swissmedic

Update of the requirements for dealing with nitrosamine impurities in medicinal products

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Overview

- Introduction
- Marketed products: Reporting and testing NDRSIs of CPCA Categories1/2 (WHY and HOW)
- Safety aspects (Ames test/ Acceptable Intake / LTL)
- Marketing authorisation processes

Requirements for dealing with NDSRIs: Brief recapitulation

Background:

- 1) **If Nitrosamine Drug Substance-Related Impurities (NDSRIs) are detected, their carcinogenic potential is usually unknown.** Regulators have therefore been obliged to derive limits in a time consuming and scientifically difficult process, using structurally related molecules for which robust carcinogenicity data were available for “read across”. **Marketing authorisation holders often had to wait for months for Health Authority feedback regarding limits to be applied for NDSRIs.** In addition, some published limits for NDSRIs derived via this SAR process were controversially discussed based on scientific considerations.

- 2) Systematic testing of certain classes of products by the Swissmedic OMCL has shown that, in many cases, **the formation of NDSRIs was not correctly predicted by the Risk Assessments** to be performed as Step 1 of the nitrosamine evaluation procedure requested by Swissmedic (see Publication of 16.04.2021). In fact, concerning levels of NDSRIs were sometimes detected even in products whose manufacturing process appeared to be devoid of any steps facilitating nitrosylation reactions.

Measures taken in response to issue 1) unknown carcinogenic potential

- **EAT:**
  Enhanced Ames Test → negative test result → Acceptable Intake (AI) 1500ng/day (if no conflicting data)

- **Carcinogenicity Potency Categorisation Approach / CPCA:**
  Progress in the analysis of interrelationship between molecular structure of nitrosamines and their carcinogenic potential → development of a scheme to assign NDSRIs to one of 5 potency classes with corresponding AIs.

- **Intention of Swissmedic:**
  - use the CPCA to set limits for NDSRIs, unless other AIs have already been published.
  - application of LTL concept (6.7 x AI) may be considered by Swissmedic for NDSRIs in Category 1 and 2 if required to ensure medical care.

Measures taken in response to issue 2) lacking accuracy of risk assessments

- API has to be evaluated focussing on the presence of secondary amines in the molecule
- The CPCA will then be used to determine a potency category
- APIs falling into Categories 1 and 2 have to be notified to Swissmedic by 31.01.2024
- For APIs in Category 1 and 2 systematic testing is required by 30.09.2024
- Routine testing of Drug Product if NDSRI of CPCA Categories 1 or 2 is detected in a concentration above 10% of CPCA Category AI. Implementation of testing ASAP, within max. one year.
  CAPA shall be implemented within another 3 years → After 3 years, NDSRIs levels must be controlled at ≤ the internationally agreed AI or CPCA Category AI.

Organisational Topics / Housekeeping

- The slides of the Swissmedic presentation will be made available to all participants after the event.
- Questions received by e-mail before the event will be addressed during the Swissmedic presentation to the extent possible.
- Requests for clarification and other relevant questions coming up during the event can be asked via the Chat function and will be answered at the end of the event if time permits.
- Closure of the event: 12.00 a.m.

Measures taken in response to the lack of predictive power of nitrosamine risk assessements

A Modified Approach for Dealing with NDSRIs of CP Categories 1 and 2:

Why?

"This new request will add to the burden that the industry is already facing …"

"We believe that if the risk assessments were done properly and are regularly updated by the MA holders based on new understanding, it should be sufficient at this stage of the project …".

