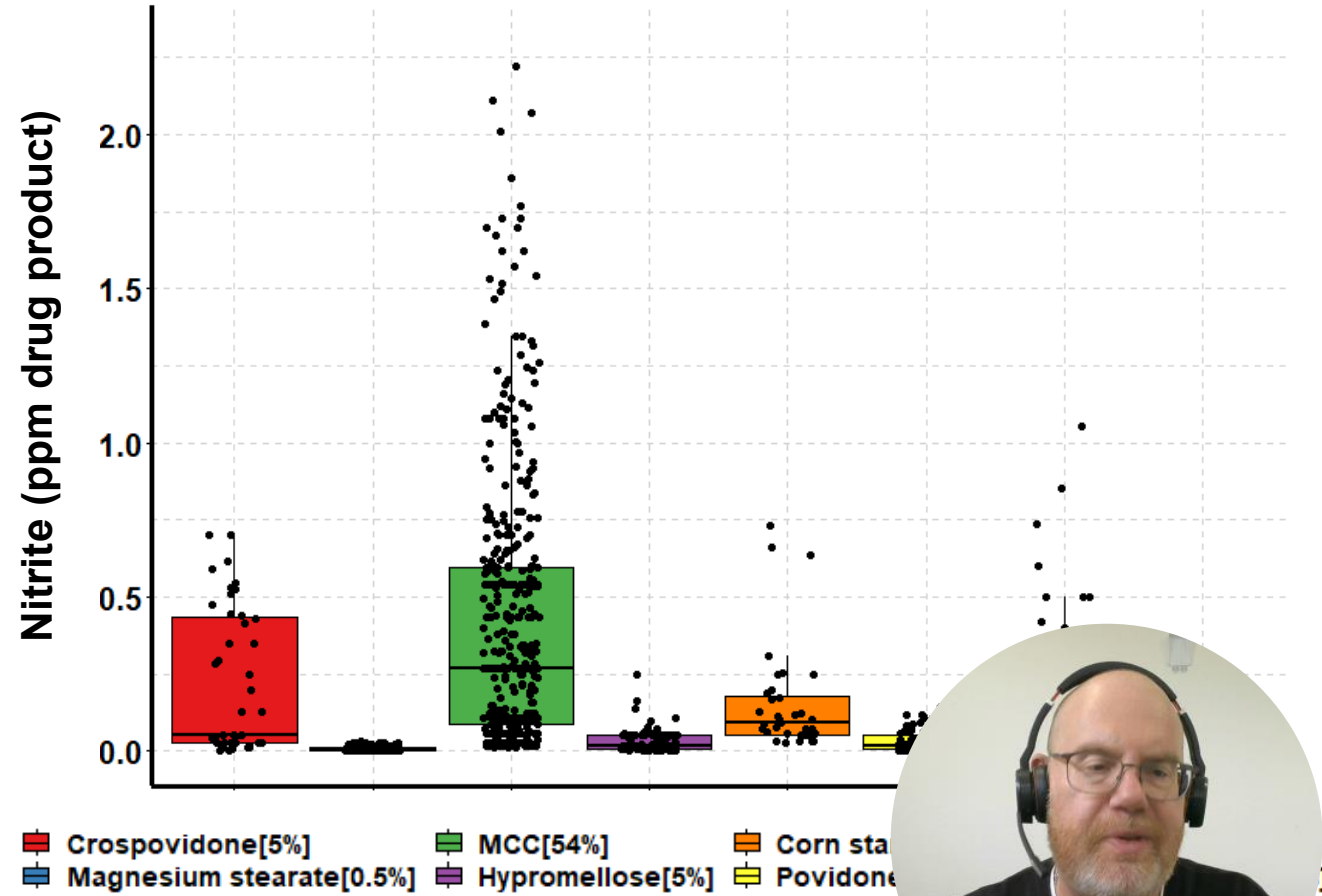


3. The overall **nitrite contribution** is typically dominated by the **highest formula % excipient**.

Nitrite results for 8 commonly used excipients



Nitrite contribution to the drug product



Inhibition of N-Nitrosamine Formation in DP



Rapid Communication

Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study



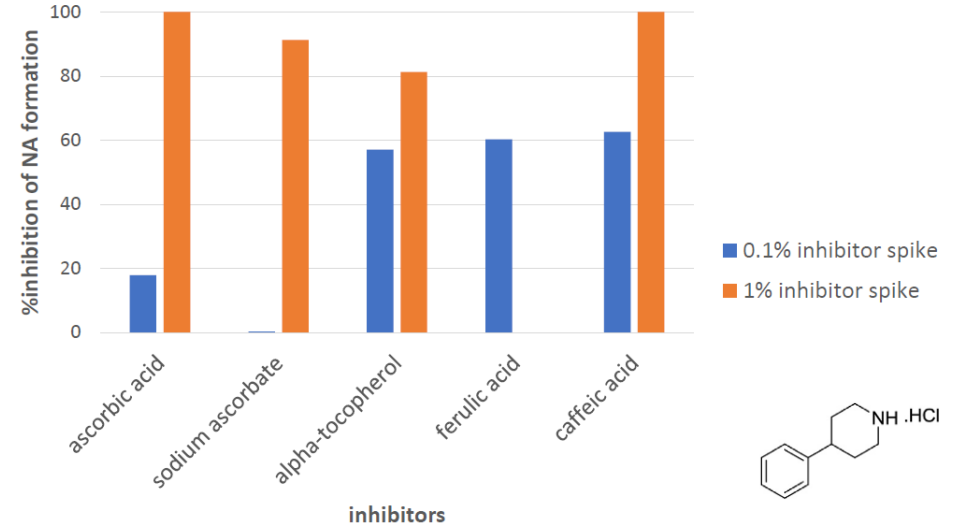
Kausik K. Nanda^{a,*}, Steven Tignor^b, James Clancy^c, Melanie J. Marota^c,
