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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

*N*itrosamine *D*rug *S*ubstance *R*elated *I*mpurities (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 (2^0) and tertiary (3^0) **amine precursors**

Table 1. Potency Categories with Acceptable Daily Intake Limits

		Potency Category	Recommended AI Limit (ng/day)
Predicted Carcinogenic Potency based on Chemical Structure ↓	*Highest*	1	18 (EMA), 26.5 (FDA)
		2	100
		3	400
		4	1500
	Lowest	5	1500 (TTC* limit in ICH M7)

*TTC = Threshold of Toxicological concern)

| 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.

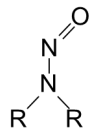
| Schlingemann, Joerg, et al. "The Landscape of Potential Small and Drug Substance Related Nitrosamines" in Journal of Pharmaceutical Sciences (2022).

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

Nitrosating agent

Vulnerable Amines

favorable conditions

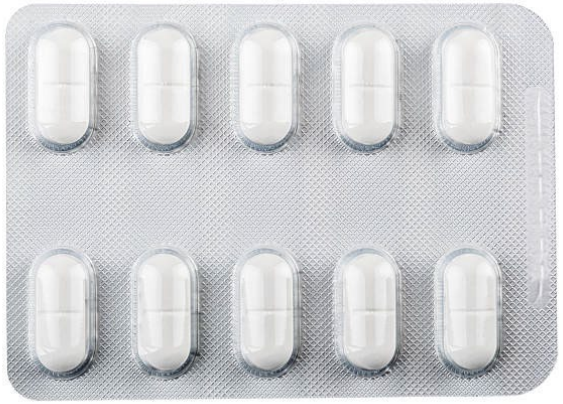
Nitrosamines 

API