Risk Assessments – even when done properly - do not reliably predict NDSRI formation

NDSRI of Category 2: Outcome of Risk Assessment vs. Results of Confirmatory Testing Swissmedic								
	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Product 8
Risk for NDSRI formation in Drug Product identified by MAH?	Yes	No	No	No	Yes	Yes, but no testing	No	No
NDSRI detected in Drug Product (OMCL Swissmedic)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NDSRI concentration > AI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (some batches < AI)
"Realistic" interim AI	6.7 x AI							

→ Confirmatory testing should be perfomed whenever an API contains a secondary amine functionality and the nitroso adduct is an NDSRI of Category 1 or Category 2

Implications

Q: "Industry notes ***the presence of a secondary amine does not automatically lead to a risk of nitrosamine formation.*** *A* ***risk assessment*** *would establish … whether nitrosation of the amine can or cannot lead to the corresponding nitrosamine and how the likely amounts of any nitrosamine compare with the acceptable intakes. … Does the* ***CPC approach*** *need to be applied for* ***all APIs containing a secondary amine****,* ***regardless of whether the drug product manufacturing process presents a risk of nitrosylation reaction or not?"***

A: As **risk assessments do not reliably predict the potential for NDSRI-formation** in Drug Products, Swissmedic expects the CPCA to be systematically applied if a product contains an API with a secondary amine functionality. If an NDSRI of CPCA category 1 or 2 can theoretically form based on the structure of the API, **confirmatory testing is mandatory.**

Implications (continued)

Q: "Complete lists of products with the potential to form NDSRIs of CPCA Categories 1 and 2 are to be submitted to Swissmedic by 31.01. 2024. ***If the theoretical assessment does not declare a potential to form an NDSRI*** *(based on de-risking principles – absence of nitrite),* ***this will not have to be part of the list.*** *Correct understanding?*

No, this is a misunderstanding. Swissmedic expects that all products containing APIs that can theoretically react to an NDSRI of CPCA Categories 1 and 2 are included in the list and subjected to confirmatory testing.

Implications (continued)

Q: "The step 1 risk assessment is not considered valid, which is in contradiction with the e.g. EMA Q&A step 1/2/3 principles. Will this be further aligned?"

A: While the Step 1 risk assessments have proven valuable in the initial assessments regarding the potential presence of nitrosamines in human medicinal products, their predictive power with respect to the formation of NDSRIs is limited. This conclusion is based on a significant amount of testing by the Swissmedic OMCL. Swissmedic has therefore taken a well-informed decision to adjust its policy.

Swissmedic regularly discusses its strategy with other regulators including the EMA and the US FDA in an attempt to achieve harmonization. Whether these other agencies will take similar steps as Swissmedic is open.

The US FDA recommends that if NDSRIs were not considered in previous risk assessments, the risk should be re-valuated until November 1, 2023. NDSRI confirmatory testing of drug products (all CP categories) and submission of changes should be completed by August 1, 2025.

What ?

Products to be assessed

Which products have to be assessed?

In scope:

- (Drug Products with) synthetic APIs containing one or several secondary amine functionalities (including peptides and oligonucleotides).

Out of scope:

- (Drug Products with) APIs devoid of nitrogen
- (Drug Products with) APIs lacking a secondary amine functionality.

  While tertiary amines etc. are also susceptible to nitrosylation, they are not currently in scope (capacity considerations). They should nevertheless be considered if there is evidence that they have the potential to be converted to nitroso derivatives of high toxicological concern.
- Nitroso-derivatives of impurities or degradation products of synthetic APIs.

  Impurities or degradation products are present at much lower concentrations than the API itself. Therefore, any nitroso derivatives of these compounds can form at low levels only. Systematic confirmatory testing for these nitrosamines at the Drug Product level is not currently being requested by Swissmedic. However, risk mitigation activities at the Drug Substance level are strongly recommended.

Which products have to be assessed? - continued

Out of scope:

- Biological products unless they contain synthetic components
- Herbal Medicinal Products without a synthetic API
- Drug Products under the Scope of ICH S9
- Veterinary Medicinal Products
- Excipients

Specific Questions regarding the products in scope:

*Q: "If there's a possibility that the **API contains a secondary amine as an impurity** (within controlled limits), but the drug product manufacturing process does not allow for nitrosylation reactions (with data supporting no nitrite impurities in the excipients), does the CPC approach still apply with results reportable by 31.01.2024? "*

*Q: **"What exactly does "NDSRI" mean: Nitrosamines directly derived from API only?** nitrosamines derived from API synthesis impurities? nitrosamines derived from API degradation products? all of them? For instance, for paracetamol: 1 nitrosamine derived from paracetamol is identified. No nitrosamine derived from its degradation product, 4-aminophenol, identified; 15 nitrosamines derived from paracetamol synthetic impurities identified".*

A: The categorization and testing requirements relate to **nitrosamines directly derived from the API only.** The nitroso-derivatives of impurities or degradation products of the API are currently **not in scope** (→ see Slide 14).

