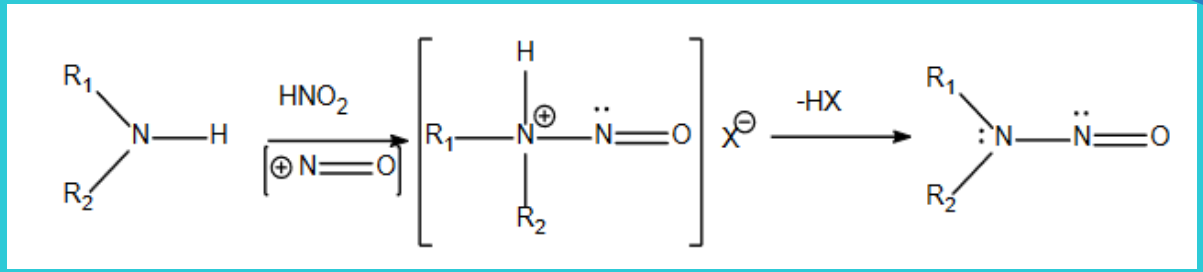
SAHPRA
South African
Health Products
Regulatory Authority

Nitrosamines Update 13/09/2024

Agenda

1. Introduction to Nitrosamines
2. Step 1: Nitrosamine Assessments – excipients, API and FP
3. Step 2: Confirmatory Testing
4. SAHPRA update
5. Questions

N-Nitrosamines



- **Class of compounds with a nitroso group bonded to an amine**
- **Probable or possible carcinogen**
- **ICH M7 recommends that mutagens be controlled to prevent cancer risk associated with exposure**

Timeline of Nitrosamines

Valsartan

NDMA identified

Ranitidine and Metformin

NDMA identified

Rifampicin and Rifapentine

1-methyl-4-nitrosopiperazine (MNP) and 1-cyclopentyl-4-nitrosopiperazine (CPNP),.

Varenicline

N-nitroso-varenicline,

Sitagliptin

7-N-nitroso-3-(trifluoromethyl) -5,6,7,8-tetrahydro[1,2,4]triazolo -[4,3-a]pyrazine (NTTP)

Sources of Nitrosamine Contaminants

Excipients and Packaging Material

- Excipients can contain reactive species
- Leaching from primary and secondary packaging

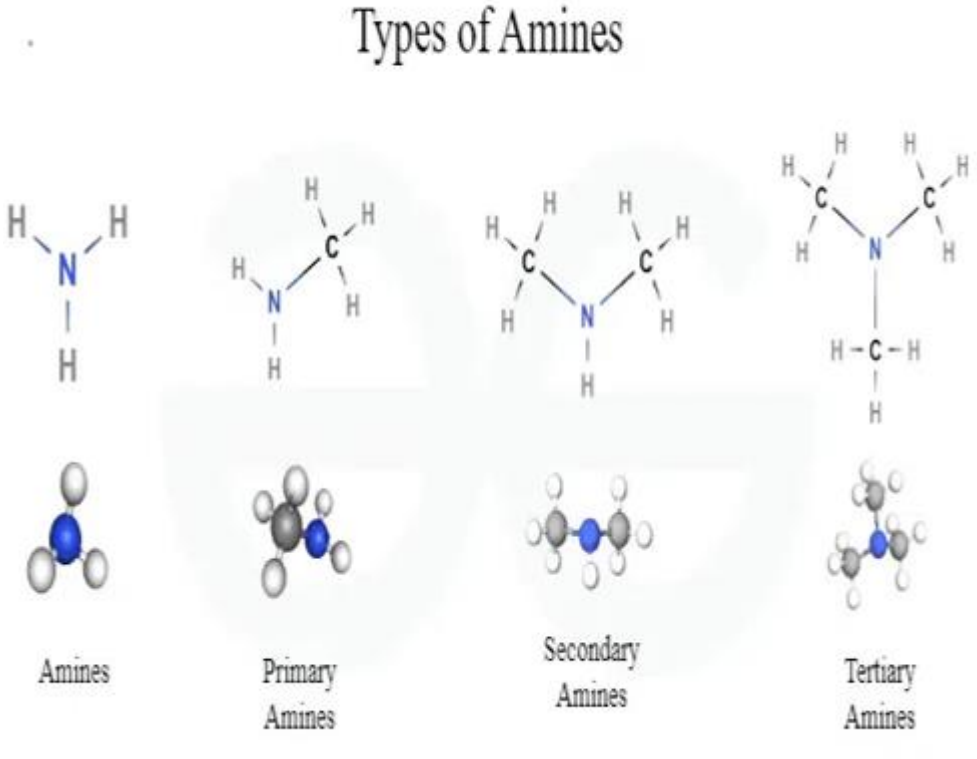
API

- Raw materials
- Recovered solvents, reagents and catalysts
- Quenching
- Process and control not optimised
- Potable water

FP

- Manufacturing Equipment
- Storage
- Repacking

Formation of a Nitrosamine Impurity



General Conditions

2 °, 3 ° & Quaternary Amines

API, intermediate, raw materials, reagents, catalysts, amide solvents, recovered solvents

Nitrosating agent

$NaNO_2$, HNO_2 NO, N_2O_3 N_2O_4 nitrosyl halides and organic nitrates. Recycled solvents

Reaction Conditions

Acidic

Stepwise Approach

Step 1: Risk Assessment

- Applicable to all synthetically produced medicines and Biological medicines that have been approved, in pre-registration and finalised but not registered.
- Submit before 31 December 2025 if no risk found

Step 2: Confirmatory Testing Results

- Required when an N-Nitrosamine impurity has been identified.
- Submit before 01 December 2026

Step 3: Submission of Variations

- Above acceptable intake limits – root cause analysis, RMP and benefit risk assessment must be submitted by 01 July 2027

Stepwise Approach

Risk Assessment

- API:

-Should begin as early as during drug development

-Review API manufacturing process

- FP:

-Evaluate degradation pathways

- Excipients:

-Based on structure

- Confirmatory testing is not expected unless potential risk is identified

Confirmatory Testing

- 6 pilot or 3 prod. batches to be tested (WHO)
- Tested using sensitive and validated methods
- Root cause analysis must be performed
- Control strategies proposed

Acceptable Intake Limit (ICH M7)

- LOQ < 10 % of limit = absence
- LOQ ≤ 30 % of limit = skip test
- LOQ > 30 % of limit = absence not known

SAHPRA Update

- Currently cataloging all risk assessments received via the inbox.
- We do not have the capacity to evaluate the risk assessments received at this time.
- Pre reg evaluates all risk assessments received with new applications.
- Post reg reviews all amendments of specifications whereby a N-Nitrosamine is being added together with the risk assessment.

Refer to the US FDA and EMA published guidance on acceptable intake limits

Questions?

Thank you