Process-related, raw materials, contaminates

Drug Product

Interactions, **excipients**, degradants



Packaging

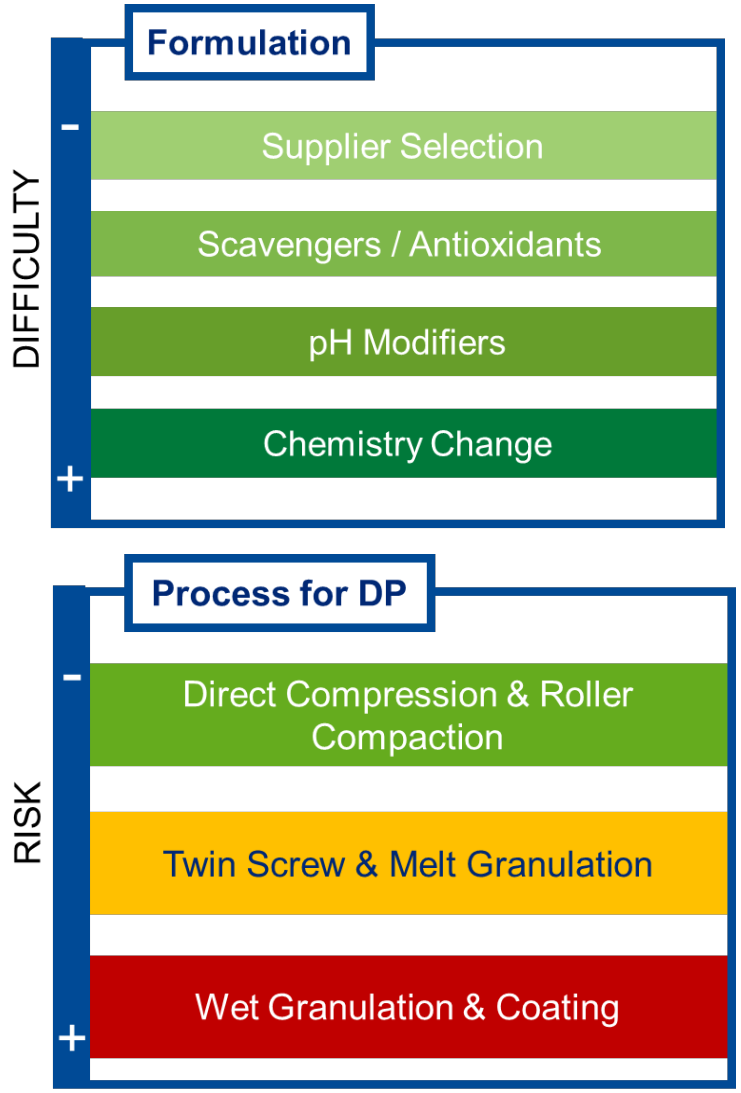
Interactions, environmental factors

- 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**

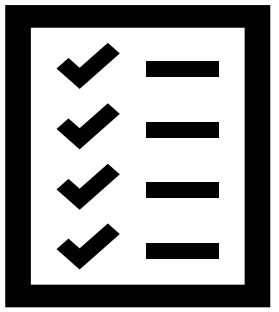
| Slide adapted from: Formation of *N*-Nitrosamines by Gary Scrivens (Pfizer), Science of Stability Conference, 2021.
| Nanda, Kausik K., et al. "Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study." Journal of Pharmaceutical Sciences 110.12 (2021): 3773-3775.
| Schlingemann, Joerg, 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



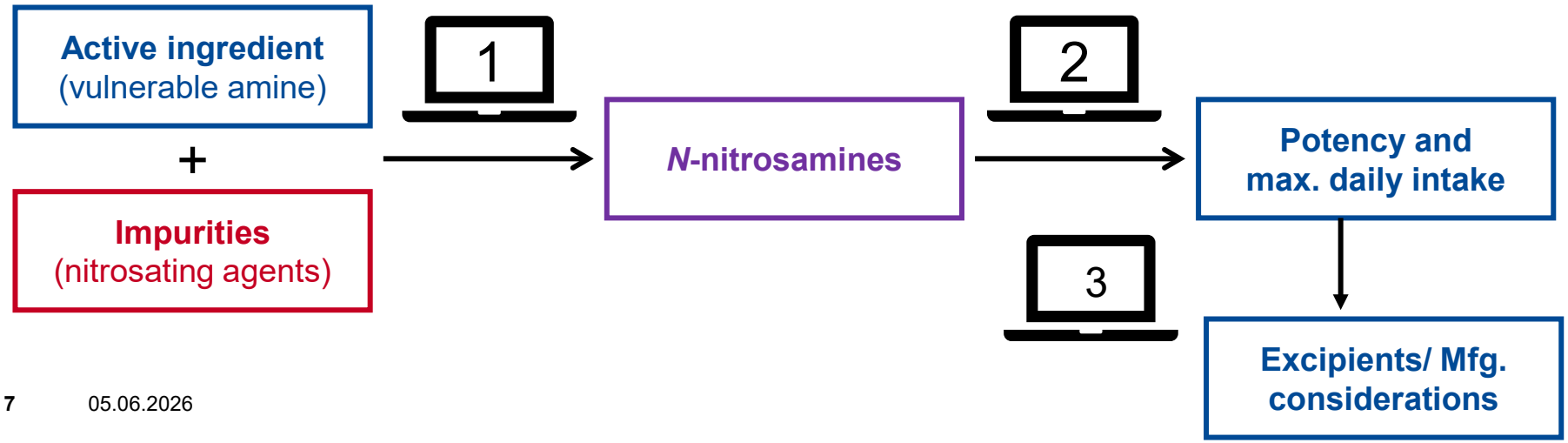
- Can **NDSRIs*** form as degradation products? If they do, which **specific NDSRIs** are most likely to be formed?
- What is the **acceptable daily intake (AI)** of these NDSRIs?
- What **maximum daily dose (MDD)** is defined in the drug label?
- If the expected intake is close to or exceeding the maximum 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*



