Checklist for the risk assessment of N-nitrosamine contamination

Guide to a company's internal assessment of the risk of contamination of the active substance and/or medicinal products with N-nitrosamines

	Yes	No
1. Is inorganic or organic nitrite used in active substance synthesis (including in the manufacture of starting materials/ intermediates)?		
2. 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?*		
3. Are recycled solvents used in active substance synthesis (including in the manufacture of starting materials/ intermediates)?		
4. Are non-dedicated equipment parts (incl. storage vessels) used in active substance synthesis (including in the manufacture of intermediates)?		
5. 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?		
6. 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)?		
7. 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?**		

If you answered YES to at least one of the above questions the final drug substance might contain Nitrosamines impurities

8. 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 9.)

The risk assessment should be completed by 01.10.2020.

9. 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 authorization 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.

* 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)

ELC can help you with:

- Preparation of risk evaluation report
- Review of the risk evaluation report
- Variation in case Nitrosamines are identified in the products