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Nitrosamine impurities in human medicines

The response of the European Medicines Regulatory Network

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Executive summary

This report provides an overview of the response of the European Medicines Regulatory Network (EMRN) to the presence of nitrosamine impurities in human medicines.

Following the discovery in 2018 of these potentially carcinogenic impurities in a group of medicines used to treat cardiovascular diseases, known as 'sartans', and later in other medicines, the EMRN initiated a number of regulatory and scientific reviews. These include Article 31 reviews of sartans and ranitidine and an Article 5(3) review for all human medicines as well as, a lessons learnt on the experience from the sartans.

Through these procedures, the EMRN established acceptable intake (AI) limits in collaboration with international regulatory partners to ensure that exposure to nitrosamine impurities remained at or below safe levels.

The network issued a call for review (CFR) for all marketing authorisation holders (MAHs) for authorised human medicines containing chemical active substances. The CFR required MAHs to institute a stepwise evaluation process to identify, assess and mitigate any risks of nitrosamines potentially present in their medicines. The CFR was later extended to medicines containing biological active substances. In addition, for marketing authorisation applications (MAAs), a requirement for applicants to submit risk assessments on the potential presence of nitrosamines was also introduced.

The EMRN also established the Nitrosamine Implementation Oversight Group (NIOG) to oversee the implementation of recommendations from the Article 5(3) review. There were also regular interactions with international partners as well as industry associations to discuss regulatory requirements and scientific information concerning nitrosamines.

These elements of the EMRN response were crucial in developing a harmonised approach in the EU for protecting patients while maintaining availability of medicines. The development of this harmonised regulatory approach for nitrosamines, as described in this report, has also supported the management and assessment of individual cases where nitrosamines have been detected in human medicines within the EU.

In terms of future developments to the regulatory framework, the latest scientific knowledge on toxicology, safety and quality aspects of nitrosamines will be reflected in an addendum to the ICH M7 guideline on the assessment and control of mutagenic impurities in order to harmonise guidance on nitrosamines across ICH members, which was initiated in June 2024.

1. Introduction

The report evaluates the effectiveness of the EMRN (which includes EMA, National Competent Authorities and the European Commission) response to nitrosamine impurities in medicines and provides an overview of the measures put in place to protect public health, while ensuring that medicines remain available for patients who need them. It also describes the refinement over time of the regulatory tools used to manage nitrosamine impurities based on evolving scientific knowledge.

Managing the potential presence of nitrosamines in medicines has been a priority for the EMRN since 2018 when EU regulators became aware of the presence of these chemical compounds in valsartan-containing medicines.

Nitrosamines are a class of chemical compounds with a nitroso functional group attached to an amine compound. These compounds can be naturally occurring or synthetic. They can be found in some foods, beverages and other consumer products as impurities.

Nitrosamines are classified as probable human carcinogens on the basis of animal studies and their detection in medicines led to a number of regulatory measures in the EU. They are also categorized as a sub-class of the N-nitroso class of cohort-of-concern (CoC) compounds in the ICH M7 guideline due to the high carcinogenic potency of some chemicals within this structural class. Despite these concerns, there only is a very low risk that nitrosamines impurities at the levels found in medicines can cause cancer in humans.

Following the initial detection of nitrosamine impurities in angiotensin-II-receptor antagonists ('sartans'), the EMRN took several regulatory actions. In July 2018, at the request of the European Commission, the European Medicines Agency (EMA) initiated an Article 31 [1] review, which resulted in additional requirements for MAHs for sartans to mitigate nitrosamine impurities in their products.

Following the review of sartans, EMA's Committee for Medicinal Products for Human Use (CHMP) conducted a second review of nitrosamines for all medicines for human use authorised in the European Union. This second review, under Article 5(3) concluded in June 2020 and provided recommendations on how to manage, detect and minimize nitrosamine impurities. In addition, the EMRN conducted a lessons learnt exercise drawing on the experience from the sartans[2].

Before the conclusion of the Article 5(3) review, the CHMP carried out an Article 31 review in which it recommended the suspension of the marketing authorisations for all ranitidine-containing medicines in due to the presence of *N*-nitrosodimethylamine (NDMA).

In 2020, the EMRN developed a framework for implementing the recommendations of the Article 5(3) review. A key aspect of the Article 5(3) framework was the Call For Review (CFR), which required companies to investigate the risk of nitrosamine impurities being present in their products. Companies were required to institute a stepwise evaluation of the risk of nitrosamine contamination for all approved human medicines within the EU, confirmatory testing when a risk was identified, and mitigation and control measures as appropriate.

To support the CFR, guidance for MAHs was made available on the websites of EMA and the CMDh (the Co-ordination group for Mutual recognition and Decentralised procedures – human)[3]. The guidance was updated regularly to reflect the latest scientific evidence.

The Nitrosamine Implementation Oversight Group (NIOG) was created to oversee the implementation of Article 5 (3) recommendations, including the CFR exercise, and to discuss related policies. Biannual meetings took place between the NIOG and Interested Parties (IPs), serving as the main interface for interacting with Industry stakeholders.

Furthermore, the EMRN was involved in international fora concerned with the management of nitrosamine impurities, such as the Nitrosamines International Technical Working Group (NITWG) and the Nitrosamines International Strategic Group (NISG).

