AESGP
VOICE OF EUROPEAN SELF-CARE INDUSTRY

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European Federation of Pharmaceutical Industries and Associations

Industry presentation

NIOG – INDUSTRY MEETING

4 MAY 2022

Feedback on the updated EMA Nitrosamine Q&A

Industry welcome the expanded Q&A in particular the possibility to test API as a surrogate for FP when warranted by the risk assessment

The expansion of root causes to include finished product is extremely helpful. As knowledge continues to evolve regarding root causes of nitrosamine impurity formation:

- With increased knowledge, there may be the need to revisit risk assessments
- manufacture process remediation to reduce or eliminate nitrosamine impurity formation will become more complex and time consuming

Industry would like to understand if further revisions of the Q&A are anticipated prior to September 2022

Key science and process discussions

How confirmatory testing plans have changed for a particular product following the evolution of science and how this has an impact on submitted step 1 responses

Company A submits a Step 1 template concluding 'Risk Identified'.

Subsequently, Company A receives additional information* which impacts the initial risk evaluation – changing the outcome from 'Risk Identified', to 'No Risk Identified'.

**e.g., correction of supplier information/documentation relating to a given excipient; or updates to risk assessment approach based on current scientific understanding.*

Company A, acknowledges authority expectations with respect to a 'Risk Identified' outcome (i.e., confirmatory testing) and understands *"…the submission of the risk evaluation template as outcome of step 1 can take place only once."* (Section 1.9, CMDh/412/2019);

However, considering the change in risk evaluation outcome, confirmatory testing is no longer justified.

Key science and process discussions

How confirmatory testing plans have changed for a particular product following the evolution of science and how this has an impact on submitted step 1 responses

Company B submits a Step 1 template concluding 'Risk Identified', on the theoretical basis that a tertiary amine could form a nitrosamine in presence of nitrosating agents.

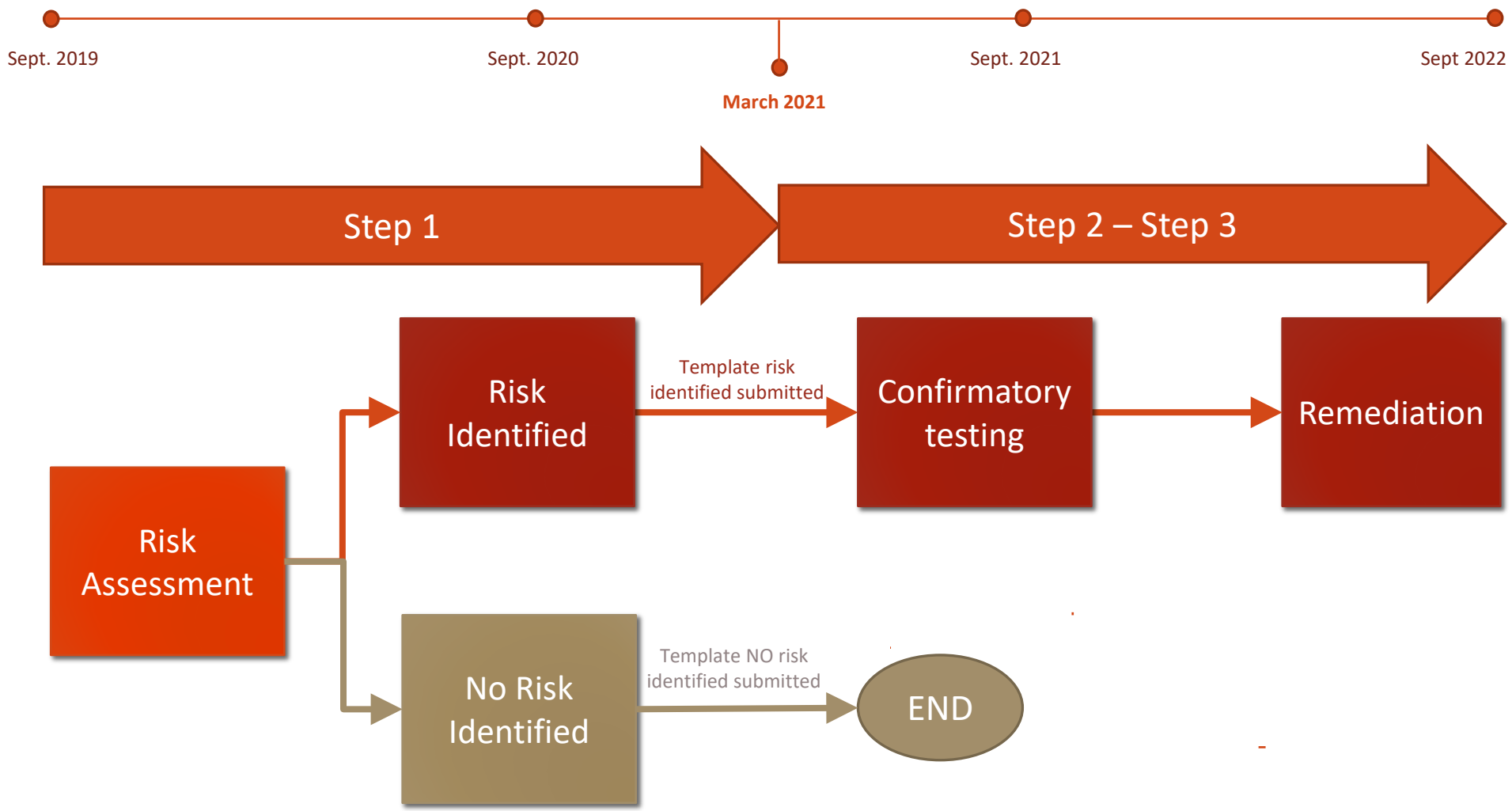
Subsequently, Company B tries to synthesise an analytical standard of the predicted nitrosamine of the tertiary API and is unable to form the nitrosamine despite extensive attempts.

