3rd meeting NIOG-Industry

Q&A update on latest scientific developments (root causes) and testing requirement simplification

Update to Q&A 4 what are the currently identified risk factors for presence of nitrosamines?

- Root causes ≠ risk factors
  - Updated based on new scientific information
  - Highlighted risk from "vulnerable amines" in API structure + trace nitrite from excipients
  - New water for injections (WFI) risk – quaternary ammonium exchange resins + NH_2Cl
  - Categorisation of root causes (API, FP, GMP)
  - Extensive referencing based on old + recent publications

Update to Q&As 8 and 15 on testing requirements

8. Possibility to conduct confirmatory testing in materials other than FP if scientifically justified
    - Already being accepted in MAAs
    - Scientific justification in PQS
    - MAH still has responsibility for the quality of the FP
15. Control point (i.e. specification) can be in API, intermediate, raw material if scientifically justified

General update of the Q&A doc:

Versions table (page 3):

- Retrospectively added for ease of identification of changes

Risk of *N*-Nitroso-API formation

The Issue

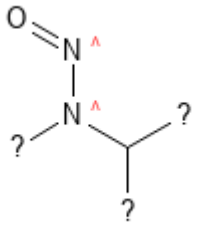
- Recent numerous step 2 testing reports of new nitrosamines derived from APIs (or impurities therein) containing ***secondary*** or ***tertiary*** amine functionality.
  - Wide range of nitrosamine contents (<18 ng/day up to 14,000 ng/day)
  - Often API is isolated as an HX salt
  - Often (but not always) formulated with common excipients by wet granulation
  - Investigations on-going
  - Some voluntary market recalls
  - Some functional group homology/overlap between reported cases
  - Many MAHs for products containing the same APIs reported "no risk" at step 1
  - For each new nitrosamine – derivation of bespoke AI required
    - Aiming to align as much as possible with other international regulatory authorities

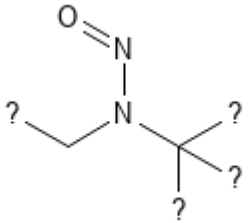
Root Cause Investigations:

- Three factors to consider:
  - Presence of amine – inherent to API (or degradant/impurity) structure
  - Presence of acid – inherent to API structure (but is it essential?)
  - Presence of nitrite – common (ubiquitous?) excipient impurity
  - Control of conditions ???
    - Conditions biggest gap in knowledge
    - Continue pre-competitive info sharing
    - Continue discussions at IP meetings as new information becomes available

What Steps is EMRN Taking?

- Rapid update of Q&A 4 (risk factors) to emphasize this specific risk (bullet 8)
- Proactive communication on EMA website + letter to industry associations
- SWP collaborating with other regulatory authorities in AIs (via NITWG)
- Considering deriving class-related AIs for groups of related APIs, e.g.





Communication of risk: website update

Active substance-derived nitrosamines (new)

New: 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.

More information on the root causes of nitrosamine impurities is available in EMA's question-and-answer document on the Article 5(3) CHMP opinion (Question 4).

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.

Guidance for marketing authorisation holders on confirmatory testing is available.

This is a precautionary step to ensure early detection of any potential risk, and to enable prompt regulatory action if necessary.

There is no immediate risk to patients who are taking these medicines. Patients who have any questions about their treatment should speak to their doctor.

Authorities will provide updates as necessary.

- EMA nitrosamine webpage updated and message to Industry associations circulated for awareness

What Action Should Industry Take?

- Evaluate this highlighted risk for products in your dossiers
- Refer to Q&A 5 in published guidance:

5. What to do if after completing step 1 and /or step 2 new information (e.g. related to a new potential root causes) is identified?

In line with their control strategy, once steps 1 and 2 are completed, MAHs together with API and FP manufacturers are expected to maintain the quality of their product throughout its lifecycle and therefore to review the outcome of the risk evaluation and testing as and when new information (e.g. on potential root causes for nitrosamine formation or contamination) becomes available. Appropriate timelines for conducting the risk evaluation and testing for the newly identified risks should be implemented depending on the level and impact of the risk identified. The same approach is also valid in case, after finalisation of a MAA, a new potential risk for nitrosamines is identified.

EMA and CMDh will continue to publish any newly identified sources of nitrosamine impurities on their websites.

Re-Visit Step 1 Risk Evaluations:

- Presence of relevant nitrosatable amine functionality in the API is to be considered a risk factor.
  - Secondary amines are a clear risk
  - For tertiary amines, dealkylative as well as direct nitrosation should be considered.
- Reconsider step 1 conclusions based on this evidence and if the risk is confirmed, proceed to step 2 confirmatory testing.

Communication of risk - discussion

- How does industry expect to receive communication on new risk information form regulatory authorities? Is the current approach acceptable?
- What is the role of the industry associations in sharing nitrosamine risk information?
- How does industry share information between industry members to support the call for review?

Industry presentation Risk of N-Nitroso-API formation

Short update on progress of call for review (industry)

Organisation of future IP meetings with QWP and/or SWP experts on nitrosamines

Organisation of future meetings with Industry Stakeholders

- Please refer also to email communication sent to EU trade associations contacts from PPTA, IPFA, EuropaBio, EFPIA, AESGP, APIC/CEFI, EUCOPE and Medicines for Europe on 30 March 2022

- European medicines regulatory network supports more flexible interactions with industry associations on the nitrosamines topic

- Meetings can be organised on an ad hoc basis **if warranted** by the availability of **new scientific information** in the area of Quality and/or Safety

Organisation of future meetings with Industry Stakeholders

- Relevant topics in the area of Quality and/or Safety are included in the NIOG workplan as presented at the NIOG/industry TC on 8 December 2021
  - finished product root cause understanding
  - predictive purge calculations
  - data on structural features or other properties that would de-risk a nitrosamine
  - data on potential endogenous API-nitrosamine formation
- Suggested industry to nominate a topic lead who will lead and be responsible for communication with EMA.
- Suggested industry to develop industry workplans with key deliverables
- To submit or inform about new scientific information and to put forward a meeting request please write to nitrosamines.review.CAP@ema.europa.eu, cc industry@ema.europa.eu

Harmonised approach to post-authorisation procedures: submission of nitrosamine risk assessments in Line Extension and variation procedures

What the published guidance says:

19. What is the approach for line extensions and variations applications not linked to changes required as part of article 5 (3) recommendation?

No risk evaluation is generally necessary when submitting line extension or variation application. The risk evaluation is only required to be submitted for products in scope of the call for review as reported in Q&A 3.

Nevertheless, in some exceptional cases questions on the presence of nitrosamines in the product may be raised if a potential risk is identified during the assessment.

Nitrosamines EMEA-H-A5(3)-1490 - Q&A Art. 5(3) Implementation_17th March for CHMP - updates to Q&As 4 8 15 (europa.eu)

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.

CMDh_412_2019_Rev.15_2021_12_clean_-_PG_to_MAHs_on_nitrosamines.pdf (hma.eu)

To ensure a harmonised approach:

- Please refer to published guidance (no change is proposed)
- Submit a nitrosamine risk assessment if a specific risk linked to the Line Extension or variation procedure has been identified
- If not, submission of a nitrosamine risk assessment is *not required* (→ call for review)

- In parallel, we are also clarifying the approach for post-authorisation procedures to the network to ensure a harmonised approach

Any questions?

Further information

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

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