swissmedic

Swissmedic online information event from September 20, 2023

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

Date (of document): 31 October 2023; revised 30 January 2024

Questions and Answers

This document is a compilation of the additional questions submitted by participants via the chat during the online information event from September 20, 2023. The questions have been anonymized and left as received as not to alter the inquiries. This Q&A document should be read in conjunction with the presentation “Update of the requirements for dealing with nitrosamine impurities in medicinal products”.

Contents

Rationale for new process in Switzerland

- **Question: Is it possible to be more specific in terms of the 8 products: Are they related to 8 different APIs and across several different classes ? e.g. B blockers / ACE inhibitors ? Would all still be cat 1 / 2 based on the CPCA? different APIs and across several different classes ? e.g. B blockers / ACE inhibitors ? Would all still be cat 1 / 2 based on the CPCA?**

- **Question: Can Swiss Medic share more info on the testing experiences of the Agency, in particular the amount of testing performed and how many different NDSRIs gave unexpected results** (Questions relate to slide 9)

  Answer: The 8 drug products listed on slide 9 all contain the same API and represent drug products from different MAH/manufacturers on the Swiss market. The nitrosamine impurity detected belongs to CPCA category 2.
  The slide can be considered representative of the NDSRI situation in general. The Swissmedic OMCL has undertaken systematic testing of a representative number of drug products containing APIs potentially susceptible to nitrosylation. Products with these APIs are typically used in long-term treatments (months to years). For each product we analyzed all galenical forms available on the Swiss market. In only approximately 20% of the cases, the risk assessment by the marketing authorization holder or the drug product manufacturer had correctly predicted the outcome of the analytical tests performed by the Swissmedic OMCL, i.e., the presence of significant amounts of the nitroso derivative of the API. Even in case their assessment indicated a potential risk for the formation of an NDSRI in their product, testing was often not initiated or only upon our request. Overall, for drug products containing an NDSRI we received test results from marketing authorization holders in only about 10% of the cases. In the case of NDSRIs of CPCA category 1 or 2, testing by the Swissmedic OMCL most often revealed that the AI was exceeded, sometimes by > 50-fold.

- **Question: FDA does not request to test systematically all category 1 and 2 products independently of the risk assessed** (Question relates to slide 20)

  Answer: It is correct that in the absence of an identified risk FDA does not request systematic testing of all category 1 or 2 products. However, the results of an extensive testing exercise performed by the Swissmedic OMCL clearly indicate that risk assessments do not reliably predict the risk of NDSRI formation in Drug Products, justifying the Agency's request for confirmatory tests also in the absence of documented risk factors.

In Scope / Out of Scope: product classes

- **Question: Is this new requirement limited to chemical drugs?**

  Answer: Yes. Please refer to slides 14 and 15 of the Swissmedic presentation regarding products in scope or out of scope.

- **Question : It is concerning to see peptides and Oligos also in scope - can you expand on why this was decided and if this is evidence based. Even what the NDSRIs are in this case that would fall into Cat 1 and 2.**

- **Question : To the above point can you clarify if you have considered the possibility of metabolism of such large molecules by CYP enzymes.**

- **Question : Large molecules such as peptides and oligos cannot enter the active site of CYP enzymes and hence cannot be bioactivated to form a reactive diazonium specie. In that context, can Swissmedic comment on the need to include them in the Cat 1 and Cat 2 CPCA request?**

- **Question : In den Informationsveranstaltungen wurde erwähnt, dass Peptide ausgenommen sind, es sei denn, sie werden auf synthetischem Wege hergestellt. /** In the information event it was mentioned that peptides are not in the scope unless they are manufactured via synthetic routes (Questions relate to slides 14 and 42)

  Answer to 4 preceding questions: In response to the above comments and in contrast to what was stated during the online event, we would like to clarify that reporting by January 2024 of NDRSI CPCA Cat.1 and 2 and analytical testing is not required in the case of peptides and oligonucleotides. However, nitrosamine risk assessments should systematically be performed for peptides and oligonucleotides which have a synthetic component in their structure or which were produced by a synthetic chemical process (see EMA Q&A). In case that a risk has been identified, confirmatory testing should be conducted. This approach is in line with that of other regulators.

