EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2nd Meeting of the NIOG-Industry

08th December 2021

EMA status update on call for review

- Presented by Maria Filancia

Call for review: state of play for CAPs (07/12/21)

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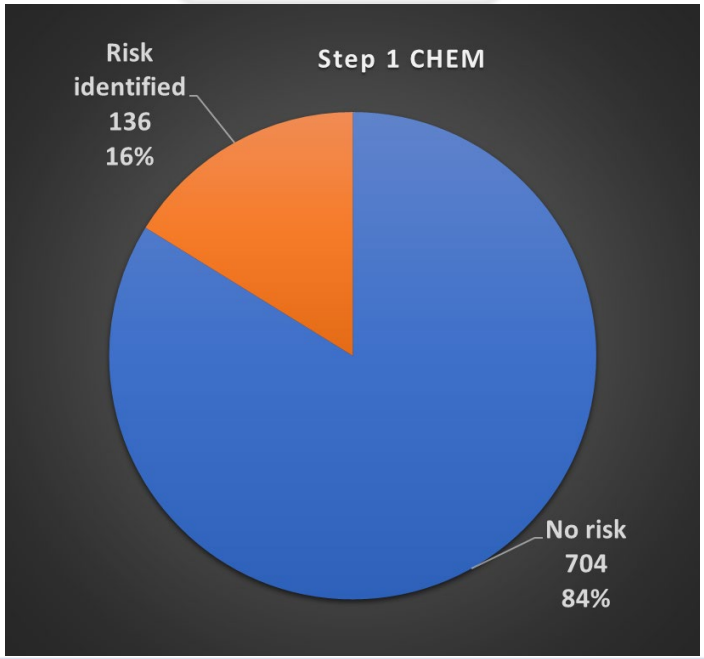
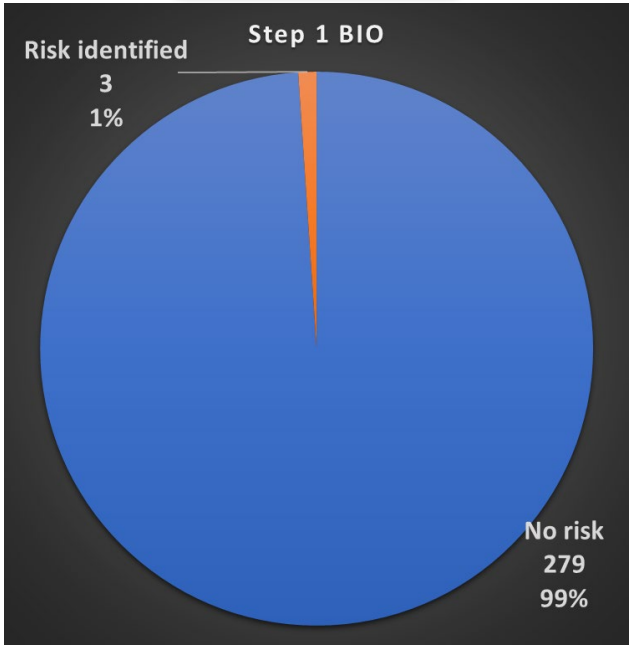
Step 1 response rate CHEM: 98%



- **16 CAPs no response provided**
- **40 CAPs discrepancy with Art.5 (3)**

Step 1 response rate BIO: 92%



- **26 CAPs no response provided**
- **6 CAPs discrepancy with Art.5 (3)**

Call for review: state of play for CAPs (07/12/21)

