

# Policy Position

## Addressing the potential formation of N-Nitrosamines impurities in human medicinal products with chemically synthesized active pharmaceutical ingredients: Industry Actions and Recommendations

### **SUMMARY OF KEY MESSAGES AND RECOMMENDATIONS**

#### **1. The potential formation of N-Nitrosamines impurities, as a global concern, needs a proportionate and aligned global response taking account of the current scientific knowledge**

- The impact of this issue on the quality and safety of medicinal products needs to first be fully understood and the balance of benefit/risk relative to environmental factors carefully weighed for suitable actions to be undertaken by pharmaceutical manufacturers and National Regulatory Agencies (NRAs).

#### **2. Regulatory reporting must be streamlined and proportionate, focusing on risk to patients, and to minimize the burden for both industry and NRAs:**

- Where an immediate risk to patients is identified, this will be promptly and appropriately communicated to NRAs;
- Outcomes of the completed risk evaluations on drug products will be reported, where requested by NRAs (full risk evaluations will be available upon request, i.e. not routinely reported);
- Interim progress on risk evaluations of APIs, if requested by NRAs, could be reported;
- Companies will make an appropriate regulatory submission, where applicable, to introduce any required changes to the manufacturing process and/or control strategy necessary to control nitrosamine impurities in APIs and/or drug products.

#### **3. Industry actions taken to date and further recommendations to evaluate the risk for the presence of nitrosamine impurities in human medicinal products:**

- a. Risk evaluations are initially focused on the synthetic active pharmaceutical ingredients;
- b. Risk evaluations for drug products require adequate time because the understanding of risk factors is evolving, and one API is often used in multiple products;
- c. Risk evaluations require timely provision of information by all suppliers along the supply chain:
  - Industry and Agencies should develop aligned communications regarding stakeholders' obligations for the provision of information to support risk evaluations;
- d. The ICH M7<sup>1</sup> principles on impurities classification with respect to mutagenic and

<sup>1</sup> ICH M7: Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

carcinogenic potential and resulting control actions generally apply to nitrosamines, but could benefit from additional specifics:

- ICH M7 should be revised to specifically address how its principles should be applied to the assessment and control of certain cohort of concern impurities such as N-nitrosamines.

**4. Confirmatory testing should only be conducted on representative products where a significant risk is identified.**

**5. Remediation of manufacturing processes: current GMPs (cGMP) for Drug Substance and Drug Products are suitable and do not need to be changed.**

- cGMP best practices to address N-nitrosamines impurities should be supported by aligned communications from industry associations and inspectorates.

**6. Any revision of regulatory standards and guidelines that may be necessary to protect public health should be science driven and harmonized globally.**

- If any changes are needed to public Quality standards in Pharmacopoeias, the requirements should be globally harmonized.

## **KEY MESSAGES AND RECOMMENDATIONS**

In 2018, N-nitrosamine<sup>2</sup> impurities were found in a number of anti-hypertensive medicines in the 'sartans' class which resulted in specific product recalls and the actions by NRAs around the world to set strict new manufacturing requirements for these medicines. More recently, nitrosamines have also been reported in ranitidine, nizatidine and metformin products, and several NRAs (e.g. EMA Information notice 26 September 2019 and the WHO [information note](#)) have directed the pharmaceutical industry to review all medicinal products containing synthetic Active Pharmaceutical Ingredients (APIs) for the presence of nitrosamine impurities and to remediate manufacturing processes, if necessary.

The pharmaceutical industry is fully committed to providing patients across the globe with high quality, safe and effective medicines. Patient safety remains our industry's utmost priority, and this position paper describes actions being taken and recommendations from the industry to address the concerns with nitrosamine impurities as quickly and efficiently as possible, while maintaining patients' safety.

**1. The potential formation of nitrosamines impurities, as a global issue concern, needs a proportionate and aligned global response taking account of the current scientific knowledge**

The manufacture of medicines is usually ensured through global supply chains involving local regulatory oversight by different agencies in the different countries where suppliers are located. The scope of the review for the presence of nitrosamine impurities in drug products will require many companies to review hundreds of APIs and thousands of products approved

---

<sup>2</sup> N-nitrosamines are then referred as 'nitrosamines' throughout this document

and supplied globally, necessitating requests for information from thousands of API, excipient and packaging suppliers, and other third-party manufacturers.

The risks to patients appear to be relatively low based on currently available information published by NRAs – e.g. the Sartans exercise has shown that impurities were either not found or were present at very low levels – see: [EMA reference](#). Therefore, the impact of this issue on the quality and safety of medicinal products needs to first be fully understood and the balance of benefit/risk relative to environmental factors carefully weighed for suitable actions to be undertaken by pharmaceutical manufacturers and NRAs.

