swissmedic

Requirements for Dealing with Nitrosamine Impurities in Medicinal Products

In September 2022, Swissmedic last updated its instructions to Marketing Authorisation Holders on how to address the issue of nitrosamine impurities of pharmaceutical products. Since then, the field has evolved considerably:

While initially, nitrosamine impurities detected in medicines were small molecules (such as NDMA and NDEA) which formed during the manufacture of active substances (APIs) and could be eliminated or controlled at the API-level, an increasing number of so-called NDSRIs (nitrosamine drug substance related impurities), i.e., nitrosamines derived from the active substances (APIs) themselves, have recently been detected. NDSRIs most often form at the Drug Product level, as a result of a reaction between the API and residual nitrite in commonly used excipients.

With this communication, Swissmedic wants to address two problems specifically associated with this new class of nitrosamines:

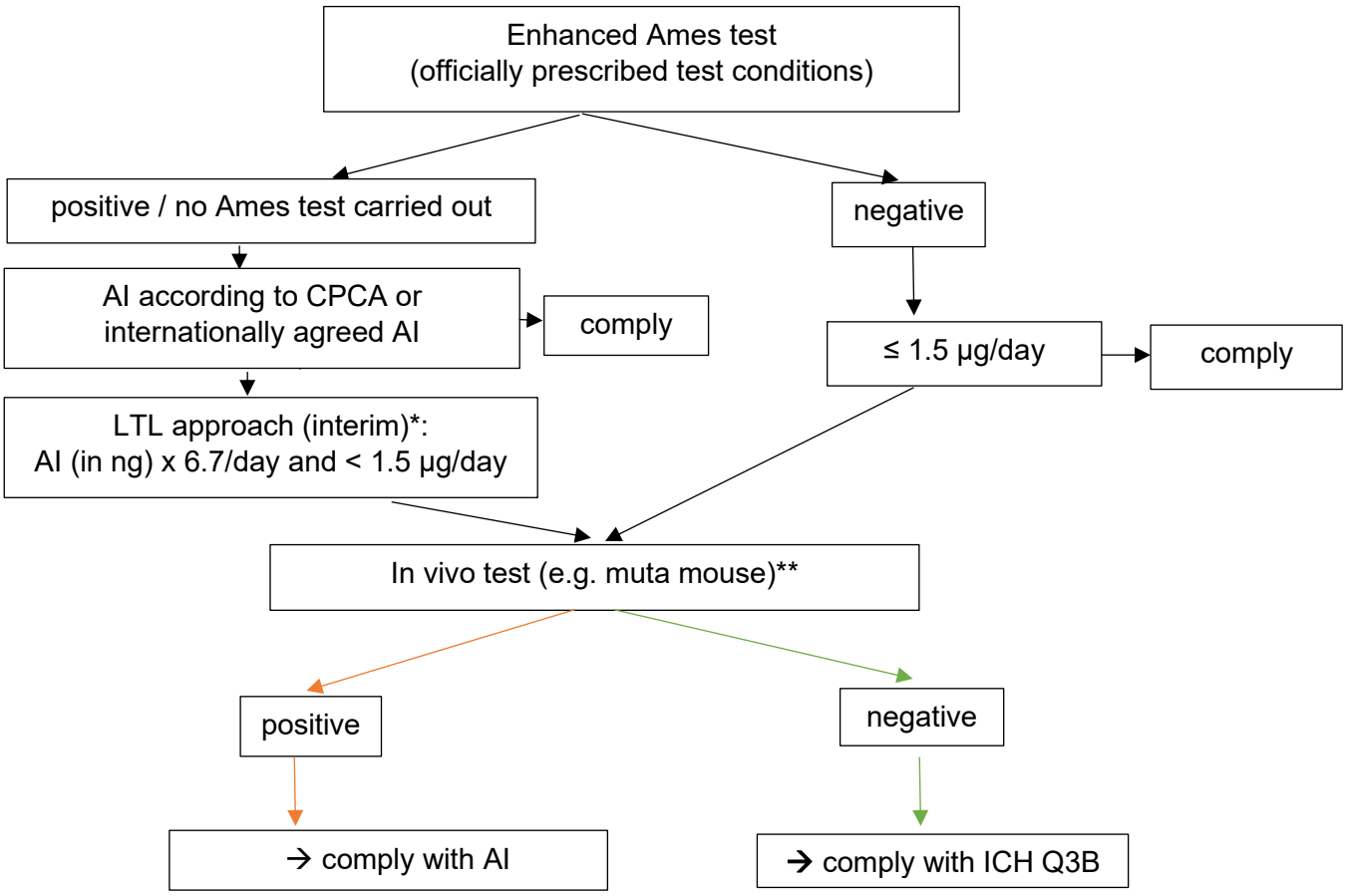
1) If NDSRIs are detected, their carcinogenic potential is usually unknown. Regulators have therefore been obliged to derive limits in a time consuming and scientifically difficult process, using structurally related molecules for which robust carcinogenicity data were available for “read across”. Marketing 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.

To address issue 1), Swissmedic has decided to adopt the following novel approach regarding NDSRIs:

- In case a negative Ames test result is available for an NDSRI and the test has been performed according to Annex 3 of EMA/409815/2020 Rev.17, Version of 28 July 2023 (“Enhanced Ames Test”), the test result will, in the absence of conflicting data, be considered sufficient evidence to justify an acceptable intake (AI) of 1500 ng/day.
- Significant scientific progress has been made in recent months in the analysis of the interrelationship between the molecular structure of nitrosamines and their carcinogenic potential. Regulators have therefore developed a scheme (Carcinogenicity Potency Categorisation Approach/CPC-Approach) how to assign NDSRIs to one of 5 potency classes with corresponding Acceptable Intakes (AIs). Details of this scheme are provided in Annex 2 of the recent update of the EMA Nitrosamine Q&A document (EMA/409815/2020 Rev.17, Version of 28 July 2023).

  Swissmedic intends to use the CPC-Approach to set limits for NDSRIs unless other limits have already been / are being agreed for a specific NDSRI (see Appendix I of the EMA Nitrosamine Q&A document (EMA/409815/2020 Rev.17, Version of 28 July 2023) for a list of published AIs). In addition, Swissmedic may apply the Less Than Lifetime (LTL)-concept of ICH M7 to set interim limits of up to 6.7x the class AI for Category 1 and Category 2 products if required to ensure medical care.

The new general policy regarding NDSRIs is summarised in the scheme on page 2. Swissmedic reserves the right to reconsider or modify its position at any time and/or apply different standards if required from a public health perspective.



*: LTL based on market supply situation

**: unless an internationally agreed AI has been defined based on in vivo data

In response to issue 2), Swissmedic requests you to take the following measures:

- The APIs in your product portfolio are to be systematically analysed regarding the presence of structural elements (secondary amines) susceptible to nitrosylation.
- If secondary amines (and thus the potential for NDSRI-formation) are identified, the CPC-Approach has to be applied to assign the NDSRI to the corresponding potency category.
- 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.
- Systematic testing for the presence of NDSRIs of CPCA Categories 1 and 2 is to be performed by 30.09.2024.
- If an NDSRI of CPCA Category 1 or 2 is identified in the tests and its concentration is above 10% of the CPCA Category AI, routine testing is to be implemented as soon as possible (within maximum 1 year), and CAPA (including submission of variations, e.g., reformulation of product, changes to manufacturing process) shall be implemented within another 3 years to reduce the concentration of the NDSRI below the internationally agreed AI or if not available the CPCA Category AI.
- A dedicated regulatory roundtable with industry to address questions arising from this approach will be organised.

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Wegenast
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