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AI Assisted Generic Formulation & Nitrosamine Risk: Algorithmic Workflows

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Agenda

- How are nitrosamines formed?
- Controlling nitrites in drug products
- Ways to mitigate nitrites in a drug product
- Digital tools for predicting nitrosamine formation
- Research gaps in nitrosamine mitigation (CMC + NDSRI)
- Conclusions

Nitrosamine Drug Substance Related Impurities (NDSRI): Regulations of N-Nitrosamines in Pharma



- Some **maximum acceptable API-related nitrosamine daily intakes are extremely low**, with limits and potency assignments varying slightly across regulatory agencies
- **~ 40% of APIs may be susceptible to forming N-nitrosamines** with varying potencies depending on the type and presence of **vulnerable secondary (2^o) and tertiary (3^o) amine precursors**

Table 1. Potency Categories with Acceptable Daily Intake Limits

Potency Category		Recommended AI Limit (ng/day)
<i>Predicted Carcinogenic Potency based on Chemical Structure</i> ↓	<i>Highest</i>	18 (EMA), 26.5 (FDA)
	2	100
	3	400
	4	1500
	<i>Lowest</i>	1500 (TTC* limit in ICH M7)

*TTC = Threshold of Toxicological concern)

3 | Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs): Guidance for Industry, FDA, August 2023;
| Questions and answers for marketing authorization holders / applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, EMA, October 2023.
| ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, EMA, July 2023.
| Schlingemann, Joerg, et al. "The Landscape of Potential Small and Drug Substance Related Nitrosamines" in Journal of Pharmaceutical Sciences (2022).

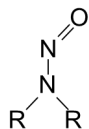
How do *N*-nitrosamines form in Drug Products?

Nitrosating agent

Vulnerable Amines

*favorable
conditions*

Nitrosamines



API

Process-related,
raw materials,
contaminates



Drug Product

Interactions,
excipients,
degradants



Packaging

Interactions,
environmental factors

- At the highest level, a **nitrosating agent** and **vulnerable amine** can react under favorable conditions to form a **nitrosamine**
- *Favorable conditions* are a function of pH, humidity/moisture, temperature, and proximity
- Nitrosamines can be generated during API production, within a drug product, or under packaging
- **Excipients can contribute to nitrosamine risk mainly as part of the drug product**

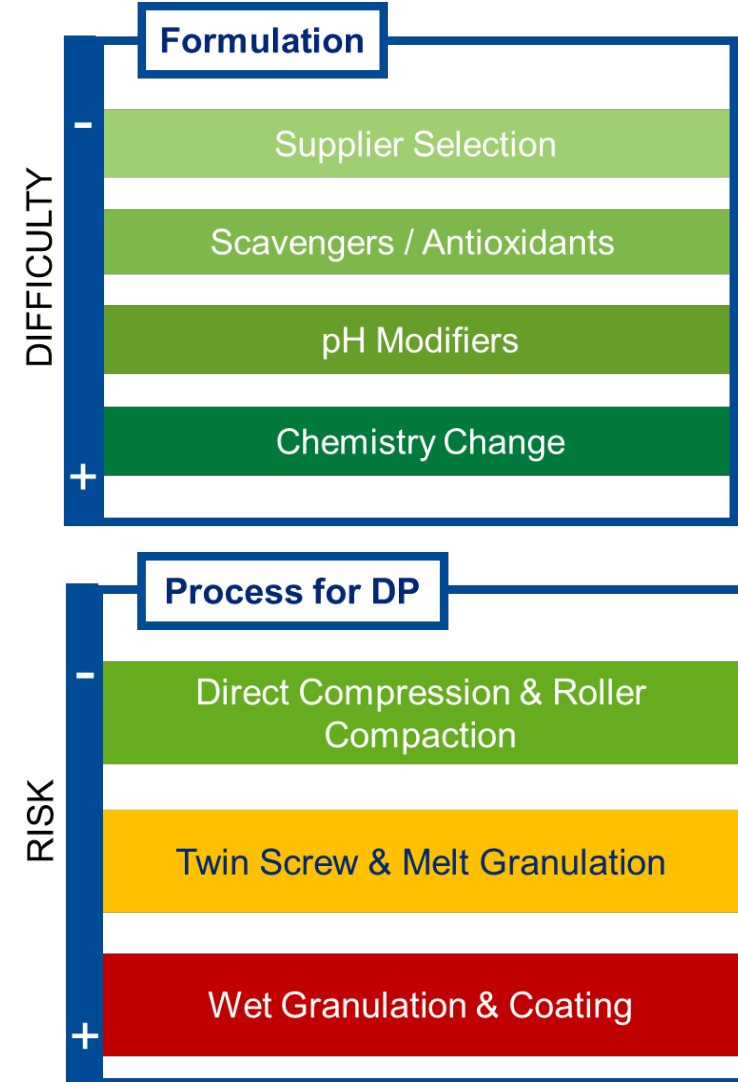
| Slide adapted from: Formation of *N*-Nitrosamines by Gary Scrivens (Pfizer), Science of Stability Conference, 2021.