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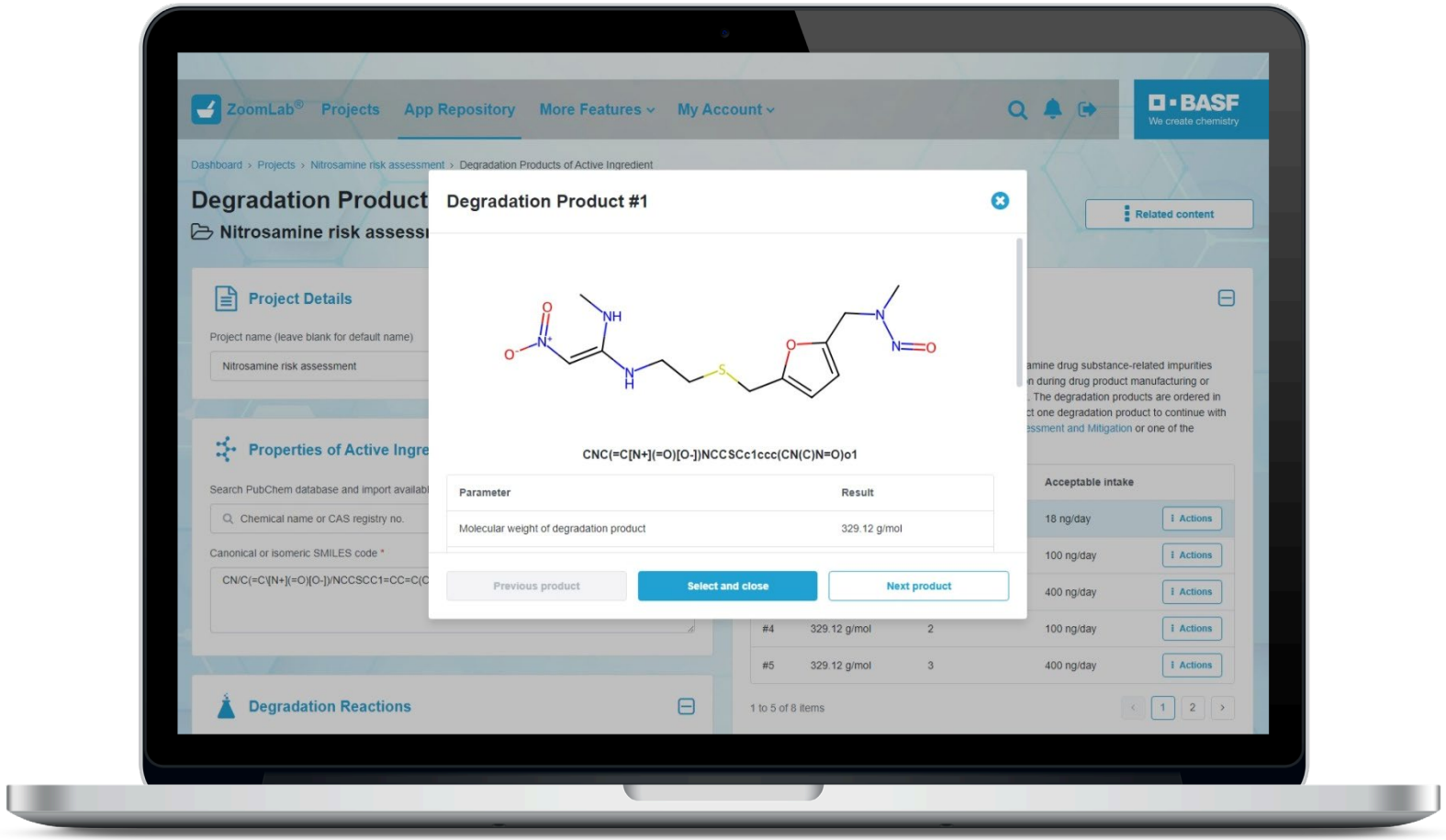
The app „Degradation Products of Active Ingredient“ predicts the chemical structures of potential NDSRIs (1)