Leonardo R. Allain^b, Suzanne M. D'Addio^a

^a Discovery Pharmaceutical Sciences, MRL, Merck & Co., Inc., West Point, PA 19486, USA

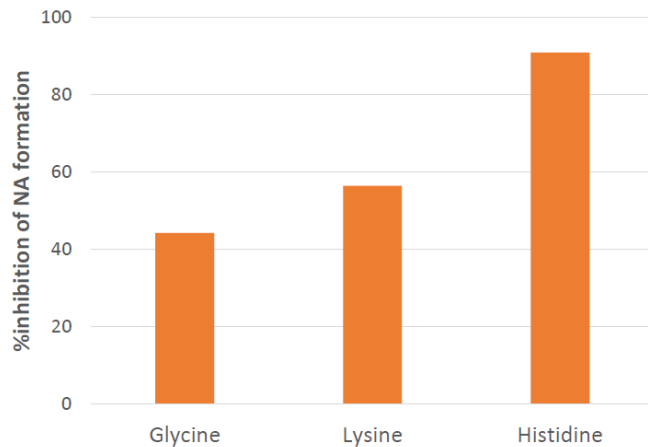
^b Analytical Sciences, MRL, Merck & Co., Inc., Rahway, NJ 07065, USA

^c Oral Formulation Sciences, MRL, Merck & Co., Inc., Rahway, NJ 07065, USA

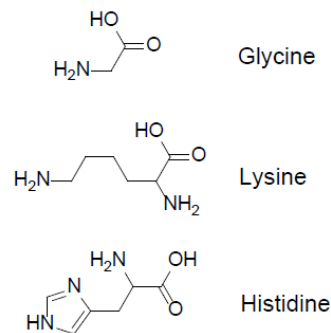
Accelerated Studies (50 °C/75% RH, 1 mth): Tablet



