medicines for europe
better access. better health.

Nitrosamines survey results

Implementation of nitrosamines guidance throughout EU MSs

Nitrosamines

- Medicines for Europe members are experiencing high variability across EU MSs when it comes to the implementation of the nitrosamines guidance.
- A survey was circulated internally to clarify this lack of harmonisation – detailed results will be presented during the next NIOG meeting
- Out of 18 companies that replied to the survey, 9 companies (50%) reported issues in terms of lack of harmonisation related to market actions, LTL approach and t-AI – higher impact for multi-market companies.
- **Six** companies reported that recalls of medicines/ halt of distribution to the market are **already taking place or expected to take place soon**. Impact on the following therapeutic areas: CNS, antihypertensive, antidiabetics, antithrombotic agents and overall high risk for products taken longer than 10 years.

Nitrosamines

- The stop of medicines distribution will lead to drug shortages that is still not visible. Drug shortage will be visible after the consumption of the product from the market.
- Proposed solutions:
  - Approach where lead country is assigned to one specific product could be used as a starting point to increase level of harmonisation across EU MSs.
    - Lead country could take responsibility for harmonisation of actions to be taken for specific products across EU MSs.
  - Alternatively, the EMA could implement a centralised process where MSs would have a platform to agree at EU level on implementation measures required for the various products.

Misalignment between NCAs and EMA

- CPCA calculations are being treated as an absolute truth with respect to Acceptable Intake (AI) by some national health authorities. In some cases, variations are being demanded despite the fact that other approaches such as read across, negative result of EAT or in vivo mutagenicity study are considered and may overweight the CPCA calculated AI. Alternatively, theses CPCA AI levels could be considered as temporary until the weight of evidence has been considered.
- Impact on patient access to the drugs
- Specificity of indications/product
- Risk benefit for patient

Control of impurities in the API

CEP control limits

- Formation of NDSRIs occurs mostly in Finish Product

  → Setting the API specification at the AI does not leave any room for formation in the FP and can make an API unsuitable without the application and registration of a tighter limit

  → MAH does not have the visibility to the DMF close part and risk assessment performed by the CEP holder

- If the AI is revised in the guidance based on new weight of evidence this will trigger CEP revisions

  →unnecessary CEP revisions

  →risk to supply – API in stock might become obsolete

  →delay due to highly sensitive methods transfer to introduce the limit

  →Each CEP approval can result in the need for multiple FP post-approval variations

- Precursors of nitrosamine present in the API controlled as regular impurities

Proposal

- When the risk of contamination is confirmed, a limit should be set based on the capabilities of the API supplier process but not at the AI. To introduce testing "For information only" until an AI is established based on data for the API supplier

Remediation challenges

Large portfolio companies

- Process that occurs in parallel of reviewing previous risk assessments in view of new root causes identified and consequently testing new product with a newly risk identified
- Number of investigation to perform
- Availability of remediated excipients
- Lengthy discussion with suppliers when relevant
- Time to implement remediation with actual tools available
- No visibility of the stability at the time we introduce the specification
- Analytical capacity and time to implement testing
- Need to prioritize the remediation activities
- Updates of AIs based on further weight of evidence provided by the industry→ planning/re-prioritizing activities

Suggest to allow interim limit for up to 3 years to implement the CAPA starting from the day the risk was confirmed

AESGP

VOICE OF EUROPEAN SELF-CARE INDUSTRY

AESGP Member scientific/procedural questions on the practical implementation of EMA/409815/2020 Rev. 16-19

Association of the European Self-Care Industry (AESGP)

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AESGP

AESGP – Medicines for Europe joint letter

- Letter co-signed by AESGP and MfE submitted on 27 October following the publication of the updated Q&A document
- Aggregated questions from members organised in two categories: Scientific and Procedural
- As requested, some questions were prioritized to be brought in the attention of the NIOG for this meeting, while other remain in writing to be addressed at a later date.

QUESTIONS WITH A SCIENTIFIC BASIS

1. LESS THAN LIFETIME (Q22)

The interpretation of the footnote to the Table in Q22 restricts the limit being applied to a product to 1500 ng/day, except where established AI's are already > 1500 ng/day or the nitrosamine is a CPCA category 5 or negative in the EAT. This effectively limits CPCA Category 3 and 4 to a similar limit as applied to Category 2 for short term use during CAPA.

- **Have we interpreted the guidance as it is intended to be applied?**
- **Has this approach been discussed and harmonized with the international group (NITWG)?**

2. MOLECULAR WEIGHT ADJUSTMENTS

- **Please confirm whether NIOG is evaluating to address the impact of molecular weight on the potency of nitrosamines?**
- **Should we anticipate any changes to CPCA AI classification?**

3. RE-SUBMISSION OF RESULTS OF CONFIRMATORY TESTING

MA Holders have submitted results of confirmatory testing to either NCAs or EMA, as appropriate.

- **Please confirm whether MA holders are expected to resubmit the Step 2 outcome, to consider CPCA limits where NDSRI's have been reported, as indicated by the report of the CMDh meeting held on 18-20 July 2023.**

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Background to Question #1:

QUESTIONS WITH A SCIENTIFIC BASIS: Less than Lifetime (Q&A #22)

Could the NIOG please provide clarifications on the following points in the updated texts:
Specifically, the footnote relating to the calculation of LTL AI in Q22

N-Nitrosamine exceeding AI detected in any drug product.
CAPA required.

→ LTL applied (on temporary basis) while CAPA activity ongoing

→ NCA/Lead authority communicates approach to MAH

→ MAH implements CAPA's
Temporary limit superseded.

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

*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 guidance caps the LTL AI to 1500 ng/day (**for both CPCA and established AI's?**)
- **LTL appears to offer limited or no leeway to managing nitrosamines that are in CPCA Categories 3 & 4 respectively during CAPA. What is the rationale for this capping?**
- ICH M7(R2) allows application of LTL without any cap (i.e. can exceed 1500 ng/day).

Increased potency ↑

CPCA Category	CPCA AI (ng/day)	LTL Up to 12 months (ng/day)	LTL >12 months (ng/day)
1	18	239	121
2	100	1330	670
3	400	1500	
4	1500	1500	
5	1500	19950	10050

AESGP

Background to Question #2:

QUESTIONS WITH A SCIENTIFIC BASIS

- Considerations of molecular weight adjustments.

The publication (Nitrosamine acceptable intakes should consider variation in molecular weight: The implication of stoichiometric DNA damage – ScienceDirect) is showing the impact of low molecular weight Nitrosamines versus higher molecular weight Nitrosamines on its capability to damage the DNA, which should be considered in the setting of limits process of Health Authorities. Could you please confirm the NIOG is looking into this?

Fine, J., Allain, L., Schlingemann, J., Ponting, D. J., Thomas, R., & Johnson, G. E. (2023). Nitrosamine acceptable intakes should consider variation in molecular weight: The implication of stoichiometric DNA damage. Regulatory Toxicology and Pharmacology, 145, 105505. https://doi.org/10.1016/j.yrtph.2023.105505.

Background to Question #3:

QUESTIONS WITH A PROCEDURAL BASIS

We have become aware of expectations from some Authorities that following the publication of Appendix 1 with listed AI levels as a separate document on the CMD(h) website that MA Holders were expected to check this list and resubmit their former answer at Step 2. In light of the fact that there is no formal request to resubmit Step 2 from EMA, could you please confirm that the earlier request to resubmit is now obsolete?

CMDh (2023). Report from the CMDh meeting held on 18-20 July 2023. Call for review for chemically synthesised and biological medicinal products regarding nitrosamine impurities. 28 July 2023. EMA/CMDh/328639/2023.

QUESTIONS WITH A PROCEDURAL BASIS

The process towards a guided AI – interpretation and procedural hurdles faced by applicants of nationally authorized products: selected questions

- Can the NIOG comment on the coordination mechanism between the LMS, the other NCA and the EMA? Applicants see that the LMS system does not warrant the LMS bringing an internally coordinated message to the applicant, but also that the LMS (or NCA in case of no LMS) does not always transfer the AI proposal to the European network based on a marginal assessment.

- Can the NIOG provide transparency on the mechanisms to reach international alignment on AIs in the NITWG? Does this apply for all Q&A 10 options for AI setting?
  - Does the willingness of the applicant to give consent for sharing the WoE package with NITWG members via the EMA influence the possibility to assign a readacross based AI?
  - Do the NcWP/NS OEG discuss only positively assessed readacross cases in the NITWG?
  - Have any new members joined the NITWG since the EMA 2021 annual report listed the NITWG members?
  - While the NITWG currently doesn't have an external face, can Industry in the future enhance the NITWG assessment by collectively addressing the NITWG with structured position papers on readacross?
  - In case none of the NITWG members supports a readacross case NcWP (NS OEG) has positively assessed, would that make publication of the related AI in Appendix 1 unlikely? Or does NITWG decision making bind the EMA, and if so what kind of voting system is applied?