| Nanda, Kausik K., et al. "Inhibition of *N*-Nitrosamine Formation in Drug Products: A Model Study." Journal of Pharmaceutical Sciences 110.12 (2021): 3773-3775.

4 | Schlingemann, Joerg, et al. "The Landscape of Potential Small and Drug Substance Related Nitrosamines in Journal of Pharmaceutical Sciences (2022).

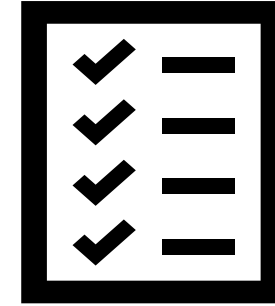
Formulation Approaches for Nitrosamine De-Risking

- **Start with low nitrite excipients and understand variability (lot/supplier)**
- **Use inhibitors/scavengers where justified (risk-based)**
- **Manage pH and moisture/water activity as key drivers**
- **Select manufacturing process to minimize amine–nitrite conversion (scenario-based)**



Nitrosamines - Key Questions for Pharmaceutical Manufacturers

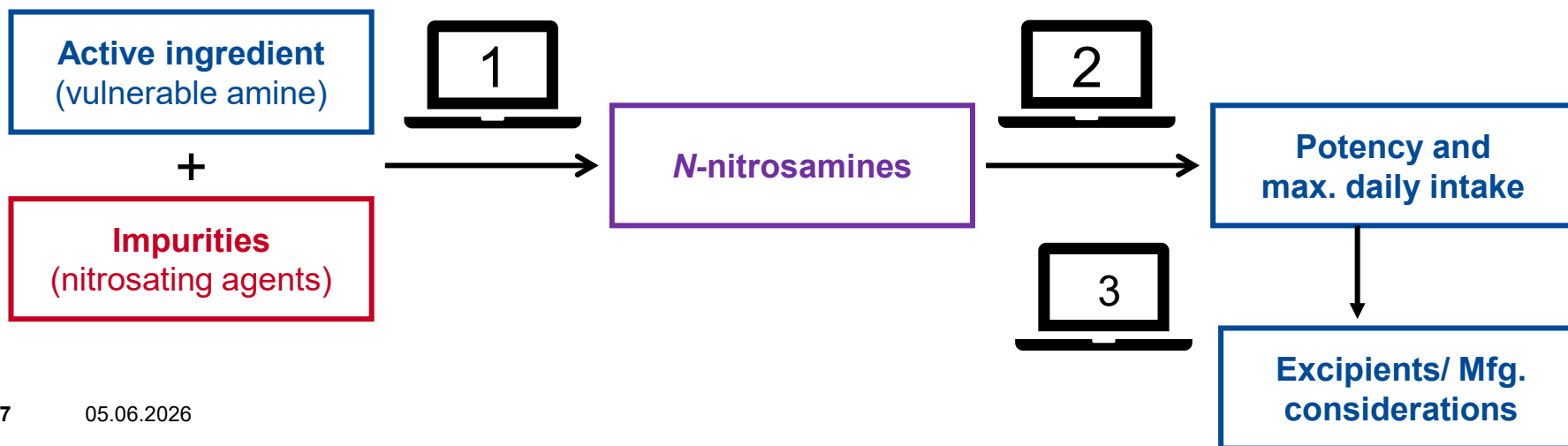
- Can **NDSRIs*** form as degradation products? If they do, which **specific NDSRIs** are most likely to be formed?
 - What is the **acceptable daily intake (AI)** of these NDSRIs?
 - What **maximum daily dose (MDD)** is defined in the drug label?
 - If the expected intake is close to or exceeding the maximum daily dose:
 - ▶ How do I **reduce the amount/risk** of nitrosamine formation?
- **Risk-assessment for different formulations and processes in drug manufacturing**



A Digital Assistant- ZoomLab® includes apps that help formulators assess the risk for nitrosamine formation in DPs

“As a formulator, I not only want to estimate the risk of nitrosamine formation, but also, be able to-