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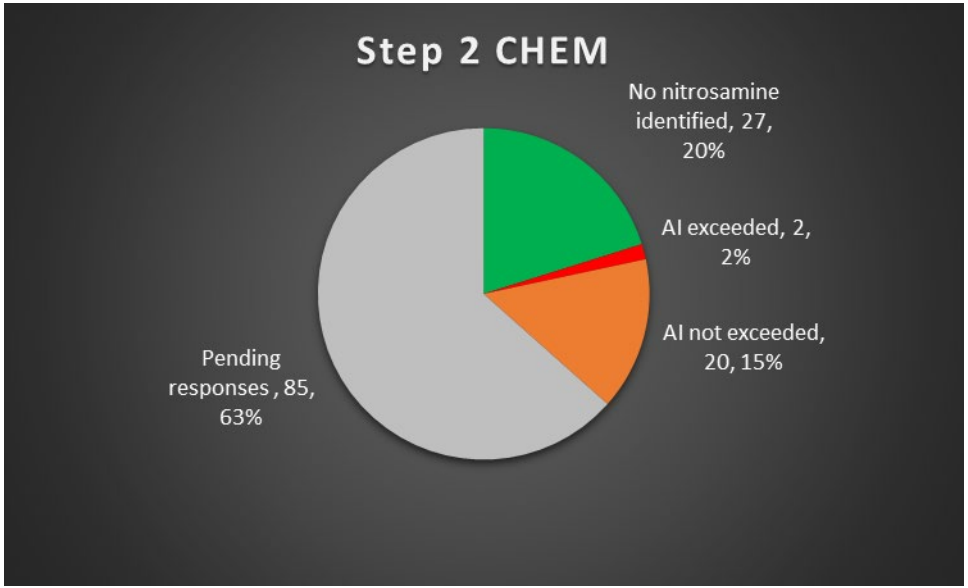
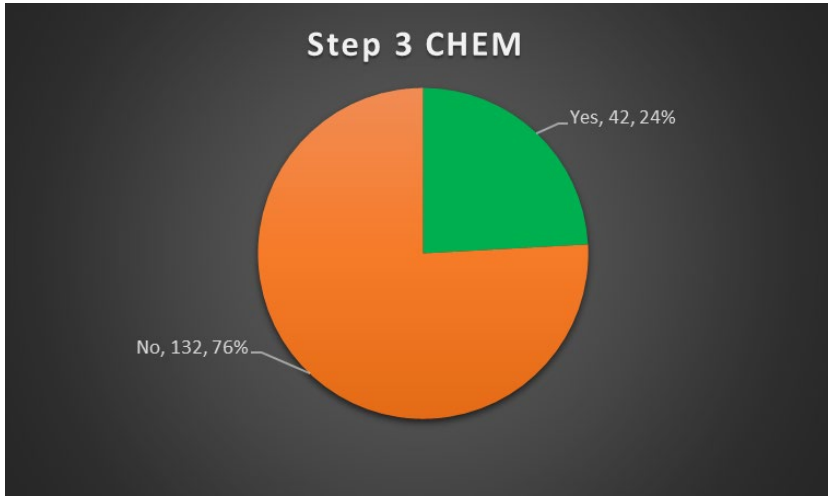
Step 2 response rate CHEM: 38% of products identified at risk



Step 2 response rate BIO: 0%

- ✓ **Scenario a**: varenicline, metformin in all cases the risk was managed.
- ✓ **Expected date for step 2 results**: end 2021-September 2022.

Call for review: state of play for CAPs (07/12/21)



- ✓ **Variations were submitted in 24% of cases. Includes all instances where a variation linked to nitrosamines was submitted (all scenarios).**

EMA update on progress of NIOG Workplan and discussion on outstanding issues to prioritise in 2022

- Quality topics
- Safety topics
- Multidisciplinary topics
- Procedural topics

Quality topics

Preented by Rob Bream

Workplan progress in 2021

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Topic raised by Industry	Description	Priority	Status
1. New science around nitrosamine formation	New scientific evidence around nitrosamine formation, risk factors and root causes including risks associated with biologics	High	On-going
2. Investigations and root causes	New root causes and investigation findings • Update on Metformin root cause investigations	High	On-going
3. Purge studies and calculations	The use of tools from ICH M7 to discharge risk, for example, purge studies and calculations	Medium	On-going
4. Analytical methods	Technical aspects of analytical methods	Medium	On-going
5. Devices and administration sets	Risk factors associated with brief contact with such materials (not container closure)	Low	On-going
6. Amend policy for confirmatory testing based on industry proposals for rationalisation	Evaluate amending policy for cases where testing may not be needed or could be reduced	Medium	On-going

Quality Topics – 1. New Science Around Nitrosamine Formation

- Extensive discussions at IP meetings, conferences and other workshops. Key new information as understanding develops:
  - Quality of raw materials (e.g. Lhasa excipients DB)
  - Kinetic/mechanistic understanding (e.g. industry kinetics models)
- But some topics are not yet mature:
  - Solid state/surface understanding still developing (cf metformin)
  - Packaging (not aligned on extent of risks)
  - Biologics (theoretical discussion only)

Quality Topics – 2. Investigations and Root Causes

- Extensive discussions at IP meetings, metformin white paper:
  - Info sharing on learnings between regulators at NITWG
  - Some general learnings but still case by case (metformin)
  - Vulnerable amines in APIs seems to be biggest source of new cases (see safety slides)
  - Control of formulation conditions seems key to mitigation if amine and trace nitrite are present – much still to learn

Quality Topics – 3. Purge Studies and Calculations

- Application of ICH M7 tools – some theoretical discussion at IP meetings, workshops
  - No solid data on (small molecule) nitrosamine purge in Lhasa database
  - Amphiphilic molecules, mixed solvent systems
  - Purge data from purification of biologics also missing
  - Current policy – ICH M7 option 4 only accepted on the basis of actual purge data

Quality Topics – 4. Analytical Methods

- Discussions at IP meetings, NITWG, conferences and other workshops.
  - Beware of false positives – learnings for method development
  - Factored in by OMCLs during development
  - Sharing of info amongst industry key
  - At the limit of sensitivity for high daily dose compounds