Company B follows Q&A #8, in which it is recognised that it may not be possible to form the nitrosamine. The **internal** risk assessment is updated to reflect that the standard cannot be formed and a 'no risk' conclusion is recorded.

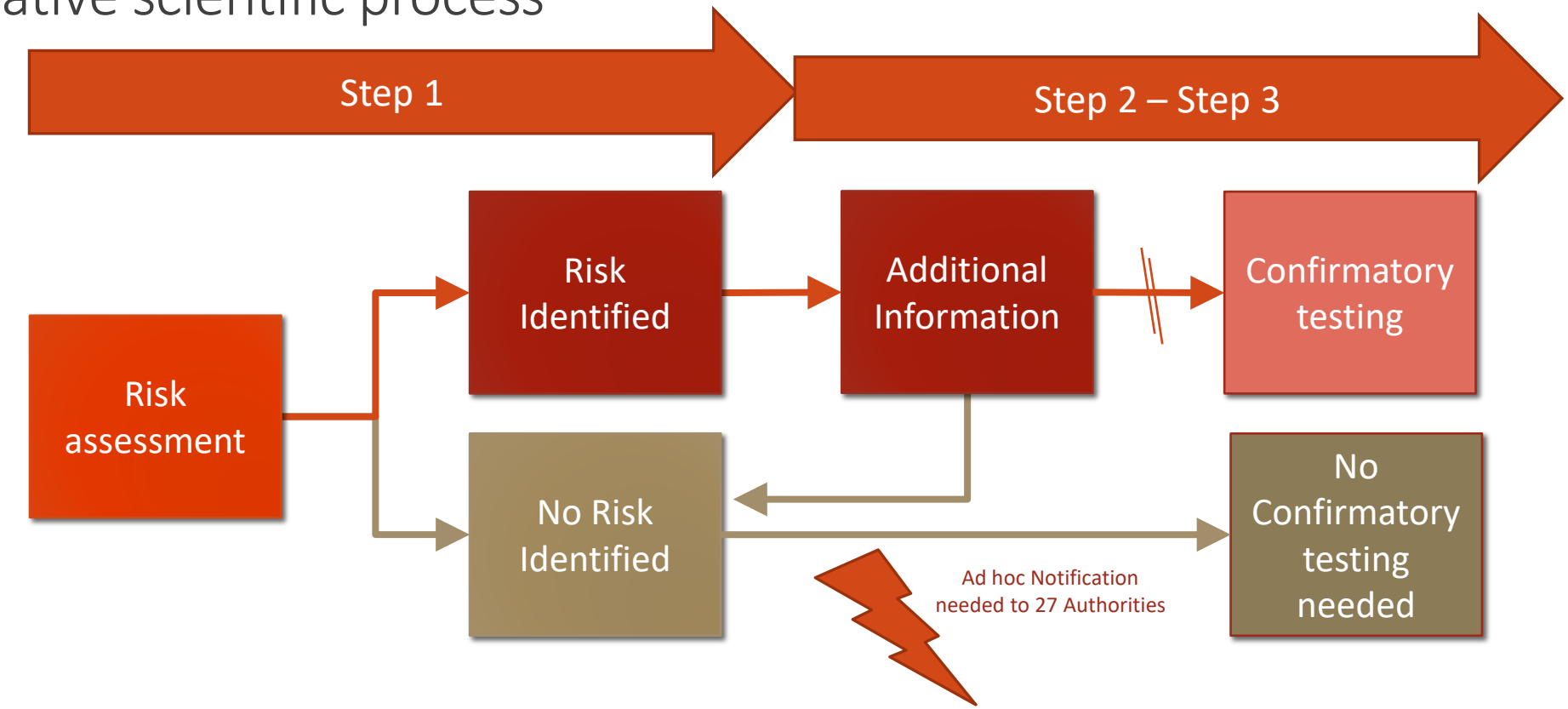
Current step 2 reporting mecanism does not include an option where the derisking process has concluded that CT is not relevant