How?

Steps to be taken …

How to proceed: Stage 1 - Paper assessment

- Identify all APIs that contain nitrogen
- If nitrogen is present: Are there any secondary amine functionalities?
- If yes: Which NDSRI(s) could form?
- Identify the CPCA Category of the NDSRI(s) by consulting the CPCA-lists published by the EMA, the US FDA and Health Canada.
  If the CPCA Category of «your» NDSRI is not yet listed, perform the assignment as described in Annex 2 of EMA/409815/2020 Rev.17 Corr. (see also Slide 37)

  Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation_ QA10_revision 17_Jul23_CLEAN (europa.eu)
- Report the results of the paper assessment until **31.01.2024**
- If the paper assessment identifies an NDSRI of category 1 or 2, proceed to confirmatory testing.

Specific questions regarding Stage 1 (paper assessment)

*Q: "If there is **no secondary amine** in the API, **is the MAH required to report anything?"***

*Q: "Has the **list to be submitted** to Swissmedic by 31.01. 2024 to **include only the products in Categories 1 and 2 or the complete evaluation** (CPC-Approach) performed for all the identified secondary amines? Is a template for data submission available?*

A: All MAHs are expected to submit a **list of all synthetic APIs** and the corresponding Drug Products in their portfolio. **APIs that can form NDSRIs of Category 1 or 2 should be marked** on this list, and the structural formula of the NDSRIs and the CPCA category should be indicated. For **the remaining APIs** it should at least be **confirmed** that the outcome of the assessment by the MAH has been that **no Category 1 or 2 NDSRI can form.** Alternatively, **the CPCA category** can be indicated **(preferred).**

A report has to be submitted by all MAHs, even if the APIs of their products cannot form NDSRIs of Categories 1 or 2. A template for reporting the results is under preparation.

Specific questions regarding Stage 1 (paper assessment), continued

Q: "Requests to submit lists of potential [CP Category 1 and 2] NDSRIs is a unique request of Swissmedic, and not aligned with positions taken by other regulatory authorities".

The Potential for NDSRI-formation should have been identified and reported in the internationally aligned Step 1 risk assessments. However, existing risk factors remained unidentified in more than just a few exceptional cases according to analytical data of the Swissmedic OMCL. The step now taken by Swissmedic should therefore be considered a data-triggered follow-up in the context of the on-going evaluation of nitrosamine impurities rather than an entirely new measure.
The position of the US FDA is similar to that of Swissmedic (see Slide 12).

Stage 1 (paper assessment): Concluding remarks

- Swissmedic's request to perform a specific assessment to identify potential Category 1 and 2 NDSRIs (nitroso adducts of the API) is based on analytical data by the Swissmedic OMCL. These data indicate that **the risk for NDSRI formation was significantly underestimated** in the Step 1 assessments of the internationally aligned nitrosamine evaluation procedure.
- The approach is clear-cut, and the strategy is **risk-based** in that it **focuses on nitrosamines (nitroso adducts of APIs) with high toxicological potential.**
- Prioritization criteria in addition to the CPCA category – such as duration of treatment, dose level etc. - can be defined within the framework of the approach if this should prove necessary.

How to proceed: Stage 2 – Analytical testing

- Tests must be performed at the **Drug Product** level.
- Key issue: Optimisation of the **extraction conditions.** Test several extraction media !
- Ideally, the test method should be able to detect NDSRI levels < 10% of the AI
- Type and amount of samples to be tested: See the EMA Q & A Document, Point 8: Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation_QA10_revision 17_Jul23_CLEAN (europa.eu)
- The concentration of some NDSRIs strongly increases over the shelf-life while that of others remains virtually constant → **Batches of different age, including batches close to the expiry date, should be tested.** All active API suppliers should be covered.
- The availability of reference materials can be a bottleneck. It is strongly recommended that procurement be coordinated among affected MAHs.

How to proceed: Stage 2 – Analytical testing (continued)

- **The test method that will work in all cases does not exist.** The methods published to detect “small” nitrosamines such as NDMA and NDEA cannot be directly applied for the detection of NDSRIs.

- It is suggested that MAHs consider the joint development of test methods.

Stage 2 – Analytical testing: Specific questions

Q: Which molecules exactly do we have to look for in the tests?

Swissmedic requests you to specifically test for the presence of the **Category 1 and 2 NDSRIs identified in your paper assessments**.

Q: Please explain the meaning of "systematic testing" in the letter sent out to the Swiss QPs.

Systematic testing means that **confirmatory testing** for NDSRIs of CPCA categories 1 and 2 **must always be performed** at the Drug Product level if an API contains secondary amines. Whether routine testing has to be implemented depends on the outcome of the confirmatory tests.

Q: Systematic testing for the presence of NDSRIs of CPCA Categories 1 and 2 is to be performed by 30.09.2024. If the NDSRI is not able to be synthesized: what should be done?

The issue should be reported to Swissmedic with appropriate documentation. Swissmedic will then decide on the further steps.

Stage 2 – Analytical testing: Specific questions (continued)

Q: Will the authority share examples of methods of analysis for quantitation of NDSRI in category 1 and 2? Will the authority provide minimum requirements for methods validation's characteristics (i.e. parameters to be investigated, acceptance criteria, etc)?

Swissmedic is open to discuss specific issues regarding method development and validation with MAHs. It is, however, within the responsibility of MAHs to define, *e.g*. the minimum requirements for method validation.

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What needs to be done upon completion of confirmatory testing?

- The results of confirmatory testing must immediately be reported to Swissmedic.
- Positive test results, even when exceeding the CPCA AI (or a published substance specific AI), will not automatically result in market action. The Institute will consider the supply situation, the NDSRI content of competitor products with the same API, and other relevant factors such as medical need before taking any decisions.
- If test results for a particular product are systematically < 10% of the AI of the respective NDSRI, no action will usually be required.
- If test results are > 10% but systematically below 30% of the AI, Swissmedic will typically request the introduction of skip testing for product release.
- If test results are > 30% of the AI but do not exceed the AI, analytical testing of all newly manufactured batches of the affected product will have to be introduced within 1 year.
- If test results are above the AI, an interim AI has to be agreed upon with Swissmedic, and routine testing will need to be implemented within 1 year max. to demonstrate conformance.

What needs to be done upon completion of confirmatory testing? (cont'd)

- The application of the LTL principle will be considered for setting interim limits as discussed in more detail later.
- After 3 years, NDSRIs levels must be controlled at ≤ the published substance specific AI or the CPCA Category AI.
- If a company intends to use the "read-across" concept to support a proposal for a substance specific AI above the CPCA limit or for an interim AI, Swissmedic expects the submission of a data package of high scientific quality.

Stage 2 (analytical testing): Concluding remarks

- The availability of comprehensive analytical data for NDSRIs of CPCA Category 1 or 2 will enable Swissmedic to take **balanced decisions** for groups of product with the same API regarding
  - any corrective actions to be imposed and, in particular,
  - any market action that might need to be taken.

- The generation of analytical data for all products with “critical” APIs will ensure that **MAHs who detected a risk for NDSRI formation** will **not be at a disadvantage relative to others who overlooked it.**

Comments on timelines and international harmonisation

Swissmedic has received numerous comments that the strategy communicated by the Institute is not fully aligned with that of other authorities, and in particular, with that of the EMA.

