4th meeting NIOG-Industry

Update on workplan progress

- Quality, safety and regulatory developments

Main Quality Developments

- Continued discussions with industry and international regulators to better understand risk factors associated with NDSRI formation in FPs, and to identify effective CAPAs
  - Guidance updated as information becomes available (when justified)
- Paper on risk factors to be published in collaboration with NITWG (JPS, submitted)
- Work has begun on drafting/updating guidance as indicated in sartans LLE report
  - Chemistry of active substances (concept paper and public comment phase complete)
  - How to use a CEP in the context of a MA(A) (additional data to be included in module 3)

Main Safety Developments

- NSOEG input into new tAI while AI is being established and interim AI during CAPA implementation approaches
- NSOEG continue to work on establishing AIs and harmonising positions with international partners
- NSOEG continues to develop approaches to AI establishment with international partners
  - Increasing number of NDSRIs
  - Broadening, if possible, the number of surrogates for read-across approaches e.g., by using the lower confidence interval limit as point of departure for less robust studies, where appropriate
  - Considering science and evidence-based alternative approaches to establishing AIs

Main regulatory developments

May 2022

Q&A20: clarifications on regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI.

June 2022

- Q&A5: clarification on risk revision.
- Q&A10: clarifications on how to set limits for products containing salt, hydrate or solvents from API.
- Q&A14: link to risk evaluation optional template.

July 2022

Q&A3: allow amendments of step 1 responses and extension of step 3 deadline for chemical medicines.

Main regulatory developments

October 2022

Q&A21: temporary universal AI.

Coming next

Q&A22: draft interim limit approach during CAPA implementation.

- Applied by the lead authority to all authorised medicines in case of scenario A (AI exceeded) when CAPAs needs to be implemented in order to mitigate/avoid presence of nitrosamine exceeding the AI.
- Applied to medicines with short/intermittent duration of treatment not exceeding the 10 years and with CAPA implementation timeline up to 3 years from the establishment of the forma AI.
- Outcome communicated by the lead authority to RAN and concerned MAH in the context of case assessment.
- No variations to be filed but monitoring through GMP compliance.

Treatment duration	Up to 12 months	>12 months up to 10years
Interim limit	13.3 x AI*	6.7xAI*

*In any case the limit should not exceed 1.5 µg/day unless the established AI (Table 1, Q10) is > 1.5 µg/day.

Flexible approach to limits for market actions

- Several scenarios where it may not be possible to release product based on default 18 ng/day limit or CHMP adopted limits
- Authorities may consider higher temporary limits for market action proposed for a limited period

While NCWP evaluates definitive long term limit:

- QSAR and read across
- Consultation with international partners
- Adoption by CHMP and publication

MAH determines and implements CAPAs to achieve adopted AI

- Amend process or other modifications
- Generation of supporting data
- File variation and implement change

New nitrosamine reported

Up to 1 year

Up to 3 years

t-AI: 178 ng/day

Treatment·duration¤	Up·to·12·months¤	>12·months·up·to·10years¤
Interim·limit¤	13.3·x·AI*¤	6.7xAI*¤

*In·any·case·the·limit·should·not·exceed·1.5·µg/day·unless·the·established·AI·(Table·1,·Q10)·is·>·1.5·µg/day.¶

Progress update of call for review for medicines with chemical and biological active substances

Industry presentation on outstanding issues and priorities for 2023

Any questions?

Further information

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

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