Checklist for the risk assessment of N-nitrosamine contamination

This checklist serves as a guide to a **company's internal** assessment of the risk of contamination of the active substance and/or proprietary medicinal product with N-nitrosamines.

Product name:		**Authorisation number:**	
Active substance:			
1. Active substance manufacturer:	Name:	Address:	
2. Is inorganic or organic nitrite used in active substance synthesis (including in the manufacture of starting materials / intermediates)?		YES ☐	NO ☐
3. Are potential nitrite sources present in active substance synthesis (including in the manufacture of starting materials / intermediates), or could impurities with nitrites or nitrite sources be present in input materials, solvents or excipients?*		YES ☐	NO ☐
4. Are recycled solvents used in active substance synthesis (including in the manufacture of starting materials / intermediates)?		YES ☐	NO ☐
5. Are non-dedicated equipment parts (incl. storage vessels) used in active substance synthesis (including in the manufacture of intermediates)?		YES ☐	NO ☐
6. Do you have incomplete information on the synthesis pathway (including starting materials and intermediates) and are thus unable to answer any of the above questions?		YES ☐	NO ☐
If you answered YES to at least one of questions 2 to 6 → proceed to 7. Otherwise proceed to 11.			
7. Are secondary or tertiary amines (e.g. triethylamine, diisopropylethylamine (Hunig's Base=DIPEA), N-methylmorpholine (NMM), tributylamine (TBA)) used in active substance synthesis (including the manufacture of precursors / intermediates)?		YES ☐	NO ☐
8. Are amine sources present in active substance synthesis (including in the manufacture of starting materials / intermediates), or could amines or amine sources be present as impurities in input materials, solvents or excipients?**		YES ☐	NO ☐

If you answered YES to at least one of questions 7 or 8 → proceed to 9. Otherwise proceed to 11.

9. Please produce a comprehensive risk assessment on the formation and potential occurrence of nitrosamines in the final drug substance.

The following aspects, at least, should be discussed:

- Is it chemically conceivable that nitrosamines could occur in the synthesis process?
- Could nitrosamines be introduced into the process by the input of substances (e.g. via recycled solvents) or via a side-reaction?
- What nitrosamines might be formed (chemical substance names) and where in the process might they form (attach flowchart)
- If it is possible for nitrosamines to form: Please carry out a toxicological assessment (incl. details of tolerable quantities and discussion of any purging by subsequent manufacturing steps) and arrange for batch analysis data to be collected (see 10.)

The risk assessment should be completed by 15.05.2020 and submitted to the authority upon request.

10. Please analyse a representative number of API or finished product batches for the potential nitrosamine (guide value: > 20% of distributed batches, if less than 10 batches at least the last three batches). A validated and sufficiently sensitive test method should be used for the analyses.

As regards the specification of limits for the currently discussed nitrosamines, we recommend at least the following publications for guidance. The latest announcements on the EMA website should be monitored.

- *Questions and answers on "Information on nitrosamines for marketing authorisation holders"* (EMA/CHMP/428592/2019 Rev. 1 European Medicines Agency)
- *Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities* (EMA/248364/2019)

The analytical tests for nitrosamine contamination should be completed by 15.11.2021 and the analytical results submitted to the authority upon request.

* e.g. nitrates+reducing agents, HNO_3+reducing metals, urea/ammonium + hypochlorite/chlorine

** amides, amide solvents e.g. N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone)

Informing Swissmedic of a positive test result:

If analytical tests carried out during the risk assessment revealed contamination with nitrosamines above the limit, Swissmedic must be informed of this quality defect **immediately**.

To this end, the corresponding details should be entered in rows 11 to 14 and submitted to Swissmedic with the other documents.

11. Marketing authorisation holder (name, address)	
12. E-mail address/ phone number for queries:	
13. Enclosures:	
14. Date / signature of the Responsible Person:	