2. CHMP scientific assessments

2.1. Article 31 reviews for sartans and ranitidine

Sartans

Regulators became aware of the presence of nitrosamines in EU medicines in June 2018 when a manufacturer of a valsartan-containing medicine reported the presence of NDMA. As a result, the European Commission triggered an EU review of all valsartan medicines in the form of a referral under Article 31 of Directive 2001/83/EC, started on 5 July 2018[4]

During the review, conducted by the CHMP, it became clear that the NDMA formation in valsartan resulted from the use of sodium nitrite in the manufacturing process to quench unreacted azide reagents under acidic and/or thermal conditions in the presence of (aqueous) N,N-dimethylformamide, which can hydrolyse to dimethylamine.

The CHMP subsequently requested analytical data on four other angiotensin receptor blockers (candesartan, irbesartan, losartan and olmesartan) with the same reaction principle in their manufacturing process. The analysed testing data confirmed the presence of NDMA in some batches containing these active substances and, in September 2018, the scope of the review widened to cover these other active substances.

Other small nitrosamines such as e.g. *N*-nitrosodiethylamine (NDEA), *N*-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitroso-di-n-butylamine (NDBA), N-nitrosoethylisopropylamine (EIPNA), N-nitrosodiisopropylamine (DIPNA) and N-nitroso-N-methylaniline (NMPA) [5]were subsequently detected and were shown to form under analogous reaction conditions with other amines. Meanwhile, the European Directorate for the Quality of Medicines and Healthcare (EDQM) re-assessed and suspended many CEPs (Certifications of Suitability to the European Pharmacopoeia) for valsartan, irbesartan and losartan.

At the conclusion of the review in April 2019, MAHs were given two years to review their manufacturing processes, test for nitrosamine impurities, implement limits based on acceptable intake (AI) for NDMA and NDEA and make any necessary changes to minimise nitrosamine contamination as much as possible[4].

In November 2020, the CHMP updated its recommendations for this review to align them with recommendations from the Article 5(3) review for all human medicines, which concluded in June 2020. The main change concerned the limits for nitrosamines, which had previously applied to the active substance but was considered appropriate for the finished products. These limits, based on internationally agreed standards (ICH M7(R1)), should ensure that the excess risk of cancer from (multiple) nitrosamines in any sartan medicines does not exceed 1 in 100,000 for a person taking the medicine for lifelong treatment[4]. A threshold of toxicological concern (TTC) of 18 ng/day was introduced as a default limit for nitrosamines impurities where substance-specific toxicological data were not available[6].

The CHMP and CMDh published a detailed questions-and-answers (Q&A) document containing guidance on how to implement the outcome of the Article 31 review in order to support MAHs and ensure a harmonised approach among Member States when assessing relevant updates to dossiers[6].

Lessons learnt from presence of N-nitrosamine impurities in sartan medicines

In May 2019, after the conclusion of the sartans Article 31 review, the EMRN conducted a lessons learnt exercise to identify areas for improvement to prevent unexpected impurities, such as N-nitrosamines, from occurring in human medicines and to support the regulatory network's preparedness for managing similar cases of unexpected impurities arising in the future.

As part of this exercise, a meeting with stakeholders, including industry associations and other international regulatory agencies, took place in November 2019. Drawing on the experience from the sartans incident, the lessons learnt group made recommendations covering prevention, incident management, market surveillance, communication and international cooperation. These recommendations were captured in a report that was published in June 2020[3]. A plan was later published in October 2020 setting out how the EMRN intended to implement the recommendations, with information on responsibilities and indicative timelines[7].

Since 2020, the EMRN has been working to implement the recommendations from the lessons learned exercise. As of April 2025, the majority of the recommendations have been addressed.

Ranitidine

In September 2019, at the request of the EC, the CHMP started a review of ranitidine-containing medicines following reports of NDMA above the AI limit. It was postulated that ranitidine degrades over time to form NDMA, and that more NDMA can also be formed following ingestion. This review ultimately led to the suspension of marketing authorisations for all ranitidine-containing medicinal products in the EU in 2020[8]. CEPs for ranitidine, that were valid at the beginning of the referral, were suspended by the EDQM or withdrawn by the holder.[11]

The CHMP recommended conditions for lifting the suspension of ranitidine medicines, including requirements for companies to provide more data. Following a request for re-examination, the CHMP maintained the conditions for lifting the suspension of the medicines, including requirements for companies to provide more data on the possible formation of NDMA from ranitidine inside the body. As the formation of NDMA in the body was expected to be very low following a single low dose of ranitidine given by injection or infusion (drip), the CHMP amended the conditions for lifting the suspension for those ranitidine medicines.

2.2. Article 5(3) review for all human medicines

In September 2019, EMA's Executive Director asked CHMP to provide guidance in accordance with Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of N-nitrosamines in medicinal products for human use.

In making the request, in accordance with Article 5(3) of Regulation (EC) No 726/2004, the Executive Director noted that it was important to learn from the experience with sartans and take a proactive approach for other classes of medicines.

On 19 September 2019, during the first phase of the Article 5(3) review, a call for review was launched requesting MAHs for human medicines containing chemically synthesised active substances to review

their medicines for the possible presence of nitrosamines, to test all products at risk and to introduce necessary changes to the marketing authorisations within 3 years.

