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European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines

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1. Background

On 10 September 2019, a referral according to Article 5(3) of Regulation (EC) No 726/2004 was triggered by the EMA Executive Director (ED) requesting the CHMP to conduct a scientific evaluation on the presence of nitrosamine impurities in human medicines containing chemically synthesised active pharmaceutical ingredients (APIs). The procedure was foreseen to run in a 2-step approach as follows:

- 1st phase, to provide considerations for marketing authorisation holders (MAHs) of these medicines on the identification of the possible presence of nitrosamine impurities;
- 2nd phase, taking into account ongoing work for the lessons learnt on the sartans review, to evaluate all available scientific knowledge on nitrosamine impurities in these medicines and their impact on the safe use of medicines, and to consider if the current scope should be broadened to other medicinal products. This evaluation will serve as a basis to achieve a coordinated approach and response across the EU and to advise regulatory authorities (RAs) on the actions to be taken following detection by MAHs of the presence of N-nitrosamine impurities in their medicines.

As a result of the first phase of the referral, a call for review to MAHs was launched on 19 September 2019 requesting MAHs for human medicines containing chemically synthesised APIs to review their medicines for the possible presence of N-nitrosamines, to test all products at risk and to introduce changes to the marketing authorisations (MAs) within 3 years.

In June 2020, the CHMP finalised its review according to Article 5(3) and issued an Opinion by consensus requiring companies to take measures to limit the presence of N-nitrosamines in human medicines as far as possible and to ensure levels of these impurities do not exceed set limits. During its scientific review the CHMP considered several aspects, including the root causes for the presence of N-nitrosamines in human medicinal products and the measures to be taken to mitigate their presence, the development of analytical methods to identify and quantify N-nitrosamines in APIs and finished products (FPs), the calculation of the risk for exposed patients in case of detection of N-nitrosamines in medicinal products, the methodology for defining limits, the need for further studies to be conducted, and the need to extend the scope to cover other human medicines (i.e. those not containing chemically synthesised APIs).

There are 2 outcomes from the CHMP scientific review. Firstly, general guidance on how to deal with the presence of N-nitrosamines in all human medicinal products was set out. As a result, MAHs/ applicants are requested to mitigate the risk of the presence of N-nitrosamines as much as possible and to ensure the quality of their medicinal products. Secondly as a result of the Article 5(3) referral, the call to review to MAHs has been extended to include not only chemicals but also biologicals.

The European Medicines Regulatory Network (EMRN) at a dedicated meeting held on 9 July 2020 agreed a harmonised approach for implementing the outcome of the CHMP scientific review, which is set out in this paper. This approach addresses operational and organisational aspects, scientific aspects and communication aspects.

The following key success factors have been applied for implementing the Article 5(3) CHMP Opinion:

- an as simple implementation as possible from an organisational perspective;
- an as efficient implementation as possible from an operational perspective;
- ensuring alignment within the EMRN and maintaining such alignment throughout the implementation phase;
- putting in place a dedicated transparency and communication approach.

The purpose of this document is to describe in further details this approach. This document should be read in conjunction with the CHMP Assessment Report for the Article 5(3) of Regulation EC (No) 726/2004 procedure on Nitrosamine impurities in human medicinal products and the EMA and CMDh Questions and answers for marketing authorisation holders / applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral.

2. Conclusions of the CHMP review

2.1. Main conclusion

As set out in the CHMP Opinion, the presence of N-nitrosamines in human medicinal products shall be mitigated as much as possible and shall be at or below the acceptable intake (AI), based on the ICH M7(R1) guideline and calculated considering a lifetime daily exposure. This should be achieved by an appropriate control strategy and by the design or adaptation of the manufacturing processes aiming to prevent formation of and contamination with N-nitrosamines whenever possible.

2.2. Scope

In terms of the main conclusion, the scope not only applies to human medicinal products containing chemically synthesised APIs but has been widened to cover all human medicinal products.

Furthermore, the scope of the call for review to MAHs, which was initially started in September 2019 for human medicines containing chemically synthesised APIs, has been extended to include human biological medicinal products. This is in light of the CHMP conclusion that while the risk of N-nitrosamines being present as impurities in biological medicinal products is generally low, some biological products could be at higher risk, such as those containing chemically synthesized fragments with risk factors similar to those for chemically synthesized active substances, biologicals using manufacturing processes with nitrosating reagents, or those packaged in certain primary packaging material (e.g. blister packs containing nitrocellulose). The CHMP concluded that a risk evaluation/risk assessment for biological medicinal products should be performed taking into consideration the above mentioned risk factors as well as any other identified additional risk factors specific to an individual medicine.

