Nitrosammine: le attività regolatorie a livello Europeo

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X☐	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X☐	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	x☐	☐	☐	☐ facoltativo
2. Consulenza per una società	x☐	☐	☐	☐ facoltativo
3. Consulente strategico per una società	x☐	☐	☐	☐ facoltativo
4. Interessi finanziari	x☐	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	x☐	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	x☐	☐	☐	☐ facoltativo
7. Sperimentatore	x☐	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	x☐	☐	☐	☐ facoltativo
9. Interessi Familiari	☐	X☐	☐	☐ facoltativo

* Nome secondo il Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco approvato dal CdA AIFA con Delibera n. 37 del 13 ottobre 2020.

N.B.

< Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva>.

Riferimenti

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines/nitrosamine-impurities

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

Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (rev 21)

Appendix 1: Acceptable intakes established for N-nitrosamines on acceptable intakes established for N-nitrosamines,

Appendix 2 : Carcinogenic Potency Categorisation Approach for N-nitrosamines on the carcinogenic potency categorisation approach (CPCA),

Appendix 3 : Enhanced Ames Test Conditions for N-nitrosamines on the enhanced AMES test (EAT) protocol.

CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines

CMDh Templates (incl. the “Template for nitrosamine risk evaluation in marketing authorisation applications”)

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

Call for review for chemically synthesised and biological medicinal products

Marketing authorisation holders should review their manufacturing processes for all products containing chemically synthesised or biological active substances to identify and, if necessary, mitigate the risk of presence of nitrosamine impurities.

The call for review was extended to biological active substances in July 2020, as an outcome of CHMP's Article 5(3) opinion.

At all steps, timelines should be shortened and marketing authorisation holders should immediately inform authorities if findings indicate an immediate risk to public health.

Step 1: Risk evaluation

Conduct a risk evaluation to identify active substances and finished products at risk of N-nitrosamine formation or (cross-)contamination and report the outcome by:

31 March 2021 for chemical medicines;

1 July 2021 for biological medicines.

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

Call for review for chemically synthesised and biological medicinal products

If a risk is identified for an active substance, marketing authorisation holders should submit the step 1 response template and proceed with step 2 confirmatory testing of the finished product.

If no risk is identified for an active substance, marketing authorisation holders should conduct a risk evaluation of the finished product and submit the outcome of step 1 only when they reach a final conclusion on the active substance and finished product.

The EMA/CMDh templates should be used.

In case of NAP new applications the CMDh 'Template for nitrosamine risk evaluation in marketing authorisation applications' should be used.

Step 2: Confirmatory testing

Perform further confirmatory testing on the products identified to be at risk of N-nitrosamine formation or (cross-)contamination and report confirmed presence of nitrosamines **as soon as possible**.

For more information on the development of analytical methods, see below the EMA/CMDh Q&As.

Marketing authorisation holders should use the EMA/CMDh templates in their responses.

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

Call for review for chemically synthesised and biological medicinal products

Step 3: Update marketing authorisations

Apply for any necessary changes to the manufacturing process resulting from this review, by requesting a variation to the marketing authorisation via standard regulatory procedures.

Marketing authorisation holders should complete the confirmatory testing and submit their variation applications by:

1 October 2023 for chemical medicines

1 July 2023 for biological medicines.

The CHMP and CMDh extended the deadline for submitting variation applications for chemical medicines from 26 September 2022 to 1 October 2023 in July 2022.

The extension aims to enable companies to perform a thorough investigation and to establish any required risk mitigating actions in light of new scientific developments since 2020, **in particular those concerning active substance-derived nitrosamines.**

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

Call for review for chemically synthesised and biological medicinal products

Step 3: Update marketing authorisations

The deadlines of the call for review (steps 1, 2 and 3) for medicines containing chemically synthesised and biological active substances have passed. Any marketing authorisation holder (MAH) that has not notified relevant competent authority about identified nitrosamine impurities should report them as a matter of priority in line with the CHMP's Article 5(3) opinion as well as any updates to previous notifications, using the response templates and available reporting mechanisms previously established.