The Article 5(3) review concluded in June 2020. There are two outcomes from the CHMP scientific review. First, general guidance on how to deal with the presence of nitrosamines in all human medicinal products was set out. As a result, MAHs/applicants are requested to mitigate the risk of the presence of nitrosamines as much as possible and to ensure the quality of their medicinal products. Secondly as a result of the Article 5(3)[6] referral, the scope of the call to review to MAHs was extended to include medicines containing biological active substances.

The review set limits for (multiple) nitrosamines using internationally agreed standards (ICH M7(R1)) based on lifetime exposure. Patients should generally not be exposed to a lifetime risk of cancer exceeding 1 in 100,000 from nitrosamines in their medicines.

Companies were required to establish appropriate control strategies for both active substances and finished products. They were also required to conduct risk evaluations for the presence of nitrosamines in their products and perform confirmatory testing if a risk is identified.

The recommendations from this review also covered:

- The need to set specification limits for (multiple) nitrosamines for a particular medicinal product, in line with published AI limits.
- Flexibility in control strategies (regular testing, skip testing, omission of specification).
- Considerations for analytical method development and sensitivity requirements.
- Control options when more than one nitrosamine is present in the same product.
- Methodologies for setting AI limits for new nitrosamines where insufficient toxicity data were available, including the establishment of a class-specific TTC limit of 18 ng/day.
- Exceptions for medicines indicated for treatment of advanced cancer or where the active substance itself is genotoxic at therapeutic concentrations.
- The exceptional and temporary use of higher limits for products containing nitrosamine impurities above the AI limit but which still have a positive benefit/risk ratio.
- The need for further epidemiological studies.

Information concerning the implementation of the outcome of the Article 5(3) review for all human medicines is presented in more detail in the following sections.

3. Overview of developed approaches

3.1. Procedural

3.1.1. EMRN governance for implementation of the Article 5(3) CHMP opinion

In 2021, the EMRN established the Nitrosamine Implementation Oversight Group (NIOG) with a mandate to oversee the implementation of the recommendations from the Article 5(3) review. The NIOG was to carry out the following tasks:

- Provide non-product specific oversight of the implementation of the CHMP's Article 5(3) opinion;

- Report progress to the EMRN regarding MAH's compliance with the call for review timelines, progress with the updating of guidance and other aspects related to the implementation of the recommendations;
- Evaluate the need for updating current guidance/Q&As or for publishing new scientific and procedural guidance;
- Provide support in the drafting of guidance and delivering training to assessors;
- Address any specific matters related to the call for review that require clarification;
- Provide a link with stakeholders, including by initiating and maintaining dialogue and interaction with the pharmaceutical industry

To date, 13 NIOG meetings have taken place. In addition, 6 meetings with interested parties (industry trade associations, NIOG-IPs) have taken place to discuss scientific developments in the field of nitrosamines, as well as policy issues related to the CFR. Regulatory agencies outside the EU also participated in these meetings as observers. Meeting highlights and presentations are available on EMA's website.

3.1.2. Call for review to MAHs

On 26 September 2019, EMA and the CMDh announced the launch of the CFR exercise, requesting MAHs to review their manufacturing processes in order to identify and, if necessary, mitigate the risk of the presence of nitrosamine impurities and report back to authorities.

MAHs were requested to evaluate the risk of nitrosamines in their authorised products based on the available scientific information (step 1). If a risk was identified, confirmatory testing (step 2) should follow and, lastly, if the presence of a nitrosamine was confirmed through testing, mitigation measures should be implemented (step 3).

Response templates and information on reporting mechanisms were made available and deadlines for each step were defined. Following the conclusion of the Article 5(3) opinion, the scope of the CFR was widened to include human medicines containing biological active substances with revised deadlines for each of the steps. As the challenges in developing and validating sufficiently sensitive analytical methods to test all at-risk products became apparent, the CFR deadlines were extended for step 3 (to 1 July 2023 for medicines containing biological active substances and 1 October 2023 for medicines containing chemically synthesized active substances).

EMA and National Competent Authorities recorded a high rate of compliance for step 1 reporting from MAHs of centrally and nationally authorised products. A risk for small molecule nitrosamines (esp. NDMA, NDEA) or nitrosamine drug substance-related impurities (NDSRIs) was identified for a proportion of products containing chemical active substances, while for biological products the risk of nitrosamine contamination proved to be low. For the products where a risk was identified, confirmatory testing was performed and reported by companies and where nitrosamines were detected, additional regulatory actions were taken as described in the sections below.

For small molecule nitrosamines and NDSRIs without carcinogenicity data, a carcinogenic potency categorisation approach (CPCA) has been established based on structure-activity relationship with 5 potency categories and AI limits for each category (see Appendix 2[12] of the Q&A).

After the lapse of the deadlines for the CFR, MAHs and applicants are still expected to continue to comply with the requirements to assess, identify, control, and report any potential nitrosamine impurities throughout the product life cycle and notify relevant authorities using the established response templates. As such, MAHs should revisit initial risk evaluation as and when new information becomes

available, updating the submitted responses accordingly. Ultimately, MAHs have the legal responsibility for ensuring the quality, safety and efficacy of their medicines.

3.1.3. Guidance for MAHs

In August 2020, the EMRN published a Q&A document providing MAHs with additional guidance on how to implement the recommendations of the Article 5(3) opinion and on the CFR exercise[4].