Current template wording was set early on in the process but since then knowledge of industry and authorities has evolved very much as reflected in last version of the Q&A and does not allow e.g. derisking

Linear reporting step process…



…but iterative scientific process



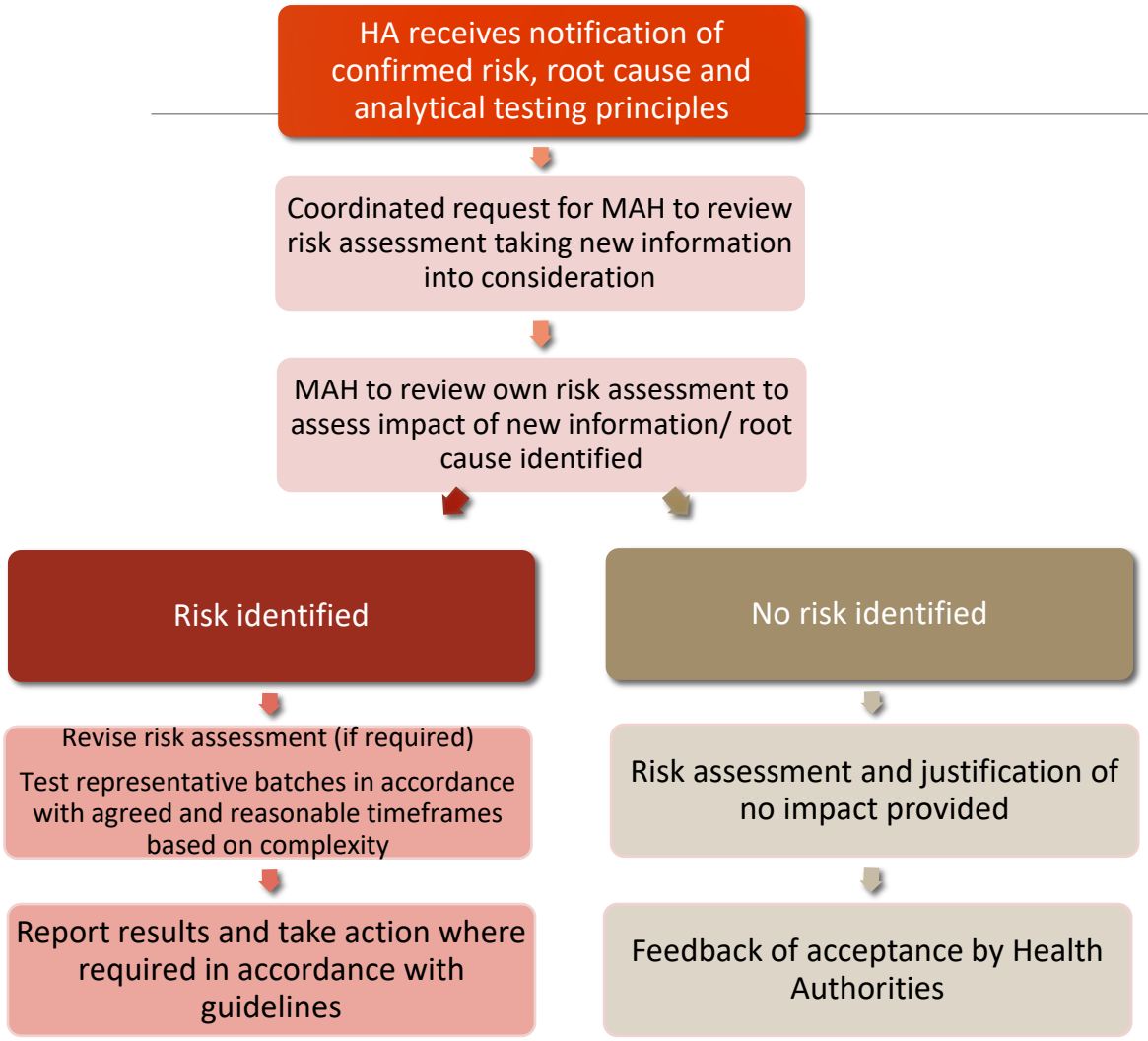
The process is iterative whereas reporting process is linear