- 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

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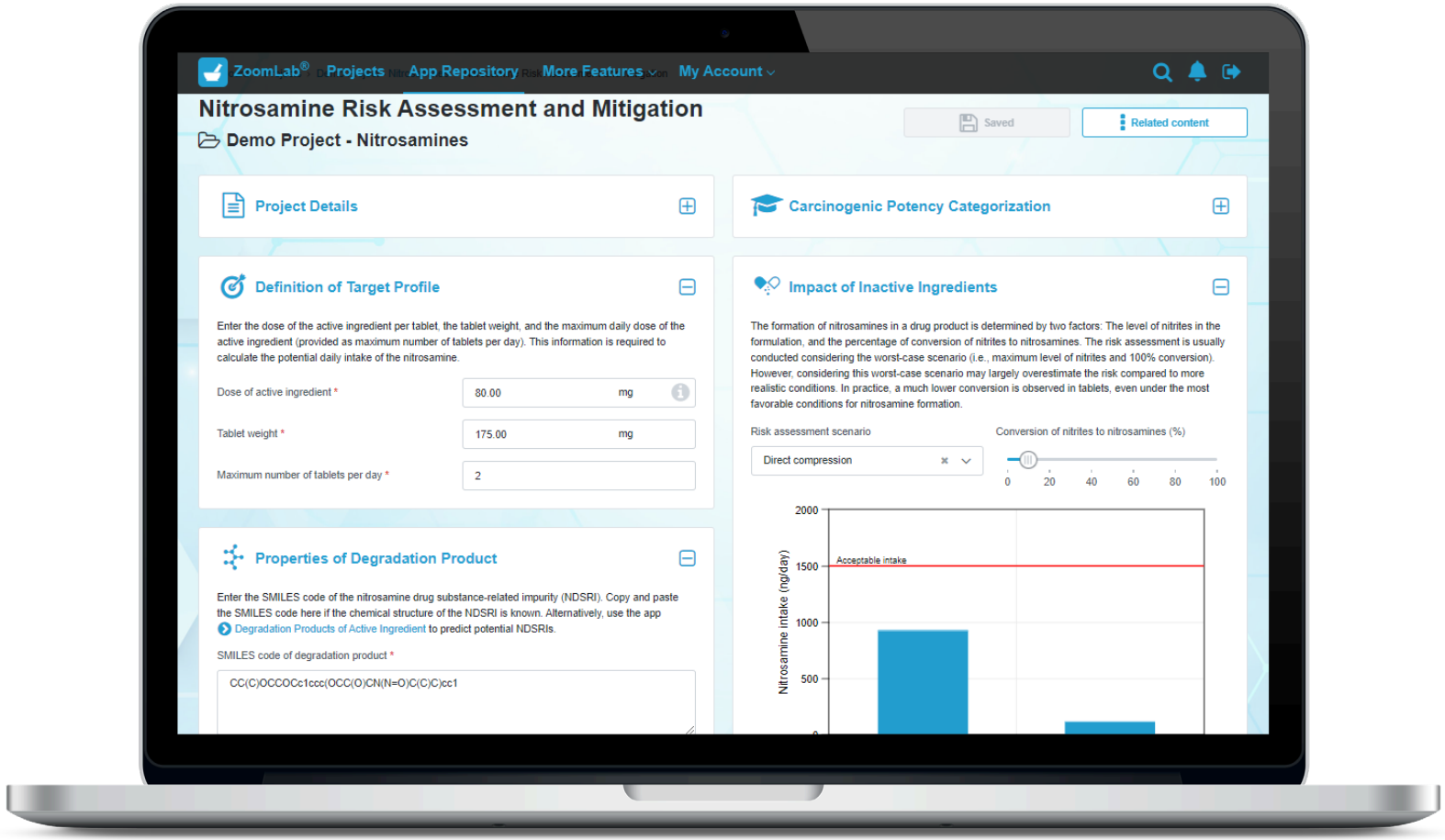
The app “Nitrosamine Risk Assessment and Mitigation” estimates the expected nitrosamine intake for a drug product (2, 3)