The document has been updated regularly in line with evolving scientific knowledge about nitrosamines and to reflect procedural outcomes of the CFR exercise. The main updates were regarding the scope of the products concerned (initially only applicable to chemical substances, and later also covering biological products) ; acceptable nitrosamine levels (the extension of the less than lifetime (LTL) approach for authorised products, initially only for critical products and later extended to all authorised products); the revision of submission timelines for confirmatory testing (extension to CFR timelines); new information on common risk factors and identified root causes; the implementation of the scientific framework (e.g. in relation to removing the temporary universal limit or non-mutagenic impurity handling) and the development of analytical test procedures (e.g. in relation to testing strategy and required sensitivity).

A major milestone was reached in July 2023, with the implementation of the carcinogenic potency categorization approach (CPCA) and the enhanced Ames test (EAT) to determine compound-specific AI limits (in ng/day), as well as the publication of the agreed AI limits for nitrosamine impurities with periodic updates.

These updates were discussed with stakeholders, including international regulators, and conveyed to industry stakeholders during regular NIOG-IP meetings.

In addition, the CMDh published a practical guidance document for MAHs of nationally authorised products (NAPs)[9]. Close collaboration between EMA, CHMP and the CMDh ensured a harmonised approach for CAPs and NAPs and early identification of areas to be further clarified.

For authorised medicines, MAHs are responsible for introducing changes to their active and/or finished products if nitrosamines are identified. They should submit a variation, as necessary, to amend their manufacturing processes, controls and specifications, product formulation, raw materials, and packaging to mitigate the risk of nitrosamines formation.

The potential presence of nitrosamines is also evaluated as part of marketing authorisation applications (MAAs). At the submission stage, applicants must submit the risk evaluation as an attachment to the marketing authorisation dossier (step 1) and, if a nitrosamine is identified, include necessary information on the mitigation strategy and confirmatory testing (step 2). If relevant information is not submitted as part of the MAA, it is requested during the MAA review process. Outstanding issues related to nitrosamine impurities have to be addressed before the final opinion, including confirmatory testing, as applicable, to ensure the benefit-risk balance of the product is not impacted. For line extensions or variations, a risk evaluation is generally not needed, because the product would have already been assessed as part of the call for review. However, a risk evaluation may be requested during the line extension or variation procedure if changes are introduced that can impact the risk of nitrosamines being present.

3.1.4. Nitrosamine case assessment workflow

The EMRN agreed a workflow[10] to support the management of the reporting of nitrosamines associated with the CFR. As products containing nitrosamines can be authorised centrally or nationally, mechanisms for harmonising the management of cases were published as part of the EMRN approach for the implementation of the CHMP's Article 5(3) opinion. The workflow sets out 4 different scenarios when confirmatory testing data are submitted during step 2:

- Scenario a: a known nitrosamine is detected in a medicinal product and the nitrosamine level exceeds the AI limit based on ICH M7 principles (1 in a 100,000 lifetime risk). The same scenario applies where there is more than one known nitrosamine detected, and the total sum of the nitrosamines exceeds the AI limit of the most potent nitrosamine, or the sum of all detected nitrosamines exceeds the 1 in a 100,000 lifetime risk.
- Scenario b: a known nitrosamine is detected in a medicinal product and the nitrosamine level does not exceed the AI limit based on ICH M7 principles (1 in a 100,000 lifetime risk), however the total nitrosamine content is more than 10% of the AI limit. The same scenario applies where there is more than one known nitrosamine detected, and the total sum of the nitrosamines does not exceed the AI limit of the most potent nitrosamine, or the sum of all detected nitrosamines is below the 1 in a 100,000 lifetime risk.
- Scenario c: no nitrosamine is detected in a medicinal product, or the nitrosamine level of the known nitrosamine is below or equal to 10% of the AI limit based on ICH M7 principles. The same scenario applies if more than one known nitrosamine has been detected and the total nitrosamine content is below or equal to 10% of the AI limit based on ICH M7 principles for the most potent nitrosamine or the sum of all detected nitrosamines.
- Scenario d: one or more new nitrosamines, for which there is not yet a defined AI limit based on ICH M7 principles, are detected in a medicinal product.

While for scenario c cases, no amendment to the marketing authorisation is expected, for scenarios a and b, the marketing authorisation should be subject to changes (e.g. via a variation or referral). Scenario d cases require, as a first step, the determination of the AI limits before recategorization as a scenario a, b or c, depending on the nitrosamine content.

For each of the above scenarios, a process was developed to ensure the best use of existing platforms (i.e. the Rapid Alert Network (RAN), the Incident Review Network (IRN)) and existing regulatory pathways for quality defects, variations and referrals).

For the establishment of the AI limits, two main approaches are established. If nitrosamines are identified with sufficient substance specific animal carcinogenicity data, the TD_{50} should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline. On the other hand, if sufficient substance specific data to derive a substance specific limit for lifetime exposure are not available, four options can be used:

- The CPCA
- Derivation by Structure-Activity Relationship (SAR) and read across
- GLP-compliant Enhanced Ames test (EAT)
- Relevant well-conducted in vivo mutagenicity study

Following the introduction of the CPCA in July 2023, the EMRN established a process flow to assess the MAH proposals for AI limits for any new nitrosamine detected in their product. The proposed AI limit is assessed and confirmed by the lead responsible competent authority (Lead Member State (LMS)/NCA rapporteurs for nationally authorised products (NAPs) and CHMP rapporteurs for centrally authorised products (CAPs)).