MAHs are reminded of their responsibilities to ensure the quality, safety and efficacy of their medicines and to adhere to the nitrosamines guidance outlined by the EU Network. MAHs and Manufacturers (both API and FP manufacturers) should work together and take precautionary measures to mitigate the risk of presence of nitrosamines during the manufacturing and storage of all authorised medicinal products.

Authorities in the EU will continue to take all necessary measures to protect patients and ensure that medicines in the EU meet the required quality standards.

https://www.hma.eu/human-medicines/cmdh/nitrosamine-impurities.html

Active substance-derived nitrosamines

Authorities in the EU are aware that some active substances are at a higher risk of formation of active substance derived nitrosamine impurities.

Such active substances contain vulnerable amine functional groups that can undergo a reaction called nitrosation (often a secondary amine). Nitrosamines are thought to form when the nitrosatable amine group in the active substances and trace nitrite impurities in the inactive ingredients (excipients) react.

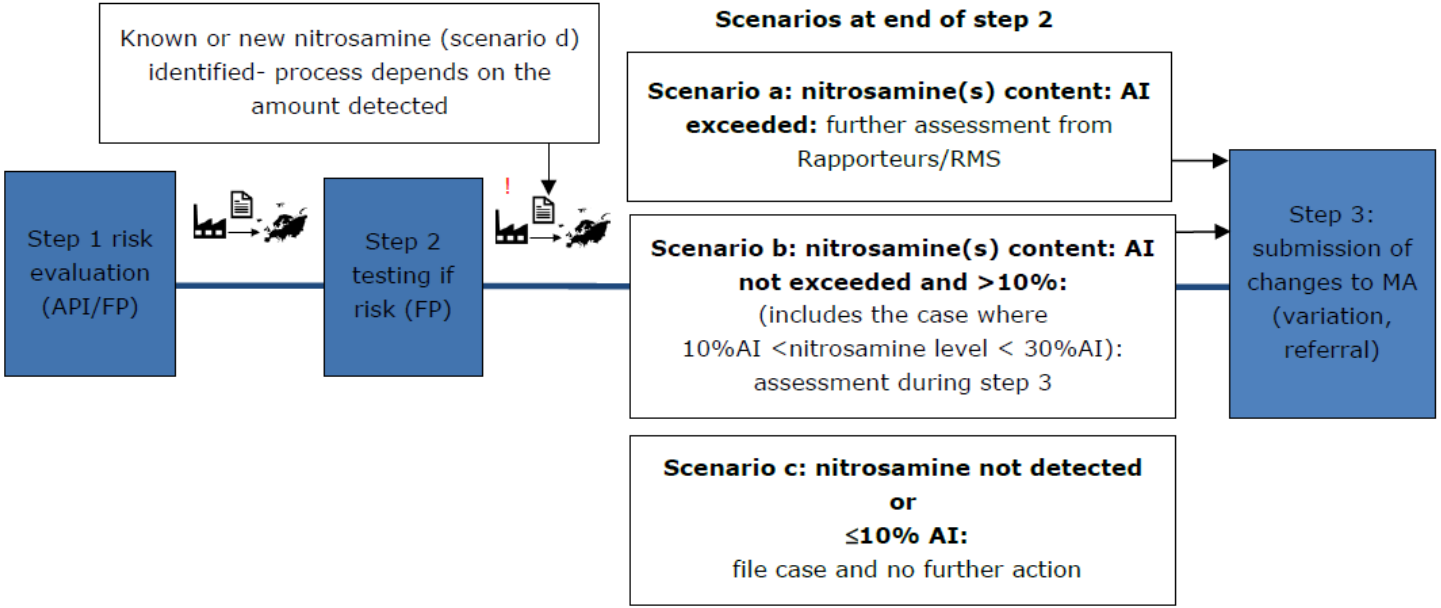
Active substances that contain secondary amines appear particularly vulnerable to this reaction, although some cases involving active substances with tertiary amines have also been observed.

All marketing authorisation holders for EU medicines should consider this risk factor in their risk evaluations as a matter of priority, if they have not already done so.