More flexibility in reporting mechanism to EMA + 27 NCAs needed

Ongoing reporting compounded with life-cycle activities increase complexity → gives additional weight for additional flexibility and reporting harmonisation

There will be a challenge to notify in time to meet step 3 deadline

Process management of ad-hoc requests



- Information of nitrosamine of concern, identified root cause and analytical testing principles should be shared to enable sufficient evaluation and correct focus
- Acknowledged that confidentiality issues may arise
- Proposal that HA will provide a checklist to MAH in order to provide key information to assist their investigation without breaking antitrust principles

Results of Nitrosamine Progress Survey

EU trade associations
April 2022

NIOG – INDUSTRY MEETING

4 MAY 2022

Survey: objective and focus

Survey objective

- Collect information to support engagement with regulators
- Understand progress towards phase 2 confirmatory testing and remediation targets

Survey Focus

- Collated responses of the set of responding companies to each trade association
- Percentage of current completion
  - Proportions as ‘NO RISK’; DETECTABLE PRESENCE; ABOVE ADI
- Estimated confirmatory testing completion by September
- Estimated remediation expected by September
- What could assist / prevent maximum adherence to the deadline?

All survey results are representative for the situation in February/March

The results shown today are the consolidated survey results of AESGP, Medicines for Europe and EFPIA

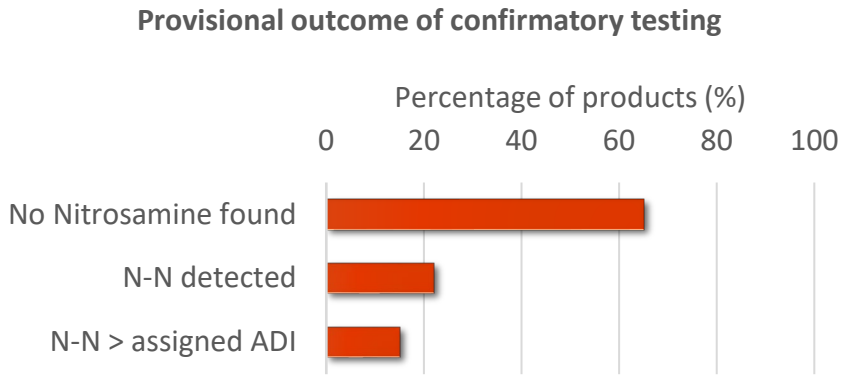
Survey Response and Findings

Confirmatory testing results

- **10% - 15%** of the overall portfolio reported to need confirmatory testing
  - based on potential risk of significant presence
  - *The percentages given below are as proportion of that 15% being tested*