Inhibition of NA Formation in Soln



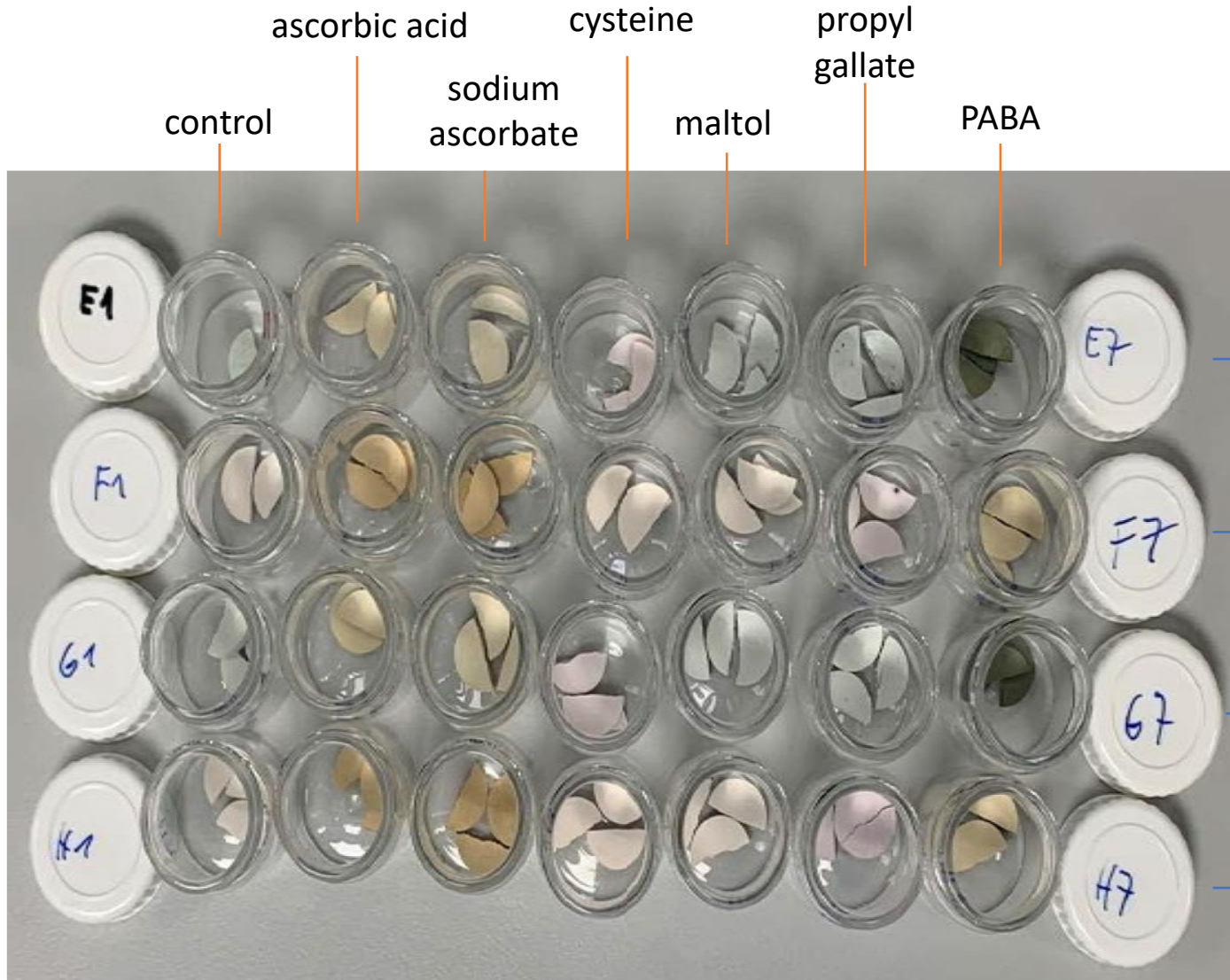
Reaction condition:
vulnerable amine 5 mM, NaNO₂ 20 mM
amino acid 100 mM
60 C, 23 h



- Study using tablets containing 4-PP HCl
- OSD and solution formulation
- Showed that at 1% level in OSD components can inhibit NA formation
- In solution phase, 1° amines can inhibit NA formation