MAHs can propose AI limits different to those derived using CPCA based on in vitro or in vivo studies. The product rapporteur (for CAPs) and LMS (for NAPs) are responsible for assessing the submitted data in consultation with the Nitrosamine Safety Oversight Expert Group (NS-OEG) experts. Depending on the outcome of the assessment, AI limits in Appendix 1 may be revised and amended.

Scenario a cases are managed through quality defect procedures[11] with the product rapporteur leading the assessment of MAH data and proposed actions (i.e. CAPA) to determining the need for market actions. If market action is needed as a potential response to identified scenario a cases, the EMRN is responsible for issuing and circulating notifications of product recalls within the rapid alert network (RAN) and informing international partners in accordance with the established recall procedure.

In case of potential shortages, the RAN is supported by Medicine Shortages Single Point of Contact Working Party (SPOC WP) which advises on product criticality. Regulatory authorities may consider implementing ad interim measures, such as the less-than-lifetime (LTL) approach during the corrective and preventive action (CAPA) implementation period (3 years from AI limit establishment) applicable to authorised human medicinal products. These measures are intended to ensure the continued availability of safe and effective medicines, while further root cause investigations are carried out.

Additional considerations apply for critical medicinal products under exceptional circumstances and the CHMP can request the Nitrosamines Multidisciplinary Expert Group (NMEG) to propose an ad interim AI limit that would allow sufficient supply to patient while safeguarding patient health.

When potential public health threats arise, regulatory authorities need to work together effectively to mitigate risks. The IRN was established by the EMA to coordinate actions across the EU. The IRN has so far held 8 teleconferences in relation to nitrosamines to consider risk minimisation measures in human medicines, regulatory procedure reviews (e.g. Article 31 reviews) and communication activities.

3.2. Safety

Nitrosamines are mutagenic carcinogens on the basis of animal studies and are classified as probable human carcinogens. Nitrosamines need to be metabolically activated to express their mutagenic activity. In the ICH M7 guideline on assessment and control of DNA reactive (mutagenic) impurities, they are included in the class of high potency mutagenic carcinogens referred to as the cohort of concern, although some nitrosamines with structural features hindering metabolic activation or DNA adduct formation may be less potent mutagens or non-mutagenic.

The establishment of AI limits for nitrosamines in human medicinal products is performed by EU toxicology experts. Initially, AI limits were established by the Safety Working Party (SWP) but due to the increasing number of nitrosamines being reported, this task was delegated to the NS-OEG which was formed in 2022, with oversight by the non-clinical working party (NcWP), the successor to the SWP following the reorganisation of the EMA's working parties. EU non-clinical guidance for nitrosamines is published and updated in question 10 of the Q&A and associated appendices. The AI limits established by the NS-OEG are published in Appendix 1[12] of the EMA Q&A.

The approaches to the safety assessment of nitrosamines in the EU/EEA have been developed in collaboration with international regulatory partners through participation of EU experts in the Nitrosamine International Technical Working Group (NITWG) with the objective of harmonising AI limits and the approaches to nitrosamine safety assessment as far as is possible. Initially, most of the nitrosamines reported were small nitrosamines. For many of these nitrosamines, sufficient substance specific animal carcinogenicity data were available to support the establishment of the AI. However, NDSRIs were increasingly reported and now make up the vast majority of nitrosamines reported.

As robust carcinogenicity data are not available for most NDSRIs, the lack of suitable surrogates for the read-across approach posed challenges to the assigning of AI limits for these substances. Consequently, in July 2023, the EMA and international regulators introduced the CPCA and the EAT as new approaches for the AI limit assessment of new nitrosamines. The CPCA and EAT conditions have been published in Appendix 2 and Appendix 3, respectively, of the EMA Q&A.

The CPCA is a structure-activity relationship-based method that allows the rapid assignment of a nitrosamine to 5 categories, each with a corresponding AI limit between 18 and 1500 ng/day, reflecting predicted carcinogenic potency. Following implementation in July 2023, the CPCA approach has been used to place nitrosamine impurities into one of five categories based on toxicological data and chemical structure, with the aim of predicting the compound-related carcinogenic potential. For instance, impurities classified as category 1 (AI limit of 18 ng/day) are predicted to have the highest potential of causing cancer in humans (most potent), while those in category 2 (AI limit of 100 ng/day), category 3 (AI limit of 400 ng/day) and category 4 (AI limit of 1500 ng/day) are considered to have progressively lower risks. Compounds falling under category 5 (AI limit of 1500 ng/day) are not predicted to have mutagenic or carcinogenic potential.

The EAT defines the conditions which need to be satisfied for acceptance of negative tests to allow control of nitrosamines at 1.5 µg/day. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD_{50} from the surrogate substance can still serve as a point of departure for derivation of AI limit on the basis of the structure activity relationship (SAR) and read across. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of the nitrosamine as a non-mutagenic impurity (NMI) according to ICH Q3A(R2) and ICH Q3B(R2) limits.