- **25%-50% average completion** across responding companies
  - Results so far (of the 15% portfolio undergoing Phase 2 confirmatory testing)
    - Ca. 35 - 65% — No Nitrosamine found
    - Ca. 22% — N-N detected
    - Ca. 3-15% — N-N > assigned ADI ➔ **1-2% of total products show a risk**

  Company CTs likely conducted in patient-centric manner and / or based on likelihood of presence



- Many/most companies reporting a significant percentage (20% - 45%) of testing is for **structurally complex nitrosamines**
  - Setting limits for structurally-complex nitrosamines is a significant aspect of the challenge
  - Challenging analytics
- Companies are finding that some nitrosamines impurities cannot be synthesized
  - ca. 50% of complex N-Ns proposed as potentially at risk are not possible to make/test for
  - Important to have the clarification published that this can be a de-risking approach

Survey Responses and Findings

Estimated completion by September 2022

Confirmatory testing

- Varies across companies (e.g. dependent upon size of company's portfolio)
- Industry working hard to achieve the necessary CT (e.g. increasing analytical capacity)
- 50-75% of companies report that CT will NOT be completed by September
  - Ca. 60% complete
  - This percentage completion potentially reduced further by test complexity time to develop methods etc.), test volume and especially if routine N-N release testing needed (relatively high % of CTs showing >10% detected N-N)

Challenges that need to be overcome in CT are broad and common across all companies:

- Reference preparation, method development, analytical capacity etc.
- Progress also impacted by additional HA requests for testing

Changes that would make most difference to progress of CT:

- Setting acceptance limits on basis of de-risking factors (e.g. clean Ames test results, LTL limits, consistent read across limits)
- Not immediately implementing routine release testing if >10% assigned ADI

Remediation

- Some companies don't expect to need any remediation
- Companies with significant % remediation will NOT be able to complete remediation in the period to September
  - most companies estimate remediation will be < 50% complete
- Recognition needed that remediation timings will follow and **need to be decoupled from confirmatory testing schedule**

Survey Responses and Findings

Challenges

Currently for industry reporting:

- NO acceptance of limits based on duration of product use (LTL)
- NO acceptance that 'clean' Ames test can focus / minimise CT, control, remediation
  - There is a considerable % of clean Ames tests on structurally-complex nitrosamines
- LITTLE experience so far with agreement to alternate limits above default
  - Need improved process for consistent limit setting for structurally-complex nitrosamines
    - e.g. on read across limit / surrogate selection

➢ **Increased acceptance of de-risking approaches and limits** would have made a significant difference to progress

➢ The limits directly influence volume of testing, control need and remediation need

Proposals for strategic action

- Revision of CT testing schedule beyond September 22
  - The date in EU for Phase 1 was twice modified to calibrate expectations – no change for Phases 2 and 3 were made
    - ➢ **Increase awareness of actions / challenges involved in CT**
  - US FDA have Sept 2023 as target date; other HAs have sequence of dates based on 'risk of significance'

- Allow for increased time for DP remediation
  - **Increase regulatory understanding of remediation challenges.**
    - ➢ Such remediation will need to be prioritised and will take time beyond CT testing completion
    - ➢ Would allow for further time to increase understanding of specific nitrosamine hazards / de-risking approaches
  - Discussion of activities involved in remediation: types of remediation opportunities and associated activities and timelines

- Reinforce the value of science-based limit setting
  - ➢ Limits adopted determine volume of significant findings and control / remediation volume and challenge
  - ➢ Remediation below ADI / 10% of ADI should not be expected (per response to revised EMA Q&A 10)