Quality Concerns and Conclusions



- All evaluated nitrite scavengers lowered formation of NA in solution
- Ascorbic acid, L-cysteine and PABA effective in solid
- Each scavenger is case-by-case (empirical)
- Chemical compatibility of the scavenger, DS and excipients
- Appearance attributes can be an issue

N-Me Aniline HCl

N-Me Aniline HCl –
NaNO₂ spike

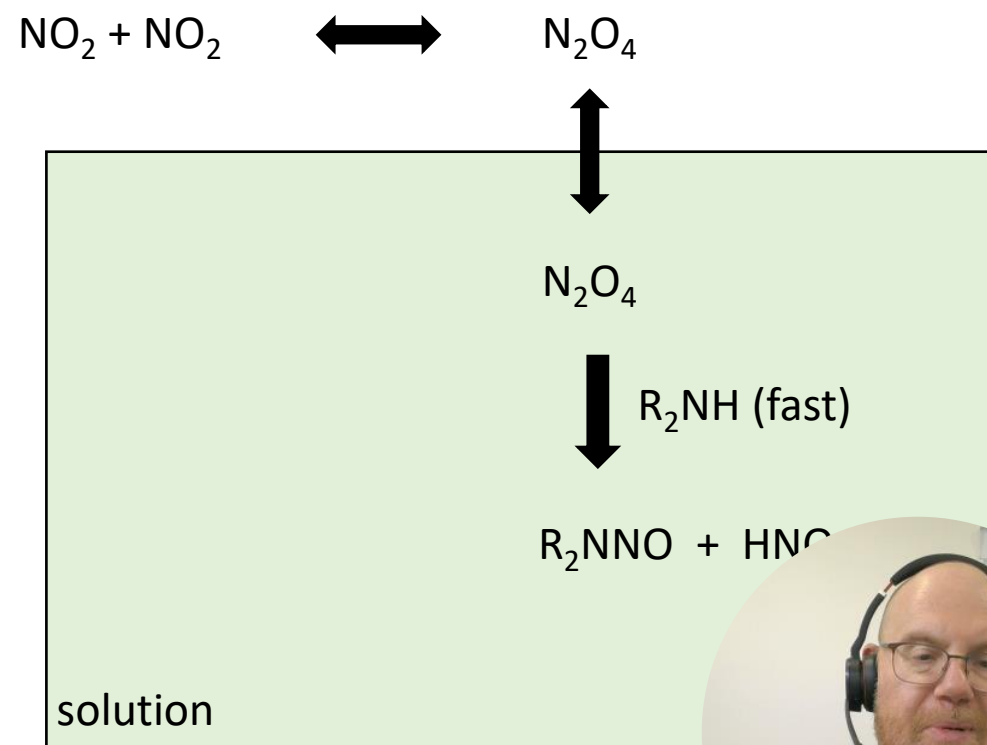
Phenyl Pip HCl

Phenyl Pip HCl –
NaNO₂ spike



Nitrosation by NOx – now raised by FDA

- Nitrosation by N_2O_4 (and N_2O_3) which are components of NOx are well preceded in the synthetic chemistry literature
 - Reactions of gaseous N_2O_4 with amines in organic solvents and under basic aqueous conditions are rapid
 - Limited published evidence that exposure of drug products to atmospheric NOx during processing can lead to nitrosamines (NDMA)
 - Also an API risk – more on this later..