If a risk is confirmed, they should prioritise confirmatory testing. If testing confirms the presence of nitrosamines, companies should immediately report their findings to the relevant competent authority.

European Medicines Regulatory Network approach

Figure 1. Overview of the call for review to MAHs



European Medicines Regulatory Network approach
Scenario A

Nitrosamine Multidisciplinary Expert group

This Expert Group is a multidisciplinary scientific group convened by the CHMP with CHMP, SWP and CMDh representatives.

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

EMA/CMDh Q&A, Q20. What are the regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI (1)?

The regulatory process dealing with the outcomes of the call for review is outlined in European Medicines Regulatory Network approach.

In case of identification of one or more N-nitrosamine exceeding the AI in the finished product, or in case that the sum of all detected N-nitrosamines exceeds the 1 in a 100,000 lifetime risk (scenario A), the following steps are taken in order to protect public health and ensure availability of critical medicines:

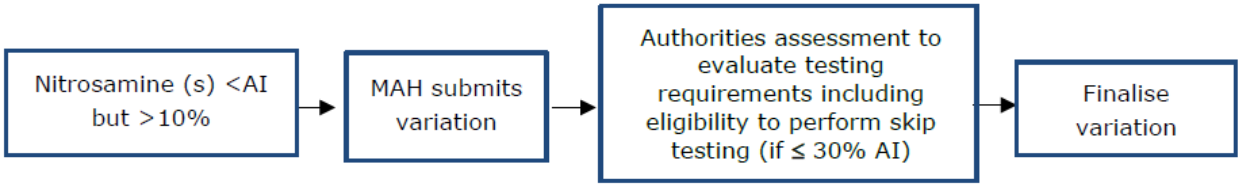
- A lead authority is identified as responsible for reviewing the information available and for providing the (preliminary) assessment of the case.
- **The RAN and the availability SPOCs are informed in order to determine the criticality of the product**.

EMA/CMDh Q&A, Q20. What are the regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI (2)?

- **The feedback from RAN and availability SPOCs is taken into account by the lead authority when providing the preliminary recommendations on any interim or eventual required market actions and on the acceptability of corrective and preventive actions proposed by the MAH**.
- The IRN is consulted 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 market actions are recommended, each National Competent Authority (NCA) will follow up in accordance with their national procedures and depending on the criticality of the product for their markets.**
- The use of an interim limit based on the LTL approach during CAPA implementation, as described in Q&A 22, may be considered, as applicable, by the lead authority and NCAs on a temporary basis for market action purposes.

European Medicines Regulatory Network approach
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……. 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.



European Medicines Regulatory Network approach

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).

Anche nel caso di presentazione di variazioni con possibile impatto sul rischio di contaminazione da nitrosammine, ad esempio per modifiche processo di produzione, introduzione di un nuovo produttore di API, l'aggiornamento del RE/RA sulle nitrosammine deve essere previsto.

European Medicines Regulatory Network approach

Scenario D ed Appendix 1

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.

Verificare sempre l'Appendix 1 delle Q&A EMA/CMDh per verificare l'Acceptable Intake (AI) di nuove nitrosammine. L'Appendix 1 è costantemente aggiornato.

https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.ema.europa.eu%2Fen%2Fdocuments%2Fother%2Fappendix-1-acceptable-intakes-established-n-nitrosamines_en.xlsx&wdOrigin=BROWSELINK

A settembre 2021 erano note 9 nitrosammine.

A settembre 2024, l'Appendix 1 riporta 172 nitrosammine con i relativi AIs, la struttura, la fonte e la categoria.

Nelle note vengono aggiunte informazioni (es. se l'impurezza è risultata mutagena in test in vivo o se è risultata negativa nei test in vivo e può quindi essere controllata secondo la LG ICHQ3A/B e non sono necessari test confirmatori).

(EMA/CMDh Q&A (Q10)

Two scenarios are foreseen for detection of new nitrosamines:

A. If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data, the TD50 should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline.

B. If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline,

1. The Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines (Appendix 2) should be used to establish the AI, unless other robust data are available that would override this AI.