- 1. Predict the chemical structure of nitrosamine drug substance-related impurities (NDSRI's)*
- 2. Calculate the maximum daily intake limit, and*
- 3. Incorporate considerations for excipients and manufacturing process*



The app „Degradation Products of Active Ingredient“ predicts the chemical structures of potential NDSRIs (1)

The screenshot shows the ZoomLab app interface. A modal window titled "Degradation Product #1" is open, displaying a chemical structure and its SMILES code: CNC(=C[N+](=O)[O-])NCCSCc1ccc(CN(C)N=O)o1. Below the structure, a table shows the molecular weight of the degradation product as 329.12 g/mol. The background interface includes a navigation bar with "ZoomLab", "Projects", "App Repository", "More Features", and "My Account". The main content area shows "Degradation Product" and "Nitrosamine risk assessment" sections. A table at the bottom lists degradation products with their IDs, molecular weights, and occurrence likelihoods.

Parameter	Result
Molecular weight of degradation product	329.12 g/mol

ID	Molecular weight	Occurrence likelihood
#4	329.12 g/mol	2
#5	329.12 g/mol	3

- Paste the **SMILES code of the active ingredient** or import it directly from the PubChem database
- Select the **degradation reactions** to be checked; initially only reaction with nitrite is available
- The machine-learning model predicts **potential nitrosamine drug substance-related impurities**
- The reaction products are ordered in **decreasing likelihood** of occurrence
- Review the chemical structures and **select one degradation product** for the “Nitrosamine Risk Assessment” app

The app “Nitrosamine Risk Assessment and Mitigation” estimates the expected nitrosamine intake for a drug product (2, 3)

The screenshot shows the 'Nitrosamine Risk Assessment and Mitigation' app interface. The top navigation bar includes 'ZoomLab®', 'Projects', 'App Repository', 'More Features', and 'My Account'. The main title is 'Nitrosamine Risk Assessment and Mitigation' with a 'Demo Project - Nitrosamines' sub-header. The interface is divided into several sections:

- Project Details:** Includes fields for 'Dose of active ingredient' (80.00 mg), 'Tablet weight' (175.00 mg), and 'Maximum number of tablets per day' (2).
- Carcinogenic Potency Categorization:** A section for categorizing the risk.
- Definition of Target Profile:** A section for defining the target profile.
- Impact of Inactive Ingredients:** A section for assessing the impact of inactive ingredients, including a 'Risk assessment scenario' dropdown (set to 'Direct compression') and a 'Conversion of nitrites to nitrosamines (%)' slider.
- Properties of Degradation Product:** A section for entering the SMILES code of the degradation product, with a text area containing the SMILES code: CC(C)OCCOCc1ccc(OCC(O)CN(N=O)C(C)C)cc1.

At the bottom right, there is a bar chart showing 'Nitrosamine intake (ng/day)' on the y-axis (0 to 2000) and 'Conversion of nitrites to nitrosamines (%)' on the x-axis (0 to 100). A red horizontal line indicates the 'Acceptable intake' at 1500 ng/day. The chart shows a single bar for 'Direct compression' with an intake of approximately 1000 ng/day.

- Enter the **dose** of the active ingredient, **tablet weight** and **maximum number of tablets per day**
- Paste the **SMILES code** of the **nitrosamine** of import it from first app
- **Select the excipients** and enter their weight fractions
- The app calculates the **potency category** and **maximum daily intake of the nitrosamine** according to the cancerogenic potency categorization approach (CPCA)
- The **contribution of each excipient** to the nitrosamine intake is estimated; **different scenarios** can be compared (e.g., direct compression vs. wet granulation)

Dashboard > Projects > New Formulation Project > Nitrosamine Risk Assessment and Mitigation

Nitrosamine Risk Assessment and Mitigation

New Formulation Project

Related content

Project Details

Project name (leave blank for default name)

New Formulation Project

Definition of Target Profile

Enter the dose of the active ingredient per tablet, the tablet weight, and the maximum daily dose of the active ingredient (provided as maximum number of tablets per day). This information is required to calculate the potential daily intake of the nitrosamine.