This is best achieved on an aligned global basis in order to protect patients worldwide as quickly and efficiently as possible, and by industry and NRAs applying science- and risk-based approaches, to build a comprehensive understanding of the root causes and actions needed to protect public health. Mechanisms to share information between Agencies and industry could be helpful to support this global approach (such information could include: root causes, analytical methods and results etc...).

Additional regulatory requests for particular data on specific products should be coordinated on a global basis, and prioritized in the light of the overall risk assessment exercise. Indeed, unrealistic national or regional regulatory deadlines for the completion of certain activities could have the unintended consequence of appearing to force the prioritization of protection of patients in one country or region over another.

Thus, and while the scientific knowledge about the safety and sources of concern is evolving, it is critical that healthcare professionals and patients receive timely and accurate information about any risks to the safety and quality of medicines, and that such risks are communicated appropriately to avoid undermining confidence in the supply of medicines.

## **2. Regulatory reporting must be streamlined and proportionate, focusing on risk to patients, and to minimize the reporting burden for both industry and NRAs**

Industry understands the importance of providing appropriate information to patients and health care professionals where a real risk is present (i.e. when the presence of a toxic nitrosamine is confirmed) and such instances will, of course, be promptly and appropriately communicated to NRAs, especially if there is an immediate risk to public health. Industry will also follow established procedures with respect to reporting ‘alerts’, as required in certain jurisdictions.

Nevertheless, the release of multiple and different reporting expectations and timelines by several Agencies worldwide has created an administrative burden that is not conducive to effective and timely communication of progress by industry.

### **Recommendations**

- Where an immediate risk to patients is identified, this will be promptly and appropriately communicated to NRAs;
- Outcomes of the completed risk evaluations on drug products will be reported, where requested by NRAs (full risk evaluations will be available upon request, i.e. not routinely reported);

- Interim progress on risk evaluations of APIs, if requested by NRAs, could be reported also;
- Companies will make an appropriate regulatory submission, where necessary, to introduce any required changes to the manufacturing process and/or control strategy necessary to control nitrosamine impurities in APIs and/or drug products.

### **3. Evaluating the risk for the presence of nitrosamine impurities in human medicinal products: industry actions taken to date and further recommendations**

The chemistry of nitrosamine formation is complex, and information has been shared between NRAs and industry on common nitrosamines that have been identified in medication thus far. It is important to continue to share knowledge as any additional nitrosamines are discovered and to ensure information is developed on the toxicity of these.

#### **a. Risk evaluations are initially focused on the synthetic active pharmaceutical ingredients**

Industry has initiated risk assessments on the presence of nitrosamines in APIs as the chemistry and manufacture of APIs is most susceptible to risks for generation of nitrosamine impurities, based on the risk factors identified from the knowledge gained from the sartans.

Trade associations have developed processes for the risk evaluation (e.g. *EFPIA API Risk Assessment process*) for use by their member companies. This may help alignment across companies, although alternate approaches may have been adopted.

#### **b. Risk evaluations for drug products require significant time because the understanding of risk factors is evolving, and one API is often used in multiple products**

It is understood that for nitrosamines to be generated in a medicinal product during manufacture and storage, an amine vulnerable to nitridation (i.e. a secondary or tertiary amine) needs to be present. Therefore, if such amines are absent from the product, the nitrosamines will not be formed in the product: this is a key aspect being used by industry to identify which drug products have a significant risk for the presence of unacceptable levels of nitrosamines.

In contrast to APIs, understanding of the risk factors leading to nitrosamine presence in drug products is not as well-developed. Indeed, the potential for the formation of nitrosamines by reactions between low levels of nitrozing agents (e.g. nitrite) in excipients and the API, during manufacture and storage of the drug product, is not well understood. Contamination of excipients by nitrosamines is also unknown, and could contribute to the daily exposure to nitrosamines due to contaminated food, beverages, and air and water pollution – see Agencies references also, e.g. [US FDA and EMA/CHMP Article 31 Sartans Referral \(page 16 of the Assessment Report\)](#).

In addition, the potential for formation of nitrosamines during certain packaging operations has been reported, but the impact still needs further investigation. To increase scientific understanding of the risk factors for nitrosamine formation in drug products, industry is investigating the conditions under which amines and nitrozing agents will form nitrosamines, including considerations for excipients and water quality.

Trade associations have developed processes for the risk evaluation (e.g. *EFPIA Drug Product Risk Assessment process*) for use by their member companies. This may help alignment across companies, although alternate approaches may have been adopted, and the identification of additional risk factors could necessitate revision of the process and potentially re-assessment of completed evaluations.

Although companies are seeking to complete the drug product risk evaluation as quickly as possible, the large number of products to be assessed and evolving scientific knowledge mean that for some companies it is impossible to meet the published deadlines.