- Maintenance of supply of products to patients ahead of remediation

Establishing ADIs & remediation of structurally complex nitrosamines

- AI feed-back in a defined timescale and based on scientific data/read across/in-vitro/in-vivo data and not default or NDEA limits: clear guidance needed
  - Impact new product launch
  - Testing burden in developing analytical methods based on 18ng/day limit
  - No remediation work initiated due to uncertainty of the limit, and whether there is a safety issue
  - No possible report of step 2 until we get feed-back on the proposed limit

Remediation challenge – excipient quality

- Excipients suppliers
  - Lhasa initiative collecting nitrites data from the industry
  - Main excipients suppliers aware of the need to reduce levels of nitrites but not necessarily ready to remediate (level of knowledge, investment needed, pharma industry not the main market)
  - Companies are approaching separately the suppliers for getting remediated excipients
  - Most of suppliers reluctant to have a limit of Nitrites in the CoA of excipients that will challenge a control strategy for FP manufacture
  - If no material with lower nitrites to remediate complex nitrosamines is available, then the only possible route is reformulation which is a lengthy and complex route.

Key science and process discussions

- Application of confirmatory testing results between products
- Safety Science topics
  - Fraunhofer Institute planning and feedback
  - e.g. establish scientific basis for read-across surrogate selection and limit setting (feedback on updated Q&A 10)
  - e.g. the value of clean bacterial mutagenicity test
  - e.g. consistent setting and communication of limits

