EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Update on activities linked to presence of N-nitrosamines in human medicines - PCWP and HCPWP

Presented by Antonio Azevedo & Robin Ruepp
Scientific Administrator, Inspection Office, / Scientific Administrator , Referrals Office
Quality and Safety of Medicines Department

# Main goals

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Ensure patient safety

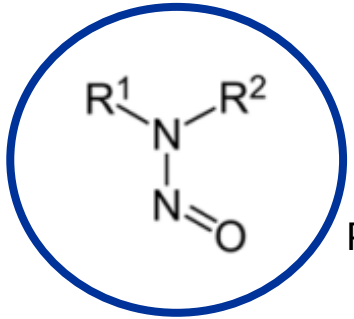
Ensure availability of critical medicines

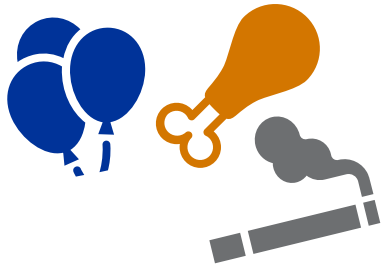
Ensure actions supported by scientific evidence

# What are N-nitrosamines?



Chemical compounds classified as probable human carcinogens on the basis of animal studies



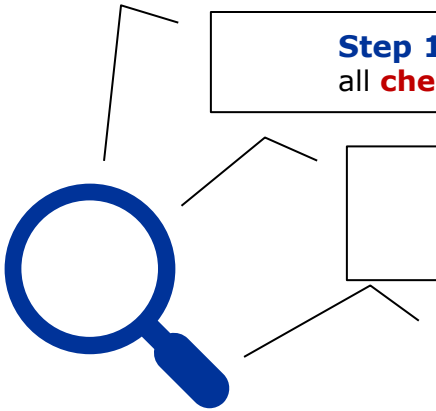



Present in trace amounts in several products, common in water and foods e.g. cured meat products, processed fish, cocoa, beer).

In pharmaceuticals Acceptable Intake (AI) limits are established for each N-nitrosamine based on a theoretical 1:100.000 excess lifetime cancer risk. From a given AI, a specific limit that takes into account the maximum daily dose and treatment duration for a certain medicine is derived. A negligible risk is linked to levels of a certain nitrosamine under the established limit.

# Nitrosamines call for review / Art. 5(3) : Industry obligations

- Nitrosamine call for review: precautionary measure for finished products containing chemically synthesised active substances started in September 2019 – 3 step process:



**Step 1 - Risk evaluation**: MAHs to perform risk evaluation of all **chemical** and **biological** medicines

**Chem.: 31/3/2021**
**Bio.: 1/7/2021**

**Step 2 - Confirmatory testing**: product where a risk has been identified in Step 1, should undergo confirmatory testing

**Chem.: 26/9/2022**

**Step 3 - Changes to the marketing authorisation**: variations should be submitted to introduce any required changes (changes to manufacturing process, packaging, excipients, product specifications etc.)

**Chem.: 01/10/2023**
**Bio.: 1/7/2023**

# What has changed since the Art. 5(3) Review?

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- 2020 – Focus on small molecule nitrosamine impurities with known high potency (robust toxicological data), mainly from API manufacturing processes

- 2022 - Extent of issue with API-derived nitrosamines (NDSRIs)
  - Most frequent cause of new step 2 "nitrosamine detected" reports
  - Common structural features of APIs
  - Continued discussions with industry and international regulators to better understand risk factors associated with NDSRI

- Publication of additional guidance as issue and scientifical knowledge on the issue evolves
  - All policies and approaches agreed since the beginning of the call for review take into consideration product criticality and benefit/risk balance

# Main regulatory developments – Nitrosamines Q&A updates

May 2022

Q&A20: clarifications on regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI.

October 2022

Q&A21: temporary universal AI.

December 2022

Q&A22: interim limit approach during CAPA implementation.

# Implementing the scientific conclusions-a network approach

European Medicines Regulatory Network approach implementing CHMP article 5 (3) Scientific Opinion

## NIOG (Nitrosamine Implementation Oversight Group)

Non product specific oversight:

- Promotion of scientific discussion with stakeholders through a dedicated workplan.
- Ensure consistent approach and guidance draft/update.

## NMEG (Nitrosamine Multidisciplinary Expert Group)

Scientific group convened by the CHMP:

- Mechanism to ensure availability of critical medicines.
- Provides guidance to authorities on consequences of stopping treatment or switching to alternative treatments vs the risk to patients from using a higher limit for a limited period of time.