- **Question: Could you confirm please that phytotherapeutic products are not concerned?**

  Answer: Phytotherapeutic products are out of scope, hence no reporting is expected. Please refer to slide 15 of the Swissmedic presentation

- **Question: Sind stabile Blutprodukte von dieser Meldepflicht ausgenommen oder müssen wir trotzdem eine Vorlage einreichen, unabhängig von der Herkunft des Wirkstoffs? /** Are stable blood products exempt from these requirements or should they be reported regardless of the origin of the active ingredient?

  Answer: Blood products are out of scope, hence no reporting is expected.

- **Question: Are homeopathic products also outside this scope?**

  Answer: Yes, homeopathic products are out of scope, hence no reporting is expected.

- **Question: Within the synthetic product category, does it make a difference whether the product is topically or orally applied? Does the product need to be tested regardless of the route of administration?**

  Answer: For topical Drug Products with synthetic APIs, the paper assessment (Stage 1) should be performed as in the case of products for oral administration. If the outcome of the paper assessment is that the API can potentially react to an NDSRI of CPCA category 1 and 2, a comment in the section "remark" of the response document shall be included (mail to market.surveillance@swissmedic.ch) to clarify whether analytical testing is needed.

- **Question: Does the same requirement apply to MAH or a manufacturer of a generic medicinal product?**

  Answer: The same requirements apply for the originator and for the marketing authorization holders of generic products. The responsibility remains with the Marketing Authorization Holder also in cases when the Drug Product is manufactured by a third party.

- **Question: Regarding complete lists of your products with the potential to form NDSRIs of CPCA Categories 1 and 2 are to be submitted to Swissmedic by 31.01. 2024, the list should include only the products distributed on Swiss market only or all the products manufactured even if some are not distributed in Swiss market?**

  Answer: The list should include all products, including those manufactured but not distributed in Switzerland.

- **Question: Are the same rules are expected for products under clinical development, whatever the development stage?**

  Answer: For clinical trials, a discussion on (potential) mutagenic impurities according to ICH M7 should be provided (structure, origin, limit justification). The level of detail necessary depends on the phase of the clinical trial.
  The provisions of ICH M7(R2) chapter 9.1. apply:
  • It is expected that the number of structures assessed for mutagenicity, and the collection of analytical data will both increase throughout the clinical development period.
  • For Phase 1 studies of 14 days or less a description of efforts to mitigate risks of mutagenic impurities focused on Class 1, and Class 2 impurities and those in the cohort of concern as outlined in Section 7 should be included. For Phase 1 clinical trials greater than 14 days and for Phase 2a clinical trials additionally Class 3 impurities that require analytical controls should be included.
  • For Phase 2b and Phase 3 clinical development trials, a list of the impurities assessed by (Q)SAR should be included, and any Class 1, 2 or 3 actual and potential impurities should be described along with plans for control. The in silico (Q)SAR systems used to perform the assessments should be described. The results of bacterial mutagenicity tests of actual impurities should be reported.
  • Chemistry arguments may be appropriate instead of analytical data for potential impurities that present a low likelihood of being present as described in Section 8.6.

- **Question: I would like to ask about the N-Nitroso HCTZ impurity. Will confirmatory testing be required for this impurity if the current AI = 0.1% = 1000 ppm based on the ICH Q3A/B? Thank you.**

Answer: N-Nitroso HCTZ does not belong to CPCA category 1 or 2 and is therefore not in scope for immediate confirmatory testing. N-Nitroso HCTZ is considered a non-mutagenic impurity with regards to its in vivo mutagenicity study results and can be controlled according to ICH Q3B (see Appendix 1 to EMA Nitrosamine Q&A)

In Scope / Out of Scope: chemical structures

- **Question: What is position of Swissmedic regarding nitrosamides?**

- **Question: Chemical question: do secondary amides (carbonyl group next to the nitrogen) fall under the secondary amines functionality to be analysed?**

*Answer to 2 preceding questions: Only secondary nitros**amines** of CPCA Cat.1 and 2 need to be reported. The CPCA was developed based on data from N-Nitrosamines and is therefore not applicable for N-Nitrosamides. Nitrosamides are, however, N-Nitroso compounds and thus part of the cohort of concern as per ICH M7(R2) and a hazard assessment should be performed.*

- **Question: According to EMA Q&A, the potency categorization approach does not apply to N-nitrosamines where the N-nitroso group is attached to a nitrogen within a hetero aromatic ring (e.g., nitrosated indole or nitrosated tetrazole). Theoretical NDSRI of this kind are in scope or not? How we should proceed?**
  (Question relates to slides 14 and 35)

  Answer: The CPCA was derived from data from N-Nitrosamines only and therefore cannot be applied to other N-Nitroso compounds. For the assessment see answer above (ICH M7 (R2)).

