FAQ

CONTROL OF NITROSAMINE IMPURITIES IN PHARMACEUTICAL PRODUCTS

1. What is the scope covered by the Guidance? Should the risk of presence of nitrosamines be considered for all human medicinal products?

The scope of this guidance covers all medicinal products for human use (containing chemically synthesised active pharmaceutical ingredients, including biological medicinal products except for non-scheduled poison, natural and health supplement products. Should any issue pertaining to nitrosamine impurities arising from products that are not within this scope, this guidance will also be applicable to such products.

2. There are no timelines mentioned. How does NPRA plan to implement the control and monitoring of nitrosamine impurities?

In general, the product registration holder (PRH)/ manufacturer is responsible to perform risk assessment by considering the whole product's lifecycle.

Should there be any safety issue (such as during evaluation or alerts), PRH must readily provide necessary data/ test results or scientific justification for the affected products (alerts) within an acceptable timeline.

The need for variation depends on the outcome of the risk assessment. If there is a risk, any changes made including changes to the manufacturing process, product specifications, etc. should be submitted.

3. Is there a standard format whereby the risk assessment should be reported?

There is no fixed risk assessment format. Reference can be made to ICH Q9 Quality risk management.

4. Is it possible to utilize reports or evaluation documents that had been shared with EMA/ USFDA?

Yes, PRH may leverage on evaluations that fulfilled the EMA and/or USFDA evaluation requirements for local reporting and submit such documents to NPRA for review.

5. Is there any preference towards US or EMA approach in performing the risk assessment and subsequently carrying out the confirmatory testing?

No, both EMA and USFDA guidance can be referred to for information on nitrosamine impurities control.

6. According to the guideline, Step 1 Risk Evaluation, should the outcome of Step 1 be communicated to the authority? If yes, is there any timeline for reporting?

For registered products, the outcome of Step 1 does not require reporting to the NPRA. The risk assessment should be retained by the PRH and made available if requested. However, the outcome may be submitted for new product registration or for product under evaluation by NPRA when necessary.

7. With regards to Step 2 Confirmatory Testing, what are the requirements in terms of analytical method?

Appropriately sensitive analytical methods for determination of specific nitrosamines in other medicinal products should be developed and validated accordingly before testing. The limit of quantification (LoQ) should be at or below the acceptable limit for the respective nitrosamine impurity.

If quantitative testing is performed to justify omission of specification, the LoQ of the analytical method employed should be ≤ 10% of the acceptable limit based on the acceptable intake (AI).

8. Is there a priority list for products based on criticality which can guide the industry in the implementation phase?

There is no priority list. We recommend that the industry consider factors such as the therapeutic indication, treatment duration, maximum daily dose taken and number of patients treated. For example, medicinal products with higher daily dose and used for chronic conditions may take priority.

9. What would be NPRA's long term plan for nitrosamine risk management as there are continued effort from ICH, EMA and other Health Authority globally to identify more nitrosamine impurities to be controlled on human use medicines?

NPRA will continue its surveillance program and perform periodic monitoring on medicinal products in the market to ensure that the safety, quality and efficacy adheres to current requirements. As a consequence, the PRH is expected to provide necessary and relevant data in a timely manner as and when requested by the authority.

10. Will NPRA only expect NDMA, NDEA or more impurities to be tested should there be a risk of presence of such impurities?

Expectation of which nitrosamine to test is wholly based on the product itself (i.e. its chemical structure, synthesis route, solvents used, etc).

11. With reference to STEP 3: RISK MITIGATION MEASURES, which departments should this be reported to?

Changes should be reported to the respective section based on the product category.

12. What does the statement "the industry shall at least develop a comprehensive plan for the conduct of risk assessment" mean?

The industry is expected to develop their own plan on how to conduct the assessments.

13. What are the guidelines to refer to when performing all 3 steps?

The following documents can be referred to:

1. 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

2. European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines

3. Control of Nitrosamine Impurities in Human Drugs Guidance for Industry (USFDA)