## NISG (Nitrosamine International Steering Group)

- Ensures sharing of information, harmonisation and scientific discussions with international authorities.
- Supported by a working group focussing on scientific discussions related to quality and safety topics – Nitrosamines International Technical Working Group (NITWG).

## Quality and Non Clinical WP expert groups

- Experts of QWP and NcWP specifically involved in the scientific discussions with stakeholders.
- Provide input on product and non product related matters including scientific approaches on setting AIs

# Conclusions

Since 2018 significant progress made in understanding and controlling the risk of presence of nitrosamines in human medicines:

- ✓ Focus on balance between patient safety and availability of medicines
  - ✓ Patient safety ensured through establishment of dedicated mechanism and groups.
  - ✓ Availability of critical medicines through Nitrosamine Multidisciplinary Expert Group (NMEG).

- ✓ Call for review: majority of medicines is not at risk of presence of nitrosamines.

- ✓ Scientific progress and harmonisation promoted with stakeholder engagement and guidance update.

- ✓ Engagement at global level with international authorities.
  - Major update expected soon with a new approach on determining limits for nitrosamines that is expected to contribute the management of products with nitrosamines while ensuring availability of supply.

# Any questions?

## Further information

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Telephone** +31 (0)88 781 6000
**Send us a question** Go to www.ema.europa.eu/contact

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# Backup slides

# What has happened so far

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**June 2018**
**SARTANS**

- Since the first report of nitrosamines (NDMA, NDEA, …) in medicines used to treat hypertension (valsartan), the investigations identified extent of the problem to all sartan substances with tetrazole ring (active substance synthesis related).
- Member States balanced need to recall batches exceeding the AI versus the need to ensure product availability.
- January 2019: Art. 31 referral established limits in sartan products.

**July 2019**
**RANITIDINE**

- Medicines used to treat indigestion, heartburn and acid reflux.
- Report of formation of NDMA in finished product, initially from independent lab.
- April 2020: Art. 31 referral suspended all marketing authorisations.

**September 2019**
**CHMP Art.5 (3)**
**Scientific Opinion**

- June 2020: provide general guidance to all human medicines and initiates in September 2019 a call for review excercise for all chemical and biological medicines for human use authorised in the EU/EEA.
- The conclusions of the sartans referral were subsequently aligned to article 5 (3) recommendations (limits, timelines, analytical approaches etc.).

# Main cases where the AI was exceeded

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**November 2019**
**METFORMIN**

- Product used to treat type II diabetes.
- Medicine supply and patients safety were ensured by establishment of interim limits by NMEG and imposing testing before release.
- The majority of companies have implemented corrective actions within 1 year and no batch with nitrosamine exceeding the AI is present on the market.

**December 2019**
**RIFAMPICIN**

- Product used in treatment of tuberculosis and other infections.
- Medicines supply and patient safety were ensured by establishment of interim limits by NMEG.
- Ongoing investigations on root cause and corrective actions to reduce nitrosamine levels.

**September 2020**
**VARENICLINE**

- Product used in smoke cessation therapy.
- Given the availability of alternative products, the company was asked to perform market recall and stop batch release until the AI limit is achieved.

Nitrosamine impurities webpage

# What has EMA done about it

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Triggered in September 2019 by EMA executive director, CHMP provided a scientific opinion in July 2020 with 2 main outcomes:

**General guidance on dealing with**

**presence of nitrosamines in human medicinal products**

- ✓ Applies to **all human medicinal products.**
- ✓ Marketing Authorisation Holders/Applicants requested to ensure the quality of their medicinal products by mitigating the risk of the presence of N-nitrosamines.
- ✓ Aspects addressed in the general guidance relate to the principle of mitigation, the calculation of limits, etc.