2.3. Setting limits for N-nitrosamines in human medicinal products

The CHMP review concludes that a limit based on the ICH M7(R1) principles for "cohort of concern" substances (AI limit corresponding to a theoretical excess cancer risk of <1 in 100,000) considering a lifetime daily exposure should be calculated for individual N-nitrosamines in human medicinal products. Limits agreed by the Safety Working Party (SWP) for some specific N-nitrosamines are set out in the CHMP Opinion for reference.

In cases where the presence of more than one N-nitrosamine is confirmed in the API and/or the FP, two approaches can be used to set limits:

- the total daily intake of all identified N-nitrosamines should not exceed the limit of the most potent N-nitrosamine identified;
- the total risk level of the sum of all detected N-nitrosamines should not exceed a 1 in a 100,000 lifetime risk.

In case no limit has yet been set for the detected N-nitrosamine (i.e. a new N-nitrosamine), the TD_{50} should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in the ICH M7(R1) guideline. In case of insufficiently robust data to derive a limit:

- a class specific threshold of toxicological concern (TTC) for N-nitrosamines of 18 ng/day can be used as the default option;
- an approach based on structure-activity-relationship (SAR) considerations to derive an acceptable intake limit can be used if appropriately justified.

For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines, as specified in the Q&A document for the ICH S9 guideline. If the active substance itself is mutagenic or clastogenic at therapeutic concentrations, N-nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH M7(R1).

Exceptionally when a single N-nitrosamine cannot be kept below the limit defined in the CHMP Article 5 (3) Opinion or the total risk level of the sum of more than one detected N-nitrosamine cannot be kept below a 1 in 100,000 lifetime risk, acceptability of higher limits may be considered by competent authorities based on a benefit-risk assessment. In such instances the "less-than lifetime" (LTL) concept in ICH M7(R1) may be considered by the competent authorities (CAs) for the range of a temporarily acceptable exposure until further measures can be implemented to reduce the contaminant to levels at or below the limits defined above.

2.4. General principles to be followed by pharmaceutical companies

In order to fulfil their obligations as set out in the call for review to MAHs, the applicants shall carry out a risk evaluation/risk assessment of manufacturing processes of APIs and FPs for the presence of N-nitrosamines as part of their marketing authorisation applications (MAAs). Likewise, MAHs shall undertake this risk evaluation/risk assessment for authorised medicinal products as part of the aforementioned call for review to MAHs for human medicines containing chemically synthesised APIs and human medicinal products containing biological active substances. Detailed information about the various steps, the timelines and instructions for reporting are set out on the EMA and HMA websites and further explained in the Q&A for the implementation of the Article 5(3) referral.

As a result of the call for review to MAHs for authorised medicines or for new MAAs, the MAH/applicant should forthwith inform CAs if N-nitrosamines are identified, irrespective of the amount detected. For authorised medicines in scope of the call for review, MAHs are required to use dedicated templates and contact points as outlined on the EMA and CMDh websites.

If the N-nitrosamine(s) identified exceed(s) the AI limit based on the ICH M7 principles, an investigation report should be submitted as part of the step 2 response (see chapter 3.1. for further information), which will subsequently be subject to a benefit/risk evaluation by the CAs in application of the process outlined in chapter 3.

Going forward, the MAHs should implement a control strategy regarding N-nitrosamines for their active substances and FPs, which should include current and prospective measures to minimise the risk of generation/contamination with any N-nitrosamine and control any future change that may impact on this risk.

3. Process for the detection of N-nitrosamines in medicines

3.1. Harmonisation of the approach and scenario setting

Following the conclusion of the referral, the timelines for the ongoing call for review to MAHs for human medicines containing chemically synthesised APIs are extended. In addition, the scope of the call has been extended to human medicines containing biological active substances with different timelines in line with the timeframes initially set for medicines containing chemically synthesised APIs and this to allow ample time for MAHs to undertake the necessary follow-up actions.

The call for review consists of the following 3 steps:

- Step 1: MAHs to perform a risk evaluation to identify if APIs and/or FPs could be at risk of presence of N-nitrosamine in accordance with the principles outlined in Q&A 7 of the Q&A for the implementation of the Article 5(3) referral:
  - to be undertaken before 31 March 2021 for human medicines containing chemically synthesised APIs;
  - to be undertaken before 1 July 2021 for human medicines containing biological active substances.
- Step 2: if a risk is identified, MAHs to proceed with confirmatory testing in order to confirm or refute the presence of N-nitrosamines, accordance with the principles outlined in Q&As 8 and 9 of the Q&A for the implementation of the Article 5(3) referral. MAHs should report the outcomes as soon as possible.
- Step 3: if the presence of N-nitrosamine(s) is confirmed, MAHs should implement effective risk mitigating measures through the submission of variations:
  - to be undertaken before 26 September 2022 for human medicines containing chemically synthesised APIs;
  - to be undertaken before 1 July 2023 for human medicines containing biological active substances.

MAHs are required to provide a response to the RAs on the outcome of step 1 and step 2 by utilising agreed published templates on the EMA/ CMDh websites.

The EMRN agreed that the RAs (EMA for centrally authorised products (CAPs), national competent authorities (NCAs) for nationally authorised products (NAPs)) should monitor pharmaceutical companies' compliance with the agreed implementation of the CHMP Opinion, which includes tracking the submission by MAHs of each step of the call for review as described above.

The EMRN agreed, on the basis of the outcome of the CHMP scientific review, a harmonised approach for addressing the detection of N-nitrosamines. As part of this approach four scenarios have been identified as an outcome to the risk evaluation/risk assessment by MAHs during the call for review to MAHs described above, depending on the N-nitrosamine and the levels identified:

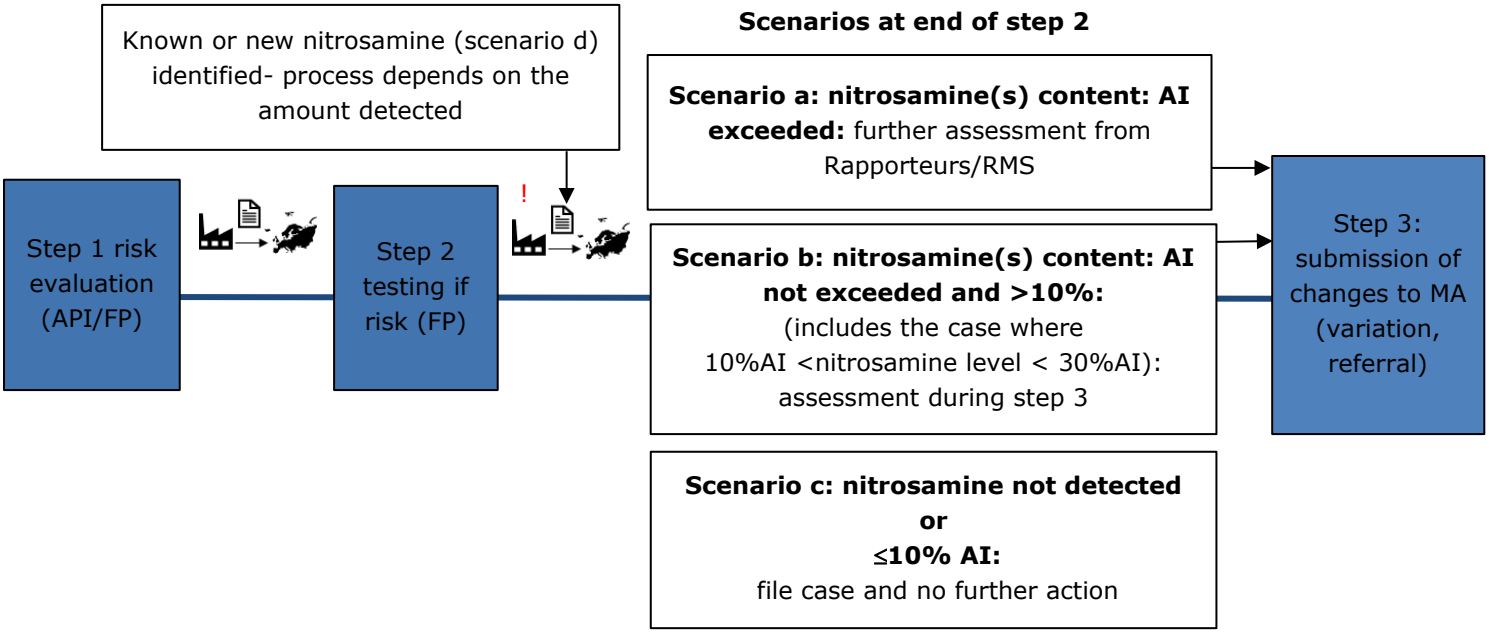
- Scenario a: a **known** N-nitrosamine has been detected in a medicinal product and the N-nitrosamine level **exceeds** the AI limit based on ICH M7 principles (1 in a 100,000 lifetime risk). The same scenario applies where there is **more than 1 known N-nitrosamine** detected, and the total sum of the N-nitrosamines **exceeds** the AI limit of the most potent N-nitrosamine, or the sum of all detected N-nitrosamines **exceeds** the 1 in a 100,000 lifetime risk.