Quality Topics – 5. Devices and Administration sets

- No discussions so far
  - Question came from industry – any knowledge to share (e.g. extractables)?
  - Factor into risk assessment as needed

Quality Topics – 6. Rationalisation of Step 2 Testing

A. Nitrosamine predicted but can't be made synthetically (likely doesn't exist)

B. Bracketing/matrixing for common blend products (worst case scenario)

- Q&As 8 and 14 updated to reflect policy

C. Using test data from 1 product to mitigate risk with similar product

- Re-discussed at QWP IP in November. Concrete examples needed. Would seem to need case by case assessment of scientific justification

D. Testing point for products where only risks are API-related

- If vulnerable amine present (API or impurity) – risk is clear and would require FP testing
- Cross-industry understanding of FP risks not yet sufficiently mature

E. Change of step 2 outcome based on further risk evaluation, scenario modelling

- Not clear what industry intend – no discussion in November

Workplan – Key Quality Topics for 2022

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Topic raised by Industry	Description	Priority	Next Steps
1. New science around nitrosamine formation	New scientific evidence around nitrosamine formation, risk factors and root causes including risks associated with biologics	High	Continue to discuss as science advances, amend guidance and policy accordingly
2. Investigations and root causes	New root causes and investigation findings, mitigation strategies	High	Continue to monitor, discuss with industry and share at NITWG. Considering publication of joint guidance on root causes.
3. Purge studies and calculations	The use of tools from ICH M7 to discharge risk, for example, purge studies and calculations	Medium	In order to consider calculation-based purge arguments, theory needs to be validated with actual purge data. Bio and Chem.
4. Amend policy for confirmatory testing based on industry proposals for rationalisation	Evaluate amending policy for cases where testing may not be needed or could be reduced	Medium	Consider impact of items 1 and 2 on testing policy and amend accordingly (items C-E on previous slide)
5. Guidance updates	Updates to guidance as recommended in sartans LLE report	Medium	Chemistry of Active Substances is the priority

Safety topics

Presented by Rhys Whomsley

Safety Topics

- Endogenous nitrosamines
- Mutagenicity assays
- SAR
- Less than Lifetime Approach

Workplan progress in 2021

EUROPEAN MEDICINES AGENCY

Topic raised by Industry	Description	Priority	Status
1. Use of Structure-Activity Relationships (SAR) to establish AIs for data-poor nitrosamines, including "complex" nitrosamines	Use of Structure-Activity Relationships (SAR) to establish AIs for data-poor nitrosamines, including "complex" nitrosamines - refinement of QSAR tools.	High	Continue to discuss as science advances, amend guidance and policy accordingly.
2. Use of in vitro assays for confirmation of non-mutagenicity for impurities	Use of in vitro assays for confirmation of non-mutagenicity for impurities and mutagenicity testing methodology.	High	Continue to discuss as science advances, amend guidance and policy accordingly.
3. Mutagenic / clastogenic APIs	Policy for control options in mutagenic/clastogenic APIs	Medium	To be discussed in SWP then with QWP and (potentially) NITWG.
4.LTL approach	Use of LTL approach in situations other than temporary alleviation of critical product shortages	Medium	Discussion in NITWG but ultimately issue for ICH M7 revision
5. How to deal with potential dis-harmonisation on AI limits	Ensure harmonisation in AI limits for: for: i) known nitrosamines ii) newly identified nitrosamines as well as the use of the LTL approach between international regulatory authorities	Medium	Completed with constant discusssion with NISG/NITWG groups and publication of recommended AI

Safety Topics - Endogenous nitrosamines

- An increasing number of NO-APIs are being reported in FPs
- The route cause seems to be nitrosation of the API by nitrite present in excipients
- By extrapolation, the conditions for nitrosation of these APIs also seem favourable in the GIT
- Further data is required to inform on possible consequences for risk assessment and control options
- A study is being proposed under the framework contracts – expected to be signed in December 2021

Safety Topics - Mutagenicity assays

- According to ICH M7, substances testing negative in Ames tests can be controlled as non-mutagenic impurities (ie according to ICHQ3A/ICHQ3B)
- A high level of confidence in a negative Ames test is required before a nitrosamine can be controlled to limits of non-mutagenic impurities
- There are concerns that conditions used in the Ames test may not be optimal for the rate limiting metabolic activation step (e.g solvent choice and concentration) and some carcinogenic nitrosamines elicit negative Ames tests
- Industry are generating further data on a wide range of nitrosamines although the supply of test substances of sufficient purity is problematic
- A study is being proposed under the framework contracts – expected to be signed in December 2021