- **Question: Is the secondary amines identification for CPCA application, is only referred on APIs structure or also in any known related substance?**

- **Question: If an impurity of an API has secondary amines is assessment needed for that impurity?**

- **Question: The question shown about an API which contains a secondary amine as an impurity was answered to be in scope. Is this not contradictory to the statement that vulnerable impurities are out of scope** (Questions relate to slide 16)

- **Question: Could you elaborate on the applicability of the request of CPCA 1&2 testing for the impurities? Tertiary amines have been put out-of-scope per the presentation, nevertheless majority of the…** [text missing] **Are these in scope**? (Question relates to slide 14)

  Answer: Swissmedic has chosen a pragmatic approach focusing on NDRSIs with high potency (CPCA Cat.1 and 2) and the potential to accumulate to high concentrations in the Drug Product. Therefore, the scope of mandatory CPCA categorisation and analytical testing has deliberately been restricted to the potential nitroso derivatives of the APIs themselves. All other NDSRIs, i.e. potential nitroso derivatives of impurities of the API do not need to be reported by January 2024 and do not fall under the testing requirement.

  Swissmedic is well aware of the limitations of this approach. For example, it is fully acknowledged that APIs with tertiary amine functionalities can contain secondary amines as impurities, sometimes to a considerable extent, and/or, can be converted to relevant concentrations of secondary amines. Clearly, such impurities can react to nitrosamines in the same way as APIs, and it is for practical, not scientific reasons that they are not specifically addressed in the present round of evaluation. Nevertheless, marketing authorisation holders should give due consideration to any nitrosylated impurities of the API, especially to potentially highly potent ones, within the framework of the on-going world-wide nitrosamine risk evaluations. The same applies to any nitroso adducts of urea derivatives, guanidines, amides or carbamates in the API. Also, it should be taken into account that N,N'-substituted hydrazines are able to form nitrosamines through oxidation, and this does not require the presence of nitrites.

- **Question: The answer to question 1 on slide 20 was "yes", but the question related to a secondary amine on an impurity (not the API molecule itself). Please can you confirm if this would require the CPC approach if impurities are out of scope?** (Comment: question relates to slide 19)

  Answer: No specific assessment and no analytical testing is required in the case of impurities of the API that are secondary amines.

Deviations for CPCA Cat.1 and 2 NDRSIs

- **Question: Not all amines can form the corresponding nitrosamine upon exposure to a nitrosating agent. If a theoretical NDSRI is identified, but shown not to form from the API, can Swiss Medic accept this rationale instead of analytical data? Please note that in such an instance, the preparation of the NDSRI may not always be at all possible**

  Answer: *Swissmedic acknowledges that if, despite extensive efforts, the relevant nitrosamine impurity cannot be synthesised, this could be an indication that the nitrosamine either does not exist or that there is no risk that it can be formed. In such cases, it may not be necessary to conduct confirmatory testing. This should be justified case-by-case based on a thorough scientific evaluation. The justification could include relevant literature, information on structural features and reactivity of the parent amine, stability of the nitrosamine and experimental data to illustrate the efforts made to synthesise and to analyse the impurity (see EMA Q&A 14).*

Drug substance versus drug product

- **Question: In case the drug product is API filled into caps only, is it sufficient to perform the testing on the API only**

  Answer: No, the tests must be performed at the Drug Product level to exclude unexpected reactions of the API upon contact with e.g., process aids, with the capsule shell or with packaging components during Drug Product manufacture.

Testing and Reporting

- **Question: On slide 45: can you clarify "confirmatory test data": would this require a validated method, or if values are sufficiently low below 10% of AI, will a qualified, fit-for-purpose method be sufficient**

  Answer: It is the responsibility of the marketing authorization holder to define the amount of validation data needed to demonstrate that an analytical method is fit for its purpose. In the situation described, the use of a limit test may be an appropriate approach to minimize the validation efforts needed.

- **Question: Can data from stress experiments be used as supporting evidence as well?**

  Answer: Data from stress experiments are supportive but will be considered a valid surrogate for analytical data only in exceptional cases.

- **Question: Was tun, wenn ein Produkt mehr als einen API-Hersteller registriert hat? /** What are the requirements if there is more than 1 API-manufacturer for a product (2-3 manufacturers for backup)?