While we strive for global harmonisation to the extent possible, the deviating request by Swissmedic is backed up by the analytical data of the Swissmedic OMCL and considered inevitable from a public health perspective.

Swissmedic takes note of the critical comments regarding the feasibility of the September 2024 deadline for submitting the results of confirmatory testing. The Institute acknowledges that the deadline is ambitious but nevertheless expects that, in the interest of patients, MAHs do their best to meet it.

Safety aspects

Enhanced Ames Tests (EAT)

- The NITWG (Nitrosamine International Technical Expert Working group) has agreed on test conditions for bacterial mutagenicity evaluations to reliably assess mutagenicity of nitrosamines
- Health authorities have published these conditions to globally harmonise the expectations (*e.g.* EMA Q&A Annex 3 [1])
- Core aspects:
  - Tester strains: *S. typhimurium* TA98, TA100, TA1535, TA1537, and *E. coli* WP2 uvrA (pKM101)
  - Pre-incubation method, 30 min
  - 30% rat and hamster liver S9
  - Organic solvent concentration as low as possible (no interference with metabolic activation)
  - Two positive nitrosamine controls (justify if relevant mechanism)

[1]: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products

Ames Tests – general aspects

- Swissmedic accepts a negative EAT result to justify an AI of 1.5 µg/day (alignment with EMA)
- If company intends to apply limits > CPCA Cat.1/2/3 AIs or > the interim CPCA Cat.1/2 AI x 6.7, *i.e.* 120 or 670 ng/day, an EAT with negative results has to be provided.
- The purified nitrosamine in question needs be tested (*i.e.*, nitrosamine impurity, N-Nitroso-API adduct or any other NDSRIs, incl. degradation products)
- There is no value in testing the finished product in the Ames test
- Nitrosamines in drug products within the scope of ICH S9 should be controlled according to ICH Q3B (R2).

Ames Tests c’ted

- If an MAH wishes to apply an AI above the CPCA AI it is up to the company to decide if priority is given to analytical or Ames testing. Work- and data sharing initiatives (*e.g.,* Lhasa, EFPIA) are highly encouraged to enlarge knowledge and to avoid redundancies
- Data sharing with regulators and approval for data sharing with other regulators participating in the NITWG is crucial to speed up processes and to avoid redundant testing and repeated revision of AIs
- There is a transition period of one year to conduct Ames tests to justify AIs > Cat. 1/2 AIs or interim Cat. 1/2 AIs x 6.7; draft reports may be acceptable for initial decision making

Acceptable Intakes (AIs) derived from the CPCA

- The main goal of international regulatory working groups (NISG/NITWG) is the harmonisation of acceptable intakes (and procedures) for nitrosamines
- The CPCA was introduced to guarantee a harmonised and more consistent setting of AIs
- CPCA categories are internationally harmonised
- Thus, only few changes of AIs are expected in the future
- Still, knowledge evolves and has to be taken into consideration. This may result in a refinement of some CPCA criteria in the future
- Industry is encouraged to actively share data to substantiate science- and risk-based approaches
- Depending on new data, whole drug classes may potentially be classified of low/no carcinogenic risk in the future

Carcinogenic Potency Categorization Approach (CPCA)