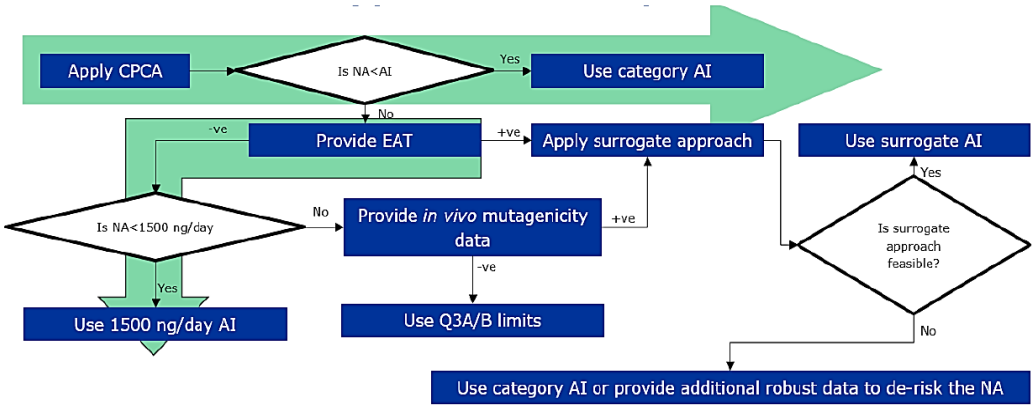

Figure 1. Process-flow for establishing AI limits

Currently, the LTL approach in ICH M7 cannot be applied routinely to nitrosamines. A limited and temporary application of the LTL is permitted in certain circumstances, as described in the EMA Q&A (question 22), to control the presence of nitrosamines exceeding the AI limit during CAPA implementation (up to 3 years following AI limit establishment).

The paradigms for the safety testing and assessment of nitrosamines are continually evolving with the generation of new data by industry, academia and regulators working individually and in collaboration. These include data from EMA-funded studies conducted by the MUTAMIND consortium led by the Fraunhofer Institute, and nitrosamines research activities carried out under the umbrella of the HESI Genetic Toxicology Technical Committee (GTTC) Mechanism-based Genotoxicity Risk Assessment (MGRA) working group in which EU toxicology experts are represented.

3.3. Quality

The various EMA referrals and reports published up to 2020 concerning nitrosamine impurities focussed on known and theoretical root causes and recommendations for the development of analytical methods for detecting and quantifying these impurities. Based on the experience and information available at that time, the focus was mainly on small molecule nitrosamines, such as NDMA and NDEA.

A comprehensive analysis of known root causes from previous referrals and theoretical root causes based on literature data was carried out. The conclusions of these early analyses focussed mainly on reagents, solvents and catalysts used within the API manufacturing process.

Several cases of small molecule nitrosamine formation in the finished product were also reported (e.g. NDMA in ranitidine and in metformin). The origin and degradation pathways for these impurities in the finished product formulations took some time to understand. In addition, certain risks associated with blister pack sealing were highlighted. Furthermore, the potential presence of trace nitrite in excipients was flagged as a potential root cause of nitrosamine formation taking place in finished product formulations. As a result, the recommendation was made for any analytical testing to be carried out on the finished product to ensure no risks were omitted from consideration. Finally, while the risk of nitrosamine formation in biological products was considered to be low, it could not be ruled out based on available science and therefore, risk assessments were also requested for biological products.

A review of published and pharmacopeial analytical methods used to detect and quantify these impurities was also carried out. The majority of these methods were designed to detect and quantify small molecule nitrosamines with established AI limits based on robust toxicology data. Recommendations were made on the required analytical sensitivity, as well as ruling out false positive or negative results from interference or sample contamination or instability. Recommendations were also made on the number of batches to be tested to ensure representative sampling.

Since these initial reports and as a result of confirmatory testing and subsequent root cause investigations recommended in the CFR, significant advances in the understanding of risk factors for nitrosamine formation have been made. These have been summarized [13] in a review paper which has been published by NITWG, a group of regulatory agencies. These scientific developments have been discussed, along with other issues associated with confirmatory testing, during interactions with stakeholders (industry, other regulators, and EU safety/toxicology experts) and guidance has been updated regularly to highlight newly discovered risk factors or to account for changes in e.g. safety/toxicology policy.

A summary of these developments and associated changes to published guidance since 2020 is given below:

- A recognition that if a nitrosamine impurity could not be synthesised despite extensive efforts, then it is unlikely to form. Confirmatory testing would not therefore be needed for theoretical nitrosamines that do not form in practice.
- Allowances for testing only certain strengths based on the worst-case scenario when a product is available in multiple strengths and extrapolation of the results is appropriate.
- Further guidance on testing and specification requirements in cases where more than one nitrosamine is present in the same product to ensure the overall lifetime cancer risk does not exceed 1 in 100,000. This could be a fixed approach where a fixed limit is set for each nitrosamine present. Alternatively, a flexible approach was developed whereby each nitrosamine is specified at its AI limit in ppm/ppb and an additional limit for total nitrosamines is required.
- As risk factors associated with active substance and finished product processes were better understood, an allowance was made to conduct confirmatory testing in the active substance, its precursor intermediates or raw materials as surrogates of the finished product provided that no further risk factors exist downstream of the tested materials. By analogy and based on an understanding of risk factors, specification limits could be set in raw materials, intermediates, or the active substance in lieu of the finished product.
- Scientific updates to guidance on risk factors and root causes as further data emerged.

