GUIDELINE ON CONTROL OF NITROSAMINE IMPURITIES IN PHARMACEUTICAL PRODUCTS

NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH, MALAYSIA
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PREAMBLE

This **GUIDELINE ON CONTROL OF NITROSAMINE IMPURITIES IN PHARMACEUTICAL PRODUCTS** is jointly established by the National Pharmaceutical Regulatory Agency (NPRA) and the pharmaceutical industry associations namely Pharmaceutical Association of Malaysia (PhAMA), Malaysian Organisation of Pharmaceutical Industries (MOPI) and Malaysian Association of Pharmaceutical Supplier (MAPS).

This guideline shall be read in conjunction with the current laws and regulations together with other relevant legislations and guidance documents where applicable, governing products for human use in Malaysia.

The written laws shall take precedence over this guideline in any event of discrepancy.

The NPRA may request for information or specify conditions not described in this guideline that are deemed necessary to ensure the quality, safety and efficacy of the products.

Regular review of current policy will continue, considering the global regulatory environment to allow for timely and pertinent changes.

Changes to the guideline may be made when necessary by the NPRA and Product Registration Holder is advised to refer to the NPRA website for latest updates on the control of nitrosamines impurities in products.

The NPRA reserves the right to amend any part of the guideline whenever it deems fit.

Any enquiry on nitrosamine impurities may be submitted to:

National Pharmaceutical Regulatory Agency,
Ministry of Health Malaysia,
Lot 36, Jalan Profesor Diraja Ungku Aziz (Jalan Universiti),
46200 Petaling Jaya,
Selangor,
Malaysia.
(e-mail: npra@npra.gov.my)

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1. INTRODUCTION

Since the detection of nitrosamine impurity in a valsartan-containing medicinal product in June 2018, the impurity has also been detected in several other human medicinal products in subsequent years following close monitoring of both the pharmaceutical industry manufacturers and regulatory agencies.

2. SCOPE

The scope of this guidance covers all pharmaceutical products for human use (containing chemically synthesized active pharmaceutical ingredients (API), including biological products except for non-scheduled poison, natural and health supplement products. However, if any issue pertaining to nitrosamine impurities arise in products that are not within this scope, this guidance will also be applicable.

3. CONTROL OF NITROSAMINE IMPURITIES

As nitrosamine impurities are identified as probable human carcinogen, safety issues following the discovery have been of major concern. With this emerging safety concern, this guidance document pertaining to steps on mitigating and preventing the presence of nitrosamines above acceptable levels in pharmaceutical products has been developed.

Reference can be made to European Medicines Agency (EMA) and United States Food and Drug Administration (USFDA) guidance for more information on nitrosamine impurities control. The Product Registration Holder (PRH) may leverage on evaluations that fulfilled the EMA and/or USFDA evaluation requirements for local reporting.

Identified Risk Factors

N-Nitrosamines can arise in a finished product from various root causes. The most identifiable risk factors are linked to **manufacturing process and storage** of API and/ or finished products. Additionally, there are also risk factors that are related to Good Manufacturing Practice (GMP).

a) Risk factors related to the **manufacture** of the API:

1. Use of nitrite salts and esters, or other nitrosating agents in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process.

2. Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process.

3. Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process.

4. Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing process or during storage. Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).

5. Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts).

6. Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents.

7. Carry-over of nitrosamines deliberately generated (e.g. as starting materials or intermediates) during the manufacturing process.

b) Risk factors related to the finished product:

8. Reaction of nitrosatable nitrogen functionality in APIs or their impurities/ degradants with nitrosating agents present in components of the finished product during formulation or storage.

9. Degradation processes of API, including those induced by inherent reactivity (e.g. presence of nitro-alkyl, oxime, or other functionality) or by the presence of an exogenous nitrosating agent.

10. Oxidation of hydrazine or other amine-containing functional groups present in API or their impurities/degradants (e.g. from hydrazones and hydrazides), either in API manufacturing processes or during storage.

11. Use of certain packaging materials. Relevant nitrosamine contamination has been observed in primary packaging of finished products in blister with lidding foil containing nitrocellulose.

12. Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase

c) Risk factors related to Good Manufacturing Practice (GMP):

13. Cross- contamination between different processes being run successively on the same manufacturing line (e.g. from contaminated solvents or process equipment due to improper equipment of facility cleaning).