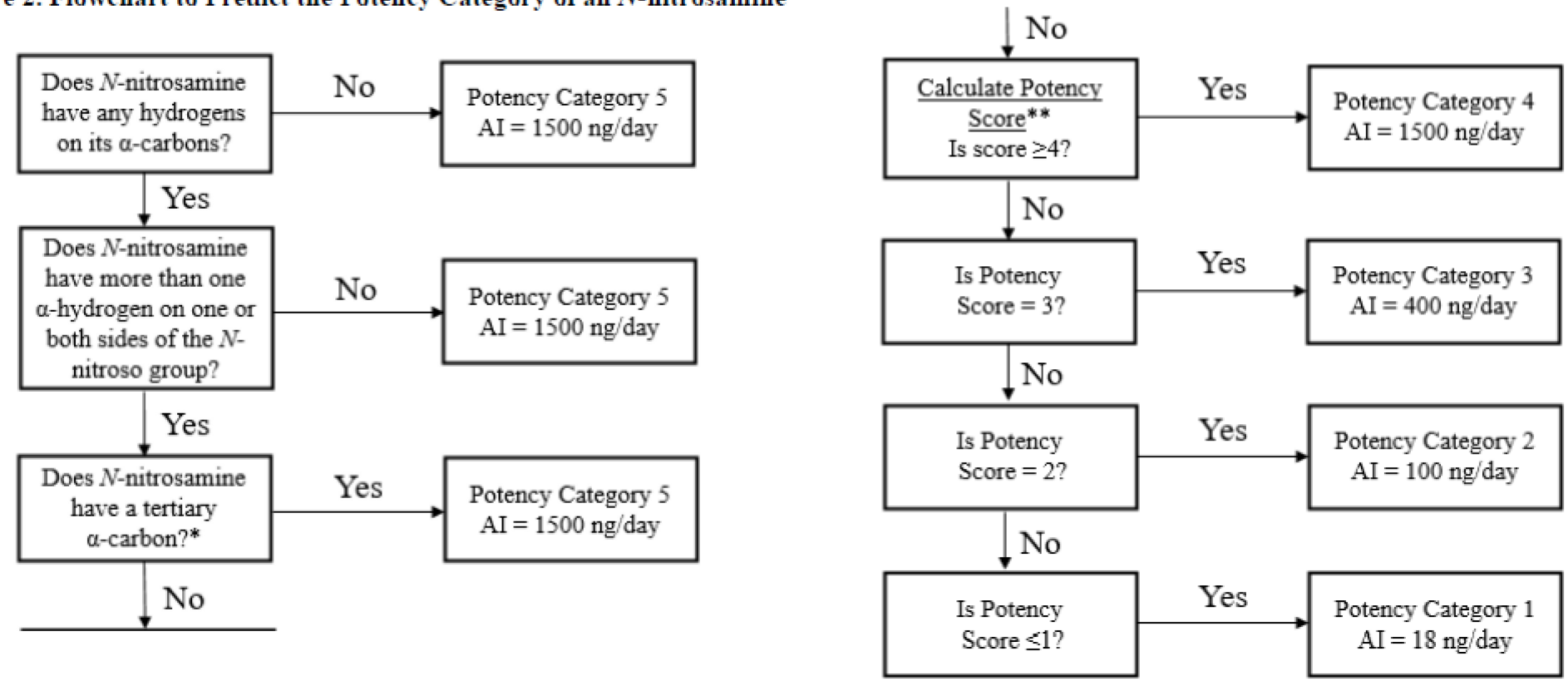
- Structure-activity relationship (SAR) analysis of a set of 84 nitrosamines for which sufficiently robust carcinogenic data were available → clusters/categories of nitrosamines defined that fall within in certain potency class
- Recent scientific publications were taken into consideration (see details, *e.g.* EMA Q&A [1] Annex 2)
- Based on the chemical structure of a nitrosamine, its carcinogenic potency can be predicted

Potency Score = α-**Hydrogen Score** + **Deactivating Feature Score** (sum all scores for features present in the *N*-nitrosamine) + **Activating Feature Score** (sum all scores for features present in the *N*-nitrosamine)

[1]: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products

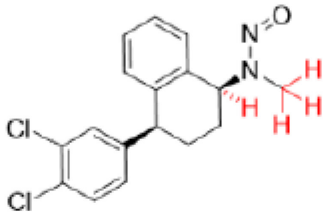
Carcinogenic Potency Categorization Approach (CPCA)

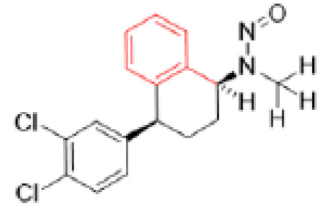
Figure 2. Flowchart to Predict the Potency Category of an *N*-nitrosamine



Carcinogenic Potency Categorization Approach (CPCA)