- 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)

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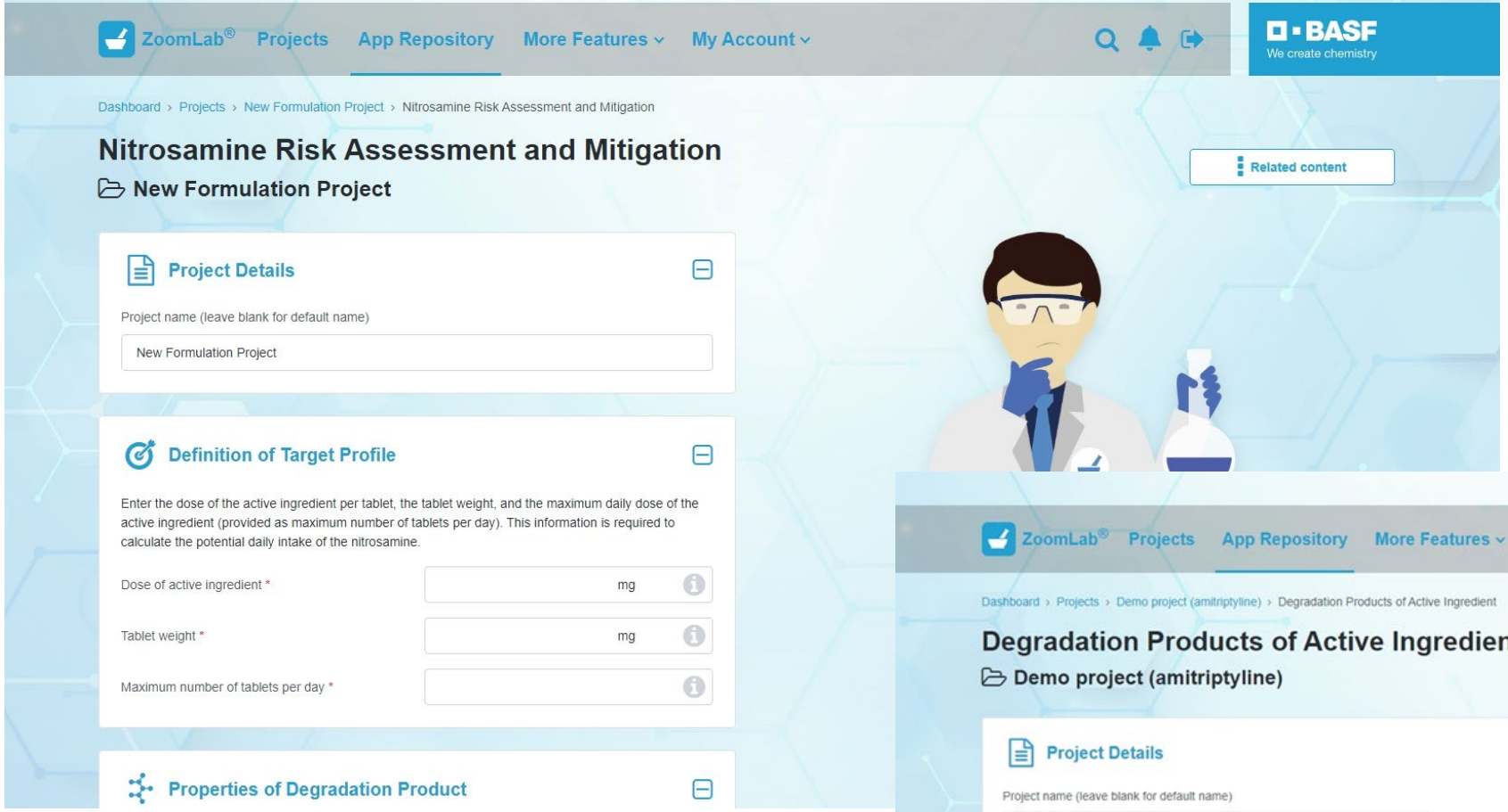
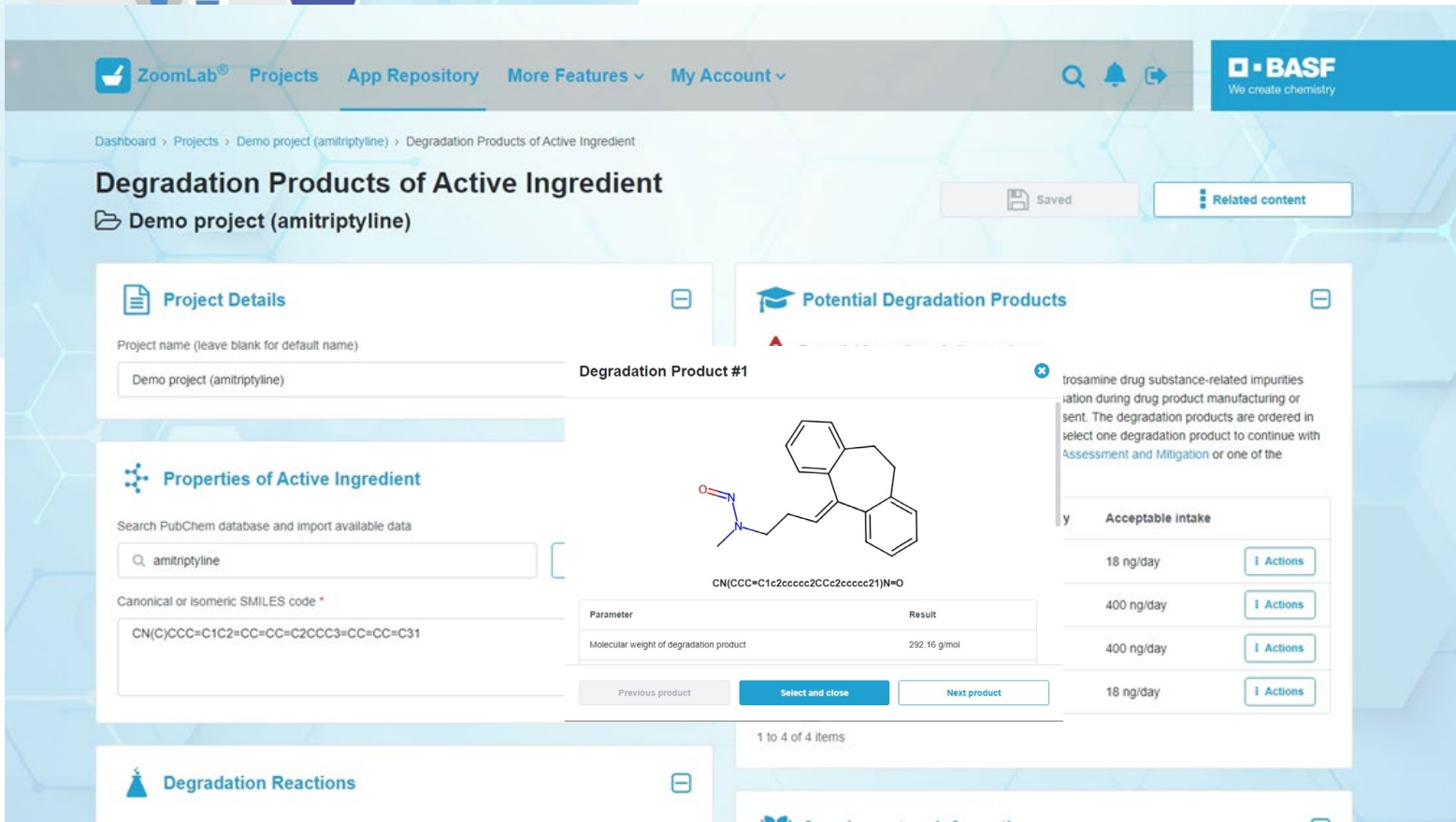