- Industry appreciates the first negative EAT acceptance, the case of *N*-nitroso-sertraline, of 28 September 2023, less than 3 months after the 7 July 2023 EAT guidance introduction. Is a 3 months assessment period for a negative EAT representative in case of submission via the NCA? Do prioritization mechanisms apply?

The requested background for the questions is provided in the next slides labeled as "NIOG PREREAD" (not up for presentation).

QUESTIONS WITH A PROCEDURAL BASIS

- We kindly ask you to clarify the process to be followed for MAHs to request consideration of a proposed AI, using the approach outlined in Q10 A, B(1, 2, 3, 4)?

Q10-A
NDSRI TD50 data

Q10-B1
CPCA

Q10-B2
Negative EAT

Q10-B3
Readacross

Q10-B4
Negative in vivo mutagenicity study

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QUESTIONS WITH A PROCEDURAL BASIS

Q10-B3 Readacross

- We kindly ask you to clarify the process to be followed for MAHs to request consideration of a proposed AI, using the approach outlined in Q10 A, B(1, 2, 3, 4) ?

Applicant submits a justification for CPCA derogation: Justified readacross proposal, e.g. to the **LMS** or the **NCA** in case of a NAP.

LMS gathers information for sharing within EMA network.

CMDh consultation.

CHMP to request NcWP, NS OEG to evaluate CPCA derogation possibilities.

NS OEG assesses the case.

NS OEG assessment: international alignment in **NITWG** subgroup SAR.

CHMP to endorse the NcWP, NS OEG evaluation (**CMDh** consultation) and NDSRI-specific AI to be published in **Appendix 1**.

Applicant to discuss with **NCA** an application of **LTL**; **NMEG** escalation in case of exceeding the limit.

Is it possible that the absence of case data transfer from NCA to EMA has resulted in a lack of published limits or an assessment of proposed limits?

Is there an opportunity to foster greater transparency in both the procedure and the end results?

AI not accepted: prevalence of possible root causes?

Has the NIOG quantitatively evaluated which root causes are the most prevalent ones for readacross AIs not being accepted and published (in case where a CPCA-based AI is and isn't published in Appendix 1)?

E.g.

- The LMS or NCA does not transfer the proposal to the network based on a marginal assessment.
- The Committees do not support the expert evaluation of the AI based on a marginal assessment and do not give an assessment mandate to NcWP.
- The NcWP and NS OEG reach a negative assessment of the case.
- The NcWP and NS OEG can't assess the case based on the documentation presented.
- The NcWP and NS OEG reach an inconclusive assessment of the case and put the case on hold.
- The NcWP and NS OEG evaluate incompatible proposals and data of different applicants or insufficient support for readacross across applicant proposals (in case generics).
- The NcWP and NS OEG reach a positive assessment of the case, but these groups and/or the Committees take(s) into account an important negative assessment prevalence of NITWG members.

Q10-B2 Negative EAT

7 July 2023

Publication of EAT guidance

28 September 2023

Publication of negative EAT acceptance *N*-nitroso-sertraline

Applicant submits a justification for CPCA derogation based on negative EAT, e.g. to the **LMS** or the **NCA** in case of a NAP.

LMS gathers information for sharing within EMA network.

CMDh consultation.

CHMP to request NcWP, NS OEG to evaluate acceptance of negative EAT.

NS OEG assesses the case.

In case NS OEG assessment is positive: is there international alignment in NITWG?

CHMP to endorse the NcWP, NS OEG evaluation (**CMDh** consultation) and NDSRI-specific AI to be published in Appendix 1.

Applicant to discuss with **NCA** an application of LTL; **NMEG** escalation in case of exceeding the limit.

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Questions to NIOG

- A number of companies have recently had formal requests from some regulatory agencies with involvement in the Nitrosamine Strategic Group (NISG) and the Nitrosamine Technical Working Group (NITWG) to share information from nitrosamine investigations with international partners. **Industry requests further clarity from NIOG as to what information is currently being shared between agencies via the NISG, NITWG and other similar inter-agency fora?**

- *In prior discussions, the importance of the less-than-lifetime approach for products under development has been highlighted by industry. The EMA Q&A document does not yet address this aspect.* ***Can NIOG provide guidance if this aspect will soon be addressed in a future Q&A revision, or via the ICHM7 revision etc.***