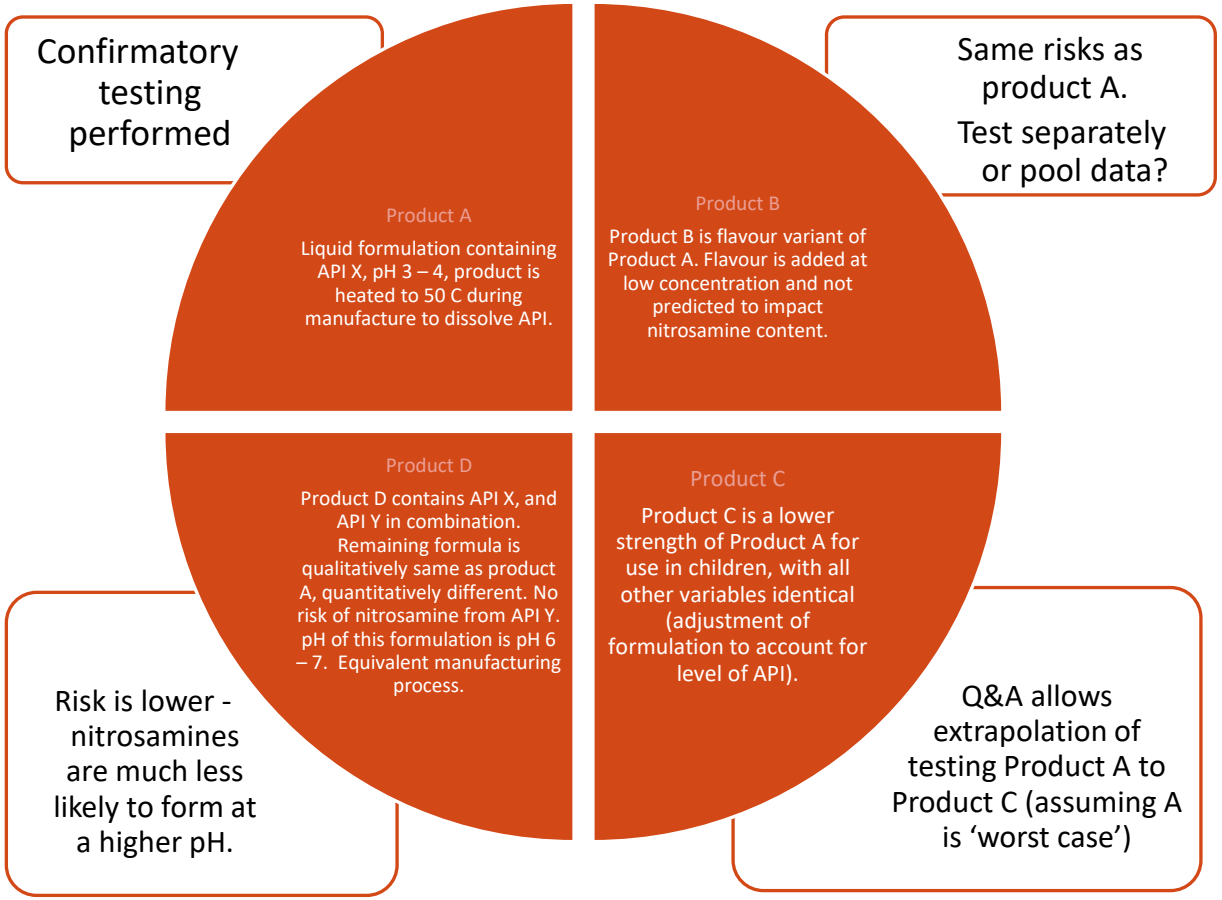
Key science and process discussions

De-risking – extrapolation of confirmatory testing results to similar formulation

EMA/409815/2020 Rev.8, Q8 is appreciated nonetheless it address one situation (lower dosage form)

Could be expanded to address equivalent situations (eg similar formulations and combination of APIs) arising in selfcare sector

Template/ reporting mecanism could be made more flexible to allow reporting of all derisking situations



Key science and process discussions

Safety science topics

- Fraunhofer planning and feedback
- e.g. establish scientific basis for read-across surrogate selection and limit setting (feedback on updated Q&A 10)
- e.g. the value of clean bacterial mutagenicity test
- e.g. consistent setting and communication of limits

Safety Science Topics

Work being conducted by Fraunhofer Institute - Important to plan this work cognisant of all information across all stakeholders

- HESI meet on 2nd May

Industry have conducted significant number of Ames tests

- **Simple nitrosamines:** This included repeat testing of ~16 compounds that were reported to be inconclusive or negative in the Ames that were carcinogenic in rodents. The data supports the position that for N-nitrosamines an OECD aligned bacterial mutagenicity test is predictive of rodent carcinogenicity. Repeat testing of ~16 additional compounds are planned (for details see footnote)
- **Structurally-complex nitrosamines:** Testing in an OECD aligned bacterial mutagenicity test is have produced both positive and negative outcomes nitrosamines (the the details of which have been shared with various regulatory agencies). The outcomes of which would support alignment with ICH M7 and ICH Q3A/B in terms of hazard-based limit setting that impacts on CT and Remediation needs

Industry are beginning to conduct in vivo mutagenicity & genotoxicity tests of structurally-complex nitrosamines –

Intent

- To correlate in vitro Ames result with in vivo rodent results
- To increase acceptance of bacterial mutagenicity 'negative' outcome
- Predictivity of bacterial mutagenicity outcome for nitrosamines
- Predictivity of in vivo test result after bacterial mutagenicity test
- Predictivity of potency of structurally-complex nitrosamine's toxicity
- Data would allow alignment with ICH M7 i.e. the in vitro evaluation of the potential mutagenicity of nitrosamine impurities

EFPIA companies have completed OECD compliant bacterial mutagenicity studies on the following nitrosamines (145438-96-6[a,c], 30533-08-5[a, b,c] , 601-77-4[a, b], 67856-65-9[a, b], 31820-22-1[a, b], 937-25-7[a], 10595-95-6[b], 1116-54-7[b], 86-30-6[c], 55-18-5[c], 62-75-9[c], 3398-69-4[c] 16339-04-1[c] , 2504-18-9[c], 75881-18-4[c] and have additional studies planned on the following nitrosamines (60391-92-6[a, c], 52322-22-2[a], 924-46-9[b], 60599-38-4[b], 53609-64-6[b], 5632-47-3[c], 61034-40-0[c], 625-89-8[c], 81795-07-5[c], 91308-71-3[c], 13256-13-8[c], 14026-03-0[c], 15973-99-6[c] , 91308-69-9[c], 91308-70-2[c], 26921-68-6[c]) that collectively have been reported as being rodent or non-rodent carcinogens with limited or inconclusive mutagenicity data. Data is being published and/or will be shared via external collaborations (e.g. ILSI HESI, Lhasa Limited, Leadscope, MCASE). Rationale for testing derived from (a) Thresher, 2020 (b) Rao 1979 (c) Lhasa Leadscope 2021).