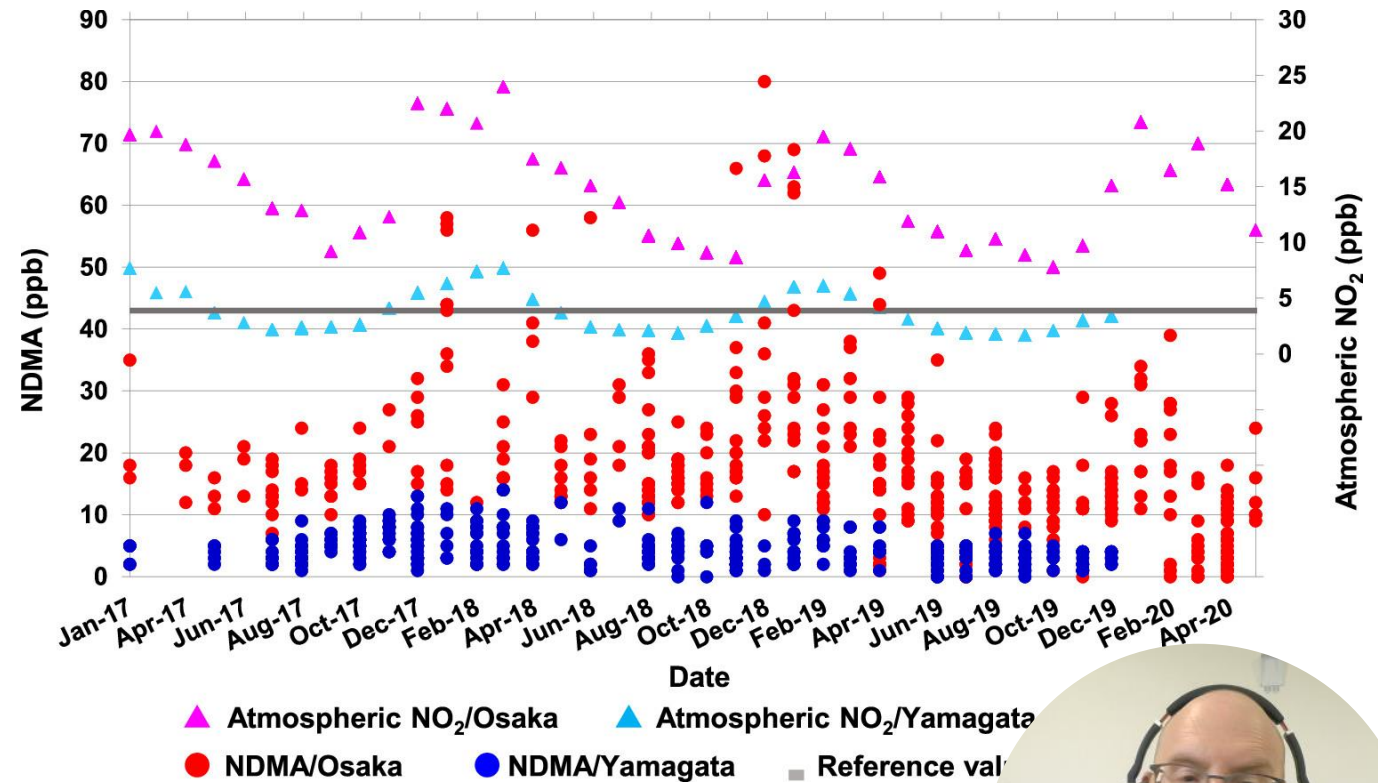
Challis, B. C.; Kyrtopoulous, S.A., *J. Chem. Soc., Perkin Trans.1*, **1979**, 299 & *J. Chem. Soc., Perkin Trans.2*, **1978**, 1296 – gaseous nitrogen oxides

Fukumoto, S. et al. *Org. Process Res. Dev.*, **2023**, 27, 2123 – NDMA in metformin product



Other risk factors? NOx

- Evidence recently published showing potential risk
- Fukumoto et al *Org. Process Res. Dev.* 2023, 27, 2123–2133
 - Found that dimethylamine (DMA) in the active pharmaceutical ingredient (API) used in the manufacturing process and nitrogen dioxide (NO₂) in the atmosphere had considerable influence on the formation of NDMA in metformin drug products.
- Under further investigation....



Nitrosamines - Future

ICH M7 addendum is critical

CPCA helps but it is not a long term solution

Key areas for ICH M7 to address

Durational Limits – Haber’s Law

Use of modelling and other approaches – purge

Scavengers – better understanding

Additional in vitro and in vivo testing and correlation

Appropri