- Scenario b: a **known** N-nitrosamine has been detected in a medicinal product and the N-nitrosamine level does **not** exceed the AI limit based on ICH M7 principles (1 in a 100,000 lifetime risk), however the total N-nitrosamine content is **more than 10% of the AI limit**. The same scenario applies where there is **more than 1 known N-nitrosamine** detected, and the total sum of the N-nitrosamines does **not** exceed the AI limit of the most potent N-nitrosamine, or the sum of all detected N-nitrosamines is **below** the 1 in a 100,000 lifetime risk. Scenario b includes the situation where the N-nitrosamine level is above 10% but below 30% (in such case if the AI is consistently below 30% then the company can apply for skip testing, see chapter 3.2.3. for further information).
- Scenario c: **no** N-nitrosamine has been detected in a medicinal product or the N-nitrosamine level of the known N-nitrosamine is **below or equal to 10% of the AI limit** based on ICH M7 principles. The same scenario applies in case **more than 1 known N-nitrosamine** has been detected and the total N-nitrosamine content is **below or equal to 10% of the AI limit** based on ICH M7 principles for the most potent N-nitrosamine or the sum of all detected N-nitrosamines.
- Scenario d: one or more **new** N-nitrosamines have been detected in a medicinal product which have not yet been assessed in the frame of the Article 5(3) CHMP Opinion.

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

In order to further explain the link between the possible outcomes from the call for review to MAHs and the aforementioned scenarios, a graphical interpretation of the call for review to MAHs is provided in Figure 1 below.

Figure 1. Overview of the call for review to MAHs



As depicted in the workflow above, the possible scenarios for dealing with the outcomes of the call for review to MAHs at step 2 are scenarios a, b and c. In addition, in cases where a new N-nitrosamine is identified, the process for dealing with scenario d is applied before a decision is made regarding which other processes (i.e. those for scenarios a, b or c) are subsequently applied to manage the case.

3.2. Detailed description of the various scenarios

3.2.1. Process for scenario a

Upon conclusion of step 2, the MAH confirms that a known N-nitrosamine is present in a medicinal product and the N-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 1 known N-nitrosamine detected, and the total sum of the N-nitrosamines exceeds the AI limit of the most potent N-nitrosamine, or the sum of all detected N-nitrosamines exceeds the 1 in a 100,000 lifetime risk.

Depending on the route followed for the authorisation of a medicinal product, different leads are responsible for performing the scientific assessment. These are referred to in this document as "Leads" (see also chapter 5.1. for more information).

If the product(s) impacted are registered as CAPs only, or if CAPs and NAPs are impacted, the Lead for the scientific assessment of the case will be the CAP Rapporteurs. The role of the Lead will be to review the information available and undertake an assessment of the case and to provide recommendations.

If the product(s) impacted are only NAPs the authority to lead the assessment will be an NCA. For products authorised via the Mutual Recognition and Decentralised Procedures (MRPs/DCPs) the Reference Member State (RMS) will take the lead role to undertake the assessment and to provide recommendations.

EMA, the CHMP, the CMDh and the RAN can provide coordination in cases where multiple CAPs, NAPs/MRPs/DCPs are affected in line with the principles reported in chapter 5.1.

The RAN is informed in parallel in order to initiate a criticality assessment for each concerned Member State (MS). It is the responsibility of each member of the RAN to liaise with the national SPOC (single point of contact) for the identification of possible shortages, if needed.

In their assessment the Rapporteur/NCA/RMS will review the company's investigation report and CAPAs (Corrective and Preventive Actions) and will provide recommendations on required market actions and the acceptability of the CAPAs. The RAN criticality assessment will also be taken into account by the Lead in order to understand if shortages are foreseen by an eventual market action (recalls or suspension of supply). If a product recall is recommended each member of the RAN will follow up in accordance with their national procedures and depending on the criticality of the product for their markets. The LTL concept may be considered by the lead authority and NCAs on a temporary basis for market action purposes for critical products as outlined in the Article 5(3) CHMP Opinion.

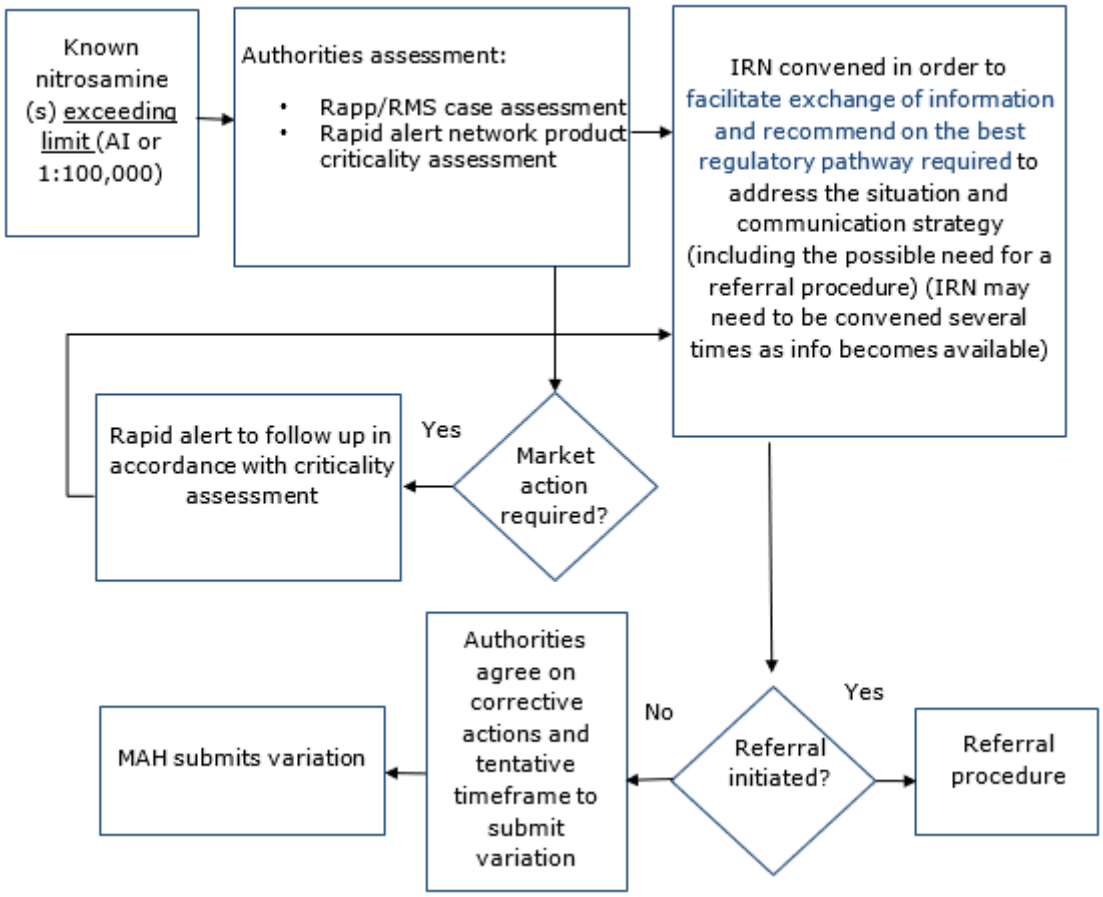
The IRN is convened in order to facilitate the exchange of information and to evaluate whether additional measures are needed or whether a different regulatory pathway is warranted.

If the case is such that standard measures are considered sufficient to control/mitigate any risk to public health, the Rapporteur/NCA/RMS will liaise with the concerned MAH to discuss corrective actions and a timeline for submitting the required variation to the MA.

If the case is such that a different regulatory pathway is needed (e.g. a referral procedure) then the dedicated process is followed.

The workflow for scenario a is provided in Figure 2 below.

Figure 2. Process for scenario a



3.2.1.1. Use of interim limits

Exceptionally, when a single N-nitrosamine cannot be kept below the established limit or the total risk level of the sum of more than one detected N-nitrosamine cannot be kept below a 1 in a 100,000 life-time risk, the MAH should submit to the relevant CAs forthwith an investigation report including the potential/identified root cause(s), preventive/corrective actions and a thorough discussion on the impact on the benefit/risk balance including all relevant considerations (e.g. medical need, daily dose, duration of administration and treatment alternatives, potential patient risk in case of drug shortage). Acceptability of higher limits is then decided by the relevant CAs on a case-by case basis, after having performed a benefit/risk evaluation. In such instances, the LTL concept in ICH M7(R1) may be considered by the CAs.

3.2.1.2. Mechanism to define the interim limits

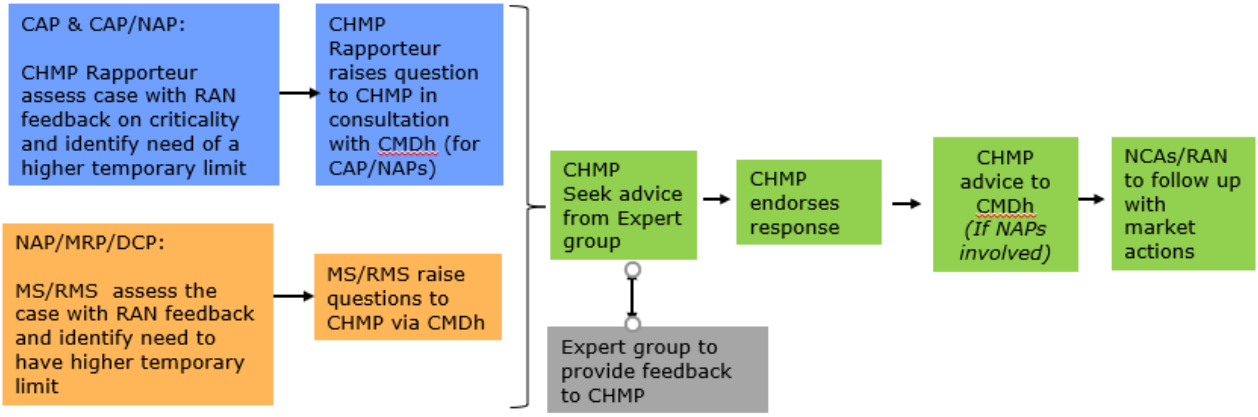
In case of scenario a (AI exceeded), the following options should be considered:

- If therapeutic alternatives are available and there is no risk of shortages, CAs can take market actions as needed by applying the AI (no need of setting an interim limit).
- If therapeutic alternatives are not available and there is a risk of shortages across all or several MSs an interim limit is required.

When the establishment of an interim limit is envisaged the following process is followed:

1. Following assessment of the case by the product Rapporteur (for CAPs and CAPs/NAPs) and by the RMS (for NAPs/MRPs/DCPs) including RAN criticality assessment, a question is raised (by the Rapporteur only for CAPs or in consultation with the CMDh for CAPs/NAPs) to the CHMP.
2. The question will focus on benefit-risk assessment considerations on the consequences of stopping treatment or switching to alternative treatments versus the risk to patients from using a higher limit for a limited period of time and the potential need for additional risk minimisation measures. The question will also include advice on the most appropriate methodology including the coefficient factor to be applied in setting interim limits, as well as an indicative threshold and maximum duration period allowed for its application.
3. Before concluding the CHMP consults a multidisciplinary scientific group (the Nitrosamine Multidisciplinary Expert Group), see below.
4. The CHMP will endorse the response before providing feedback to the Rapporteurs/CMDh (feedback will be sent to the CMDh when NAPs are involved).

Figure 3. Process to be followed for identifying interim limits



3.2.1.3. Composition of Nitrosamine Multidisciplinary Expert group

This Expert Group is a multidisciplinary scientific group convened by the CHMP.

The general composition of the group is as follows:

- CHMP representatives (link to Art 5(3) Rapporteurs to ensure consistency).
- CAP Rapporteur or the RMS Rapporteur in charge of the procedure, as appropriate.
- SWP representatives.
- CMDh representatives (CMDh nitrosamine group (part of the Nitrosamine Oversight Implementation Group (NIOG), see chapter 5.2 to ensure a link with the CMDh & CMDh lead in the case of NAPs)

Additional expertise may be needed on a case by case basis.

Further details on N-nitrosamine limits including the requirements for the analytical methods are provided in the CHMP Opinion.

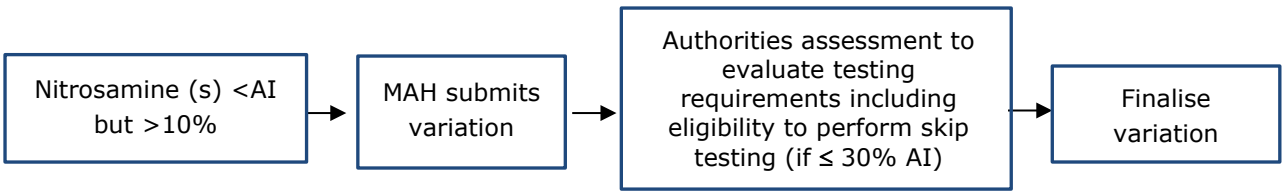
3.2.2. Process for scenario b

Upon conclusion of step 2, the MAH confirms that one known N-nitrosamine is present and the N-nitrosamine level does not exceed the AI limit based on ICH M7 principles (1 in a 100,000 lifetime risk), however the total N-nitrosamine content is more than 10% of the AI limit. The same scenario applies where there is more than 1 known N-nitrosamine detected, and the total sum of the N-nitrosamines does not exceed the AI limit of the most potent N-nitrosamine but is more than 10% of the AI limit, or the sum of all detected N-nitrosamines is below 1 in a 100,000 lifetime risk.

A variation is required to be submitted in order to introduce a limit in the specification of the FP. During the assessment of the variation the RAs will evaluate the eligibility to perform skip testing (e.g. testing on pre-selected batches and/ or at predetermined intervals). In this case the MAH should be able to prove that the content of the N-nitrosamine(s) is consistently below 30% of the AI limit.

The workflow for scenario b is provided in Figure 4 below.

Figure 4. Process for scenario b



3.2.3. Process for scenario c

Upon conclusion of step 2 the MAH confirms that no N-nitrosamines have been identified or that the levels of the N-nitrosamine (s) detected are consistently below 10% of the limit based on ICH M7. The notification is recorded by the concerned Competent Authority and no further action is needed.

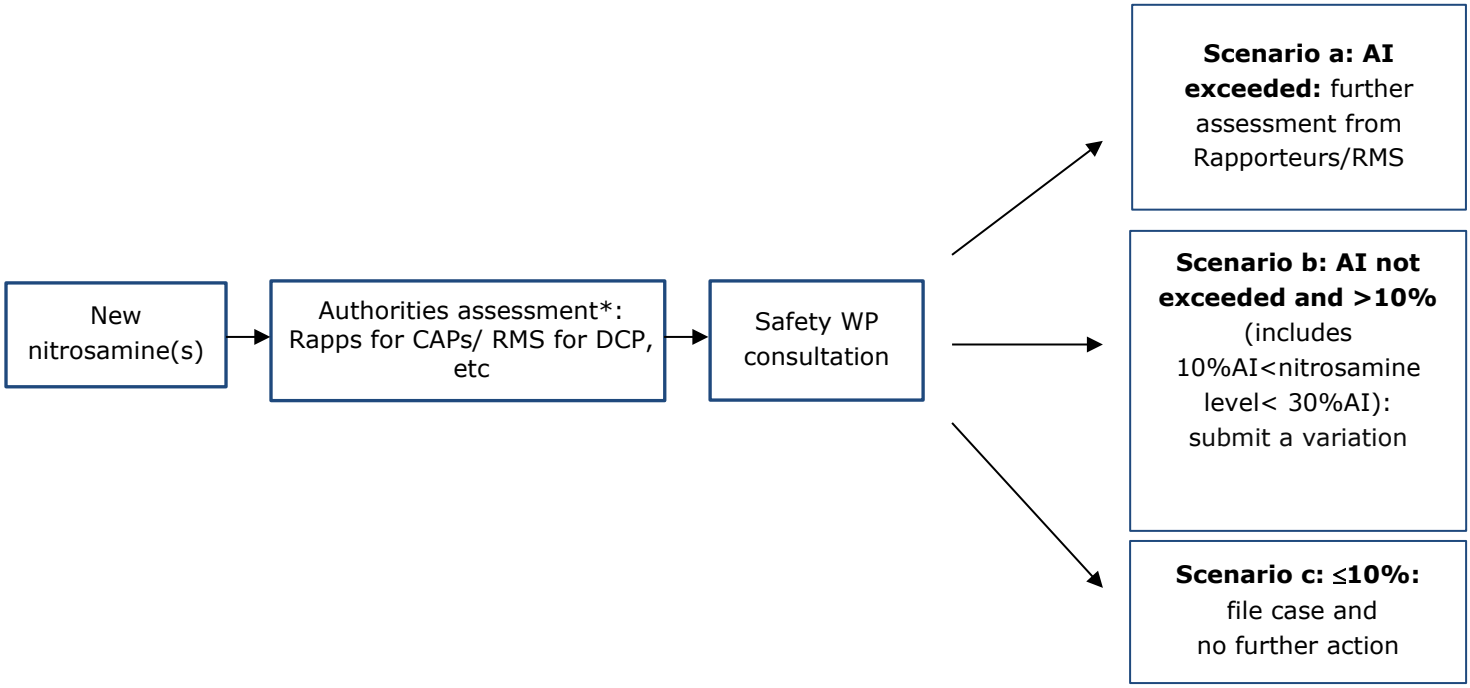
The MAHs together with API and FP manufacturers are expected to review the outcome of the risk evaluation and testing as and when new information becomes available (e.g. on potential root causes for N-nitrosamine formation or contamination).

3.2.4. Process for scenario d

Upon conclusion of step 2 the MAH confirms that one or more new N-nitrosamine(s) have been detected. In order to decide which scenario (a, b, c) is applicable, an additional step is required to determine the limit of the new N-nitrosamine. The MAH should use the instructions in the Q&A published by EMA and the CMDh to calculate a substance specific limit for lifetime exposure as recommended in the ICH M7(R1) guideline, the class specific TTC for N-nitrosamines of 18 ng/day, or a limit based on a SAR approach. A justification of the approach taken by the MAH should be submitted, which will be assessed by the Lead (Rapporteurs for CAPS, NCA/RMS for NAPs/MRP/DCP) in consultation with the SWP.

The workflow for scenario d is provided in Figure 5 below.

Figure 5. Process for scenario d



4. Elements to consider when deciding on the regulatory pathway

As described in scenarios a and b above, as a conclusion to the call for review to MAHs and depending on the specificities of the impacted medicine(s) and the N-nitrosamine impurities identified, there are 2 possible regulatory pathways for RAs: management through approval (a) of variation(s) to the MA or initiation of a referral procedure where required.

A referral needs to be considered, for instance if the N-nitrosamine presence is intrinsic to the API (e.g. a structural feature or a metabolic formation) and/or if new elements to root causes are reported that require further extensive assessment. In all other situations the submission of variations is proposed.

Elements to consider when deciding on the best regulatory pathway include:

- product criticality (medical need, availability of alternatives);
- extent of the contamination (number of batches/products impacted/number of MSs affected);
- level of contamination (% AI exceeded);
- patients' exposure (level of contamination, daily exposure, duration of exposure);
- impacted period of time (issue present since MA?);
- potential/identified root causes linked to the manufacturing process/site/product (new root cause/intrinsic to the API).

5. Operational and organisational aspects at Regulatory Authorities' level

5.1. Roles and responsibilities

The roles and responsibilities for the RAs in the context of the implementation of the CHMP Article 5(3) Opinion are as follows:

- EMA/CHMP is responsible for the call for review to MAHs, the implementation of the CHMP Opinion and the handling of variations to MAs for CAPs;
- NCAs are responsible for the call for review to MAHs, the implementation of the CHMP Opinion and the handling of variations for NAPs;
- in cases where CAPs and NAPs (the latter including MRPs and DCPs) are affected, EMA, the CHMP, the CMDh and the RAN are involved and coordination amongst all parties is needed;
- oversight is provided by a dedicated forum, i.e. the NIOG (for further details see chapter 5.2.);
- the IRN facilitates exchange of information and reaches agreement on the best regulatory pathway in situations with a major public health impact;
- The European Directorate for the Quality of Medicines and Healthcare (EDQM) is responsible for assessing the impact on monographs (either general or product specific) on the way of setting limits for N-nitrosamines, and the Certificate of Suitability (CEP) process.

Taking the aforementioned principles into account, the Leads for the handling of N-nitrosamine impurities will depend on the authorisation route of the medicine concerned, as follows:

- for CAPs the CHMP Rapporteur will be in the lead;
- for MRPs and DCPs the RMS will be in the lead;
- for purely NAPs the concerned NCA to lead;
- in case both CAPs and NAPs are involved the CHMP is in the lead of the assessment and amongst the appointed Rapporteurs one lead Rapporteur needs to be selected;
- in cases where multiple NAPs are involved, the CMDh will decide on a case-by-case basis.

5.2. Oversight of the implementation through the Nitrosamine Implementation Oversight Group

A dedicated group has been put in place, the NIOG, with as a primary responsibility to oversee the implementation of the Article 5(3) CHMP Opinion.

5.2.1. Composition of the NIOG

The NIOG is composed of CHMP, CMDh, EDQM and EMA representatives, as follows:

- CHMP: the 2 CHMP Article 5(3) Rapporteurs, 1 Quality Working Party (QWP) member, 1 SWP member, and, if needed, a Biologicals Working Party (BWP) member;
- CMDh: 4 CMDh members;
- EMA: 3 EMA staff members, with expertise in the fields of quality, safety and market surveillance;
- EDQM 1 representative.

The group members are responsible for liaising with their committees, where relevant, and providing regular updates to them.

The NIOG is co-chaired by the CMDh and EMA; the secretariat is provided by EMA.

5.2.2. NIOG mandate

The NIOG mandate includes the following activities:

- providing non-product specific oversight of the implementation of the CHMP Article 5(3) Opinion;
- reporting progress to the EMRN in terms of MAHs' compliance with the call for review to MAHs' timelines, progress with the updating of guidance, etc;
- ensuring oversight in assessment consistency by gathering new scientific questions related to methodological aspects not captured in existing guidance, identified through escalation of queries from the CMDh, the CHMP, EMA, international partners;
- evaluating the need for updating current guidance/Q&As, or publishing new scientific guidance;
- providing support to the drafting of guidance and to the delivery of training to assessors;
- addressing any specific matter of the call for review to MAHs requiring clarification;
- providing a link with stakeholders, including initiating and maintaining a dialogue and interaction with pharmaceutical industry.