Questions and Answers for the Industry Training Workshop on Management of Nitrosamine Impurities in Therapeutic Products

This document aims to address the questions that were received during the Industry Training Workshop on Management of Nitrosamine Impurities in Therapeutic Products held on 30 October 2024.

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1. **Why is an interim acceptable intake (AI) exceeding 1500 ng/day permitted for nitrosamines classified as CPCA Category 5, but not for those in Category 4, despite both categories being allocated an AI of 1500 ng/day?**

   CPCA Categories 4 and 5 nitrosamines share the same recommended AI of 1500 ng/day, but they exhibit different metabolic properties in the body. Category 4 nitrosamines, like those classified under CPCA Categories 1, 2, and 3, remain susceptible to metabolic activation via α-hydroxylation and are thus more aligned in terms of their potential toxicity mechanisms. On the other hand, Category 5 nitrosamines are not expected to be metabolically activated. Due to this difference, Category 4 nitrosamines are treated with the same caution as Categories 1, 2, and 3 nitrosamines, despite sharing the same AI with Category 5 nitrosamines. In this regard, an interim AI exceeding 1500 ng/day is only applicable to Category 5 nitrosamines.

2. **Are there any cases so far that suggest that nitrosamine formation occurs at a higher rate under Zone IVb conditions compared to Zone II conditions?**

   Yes, this has been observed in quite a few products. If an increase in nitrosamine levels during storage is seen, nitrosamine formation under Zone IVb condition will be expected to be higher compared to Zone II condition based on the scientific principle that higher temperature results in higher rate of reaction.

3. **Which data sets should be evaluated when considering the nitrosamine testing control strategy? Only the data at release, or both the release and shelf-life data?**

   This depends on the root cause of the nitrosamine formation. Should nitrosamine levels be expected to increase during storage, it becomes necessary to assess both

the release and shelf-life data. Conversely, if no such increase is anticipated, examining release data alone would suffice.

4. **Does the method validation report need to be submitted to HSA?**

   For currently registered products, HSA may request for the report on a case-by-case basis after evaluation of the nitrosamine risk assessment. For new product applications (NDAs and GDAs), both the method validation report and results must be available and submitted in the applications.

5. **For a product with a potential risk of a nitrosamine drug substance-related impurity (NDSRI), what alternative methods, apart from confirmatory testing of the drug product, are deemed acceptable to substantiate that the product is devoid of the nitrosamine? Does a supplier declaration that excipients are free of nitrates/nitrites suffice?**

   Regarding NDSRI, options are limited beyond confirmatory testing of the drug product. However, for NDSRI with a high acceptable intake (AI), it may be feasible to estimate levels through theoretical calculations. The calculations should be based on the maximum quantity of nitrites that is present in the excipients and demonstrate that even in a worst-case scenario of 100% conversion, nitrosamine formation would not exceed the AI. The nitrite content in the excipients cannot be substantiated merely by a supplier's declaration that the excipient is nitrite-free. It must be supported by test results of nitrite levels, either from the excipient supplier or the drug product manufacturer. In such instances, the inclusion of nitrite control in the excipient specifications may be requested.

6. **What approach would HSA recommend if a monograph method/any reference for the nitrosamine impurity is unavailable?**

If the test method is not available in the monograph, product registrants/manufacturers can refer to the test methods published by the various international agencies, including HSA, as a starting point for the development and validation of analytical methods for nitrosamines in other drug substances. Click here for the test methods published by HSA.

7. **The situation regarding nitrosamine in therapeutic products keeps evolving and recommendations keeps changing. Consequently, risk assessments conducted previously may no longer be applicable and require re-evaluation. What is the anticipated timeframe for conducting these re-evaluations?**

   Nitrosamine risk assessment is an ongoing process throughout the lifecycle of a product. Re-evaluation is required whenever a new risk is identified. Product registrants should inform us of their proposed timeline for this re-evaluation. HSA may request for an expedition of this process if there is information indicating significant risk.

8. **For drug substances certified by the EDQM, can it be presumed that the nitrosamine risk associated with the drug substance has been adequately addressed?**

   Yes. However, nitrosamine risk assessment for the drug product must still be conducted.

9. **Can drug product manufacturers conduct nitrosamine testing for every batch on release, and skip testing approach for stability batches?**

   According to Good Manufacturing Practice (GMP) standards, stability testing is typically performed on one batch per year. Therefore, nitrosamine testing should be

conducted on all batches undergoing stability testing if there is a potential of nitrosamine levels increasing during storage.

10. In cases where the drug substance manufacturer has conducted a risk assessment and determined that confirmatory testing is unnecessary, or where such testing has been completed with no nitrosamine detected, is the drug product manufacturer still required to carry out confirmatory tests on the drug product?

This depends on the overall risk assessment and root cause of the nitrosamine formation. The drug product manufacturer is responsible for conducting the overall risk assessment considering the risks in both the drug substance and drug product. Confirmatory testing must be conducted on the drug product if a risk is identified in the drug product.