2. A negative result in an GLP-compliant enhanced Ames test (EAT, Appendix 3) allows control of the N-nitrosamine at 1.5 µg/day. For substances testing positive, the AI should be established using options 1 or 3.

3. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD50 from the surrogate substance can serve as a point of departure for derivation of AI by SAR and read across.

4. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of the N-nitrosamine as a non-mutagenic impurity (NMI), i.e. according to ICH Q3A(R2) and ICH Q3B(R2) limits, irrespective of the limit calculated through option 1, 2 or 3. For substances testing positive, the AI should be established using options 1 or 3.

(EMA/CMDh Q&A (Q10)

The risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless data justify route-specific differences.

Appendix 1 lists the nitrosamines for which acceptable intakes have been established by the Non-clinical Working Party. If the nitrosamine is not included in Appendix 1, MAH/MA applicants can also refer to a CPCA category from another source e.g. CPCA categories published by other regulatory authorities, but this will need confirmation to allow control of the substance at the level corresponding to that category.

……

- **Calculation of the limit when a single known nitrosamine is identified:** The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective AI in Appendix 1 (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC……;
- **Calculation of limit when more than one nitrosamine is identified in the same product**;
- **Control options for Genotoxic APIs**: …..The ICH M7 GL does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9. …..

Appendix 2: Carcinogenic Potency Categorisation Approach for N-nitrosamines

This document describes an approach for assigning an N-nitrosamine impurity (including nitrosamine drug substance-related impurities [NDSRIs]) to a predicted carcinogenic potency category, with a corresponding acceptable intake (AI) limit, based on an assessment of activating or deactivating structural features present in the molecule. In the context of this document, activating or deactivating features are defined as molecular substructures that are associated with an increase or decrease, respectively, in carcinogenic potency…….. The Carcinogenic Potency Categorisation Approach applies to N-nitrosamines bearing a carbon atom on both sides of the N-nitroso group, and where the carbon is not directly double bonded to a heteroatom (i.e., N-nitrosamides, N-nitrosoureas, N-nitrosoguanidines and other related structures are excluded). Additionally, the potency categorisation approach does not apply to N-nitrosamines where the N-nitroso group is attached to a nitrogen within a hetero aromatic ring (e.g., nitrosated indole).

https://www.ema.europa.eu/system/files/documents/other/appendix_2_carcinogenic_potency_categorisation_approach_for_n-nitrosamines_en.pdf

Appendix 3: Enhanced Ames Test Conditions for N-nitrosamines

…….For N-nitrosamines, enhanced testing conditions for the Ames assay are recommended due to the reported reduced sensitivity of the assay under standard conditions for some N-nitrosamines, such as N-nitroso-dimethylamine (NDMA). Moreover, very little is known about the sensitivity of the Ames assay to N-nitrosamine drug substance related impurities (NDSRIs), which are a recently recognized class of N-nitrosamine impurities structurally related to the drug substance. NDSRIs generally have a wider variety of functional groups present than typically found in low molecular weight N-nitrosamines (such as NDMA) historically studied.
If a standard Ames assay is conducted and produces a positive result, there is no need to conduct an additional assay using enhanced testing conditions.

All Ames assays initiated after August 2023 must comply with the requirements of the EAT protocol (Appendix 3).

https://www.ema.europa.eu/en/documents/other/appendix-3-enhanced-ames-test-conditions-n-nitrosamines_en.pdf

EMA/CMDh Q&A, Q22. What is the approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation (1)?

In accordance with the regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI, **the less-than lifetime (LTL) concept or the use of interim limits may be considered by the lead authority and NCAs on a temporary basis in order to inform market actions and at the same time ensure availability of medicines.** MAHs are expected to establish and implement the CAPAs in authorised medicines without any delays in order to ensure patients safety and product quality. Nevertheless, it is recognised that implementation of CAPAs may require some time before the MAH is able to mitigate the presence of the identified N-nitrosamine below the established AI. Therefore, **in order to avoid unnecessary risk of supply disruptions,** a harmonised approach promoting the establishment of interim limits in a streamlined way is agreed. The approach is applicable to all authorised products that have:

- CAPA implementation timeline of up to **3 years from the establishment and publication of the AI** (nevertheless MAHs are expected to expedite CAPAs implementation).

Treatment duration	Up to 12 months	>12 months
Interim limit	13.3 x AI*	6.7xAI*

EMA/CMDh Q&A, Q22. What is the approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation (2)?

*In any case the limit should not exceed 1.5 µg/day unless the established AI (Table 1, Q&A10) is > 1.5 µg/day or the nitrosamine concerns a category 5 according to CPCA or the nitrosamine is shown to be negative in an enhanced Ames test (EAT).

The approach **is not applicable** to the below instances where other approaches may be considered on a case-by-case basis in consultation with the appropriate regulatory authority:

- CAPA implementation exceeding 3 years from the establishment and publication of the AI;
- New/ongoing regulatory applications……..

The approach is intended to be evaluated by the lead authority during the assessment of the case and is expected to be communicated by the lead authority to the concerned MAH as part of assessment conclusions. ……. MAHs are expected to ensure that the implementation of adequate controls for the detected nitrosamines is done as a matter of priority. During the use of the interim limit, monitoring measures may be evaluated by the lead authority as required. **However, it is not the expectation that MAHs include these interim limits in specifications via variation.**

CMDh Guidance: Q1.6. What is the approach for new and ongoing marketing authorisation applications (MAA) (1)?

The potential presence of nitrosamines will be evaluated as part of the marketing authorisation application as follows:

- **At the submission stage**:

– Applicants are required to submit as part of their MAA a risk evaluation –including the relevant documentation - as per principles outlined in step 1. For documenting that the risk evaluation has been performed based on the current scientific knowledge and the latest version of theQ/A the Template for nitrosamine RE has to be completed and added to the documentation in Module 3.2.P.5.6. It should be noted that this template supplements the risk evaluation and does not replace a thorough assessment. It is expected that by confirming the evaluation with "yes" in this template it is assured that all risk factors are sufficiently addressed in the risk evaluation itself.

- If at this stage the risk of presence of nitrosamines in the medicinal product is already identified, the applicants are required to provide the risk assessment outlining the impact on the benefit-risk balance of the product and a risk mitigating strategy. Applicants should also submit confirmatory testing plans or confirmatory testing data.

– In case applicants have not submitted a sufficient risk evaluation, risk assessment if applicable, including confirmatory testing results or testing plans with their MAA, these should be submitted during the marketing authorisation review procedure.

CMDh Guidance: Q1.6. What is the approach for new and ongoing marketing authorisation applications (MAA) (2)?

During the MA evaluation procedure:

– If the risk evaluation was not submitted as part of the MAA, it will be requested during the MA review process as a major objection (for all products other than the exceptions listed in ICH M7). Where a risk of the presence of nitrosamine has been identified in the risk evaluation, a risk assessment will have to be provided, adequately documented and supported by confirmatory testing. This information should be submitted as part of the Day 106 responses to the list of questions.

– The procedure will be restarted after receipt of the final response independent from the quality of the response data. Any outstanding issues related to nitrosamines have to be addressed before Day 210, incl. confirmatory testing results where needed, without the possibility for post-approval commitments.

- If concerns on quality of the products are still not sufficiently addressed at Day 210, considerations on the impact of the risk evaluation/ assessment on the presence of nitrosamines in the product will be made and final decision on granting the MA will be made by the RMS in liaison with CMS.

CMDh Guidance: Q 1.7. How to deal with pending or newly submitted MRPs or RUPs or line extensions?

No risk evaluation is generally necessary when submitting an application for RUP, MRP or a line extension as the MAH had to submit it during the general call for review.

However, in some cases depending on the product a risk evaluation can be requested by the RMS or CMS during the procedure, i.e. in cases where changes are introduced possibly impacting the currently identified root causes for presence of nitrosamines as defined in EMA/CHMP/428592/2019.

However, in case a risk is already known for the basic product from the general call for review this should be adequately mitigated before the start of an MRP or RUP or line extension. The same applies in case an AI is published in EMA/CMDh Q/A, Appendix 1. In this case results of confirmatory testing and a risk assessment have to be provided in accordance with the EMA/CMDh Q/As. Otherwise, in both cases it might lead to a refusal if the requested data cannot be provided during the procedure.

Operational and organisational aspects at Regulatory Authorities' level

Roles and responsibilities (1):

- 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;
- the IRN facilitates exchange of information and reaches agreement on the best regulatory pathway in situations with a major public health impact;
- The 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 CEP process.

Operational and organisational aspects at Regulatory Authorities' level

Roles and responsibilities (2):

- 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.

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.

The NIOG is composed of CHMP, CMDh, EDQM and EMA representatives.

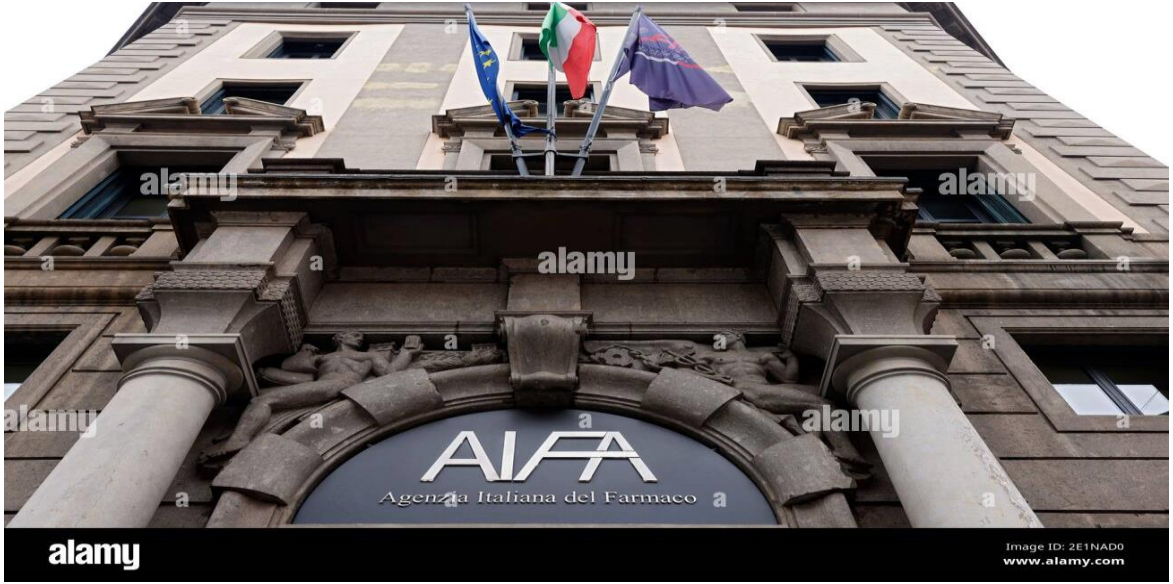
The NIOG mandate includes the following activities:

- 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.

Conclusioni

- C'è continuo confronto, coordinamento ed accordo a livello Europeo sulle questioni relative alle nitrosammine (Acceptable Intakes, criteri di valutazione, analisi di nuove informazioni, comunicazione agli operatori sanitari ed ai pazienti etc).

- L'Appendix 1 relativa alle nuove nitrosammine è aggiornato costantemente. Si raccomanda di consultarlo periodicamente e di eseguire un nuovo Risk Evaluation/Assessment qualora sia resa nota una nitrosammina API specifica e verificare ove necessario la presenza/assenza della nitrosammina nei propri lotti di medicinali.
- La deadline dello step 3 della Call for Review è già scaduta. Si raccomanda di accelerare l'attuazione delle CAPAs.
- Nel caso di domande di AIC in corso, si raccomanda di fornire tutti i dati richiesti sulle nitrosammine in corso di procedura, soprattutto usufruendo del clock stop, per evitare l'esito negativo della procedura stessa.
- Anche nel caso di RUP può essere richiesto il RA con i relativi risultati sui lotti.



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