TAROS

discovering the world of chemistry

Nitrosamine Impurities: Services for Risk Management

Taros Chemicals GmbH & Co. KG

Fall 2022

Nitrosamine Impurities - Regulatory Background

Groundbreaking regulations pose major risks for the pharmaceutical industry

According to the **FDA guidance** "Control of Nitrosamine Impurities in Human Drugs | FDA-2020-D-1530, September 2020", as well as the **assessment report by EMA** "Nitrosamine impurities in human medicinal products | EMEA/H/A-5(3)/1490, June 2020"

→ manufacturers of APIs & drug products are advised to **detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products!**

Guidance applies to all chemically synthesized APIs & drugs on the market and those under current review:

1. **Risk assessment (FDA & EMA March 31, 2021)** of nitrosamine impurities in APIs, marketed products, and products under approved and pending applications
2. **Confirmatory testing (FDA October 1, 2023; EMA September 26, 2022)** when there is any risk for the presence of nitrosamine impurities.
3. **Report (FDA October 1, 2023; EMA September 26, 2022)** changes implemented to prevent or reduce nitrosamine impurities in APIs and drug products to the regulatory body.

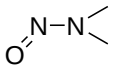
These groundbreaking regulations are expected to evolve rapidly to limit human exposure to nitrosamine impurities

- ❑ **Your product ingredients or manufacturing process might be vulnerable to nitrosamine formation ???**
- ❑ **Confirmatory testing is the last chance to prevent a potential market recall of your product ???**
- ❑ **Reference standards for reactivity assessment and risk management are commercially not available ???**
- ❑ **Need of a one-stop-shop covering chemical & analytical support as well as regulatory and strategic advice ???**

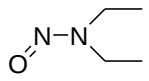
Nitrosamine Impurities - Regulatory Background

Identified nitrosamine impurities and a summary market recalls and suspensions

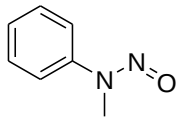
FDA has identified seven nitrosamine impurities that may be present in chemically synthesized APIs and drug products.



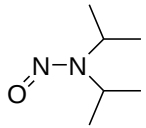
N-Nitrosodimethylamine (NDMA)



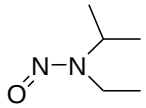
N-Nitrosodiethylamine (NDEA)



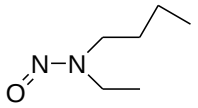
N-Nitrosomethylphenylamine (NMPA)



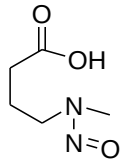
N-Nitrosodiisopropylamine (NDIPA)



N-Nitrosoisopropylethylamine (NIPEA)

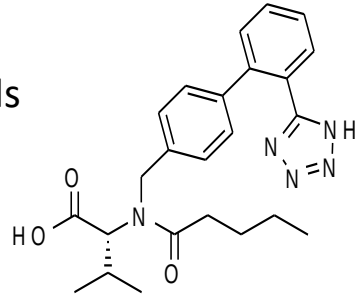


N-Nitrosodibutylamine (NDBA)

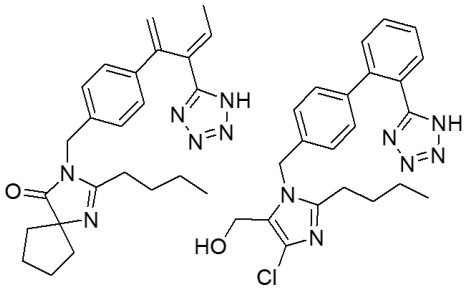


N-Nitroso-N-methyl-4-aminobutyric Acid (NMBA)

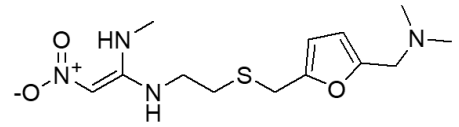
- **Valsartan**: Since June 2018, recalls worldwide and CEP suspensions



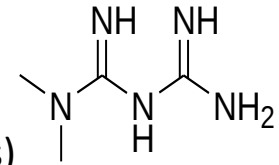
- **Ibesartan, Losartan**: Since July 2018, several recalls and CEP suspension



- **Ranitidine**: Since September 2019, several recalls (US, EU) and suspension of MA (EU, US)



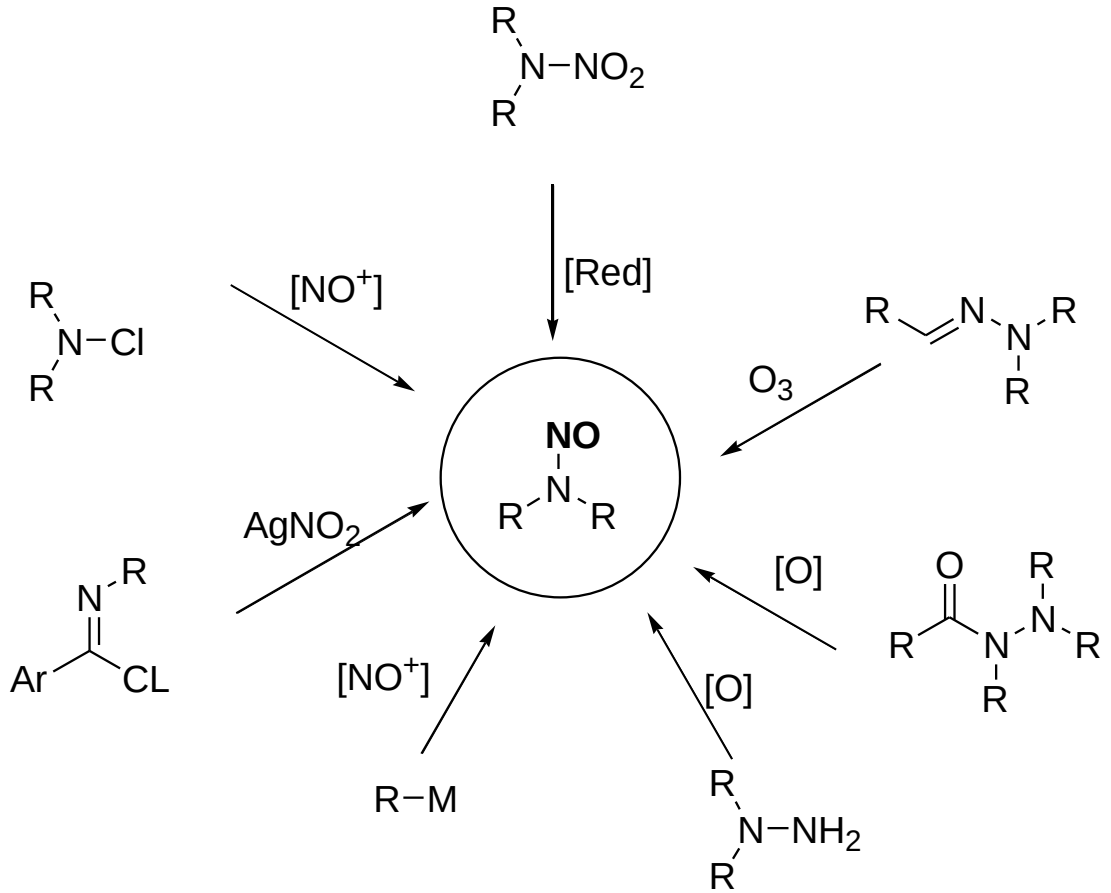
- **Metformin**: Since December 2019, market actions and recalls (extend-release dosage forms)



Nitrosamine Impurities - Chemical Background

Nitrosamines in pharmaceuticals – chemical pathways and root causes

Summary of Pathways Leading to N-Nitroso Compounds



Causes for the Presence of Nitrosamine Impurities in APIs

1. **General conditions that lead to nitrosamine formation**
2. **Sources of secondary, tertiary, and quaternary amines that can form nitrosamines**
3. **Contamination in vendor-sourced raw materials**
4. **Recovered solvents, catalysts, and reagents as sources of contamination**
5. **Quenching process as a source of nitrosamine contamination**
6. **Lack of process optimization and control**

Rocío López-Rodríguez, James A. McManus, Natasha S. Murphy, Martin A. Ott, and Michael J. Burns, Pathways for N-Nitroso Compound Formation: Secondary Amines and Beyond, Org. Process Res. Dev. 2020, 24, 1558−1585.

Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, February 2021 Pharmaceutical Quality/ Manufacturing Standards/Current Good Manufacturing Practice (CGMP), Revision 1; **https://www.fda.gov/media/141720/download**

Nitrosamine Impurities – Taros' Background

How Taros has built a proven track record of supporting pharmaceutical and biotech companies

- Your product ingredients or manufacturing process might be vulnerable to nitrosamine formation ???
- Confirmatory testing is the last chance to prevent a potential market recall of your product ???
- Reference standards for reactivity assessment and risk management are commercially not available ???

Due to our outstanding expertise in synthetic chemistry, our capabilities in analytical chemistry and handling of hazardous substances, several pharmaceutical companies engaged Taros for **comprehensive support along the process of reactivity assessment and risk management** of compounds vulnerable towards nitrosamine formation.

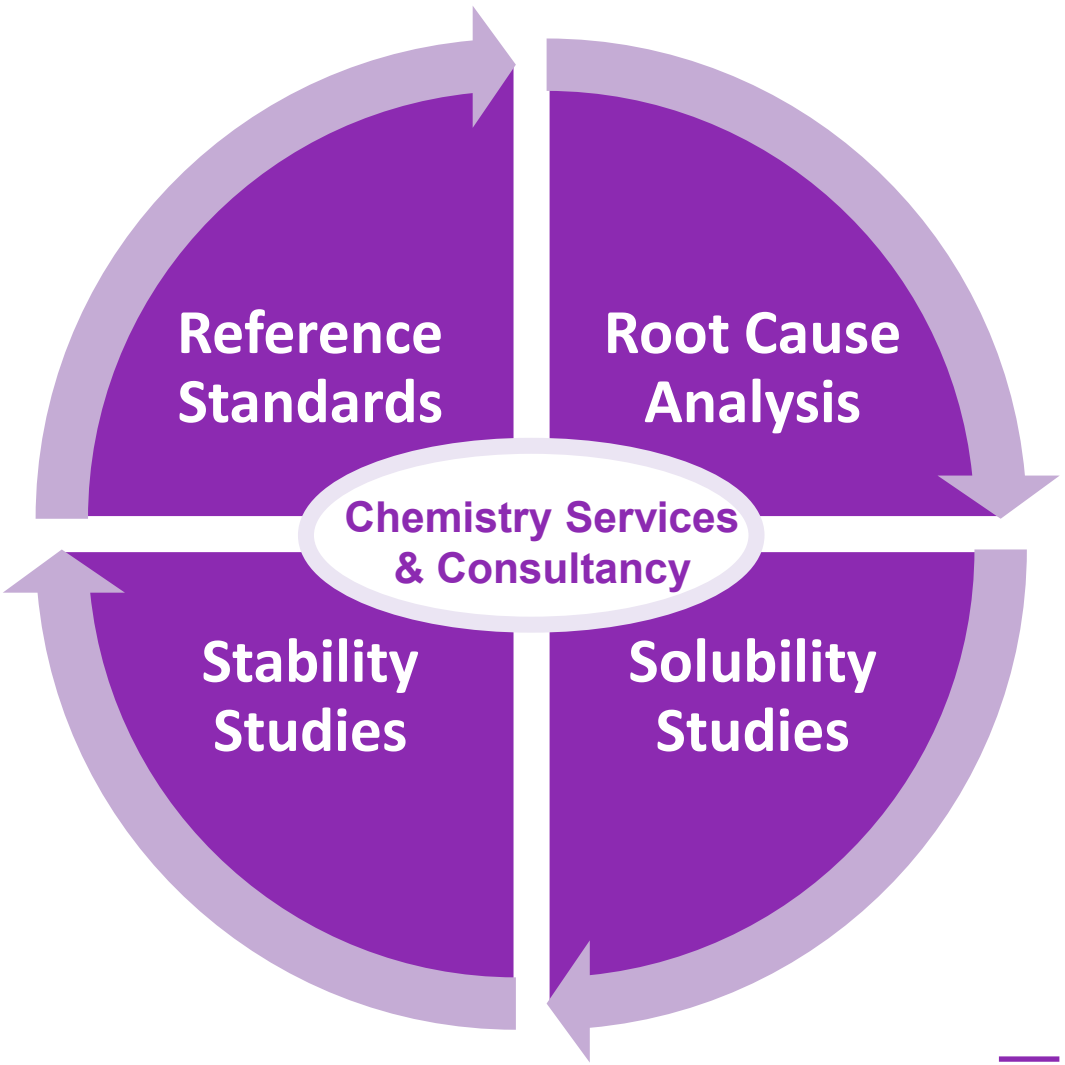
Initial customer requirements:

- Vast experience and equipment for the safe handling of highly potent APIs and nitrosamines
- Customized reference standards for biological testing of nitrosamine impurities
- Isolation of potential nitroso degradants in high purity
- Quality control and structure confirmation of synthesized nitrosamines
- Determination of detection limits (LODs) of synthesized nitroso degradants

Nitrosamine Impurities – Taros' Services

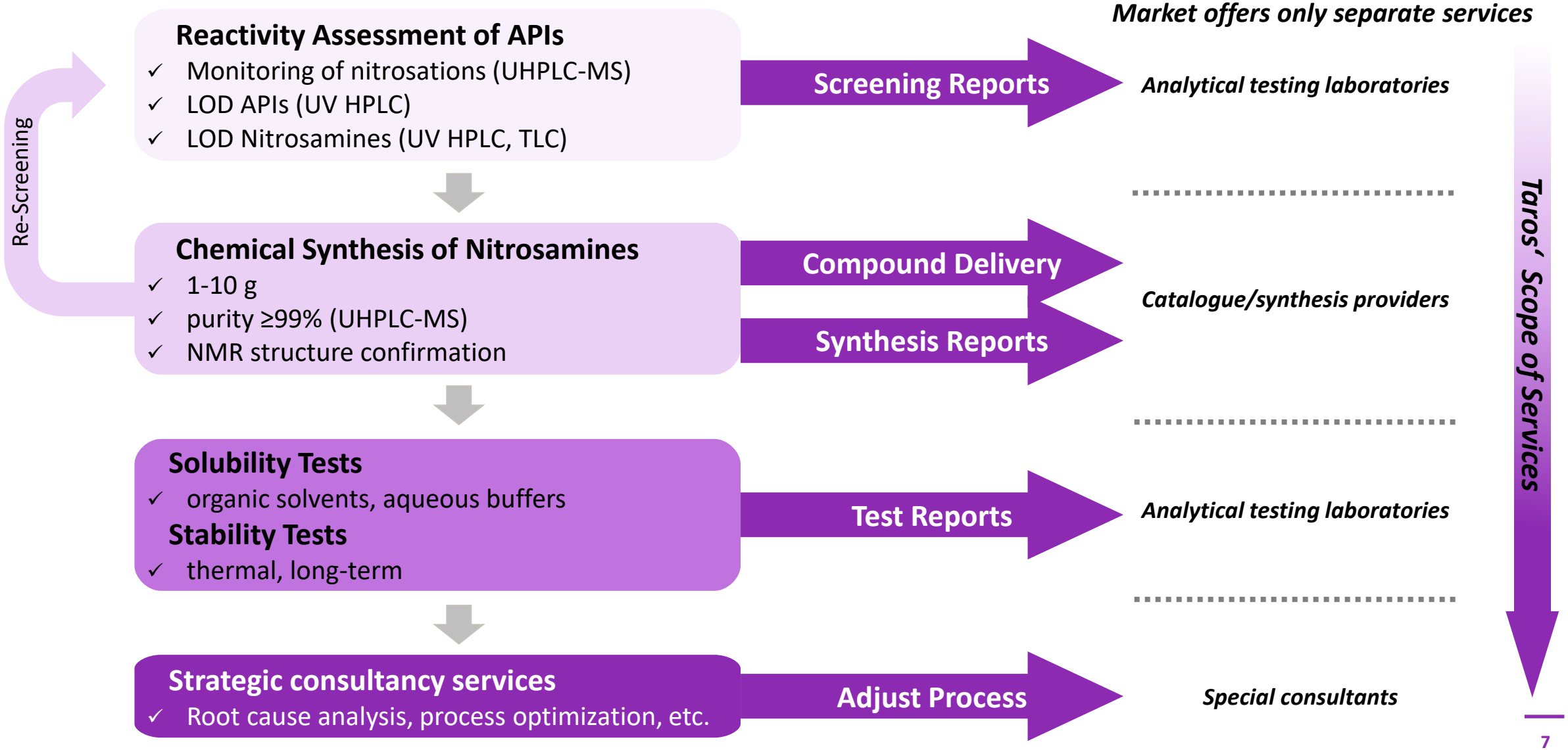
One-stop-shop services from risk assessment and confirmatory testing to process optimization

- In contrast to plain cataglogue/synthesis providers or analytical testing laboratories our customers benefit from one-stop-shop services
- Root cause analysis to trace back all starting materials and excipients besides the relevant API to uncover potential further risks
- Solubility studies to ensure reliable Ames Tests and supporting purge factor analysis to understand risk and control strategy options
- Stability studies to ensure reliable Ames Tests or assessment of shelf life and nitrosamines introduced within the synthetic process
- Further strategic consultancy on chemical and regulatory issues to adjust the clients' process according regulatory guidelines



Nitrosamine Impurities – Taros' Workflow

Our workflow from risk assessment and confirmatory testing to strategic process optimization



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