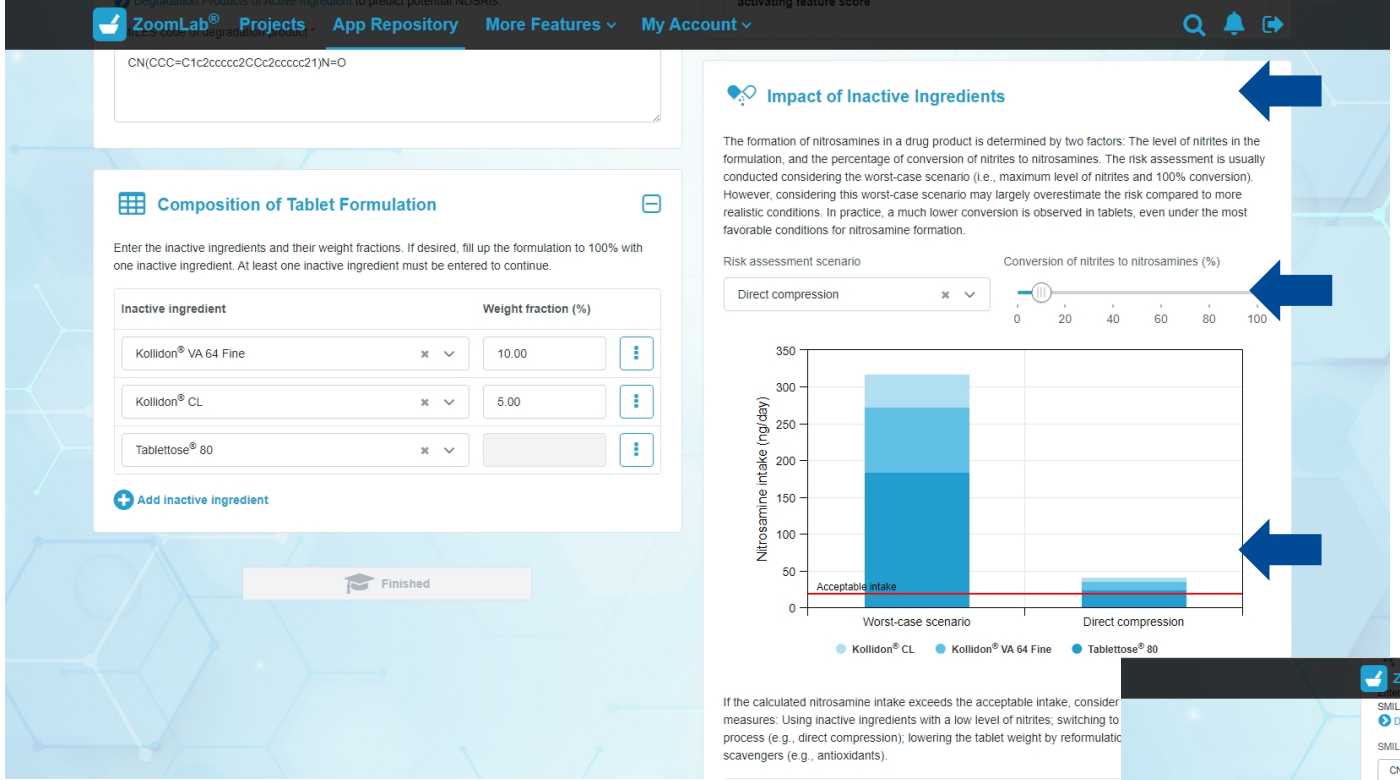
Illustrative Digital Assistant Output (Example Workflow View)