Safety Topics - SAR

- As a negative Ames assay is currently not accepted by RAs all nitrosamines without robust carcinogenicity data need to use SAR approaches if the class specific TTC of 18 ng is not used for AI.
- SAR is challenging for a multistage process involving metabolism/activation, access/reaction with DNA, repair processes with a limited pool of nitrosamines havinges robust data.
- Industry are currently working with partners to generate data on the most appropriate approach for SAR to determine if nitrosamines can be classified according to structural features.
- NITWG discussions on topic ongoing
- A study is being proposed under the framework contracts – expected to be signed in December 2021

Safety Topics – Less than lifetime approach

- CHMP does not recommend generally applying the LTL approach to *N*-nitrosamine impurities (Article 5(3)opinion) because of the potential risk of saturating DNA repair capacity at high acute nitrosamine doses.
- Industry presented a justification on the use of the LTL approach based on data on NDEA in rats.
- International regulators also do not currently advocate the LTL approach for nitrosamines and the issue would be best addressed through discussions on ICH M7 revision.

Multidisciplinary topics

Presented by Rob Bream and Rhys Whomsley

Workplan progress in 2021

Topic raised by Industry	Description	Priority	Status
Management of products with multiple nitrosamines	Provide guidance for managing cases where than one nitrosamine is present.	Medium	Under finalisation
Revision of ICH M7	Discuss revision of ICH M7	Medium	Ongoing
Policy for control options in mutagenic/clastogenic APIs	Clarify whether exception applies for all mutagenic/clastogenic APIs or just those in the scope of ICH S9.	Medium	To be discussed in SWP then with QWP and (potentially) NITWG.

Multidisciplinary Topics – 1. Multiple Nitrosamines

Discussed technical aspects in depth at November IP meeting. Two control options for multiple nitrosamines according to Article 5(3) opinion:

- Option 1: the sum of all detected *N*-nitrosamines does not exceed the limit of the most potent *N*-nitrosamine
  - Clarification that "most potent nitrosamine" is that with the lowest AI in ng/day (irrespective of M.Wt.)
- Option 2: the total risk level of the sum of all detected *N*-nitrosamines does not exceed 1 in 100,000 life-time risk
  - Risk of nitrosamines present at <10% AI is considered negligible
  - If >1 nitrosamine present at ≥10% AI, can apply fixed or flexible limits
  - Still need to mitigate presence as much as possible ≠ uncontrolled impurities in processes
  - Update to Q&A 10 underway, publication anticipated Q1 2022

Multidisciplinary Topics – 2. ICH M7 Update

Proposed updates to ICH M7

- Science not yet deemed advanced enough (e.g. SAR, Ames + other assays)
- Re-visit possibility of informal ICH discussion group at ICH MC in Q2 2022

Multidisciplinary Topics – 3. Control Options in Mutagenic/Clastogenic APIs

Topic under discussion at SWP and will then go to QWP

Draft SWP/QWP position to be presented at NITWG

Final position to be added to Q&A

Procedural topics

Presented by Robin Ruepp

Workplan progress in 2021

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Topic raised by Industry	Description	Priority	Status
1. Managing interaction with industry	Interaction between NIOG and Working Parties with industry stakeholders	High	Completed with NIOG-Industy and QWP/SWP IP meetings organsed in 2021
2. Risk assessment for line extensions and variations	Harmonisation of EU approach to risk assessments for line extensions and variations	Medium	Completed with CMDh practical guidance and EMA/CMDh Q&A 19 aligned
3. Reporting formats	Facilitate submission of step 1/2/3 responses	Medium	Completed with reporting format updated accordingly
4. Confirmatory testing when API manufacturers are currently not actively used in supply	Agreement of approach	Low	Completed with CMDh practical guidance and EMA/CMDh Q&A 3 updated

Additional procedural issues to be considered in 2022 based on feedback from Industy stakeholders.

Points to highlight

- ✓ Since March 2021 significant progress was made in term of addressing the topics included in the workplan. This was possible through the increased engagement and the sharing of information on the scientific developments.
- ✓ In 2022 the workplan will further progress in accordance with updated scientific information.
- ✓ The EU/EEA Network is open to have more agile, scientific and less formal interactions between industry and regulatory experts.
- ✓ At international level, EMA is further engaging with authorities on discussing the quality and safety topics and on how to further engage with industry – proposals for more transparency, e.g. publication of NITWG workplan.

Points to highlight

- More science is needed in order to progress on the below critical topics:
  - Mutagenicity assays
  - SAR studies
  - Investigations and root causes and related corrective actions – particularly, control of conditions if amine/nitrite combination can't be avoided
  - AI extrapolation from one substance to another

Industry short update on progress of call for review

Tour de table per EU Trade organisation

Industry update on workplan and priorities for 2022

1 cross-industry lead speaker

Any questions?

Further information

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

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