EUROPEAN MEDICINES AGENCY

# 6th meeting NIOG-Industry

07 December 2023

# Update on New Developments for Nitrosamines

# Q&A updates - July to November 2023

- Q&A 22 to extend the scope of the LTL approach to **all authorized products** – 28 July
- Q&A 20 and Q&A 21 deleting the universal temporary AI (**t-AI**) while a formal AI is established – 28 July
- Q&A 3 to inform the **deadlines for CFR** have not been extended and highlight MAH responsibilities to control, report and mitigate the detection of Nitrosamine impurities throughout the product life-cycle, by using the established procedure – 2 October
- Q&A 10 to allow the consideration by MAHs of CPCA derived AI from **alternative sources** (e.g. CPCA categories published by other regulatory authorities) – 12 October
- Removal of information in **Annexes** 2 (CPCA approach) and 3 (EAT protocol) to Appendices 2 and 3 – 12 October

# Topics currently being considered for update (1)

## Implementation of EAT

- Ames assays initiated after August 2023 to comply with EAT or they will not be accepted. Ames assays initiated before August 2023 may be accepted on a case-by-case basis and assessed according to the requirements of the EAT protocol, but they must be submitted before end January 2024.
  - EAT introduced in July 2023
  - Companies and CROs have had sufficient time to implement modified protocols
  - Ames tests performed prior to implementation have been accepted if sufficiently similar to EAT

# Topics currently being considered for update (2)

**Non mutagenic impurities**

- For nitrosamine impurities that are classified as non-mutagenic in Appendix 1 based on in-vivo mutagenicity studies, the submission of step 2 confirmatory testing is not required, and these impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2)
- For all other nitrosamine impurities, the submission of step 2 confirmatory testing is required using the established templates

# Topics currently being considered for update (3)

**Update on method sensitivity**

- Analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities.
- Update to say that when developing an analytical method, the required sensitivity should derive from the appropriate acceptable intake determined in line with the approaches described in Q&A 10. Appropriate development of the analytical method and the required sensitivity are the responsibility of the MAH/applicant.

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# Industry presentation on outstanding issues and priorities for 2024

# Options for setting an AI (Q&A Question 10)

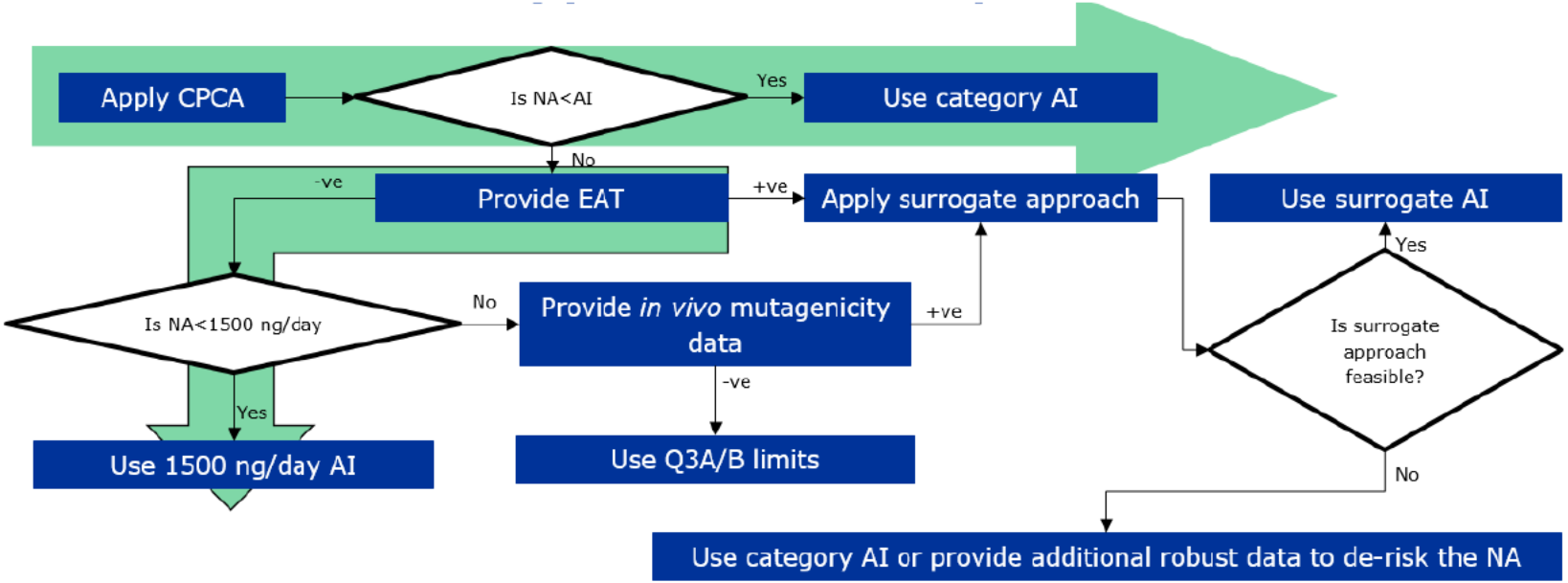
1) The Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines should be used to establish the AI.

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, i.e. according to Q3A/B 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.

# Process-flow for A.I. limit establishment



# Procedure for setting AI based on CPCA and (negative) EAT (Options 1 and 2) - current

Applicant submits a justification for setting AI using CPCA/ (negative) EAT results to the **EMA** for a CAP or the **RMS** in case of a NAP

LMS summarizes request from MAH and makes first assessment whether it agrees with the proposed AI and sends proposal NS-OEG for consultation. Consultation period is a maximum period of two weeks

**NS-OEG** assesses the case.

If NS-OEG agrees it will report back to EMA/CMDh and LMS and ensures inclusion in Appendix 1

If NS-OEG does not agree, alternative (lower) AI will be reported to EMA/CMDh and LMS and included in Appendix 1

# Procedure for setting AI based on CPCA and (negative) EAT (Options 1 and 2) - from January 2024

Applicant submits a justification for setting AI using CPCA/ (negative) EAT results to **EMA** for a CAP or the **RMS/LMS** in case of a NAP

**EMA/RMS/LMS** assesses the data

and reports the agreed AI to CMDh, MAH and NS-OEG. NS-OEG checks the AI and ensures inclusion in Appendix 1

# Procedure for setting AI based on Read-across/in vivo study results (Scenario 3 and 4)

Applicant submits a justification for CPCA/EAT derogation: Justified read-across proposal/(negative) in vivo results to the **EMA** for a CAP or the **RMS/LMS** in case of a NAP

LMS summarizes request from MAH and makes first assessment whether a higher AI using read-across/in vivo study data **is required** and brings proposal to CMDh for consultation.

**If CMDh agrees** with request for using read-across/in vivo study results to set AI, CMDh submits request to CHMP for NcWP/NS-OEG to evaluate CPCA/EAT derogation possibilities

**NS-OEG** assesses the case.

If NS-OEG agrees it brings proposal to NITWG for international alignment.

If NS-OEG does not agree, it reports back to EMA/CMDh and LMS that lower AI remains

If NITWG agrees NS-OEG will report back to EMA/CMDh and LMS; NS-OEG ensures update of Appendix 1

If NITWG does not reach agreement, NS-OEG will report back to EMA/CMDh and LMS that lower AI remains

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# Industry Tour de table

# Any questions?

## Further information

[t relevant information sources or contact details as applicable.]

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Telephone** +31 (0)88 781 6000
**Send us a question** Go to www.ema.europa.eu/contact

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