EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on activities linked to presence of N-nitrosamines in human medicines

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An agency of the European Union

Main goals

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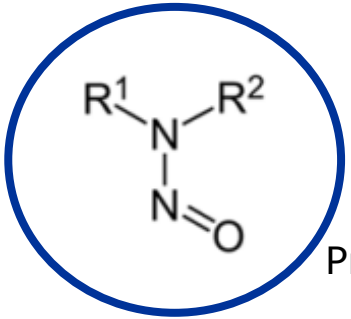
Ensure patient safety

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 and strictly regulated in all areas

In pharmaceuticals Acceptable Intake (AI) limits are established for each

N-nitrosamine. 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.

What has happened so far

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June 2018
SARTANS

- Since the first report of nitrosamine in medicines used to treat hypertension (valsartan), the investigations identified extent of the problem to all sartan substances with tetrazole ring.
- Member States balanced need to recall batches exceeding the AI versus the need to ensure product availability.
- January 2019: scientific review referral established limits in active substances.

July 2019
RANITIDINE

- Medicines used to treat indigestion, heartburn and acid reflux.
- Report of formation of nitrosamine in vivo.
- April 2020: scientific review 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.
- The conclusions of the sartans referral were subsequently aligned to article 5 (3) recommendations.

What has EMA done about it

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.

Implementing the scientific conclusions-a network approach

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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)

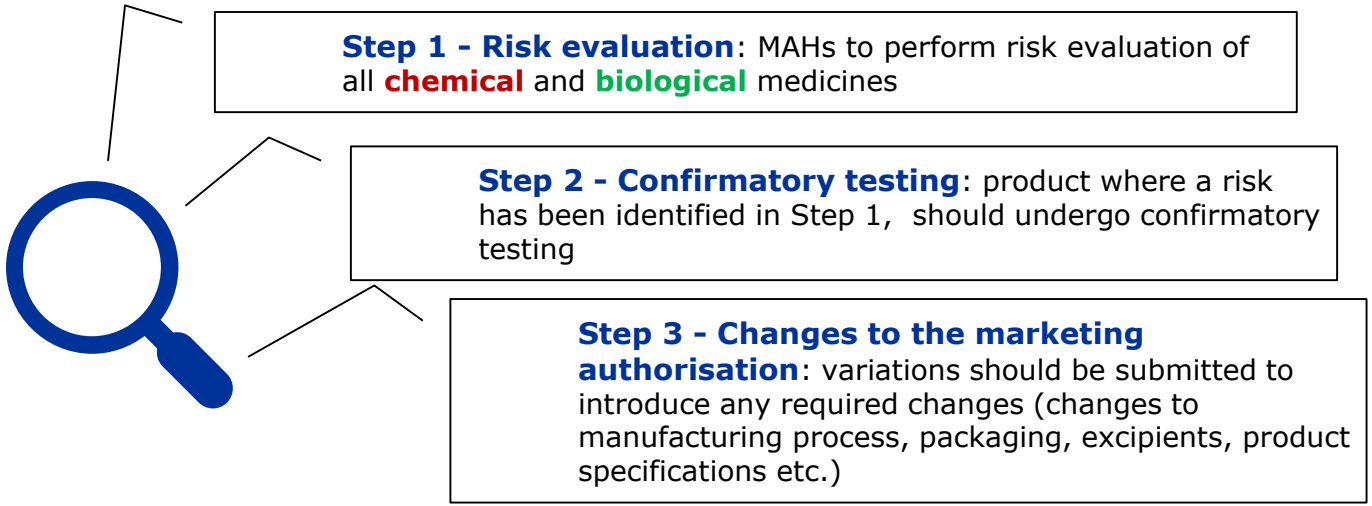
- Ensures sharing of information, harmonisation and scientific discussions with international authorities.
- Supported by a working group focussing on scientific discussions related to quality and safety topics.

Quality and Safety WP expert groups

- Experts of QWP and SWP specifically involved in the scientific discussions with stakeholders.
- Provide input on product and non product related matters.

What are the obligations of the Pharmaceutical Industry

- Nitrosamine call for review: precautionary measure for finished products containing chemically and biologically synthesised active substances



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

Chem.: 26/9/2022
Bio.: 1/7/2023

Call for review: state of play for CAPs (14/02/22)