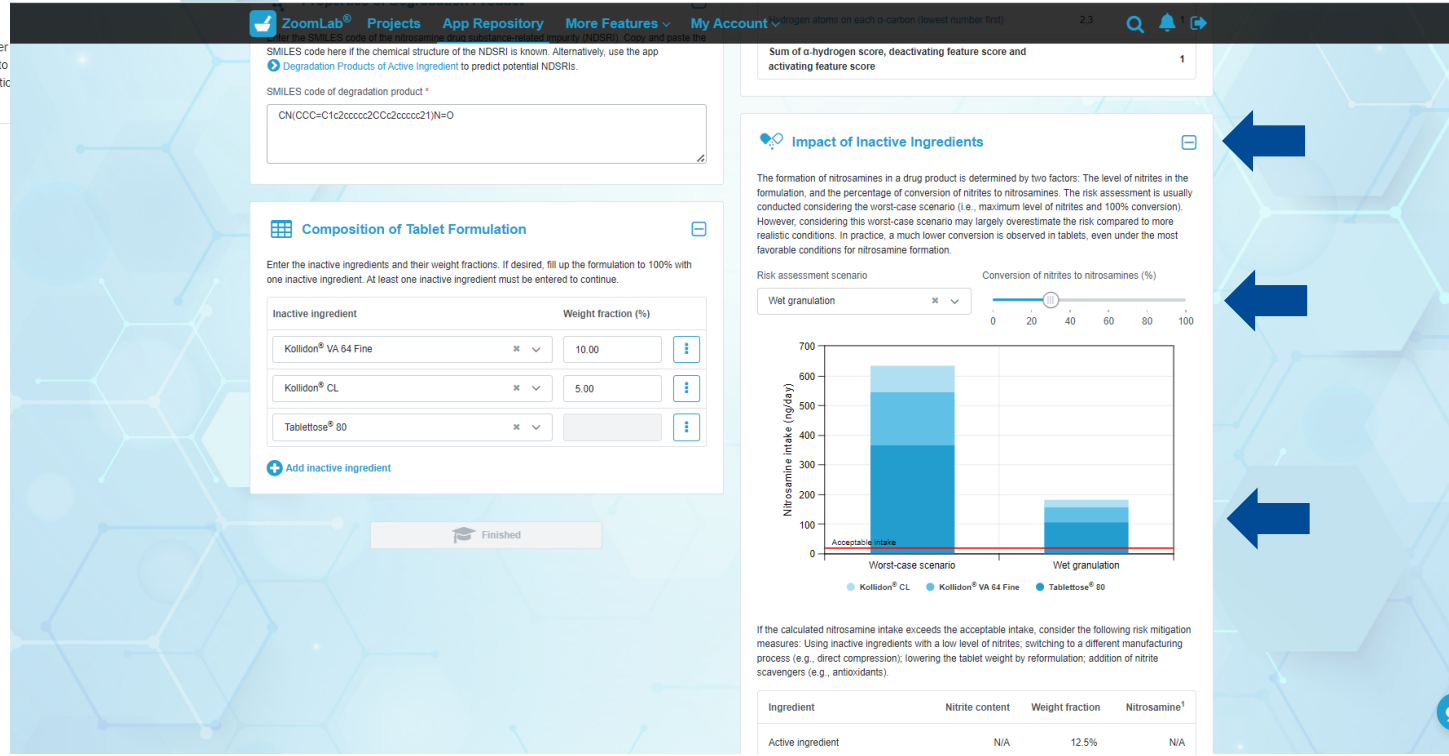




Purpose: quickly visualize candidate NDSRIs and risk drivers to prioritize confirmatory testing.

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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