**c. Risk evaluations require the timely provision of information by all actors along the supply chain**

All actors in the pharmaceutical supply chain need to understand the risk factors and expectations for the communication of key information to other stakeholders conducting the risk assessments. Failure to provide appropriate information may result in sub-optimal and/or inconsistent approaches to risk assessments (potentially leaving some risks un-addressed), resulting in uncertainties about the outcome of the assessment process and the quality of the medicinal products. It should be noted that the pharmaceutical industry may not be a key business for some suppliers of materials used in the manufacture of APIs and drug products, potentially affecting the ability and willingness to supply information requested.

**Recommendation:** industry and Agencies to develop aligned communications regarding stakeholders' obligations for the provision of information to support risk evaluations.

**d. The ICH M7<sup>3</sup> principles on impurities classification with respect to mutagenic and carcinogenic potential and resulting control actions generally apply to nitrosamines, but could benefit from additional specifics**

Pharmaceutical products should not be contaminated with significant levels of hazardous materials such as nitrosamines that have found to be potent mutagens from toxicological evaluation. Because of the ubiquitous nature of nitrosamines in the environment, an expert assessment of their safety levels as well as identification for sources of risk should be completed. Industry cannot guarantee that the presence of nitrosamines will be completely eliminated from pharmaceutical products. However, risk assessments can determine the probable sources for the generation and presence of nitrosamines and inform the use of appropriate control measures.

Trade associations have developed a position on principles (which are aligned with ICH M7 guideline) that are applicable in case of the nitrosamine evaluations (*e.g. EFPIA position with respect to Safety related aspects of EMA and Health Canada requests for N-nitrosamine evaluations*). These can be used to inform risk evaluations and decisions on the need for confirmatory testing.

Industry is working to further understand the actual toxicity of nitrosamines (in particular more complex nitrosamines than those found in the sartans). The latest information (see EFPIA safety paper referred to above) suggests that the mechanism of toxicity involves a pathway that requires particular structural elements to be present in a nitrosamine, and that without these the nitrosamine may be far less potent or may be non-mutagenic.

**Recommendation:** ICH M7 should be revised to specifically address how its principles should be applied to the assessment and control of certain cohort of concern impurities such as N-nitrosamines.

---

<sup>3</sup> ICH M7: Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

#### **4. Confirmatory testing is only conducted on representative drug products where a significant risk for nitrosamine impurities is identified**

The development of analytical methods for confirmatory testing that can reliably quantify several simple nitrosamines in drug products at very low levels is not straightforward e.g. due to the lower concentrations that may be present, difficulties with recovery from the matrix etc. The validation of such methods must be fit-for-purpose and may not need to meet all traditional ones such as described in ICH Q2<sup>4</sup>.

Furthermore, confirmatory testing should only be conducted on representative drug products where a significant risk for nitrosamine impurities is identified. Judicious use of resources to conduct confirmatory testing, both human and equipment, is necessary and may necessitate testing of representative samples (e.g. using matrixing or other approaches) rather than those from a particular country.

#### **5. Remediation of manufacturing processes: Current GMPs (cGMP) for Drug Substance and Drug Products are suitable and do not need to be changed**

Trade associations have developed a reflection paper on GMP aspects relating to the contamination of APIs and drug products by nitrosamine impurities (*EFPIA GMP considerations in relation to nitrosamines*). This considered some of the GMP root causes and risk factors, which are not directly related to the actual product or process chemistry, but which have been identified during recent investigations, including general GMP processes (e.g. Quality Agreements, Change Control...) and specific risk factors (e.g. handling of solvents and reagents, cleaning of process equipment to the required limit). It concluded that current GMPs for Drug Substance and Drug Products are suitable and do not need to be changed, but identified also a number of best practices that could reflect the 'c' in cGMP.

**Recommendation:** adoption of cGMP best practices to address nitrosamines impurities, should be supported by aligned communications from industry associations and inspectorates.

#### **6. Any revision of regulatory standards and guidelines that may be necessary to protect public health should be science driven and harmonized globally**

As noted above, industry recommends that the ICH M7 Guideline is updated to address nitrosamine impurities, and this revision incorporated into national and regional regulatory frameworks. The scope of ICH M7 includes both drug substances and drug products, but there are exclusions for certain types of materials and products.

Consequently, there may be the need to revise the quality standards for some materials used in the manufacture of medicines, if the use of these materials is found to introduce unacceptable risks for the presence of nitrosamine impurities in medicines. Such quality standards are usually found in national or regional pharmacopoeias.

**Recommendation:** if any changes are needed to public Quality standards in Pharmacopoeias, the requirements should be globally harmonized.

---

<sup>4</sup> ICH Q2: Validation of Analytical Procedures: Text and Methodology