As reflected above, the main focus up to 2020 was on potent small molecule nitrosamines formed primarily in the API manufacturing process. Since 2020, an increasing number of reports have been received of nitrosamines related to the structure of the active substance itself (NDSRIs). It has been estimated that around 40%[14] of marketed products may be at risk of NDSRI formation based on the structural features of the active substance. In general, 3 factors are required for formation of nitrosamine impurities: a nitrosatable amine, a nitrosating agent, and conducive conditions (see Figure 2). In few cases, oxidation of a hydrazine functional group can lead to NDSRI generation[13]

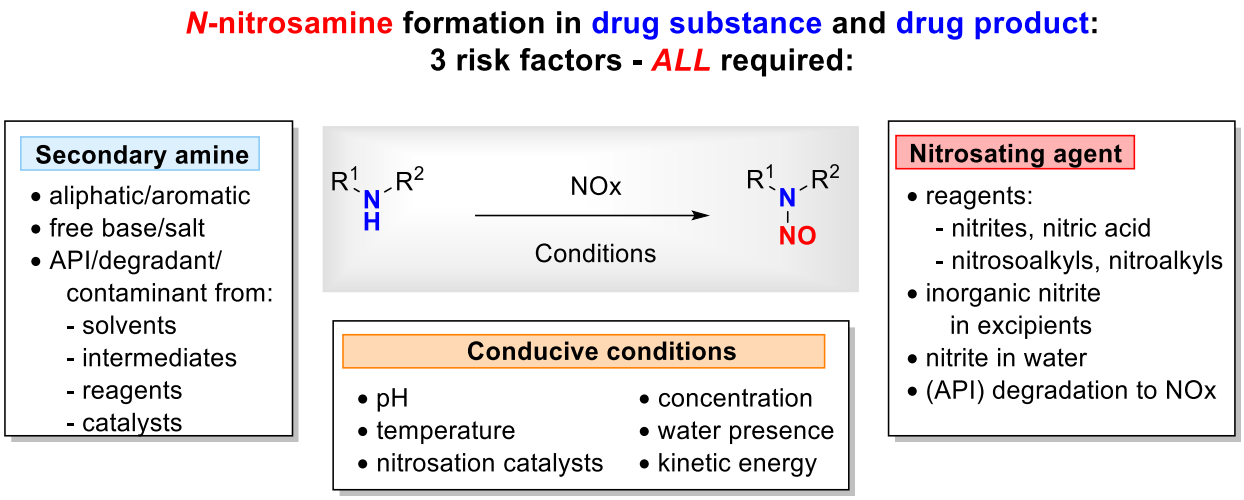

Figure 2. Conditions for nitrosamine formation in active substance and finished product

There are potentially multiple effective approaches to avoiding nitrosamine formation by carefully designing manufacturing processes for APIs. If unavoidable, they can also be removed by purification. At this stage, it is considered that formation of nitrosamines in active substance manufacturing processes is largely avoidable, provided that the risks are considered during manufacturing process development and appropriately mitigated.

Mitigating the formation of NDSRIs in finished products is more challenging because the vulnerable amine is an intrinsic (and critically important) part of the active substance and cannot be removed. Iit may not be possible to remove or reduce the nitrosating agent to sufficiently low levels, the scope for amending manufacturing process unit operations without impacting product CQAs is limited, and if NDSRIs are formed, they cannot be removed by purifying the finished product.

In those cases where nitrosamines are detected above the AI limit, various remediation strategies could be envisaged. These include reducing the nitrosating agent content to levels which sufficiently limit NDSRI formation (e.g. removing/replacing an excipient or reducing its nitrite contents) and incorporation of nitrite scavenging agents (antioxidant, amine) or pH modulator in the formulation.[13] For situations where nitrosamine levels increase during storage, more protective packaging, more restrictive storage conditions and shorter shelf-lives could be all considered. Other approaches may also be viable depending on the root cause. There have been multiple examples where the above strategies have been successfully implemented in the last few years for products marketed in the EU to ensure nitrosamine levels are kept below their acceptable intake limit.

However, the impact of changing the formulation on the finished product quality attributes (e.g. stability, bioavailability) by incorporating a new excipient should be carefully considered and investigated as appropriate.

3.4. Market surveillance

Sampling and testing of human products, considered at risk of nitrosamine contamination, was put in place following the first reports of contamination in sartan medicines. Sampling and testing were a key part of the regulatory response to manage the sartans incident but also to explore why nitrosamines came to be present in the first place. Thereafter, surveillance sampling and testing remained an important tool used to control compliance with the requirements of the CFR by the competent authorities. The Official Medicines Control Laboratories (OMCL) network, coordinated by EDQM, also developed methods for testing specific nitrosamines.

During this period, ad hoc market surveillance testing was conducted by OMCLs across the EU Member States in coordination with EMA and EDQM. Starting in 2023, EMA in collaboration with EDQM, put in place a dedicated routine programme for the sampling and testing of human medicinal CAPs where there is a risk of nitrosamine impurities. The aim of this initiative is to determine nitrosamines levels, compare these with risk assessment and test data submitted by companies and to evaluate whether the analytical methods are fit for purpose.

With respect to inspections, following the initial for-cause inspections of API manufacturing sites that were conducted in response to the initial discovery of nitrosamines in sartans, risk-based inspections were also used to verify elements of the CFR reporting. Verification during routine GMP inspections of manufacturers will continue to be considered by EU inspectorates in the future.

3.5. Medicine shortages and availability issues

Following the detection of nitrosamines in sartans in 2018, associated recalls of sartan medicines had a sizeable impact on market supply and caused critical shortages. There were concerns that dealing with the presence of nitrosamines in medicines would cause widespread shortages on the market. However, the EMRN was able to put in place measures to balance safety of patients with availability of much needed medicines, and relatively few disruptions to supply were reported.