  Answer: The confirmatory testing has to be representative of the market situation. If an API manufacturer is approved but inactive, no analytical data for Drug Product batches with API from

this source need to be submitted. However, in case API from the respective manufacturer(s) shall be used at a later stage, the MAH has to perform and submit the results of confirmatory testing.

- **Question: How should the completion of confirmatory testing be notified to Swissmedic? Specific email address?**

  Answer: The results of confirmatory testing should be submitted by e-mail to the following address: market.surveillance@swissmedic.ch. Swissmedic encourages the use of the template for reporting the results of the Stage 1 assessment for this purpose.

Ames Test

- **Question: In terms of positive controls would you anticipate that at least one of these is a NDSRI?** (Question relates to slide 31)

  Answer: It would be ideal to include a relevant NDSRI as positive control. However, the most important is that the nitrosamine control reflects the expected metabolic pathways of the NDRSI. Three nitrosamine positive control examples are mentioned in the requirements for the EAT (Enhanced Ames Test) among them an NDRSI. The sponsor should choose two suitable nitrosamine controls which reflect best the expected enzymatic activation of the test compound.

- **Question: The work of HESI relating to Ames won't read out until March - until this is complete changes to the EAT are very likely - this makes the deadline of 1`yr very tight as mosty will wait until the EAT is finalised** (Question relates to slide 31 and 33)

  Answer: The HESI work evaluates different test conditions including those that are recently recommended for the EAT. The results obtained with the recent EAT will also be accepted in the future as these test conditions are considered conservative. Thus, there is no need from the regulatory perspective to wait for the updated EAT conditions.

- **Question: As to a negative result of an EAT: can you confirm that a negative result still assumes the NSDRI to be a mutagenic carcinogen but one of low potency?** (Question relates to slide 32)

  Answer: In line with other regulators, Swissmedic considers an NDSRI with a negative result from an EAT as a potential carcinogen of low potency at the moment and accepts an acceptable intake of 1.5 µg/day. Control according to ICH Q3A/B would require a negative outcome in a relevant in vivo test (TGR mutation study).

In vivo studies

- **Question: Can the transgenic rodent (TGR) mutation assay be used to determine an AI different from the CPCA approach?**

- **Question: For a number of generics there are now in vivo transgenic data - what is the Swiss Medic position regarding both -ve and +ve TGR results in terms of limits? Do you agree with EMA that -TGR = Q3A/B ?**

  Answer: In line with EMA, Swissmedic accepts a negative result from a relevant, robustly conducted rodent transgenic assay to justify control according to ICH Q3A/B. However, not all

genotoxicity endpoints from other in vivo studies may be considered acceptable as stand-alone endpoints. For instance, a negative PigA result alone is not considered sufficient to confirm absence of mutagenicity of nitrosamines.
Recently, new approaches have been submitted to derive an acceptable intake from a relative potency comparison to other nitrosamines based on the BMD (benchmark dose) in case of positive result in an in vivo mutagenicity study. These approaches are being discussed in the NITWG. Sponsors are encouraged to share their data to enlarge the data collection.

LTL

- **Question: Cat 4 and 5 NDSRIs have an AI of 1500 ng/day, which is equal to the standard TTC for non-CoC compounds. Why are LTLs as per ICH M7 not accepted outside of remediation?**

- **Question*: Apologies if I misheard will you accept the LTL approach for cat 4 / 5 outside of CAPA framework ?*** (Questions relate to slides 38 and 39)

  Answer to questions:
  We aim for regulatory harmonization and refer to EMA Q&A in general. There is regulatory agreement that the LTL factors of 6.7- and 13.3-fold are acceptable as interim measures until further data evolve. We only divert from EMA in that we do not accept the factor 13.3x for N-Nitroso API adducts of Cat. 1 and 2. We are aligned with the EMA process for all other categories, i.e., application of LTL factors 6.7x and 13.3x (see EMA Q&A 22).