Example 7 – *N*-Nitroso-sertraline

Count of α-Hydrogens	Score	Feature Highlighted in Red
1,3	3	
No Deactivating Features Present		

Activating Features	Score	Feature Highlighted in Red
Aryl group bonded to α-carbon (i.e., benzylic or pseudo-benzylic substituent on *N*-nitroso group)	-1	
Potency Score = 3 - 1 = 2	**Potency Category 2**	**AI = 100 ng/day**

- As outlined in EMA Q&A[1], the CPCA should be used to establish the AI, unless other robust data are available that would override this AI
  A clarification or refinement of features and AI may be published in the future as knowledge evolves
- Computer tools have been published in the meantime by private institutions to facilitate automated application of the CPCA

[1]: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products

Acceptable Intakes (AIs)

- Principally, we rely on the AIs published by EMA to facilitate European-wide marketing and supply processes (SMC Nitrosamine website[1])
- We note that there are few discrepancies between published AIs in different global regions which result from different acceptance of CPCA, SAR or in vivo data
- We acknowledge that this represents a regulatory hurdle for companies, and we will continue working on the global regulatory harmonisation

[1]: Potential nitrosamine contamination – harmonised implementation (update) (swissmedic.ch)

Less Than Lifetime (LTL) Limits

- LTL limits are applicable as outlined in EMA Q&A Nitrosamines[1] (EMA/409815/2020)
- The ICH M7 LTL factor of 80 for treatments ≤ 1 month is not accepted for nitrosamines
- The interim AI is limited to 6.7x Cat.1/2 AI based on the expected carcinogenic potential typical for a Cohort-of-Concern mutagen and takes into account the risk for the cumulative intake during the 4-year transition period (1 year for analytical testing and additional 3 years until CAPA implementation)
- Interim limits higher than CPCA Cat.1/2 AI x 6.7 may be acceptable case-by-case based on a risk-benefit evaluation

[1]: Questions and answers for marketingauthorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products

Marketing authorisation processes

Marketing authorisation application (MAA) procedures

- Also with regard to MAA procedures, regulators are working towards harmonised international regulatory requirements across regions
- Procedures as described in EMA Q&As[1] (EMA/409815/2020, in particular Q&As 13-15) should be followed for Swiss submissions
- Potential or known nitrosamines in the drug product (see *e.g.,* EMA[1]/FDA[2] published lists) should be considered in the risk assessment and for the testing/control strategy
- Requirements for generic products with regard to AIs will be the same as for the originator

- [1]: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products
- [2]: FDA publications Updated Information | Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) | FDA

Marketing authorisation procedures – Risk assessments

- A risk assessment for nitrosamine formation should be submitted for:
  - New products (NA NAS)
  - Variations concerning manufacturing processes that can potentially influence formation of nitrosamines (see EMA Q&A[1] No.19)
  - Generic products (BWSmI/BWSoI)
- Products for which a risk assessment should be submitted, see EMA Q&A 1[1]
- Risk assessments should address the potential presence of nitrosamine impurities, NDRSIs incl. degradation products, and excipients irrespective of CPCA category
- Risk assessments must consider both the Drug Substance and the Drug Product level.
- If risk is known (e.g. from originator, publications) or if potential risk is identified, confirmatory testing data need to be submitted during the MAA evaluation procedure

[1]: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 2726/2004 referral on nitrosamine impurities in human medicinal products

CAPA implementation: Variations

Q "In case a reformulation of the product or changes to manufacturing process will be necessary as CAPA to reduce the level of a NSDRI below the AI, which kind of data will be requested for submission of variation (full ICH stabilities up to shelf life, accelerated stability up to six months, etc)? It will be possible to submit variation with only 6 months stability data and commit to provide the remaining timepoints?"

With regard to variations the variation guideline (Form "Variations and extensions") and EMA Nitrosamine Q&A have to be followed. Wherever requirements differ, the stricter ones apply. Please note that the level of a NDSRI must remain below its AI over the whole shelf-life.