Safety Science Topics

Establish scientific basis for read-across surrogate selection + limit setting

- Significant impact on CT and Remediation

Industry would like to seek further clarification from the Agency regarding the structure-activity-relationship (SAR) and read-across approaches to be adopted by industry to derive limits for nitrosamine drug substance related impurities.

- The establishment of most appropriate limits for structurally-complex nitrosamines is a fundamental challenge at present in Confirmatory testing and in Remediation
- A significant % of nitrosamines being tested for are structurally-complex
- Publications have been issued on read-across science (groups based on structural features around nitrosamine centre and evaluation of carcinogenicity data for family members – selection of most conservative limit in family for limit setting)
- Some signs of concerning disagreement over surrogate selection in read across assessments
  - eg nitrosamine of varenicline – regulatory limit uses allylic surrogate which is more reactive (and higher tox potency) than the NNV and its closest surrogates

Industry would value further discussion to define the general principles that are applied during the SAR and read across approaches that could be adopted by industry.

Remediation – understanding challenge, opportunities + expectations

Remediation can be focussed by understanding of root cause of nitrosamine presence

- Presence in API only – remediate by API manufacturing process change (e.g. reprocessing; change to isolations; change to process conditions / reagents)
  - Reduce levels of vulnerable amines
  - May have need for re-registration of process and / or further API stability data
- Presence from packaging only – remediate (if necessary) by change of packaging (e.g. removal of nitrocellulose)
  - Discuss regulatory process to manage multiple such changes…
- Presence driven by nitrite level in excipients – remediate by reduction of nitrite level in formula / excipients
  - IF root cause can be addressed
  - Very low levels in excipients – very much below normal pharmacopoeial controls and excipient manufacturers with significant other market for materials may not be amenable to process change
  - **This remediation approach may work for some products, but in others the levels of nitrite to be achieved may be 'too low' to robustly achieve**
- Presence from nitrosation of active substance, vulnerable amine – may need reformulation e.g. to remove and excipient or to add a nitrosamine inhibitor.
  - Significant development and scale-up effort required.
  - Some platform approaches may be suitable – but 'one size fits all' addition of inhibitor % may not work - dependent upon reactivity of amine, product type and amine loading in product
  - Also need for stability data set (clarity on what accelerated data will support setting a workable shelf-life) AND potentially for PK / BE data in some cases to manage formula change (dependent upon BCS Class)

Industry propose follow-up with QWP to understand remediation challenges and look to optimise regulatory change mechanisms

Remediation (update Q&A 10)

Industry notes with concern that the revision update included key wording related to remediation expectations –

- That “manufacturers are encouraged to improve their processes, even if they result in only very small amounts (<10% ADI)”.

Given that a product can be supplied to patients when the nitrosamine ADI is met (equating to a product being considered safe for supply), it would seem to be more appropriate to link remediation expectations to product safety (i.e. expect remediation, by process or product change, when levels are at or above ADI).

Industry considers that this should be where remediation resources are applied.

Setting the remediation expectation to the ADI would be aligned to current regulatory expectations for impurity management, where it is the expectation to supply to a safety-based limit (e.g. for other mutagenic impurities the TTC / PDE limits are expected to be met, not ALARP based approach).

- It may be possible in future, when the overall remediation need is more clear, for a company to consider remediation to lower levels (e.g. to below the 10%, or some such, agreed control expectation to remove the need for onerous ongoing routine testing of product) but this should not be a mandated expectation and such remediation should not be a requirement of supply.