Marketing authorisation processes

(revised 30 Jan 2024)

- **Question: Can you comment on how these updates will impact new marketing authorization applications? Is additional documentation going to be required (i.e., in addition to the risk assessment)?**

- **Question: Risk assessment is accepted for new submissions and confirmatory testing is only needed in case of identified risk. Does this also apply to NDSRIs? This seems different to the requirements for the existing products**. (Questions relate to slides 40 following)

  Answer to 2 preceding questions:
  MAHs/Applicants of all human medicinal products should ensure that the presence of nitrosamines is controlled and kept as low as possible. A risk assessment should be submitted for all medicinal products containing chemically synthesised APIs (see EMA Q&A 7). The risk assessment should include the assessment of NDSRIs. Any identified or known risk will require additional data irrespective of the CPCA category. Acceptable intakes for nitrosamine impurities in generic products will be the same as for the originator. Requirements for nitroso derivatives of APIs of CPCA Cat. 1 and 2 will be communicated in due time.
  As required for marketed products, confirmatory testing data are expected if N-Nitroso derivatives of the API (i.e. the directly nitrosylated API) of CPCA Cat.1 or 2 can theoretically form. However, if experimental evidence shows that the N-Nitroso derivative of the API is unlikely to form, the MAH/applicant should contact Swissmedic to clarify if analytical data are required.
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Additional questions

- **Question: According to the anti-trust law, companies are not allowed to communicate/align on actions on specific products**

  Answer: Companies should approve and consent to regulators sharing data within the regulatory working groups. Regulators are dependent on these data for science-based and fast decision making. A declaration for the consent of data sharing with NISG/NITWG is already implemented in the authorisation procedures. After the meeting, a template will be provided to declare the approval for data-sharing also for marketed products.

  In addition, it is not apparent to Swissmedic how a cartel law, e.g., the Federal Act on Cartels and other Restraints of Competition, should influence the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act).

- **Question: If the cause of formation of NSDRi will be traced to trace nitrites in excipients or APIs. And the current limits of nitrites in excipients in pharmacopoeia are not sufficient to guarantee the absence of Nitrosamine in final drug product and no producer will be available with acceptable level of nitrites. Would the Health Authorities collaborate in defining new acceptable limits for nitrites?**

  Answer: It is acknowledged that traces of nitrite contained in (certain) excipients are key to the formation of NDSRIs in Drug Products (via reactions of APIs containing NR2 (or NR3) - functions in their molecular structure or of their impurities) and that the nitrite content of excipients should therefore be reduced to the extent possible. However, depending on the API, even very low concentrations of nitrite introduced into a Drug Product might still result in NDSRI-levels in amounts above the acceptable intake.
  At this point of time, it is unclear whether a general solution of the NDSRI-problem can be achieved by setting limits for the nitrite content of excipients. The issue is being internationally discussed at the health authority level, e.g., in the Nitrosamine International Technical Working Group. More data are needed to scientifically justify limits in pharmacopoeia for nitrites in excipients. At this time, limits are not considered useful.
  It is recommended that recent publications on nitrites in different excipients be consulted for risk mitigation.

- **Question: Could Swissmedic share the analytical methods used to the Industry?**

  Answer: Swissmedic has published an analytical method for the small nitrosamines such as NDMA or NDEA. However, there is no "standard method" that will work with all NDSRIs. It is suggested that Marketing Authorization Holders cooperate in the development of analytical methods for NDSRIs to the extent possible. Swissmedic can be contacted regarding specific issues encountered during method development and will provide advice if appropriate.

- **Question: How many individual notifications of Class 1 or 2 CPCA class NDSRIs does Swissmedic estimate they will receive?**

  Answer: Recent publications indicate that about 1/3 of products fall into CPCA Cat. 1 and 2. The expected number of notifications is significantly lower, as currently, only nitrosylated APIs are to be notified. (e.g., Schlingemann et al, 2023, J Pharm Sci 112(5):1287-1304, Burns et al, 2023, J Pharm Sci, Oct 5:S0022-3549 (23, online ahead of print*).*

- **Question: It might be not the scope of the event. how far should we consider about the secondary materials such as color pigments and some free nitro-agent in nitrocellulose which might mirigate into the blister inside and forms nitrosamine impurities with API? Some custmors insists to replace such color and nitrocellulose.**

  Answer: All materials potentially introducing nitrosamines or nitrosylating agents could pose a risk and need to be duly considered (see EMA Q&A). If there is evidence that they may be involved in the formation of genotoxic impurities, corrective measures should be taken.

- **Question: When will the video of the nitrosamine event be made available?**

  Answer : Only the slides of the event and the Question and Answers will be made available. They were sent to the participants.

References

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4. EMA Nitrosamine Q&A: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, EMA/409815/2020
5. EMA Q&A Appendix 1 to Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, EMA/315970/2023
6. FDA Guidance for Industry, Aug 2023, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs), and published AIs Updated Information | Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) | FDA