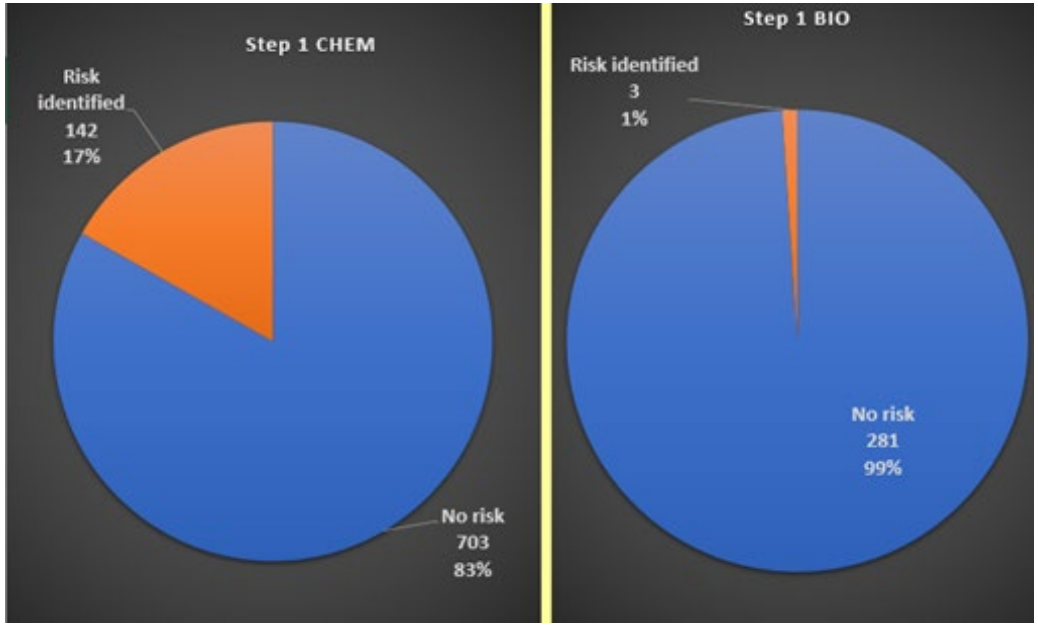
**Specific guidance relating to the call for review to MAHs**

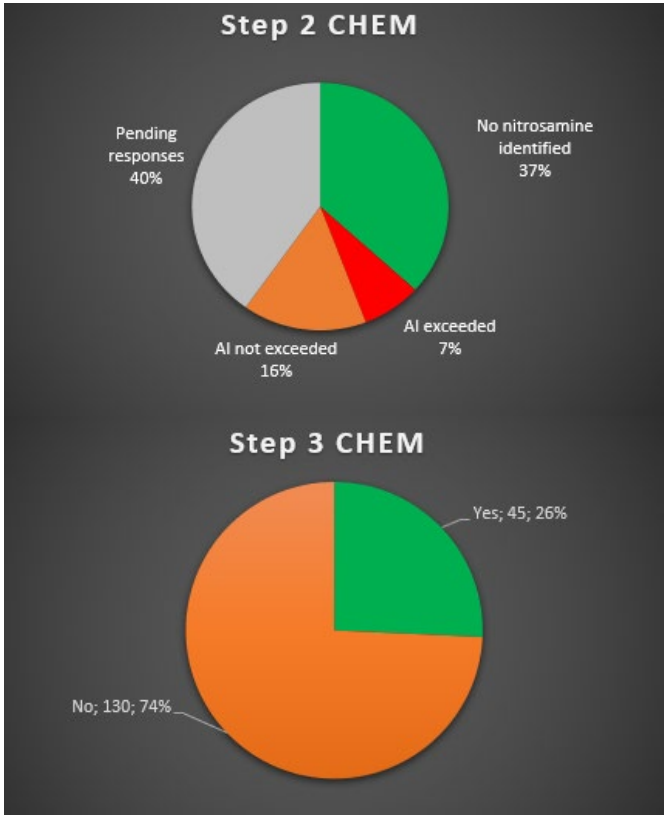
- ✓ Applies to **chemicals and biologicals**
- ✓ Procedural aspects and timelines.
- ✓ Confirmatory testing requirements for products at risk.
- ✓ Filing of variations.

## 4 scenarios identified based on presence of nitrosamines

- Taking into account the outcome of the CHMP scientific review, four scenarios have been identified:
  - Scenario a: a known nitrosamine has been detected and the nitrosamine level can not be kept below the Acceptable Intake (AI)/more than 1 known nitrosamine has been detected and the total risk level of the sum of all detected nitrosamines can not be kept below a 1 in a 100,000 lifetime risk
  - Scenario b: a known nitrosamine has been detected and the nitrosamine level does not exceed the AI and is more than 10% of the AI (same approach in case of more than 1 known nitrosamine)
  - Scenario c: no nitrosamine has been detected or the nitrosamine level of the known nitrosamine is below or equal to 10% of the AI (same approach in case of more than 1 known nitrosamine)
  - Scenario d: a new nitrosamine, not yet assessed in the frame of the Article 5(3) CHMP Opinion, has been detected

# Status of the call for review for CAPs, as of 23/06/23




- The majority of products was identified not at risk of presence of nitrosamine
- Confirmatory testing is pending for products identified at risk