14. Carry-over of impurities between process steps due to operator-related errors or insufficient detailed batch records such as inadequate phase separations during work-up procedures.

15. Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts) where the recovery is outsourced to third parties who are not aware of the content of the materials they are processing. Recovery processes carried out in non-dedicated equipment should also be considered.

    For more details on root causes, the PRH may refer to 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.

Mitigation Steps

Step 1: Risk-Evaluation

PRH are required to perform risk evaluation to identify if the API and/ or finished products could be at risk of nitrosamine presence.

Step 2: Confirmatory Testing

If a risk is identified, PRH is required to proceed with confirmatory testing in order to confirm or refute the presence of nitrosamine impurities in the finished product.

Reports on the confirmatory testing should be generated as soon as possible.

To perform testing, the applied analytical method should be sufficiently sensitive. The Limit of Quantification (LoQ) should be at or below the acceptable limit for the respective nitrosamine impurities. Most importantly, the purpose of testing also needs to be taken into account (e.g. to be set as routine testing, to support justification for skip testing or to support justification for omission of testing).

Step 3: Risk Mitigation Measures

If the amount of nitrosamine impurities exceeds the limit listed in USFDA and EMA guidance documents, PRH is required to report to the authority by providing the following documentations:

a) Test results expressed in ng and ppm.
b) Interim investigation report including (preliminary) root cause, risk mitigating plan and benefit/ risk assessment.
c) Appropriate proposal on the regulatory action if it involves batch/ batches that are currently available in the market for NPRA consideration.

Reporting Changes

In general, the outcome of the risk assessments should be made available to the authority upon request.

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

a) Variation submission may/ may not be required depending on the following scenarios:

i) Variation submission required

If the root cause has been identified in the finished product manufacturing process or storage, or nitrosamines have been detected in the finished product but the actual source of contamination remains unclear, routine testing of the finished product is required by default.

Exceptions from routine testing may be possible, if:

1. The root cause of contamination is demonstrated to be well-understood, AND
2. Levels of a single nitrosamine are consistently below 30% of the acceptable limit based on API and/or the finished product, skip-testing according to the ICH Q6A definition is acceptable.

ii) No variation submission is required

If no changes/variation needed for example there is nitrosamine detected but PRH wish to omit it from being routinely tested (omission).

Omission from the specification is only justified if it can be shown that the levels of nitrosamines are consistently ≤ 10% of the specified limit and the root cause is identified and well-understood.

New Product/ Product Under Evaluation

If the risk assessments (and confirmatory testing plan/ data/ result if necessary) are not submitted as part of the registration dossier, the documents may be requested during the ongoing evaluation process, whenever necessary.

4. IMPLEMENTATION AND MONITORING

It is of particular importance to ensure that sufficient supply of pharmaceutical products is constantly available in the market for patients use. Therefore, the implementation of control of nitrosamines shall be based on the risk benefit approach. The manufacturer is mainly responsible in ensuring the quality, safety and effectiveness of the product throughout its lifecycle and this includes but not limited to assuring that all marketed batches of pharmaceutical products do not contain nitrosamine impurity above the allowable limits. As such, PRH shall undertake risk assessments (and the subsequent steps, if necessary) for all

pharmaceutical products in the market. Considering that the risk of nitrosamine impurity is also associated with the frequency and duration of products used, the PRH may prioritize on assessing the risk of chronically used products in addition to the products which are known to have identified risk factors published by reference authorities such as EMA and USFDA.

NPRA will continue to work closely with other regulatory agency and the industry in monitoring the content of nitrosamine impurities in pharmaceutical products. In addition, the industry has also shown commitment in addressing the need for control of nitrosamines. As a result, NPRA has occasionally received alerts from other regulatory agencies and reports from PRH notifying on the detection of nitrosamine impurities in their products containing different API.

Noting the gaps, the amount of effort and resources required to fulfil the requirement on the confirmatory testing in particular, the industry shall at least develop a comprehensive plan for the conduct of risk assessment. NPRA however will continue the surveillance program and perform periodic monitoring on pharmaceutical products in the market to ensure that safety, quality and efficacy adhere to current requirements. As and when needed, the PRH is expected to provide the necessary and relevant data and information in a timely manner.

References:

1. USFDA : Control of Nitrosamine Impurities in Human Drugs Guidance for Industry
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

2. EMA : 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
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

3. EMA : 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
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities