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active pharmaceutical ingredients committee

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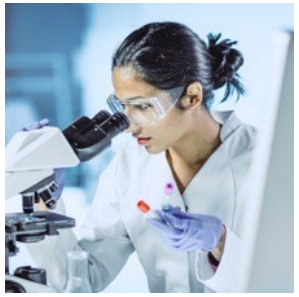
Industry Nitrosamines Update








NIOG meeting – 8th December 2021

Industry Updates

- Short update on progress of call for review:
  - Highlight of challenges with steps 2 and 3 **(MfE)**
  - Enable the use of the Ames test to discharge mutagenicity risk **(EFPIA)**
  - Updates on confirmatory testing requirements **(EFPIA)**
  - Confirm approaches to management of multiple nitrosamines – publish guidance position **(EFPIA)**
  - Update on regulatory review - clastogenic and mutagenic APIs. **(EFPIA)**
  - Industry conclusions/proposal for biological products **(PPTA/Europabio/IPFA)**

- Industry workplan for 2022
  - Industry will provide a perspective on what industry sees as the priorities and need for clarity on key topics (**Ron Ogilvie**, **EFPIA**)

Part 1

Updates on progress of call for review

Challenges

- Generic company portfolios typically large and diverse due to pricing environment
- “Same product” may be multi-sourced across different NCAs
- Single products will typically have >1 API registered for a given product across Europe

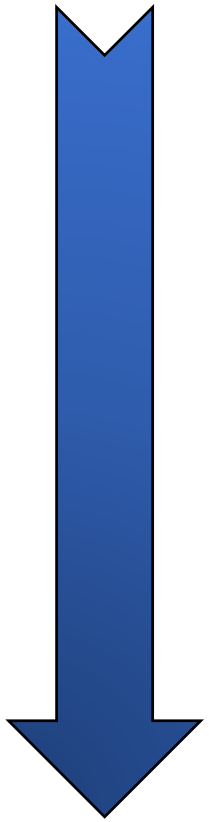
High testing burden

Timelines	•Step 1 extended by one year leaving limited time for steps 2 & 3 •Especially problematic for companies with large portfolios
HA requests	• Ad-hoc requests (e.g. sartans) compete for limited analytical testing capacity • Evolving guidance and expectations
Analytical	• Analytical method development for complex Nitrosamines takes more time • False positive results → complex analytical investigation
Remediation	• Readiness of excipient suppliers and limited material to experiment with • Excipient grades may impact product performance → batches + stability?
De-risking strategy	• Lack of practical experience or clarity on acceptance of read across approach • Lack of clear position on *in vitro* and *in vivo* requirements (e.g. role of Ames?)

Options to remediate formation of complex nitrosamines in the DP

Time and cost

Lower



Higher

Setting appropriate AI after alignment with Health Authorities

Reducing risk through use of low nitrite excipients

- Working with suppliers to decrease nitrites content in common excipients.
  - Need to establish the appropriate level for each product
  - Focusing on excipients with high load in the formulation
- Large investments from some suppliers initiated but availability of these grades will take time and consequently possibility to remediate the FP delayed

Reformulation to avoid use of identified material(s) containing nitrosating entity

- Time consuming: new development, manufacturing batches, stability, submission
- FDA suggested use of anti-oxidant, maybe more relevant for new development
- Important cost and impact the development capacity

How to deliver this ?

- Need to prevent supply disruption, especially
  - Where supporting safety studies are needed to broaden AI (very few CRO can perform TGR studies)
  - Where remediation activities, especially for complex nitrosamines, require changes to the drug product
  - Not all actions may be completed to current timeline

- Clarity in supporting data requirements
  - Consistent application in line with ICH M7
  - The timeline should be linked to clear guidance for complex nitrosamines

- Speed of decision making
  - Practical experience so far is setting AI for complex nitrosamines takes many months

Industry recommendations 1: Mutagenicity testing

- The concern that the bacterial mutagenicity (Ames) assay may not be sensitive to detect a mutagenic potential of N-nitrosamines (NA) is mainly based on publication in 1979 (Rao et al) who reported negative Ames data for some carcinogenic NA. However, the test conditions used in those studies have important technical shortcomings and are not in accordance with guideline OECD TG471 (issued in 1997).
- In contrast, more recent studies unambiguously demonstrate that the Ames assay is highly sensitive to detect the mutagenicity of NA when using sensitive test conditions (e.g., Aira 1984; Thresher et al, 2020).
- Certain test conditions are critical to ensure sensitivity of the Ames test, including exogenous metabolizing system (S9 mix) and choice of solvents. Industry has shared data with regulators at recent scientific meetings (e.g., EMA-SWP IP meetings) demonstrating that NA are readily detected in an Ames test when conducted according to OECD TG471.

Industry requests NIOG whether a robust, OECD 471-compliant negative Ames test is sufficient to de-risk a NA impurity including structurally-complex NA (e.g., DS-related NA). If not considered sufficient, what additional data will be needed to increase confidence in the reliability of the Ames test.

Industry recommendations 2 – optimised testing

- Significant global volume of Step 2 confirmatory testing which needs to be managed.
  - Confirmatory testing plans will need to be prioritised and adapted as data and lessons emerge.
  - Testing 10% of batches where potential risk identified not science / risk based - need for flexibility
  - Particularly so, where testing is to discharge negligible risk from API synthesis impurities and/or a single API batch is used in multiple drug product lots
  - Risk of overwhelming available capacity – ask to review the guidance.

- Global alignment on the use of science and risk based principles is essential to manage Step 2 testing and ensure ongoing medicines availability.

Industry recommendations 3 – where to test?

- As Step 1 and Step 2 testing data has emerged, the evidence has been building to confirm that testing in API or intermediates, rather than finished product, can be an appropriate approach to discharge risks.
- Still gaps in knowledge on processing and formulation conditions which are highest risk in drug product, where there may be vulnerable amines and trace nitrite in excipients (cf metformin discussion with QWP on 18th November)
- Where risk is associated with impurities in the API, data shows risk can be discharged by appropriate science-based controls (e.g. controls at or before API for nitrosamines or amines)

- Update to EMA guidance to accept testing in API when appropriate will enable nitrosamine risks to be addressed more rapidly and at no risk to patients.

Industry recommendations 4 – updates on risk

- Not every product reported as "*risk identified*" in Step 1 should need actual testing, considering:
  - Testing a single presentation or strength of a single product can derisk other strengths / presentations. As knowledge and understanding builds from prioritised Step 2 testing, it will also be possible for testing of one product to provide data to derisk another product.
  - Where a novel nitrosamine is not stable or synthesizable, this can impact the Step 1 risk assessment outcome (no longer an actual risk).
- Industry acknowledges the helpful and important changes made to the EMA Q&A8 ***How should confirmatory tests be conducted by MAHs and manufacturers?*** *a*nd notes reference to *"justifications documented in the risk assessment in the MAH's pharmaceutical quality system*"

- How to implement changes to testing plans and Step 1 outcomes?

Control of Multiple Nitrosamines and Mutagenic / clastogenic APIs

Multiple nitrosamines

- Industry is aligned with the EMA proposal on control of multiple impurities discussed on 18th November with QWP and BWP
- It will be important to publish this position in the EMA Q&A Guidance
    - The total risk should be managed, as described in guidance, to ensure suitable product is supplied to patient
    - It is important that 'total controls' are implemented on actual nitrosamines present in a product
    - Not factoring in 'potential nitrosamines' that are not / not likely to be present
    - Industry support the pragmatic approach outlined by QWP around control limits (see next file)

Nitrosamine risks in Mutagenic/clastogenic Active Substances

- Are there plans to update/clarify EMA guidance and when can these changes be expected ?

Option 2 – Alternatives considered

Limits:
NDMA: 96 ng/day
NDEA: 26.5 ng/day

What to do if 1 NA is < 10% AI?

- Do both NAs still need to be specified?
- Example: NDMA and NDEA present in 19:1 ratio

Alternative 1:	Alternative 2:	Alternative 3:	Alternative 4 = Option 1
NDMA = 0.95x96 = 91.2 ng/day	NDMA = 96 ng/day	NDMA = 0.95x96 = 91.2 ng/day	Sum [NDMA+NDEA] = 26.5 ng/day
NDEA = 0.05x26.5 = 1.325 ng/day	NDEA unspecified	NDEA unspecified	
Analytically challenging	Ignore NDEA	Conservative approach	Extremely conservative

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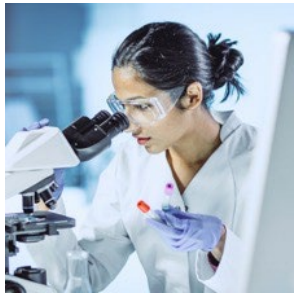
Biological Products








EMA-NIOG-Industry meeting

08 December 2021

Biological products

- STATUS STEP 1 RA FILINGS

* Filed on time (01 July 2021)
* Biologics: No risk identified
* SIGNIFICANT impact on industry resources (with no/ little benefit to product or patient safety)

- QUESTIONS

* Is EMA considering any updates to guidance specifically to biological products, based on outcomes of step 1 by industry?
* What is EMA's vision regarding a globally harmonised approach, considering biological products are out of scope of other jurisdictions, including NISWG members?

Part 2

Industry update on workplan and priorities for 2022

Workplan for 2022 – Industry Perspective

- 2022 is already set to be a very busy year – published schedule in EU for testing and remediation (challenging to meet – and not aligned internationally)
- Industry is seeking clarity and focus through 2022, rather than ‘new workplan actions’
- The concern has shifted from ‘simple nitrosamines in API manufacture’ towards ‘structurally complex nitrosamines’ and their generation in drug product.
  - This is most complex in terms of testing and remediation, especially where limits are aligned to those established for simple di-alkyl nitrosamines
- It will be important to efficiently get to clarity on the diversity of hazard associated with such structurally-complex nitrosamines
- To deliver on testing and remediation, clarity will be needed on hazard and control expectations (safety science, SAR and LTL) AND on accepted derisking information for such complex nitrosamines (many are being found to be Ames negative)
- **International alignment of expectations is of vital importance**
  - Also will be important to clarify nitrosamine inspectional focus in 2022 whilst the ongoing work completes