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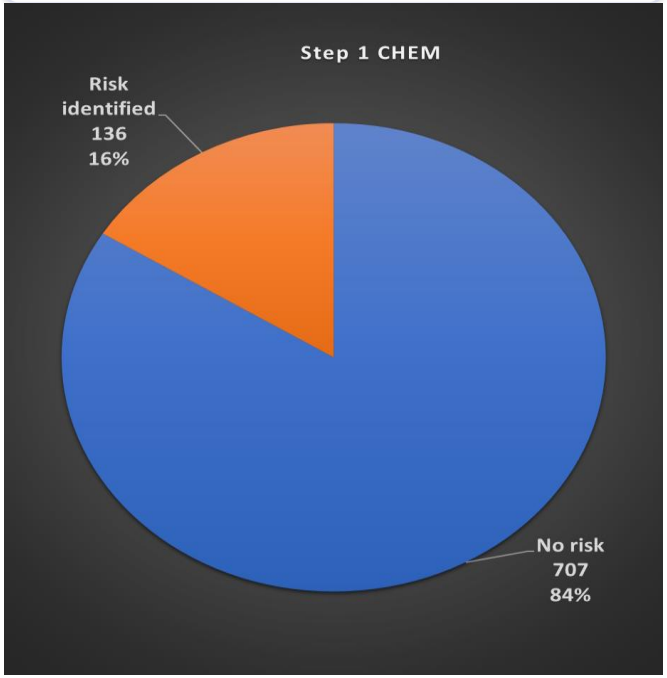
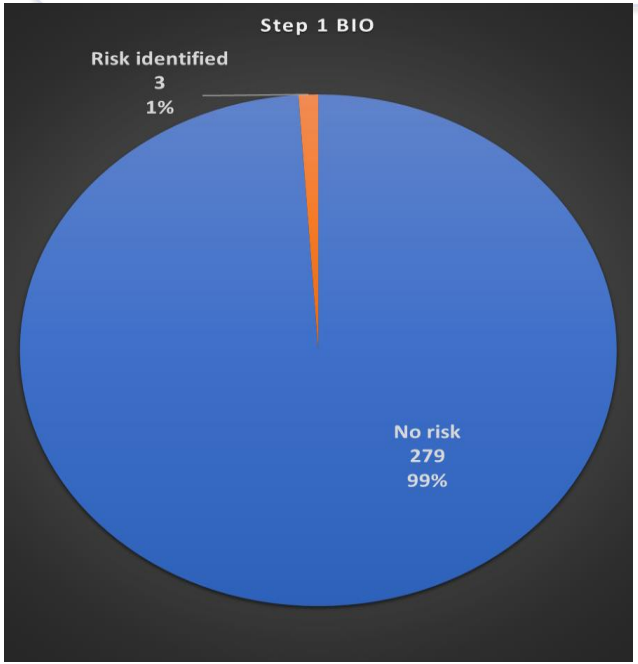
Step 1 response rate CHEM: 98%



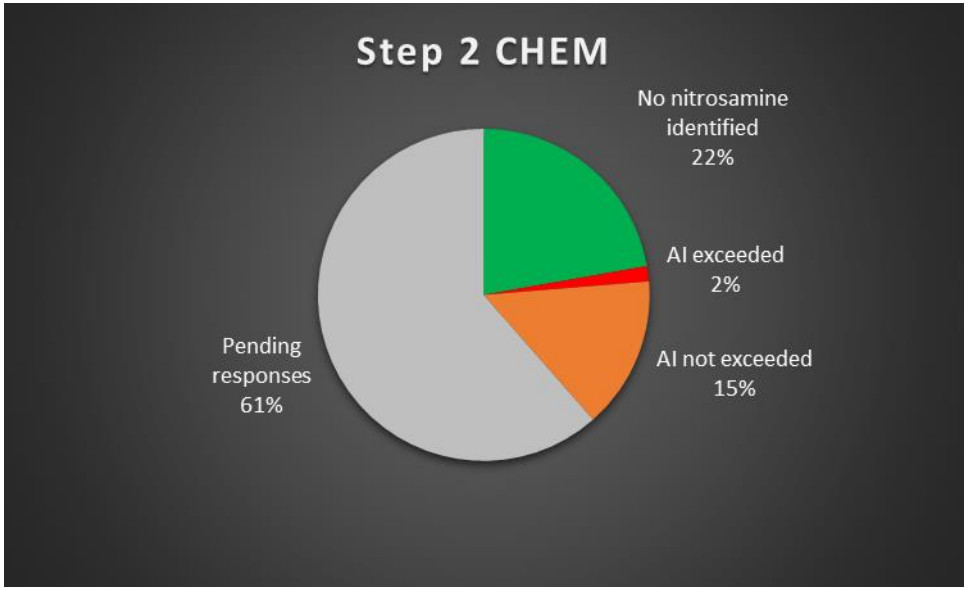
Step 1 response rate BIO: 92%



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

Call for review: state of play for CAPs (14/02/22)

Step 2 response rate CHEM: 39% of products identified at risk.
Deadline: 26/06/2022



Step 2 response rate BIO: 0%
Deadline: 01 July 2023

- ✓ **AI exceeded for substances used in CAPs**: varenicline, metformin
- ✓ **Expected date for step 2 CHEM results**: end 2021-September 2022

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.

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

Conclusions

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

- ✓ Patient safety ensured through establishment of dedicated mechanism and groups.
- ✓ Availability of critical medicines ensured by NMEG guidance.
- ✓ Call for review ongoing with step 1 results confirming that the 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.

Any questions?

Further information

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