Dose of active ingredient *

mg

Tablet weight *

mg

Maximum number of tablets per day *

Properties of Degradation Product

Project Details

Project name (leave blank for default name)

Demo project (amitriptyline)

Properties of Active Ingredient

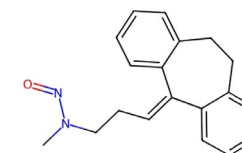
Search PubChem database and import available data

Q amitriptyline

Canonical or isomeric SMILES code *

CN(C)CCC=C1C2=CC=CC=C2CCC3=CC=CC=C31

Degradation Product #1

CN(CCC=C1c2ccccc2Cc2ccccc21)N=O

Parameter	Result
Molecular weight of degradation product	292.16 g/mol

Previous product

Select and close

Next product

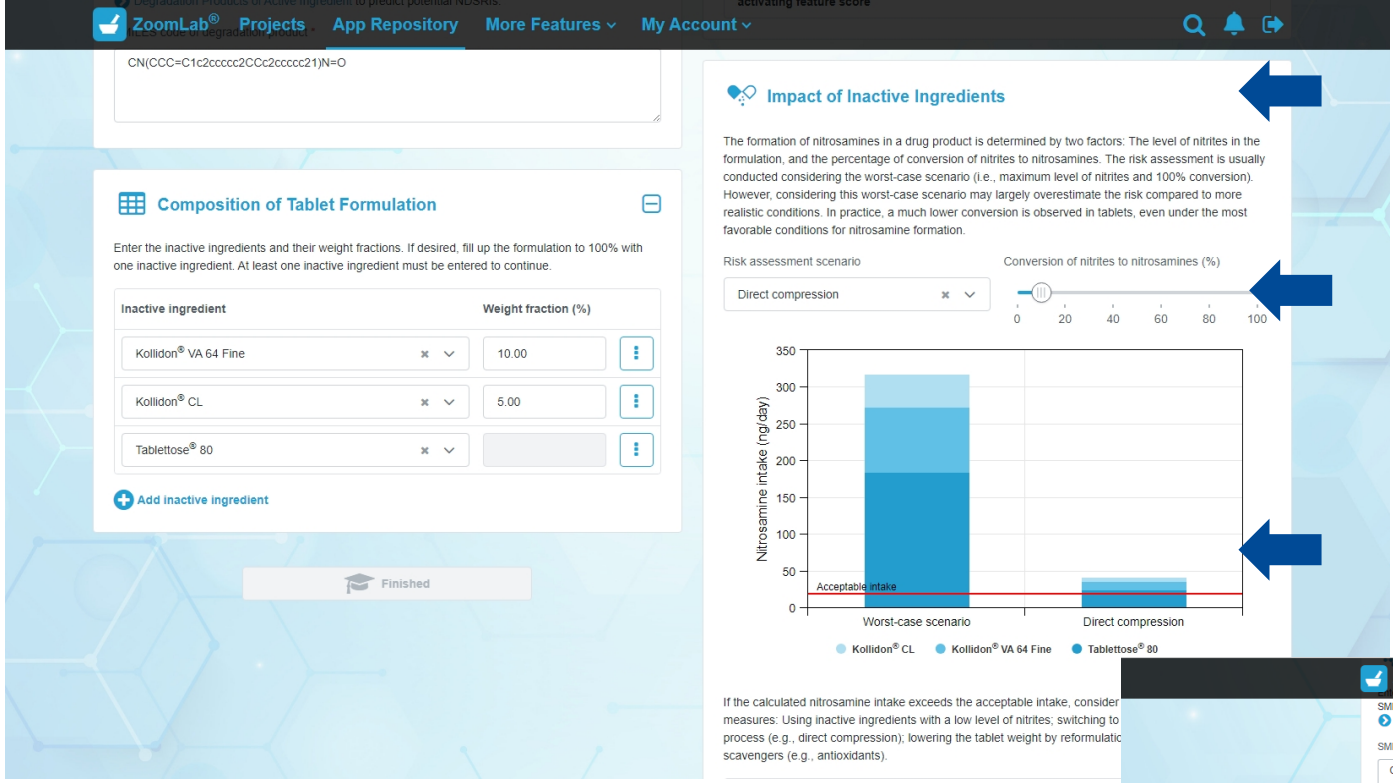
1 to 4 of 4 items

Degradation Reactions

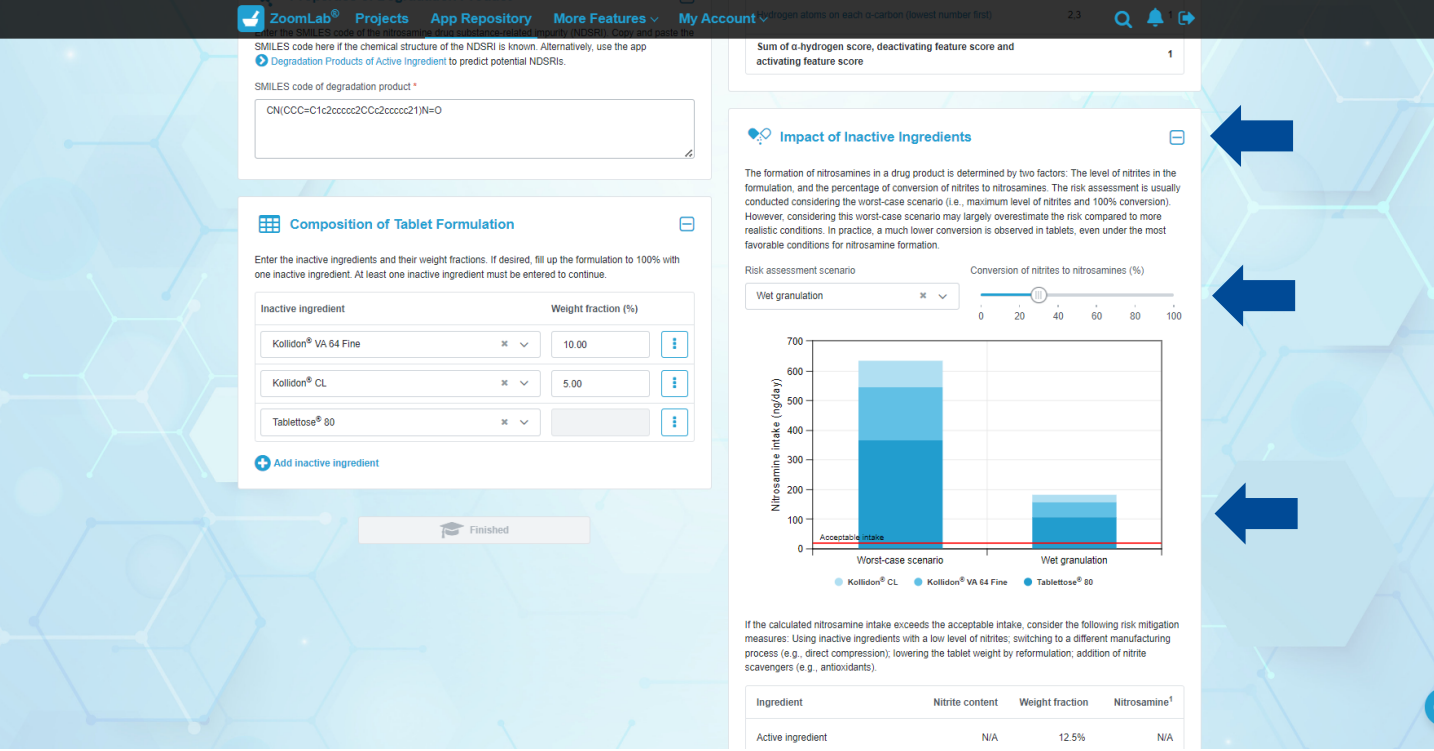
Illustrative Digital Assistant Output
(Example Workflow View)

Purpose: quickly visualize candidate NDSRIs and risk drivers to prioritize confirmatory testing.

Scenario Comparison Output (Formulation / Process Sensitivity)



Purpose: compare scenarios (e.g., DC vs WG) to identify highest-impact mitigation levers.



Industry Research Gaps in Nitrosamine Mitigation (CMC + NDSRI)

- **Understanding formation in solid oral drug products**
 - ✓ Quantify effects of pH, water activity, temperature, and time on formation rates
- **Excipient nitrite measurement and variability**
 - ✓ Harmonize low-ppb methods, inter-lab reproducibility, and uncertainty reporting
- **Process–risk relationships (scale-up ready)**
 - ✓ Predict wet granulation vs direct compression impact; define moisture thresholds
- **NDSRI potency prediction and acceptable intake confidence**
 - ✓ Expand compound-specific datasets to strengthen structure–potency relationships
- **Integrated, scenario-based risk assessment**
 - ✓ Combine API structure + excipient nitrite + process into one decision framework

Opportunity: shift from reactive testing to predictive, model-informed mitigation decisions

Summary:

- NDSRI risk is a multi-factor CMC problem: API + excipients + process + storage conditions
- The key need is predictive integration: formation science + variability + scale-up process understanding
- Scenario-based, model-informed approaches can prioritize experiments and mitigation options earlier
- Research gaps: standardized datasets, validated models, and harmonized expectations for decision-support tools

Example workflows shown are illustrative; broader validation across industry datasets is the key next step.

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