The Medicine Shortages Single Point of Contact Working Party (SPOC WP) was involved in cases of nitrosamines and were consulted on the availability of alternatives and the criticality of products identified with nitrosamines. The SPOC WP feedback on the potential risk of shortages was considered as part of the assessment of the nitrosamine cases to inform the appropriate measures.

While the SPOC WP has discussed some cases for which supply disruptions occurred, critical shortages occurred only exceptionally.

4. Engagement and communication with stakeholders and international partners

4.1. Industry, health care professionals and patients

Since the initial identification of the risk of presence of nitrosamines impurities in sartan-containing medicines, the EMRN has ensured that there was clear and timely communication with patients, healthcare professionals and industry.

Engagement with these stakeholders was achieved, in the case of EMA, through established frameworks of interaction,[15, 16] and involved the dissemination of relevant information in accordance with Agency processes and transparency rules.

Both EMA and national competent authorities have updated patients and healthcare professionals about the risks identified with medicines, ensuring that patients had a clear understanding of the risks associated with the exposure to medicines containing nitrosamine impurities and what actions regulators were taking. Some updates were provided on regulators websites. EMA and national competent authorities also responded directly to individual members of the public who had queries or concerns.

EMA's Patients and Consumers Working Party (PCWP) and the Healthcare Professional Working Party (HCPWP) received regular updates on major policy developments and availability of medicines.

Regular interactions also took place between the EMRN and industry stakeholders through meetings of the NIOG-IP. These meetings provided an opportunity for the NIOG to give updates on new guidance and for the industry associations to provide updates on their progress, highlight challenges in complying with the requested activities and present new scientific data generated by industry. It also served as a forum to share updates on scientific progress concerning safety and quality aspects of nitrosamines in advance of technical discussions within expert groups, such as the Nitrosamine Safety Oversight Expert Group (NS-OEG) and the Quality Working Party (QWP).

4.2. Collaboration with international partners

Managing the presence of nitrosamine impurities in medicines is a challenge shared by regulators across the globe. Beginning with the sartans case, information was shared between regulators, including information on guidance, referrals and other regulatory actions such as market recalls.

In 2019, the Nitrosamine International Steering Group (NISG) was created. The mandate of this group is to achieve consistency in regulatory activities between different international jurisdictions, including information on market actions and product availability. Following the launch of the CFR in the EU, other regulators launched similar activities with timelines and requirements aligned to the greatest extent, taking into account local legal frameworks. As scientific data and understanding progressed, the NISG evolved to include dedicated forums for detailed technical discussions, with the creation of the NITWG in 2020. The aim of this group is to discuss safety and quality topics related to nitrosamines and to seek technical convergence among member jurisdictions, where possible. Scientific papers on root causes/ risk factors and on the CPCA approach have been published by NITWG quality and safety sub-groups.[22],

EMA also established dedicated confidentiality agreements with other international regulators to share information on nitrosamine topics. The engagement and agreement of major milestones at global level with international authorities will remain one of the priorities of the Agency.

A dedicated communications group was also set up so regulators could share public communication (such as press releases about nitrosamines) with each other in advance of publication.

5. Areas for future development

During the ICH plenary meeting of June 2024, the creation of an implementation working group to draft an addendum to ICH M7 Guideline on assessment and control of mutagenic impurities was agreed. The addendum will focus specifically on safety and toxicology aspects of nitrosamines. Quality topics may also be included based on progress with scientific understanding. The document will provide harmonised global guidance on nitrosamines based on the available scientific data. Subject matter experts from the EMRN will participate in this work. At the start of the ICH revision process, the planned target date for the revised ICH M7 is foreseen to be May 2028[17].

In parallel, the EMRN will also continue to assess the scientific developments on the topic and to update EU guidance as needed and in collaboration with relevant stakeholders.

6. Conclusions

The EMRN has established a framework and governance structures for controlling nitrosamine impurities in medicines. The call for review launched in 2019 required MAHs to review their portfolios and conduct confirmatory testing when risks were identified and to implement adequate preventive and corrective actions if required. Reporting mechanisms were developed in order to facilitate submission of CFR responses and compliance with the requests was generally good. The EMRN has had regular and extensive interactions with industry stakeholders and international partners to discuss the latest information on nitrosamine impurities.

The science around formation of nitrosamines has developed significantly in recent years, leading to regular updates to guidance on risk factors and testing requirements. More recently, the recognition that many products on the market were at risk of NDSRI formation led to a thorough review of the genotoxic potential of these impurities and the development of the Carcinogenic Potency Categorization Approach (CPCA) and the application of an enhanced Ames test, in collaboration with international regulatory partners. At the time of this report, over 170 AI limits have been published on EMA's website, many derived from the latest scientific approaches.

The safety of patients has been carefully balanced with the need to ensure the availability of important medicines. Relatively few products have been made unavailable and patients have not been unduly exposed to nitrosamine impurities, demonstrating the success of this approach.

Authorities in the EU will continue to take all necessary measures to protect patients. EMA, together with EU national competent authorities, remind MAHs of their responsibility to actively follow the latest science and policy developments, re-visit nitrosamine risk assessments, conduct confirmatory testing as appropriate, and ensure the quality, safety, and efficacy of their medicines for the safety and well-being of patients.

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