

Policy Position

Addressing the potential formation of N-Nitrosamines impurities in human medicinal products: Industry Recommendations

In 2018, N-nitrosamine impurities, which are classified as probable human carcinogens, were found in a number of anti-hypertensive medicines in the 'sartans' class which resulted in specific product recalls. More recently, nitrosamines have also been reported in ranitidine, nizatidine and metformin products, and several National Regulatory Authorities (NRAs) around the world 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; these directions include the [EMA guidance to MAHs](#), first issued in September 2019 and revised in August 2020, the WHO [information note](#) and the more recent [US FDA guidance](#). Some regions have since extended the requirements to include all medicinal products, i.e. beyond those containing synthetic APIs.

The biopharmaceutical R&D-based industry is fully committed to providing patients across the globe with high quality, safe and effective medicines. Patient safety remains our utmost priority, and this position paper describes industry's recommendations to address concerns with nitrosamine impurities as quickly and efficiently as possible to protect public health.

This second edition of the industry global position paper reflects progress and developments in scientific understanding since the [June 2020 version](#).

1. Regulatory reporting requirements must be harmonized, streamlined and proportionate, focusing on patient safety, while minimizing the burden for both NRAs and industry.

IFPMA and its members fully understand 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 be promptly and appropriately communicated to NRAs, especially if there is an immediate risk to public health.

IFPMA and its member companies remain committed to reporting the outcomes of the completed risk evaluations on drug products, where requested by NRAs (full risk evaluations will be available upon request, i.e. not routinely reported); where an immediate risk to patients is identified, this will be promptly and appropriately communicated to NRAs.

Furthermore, IFPMA member companies will make the appropriate regulatory submissions, where necessary, to introduce any changes to the manufacturing process and/or control strategy necessary to control nitrosamine impurities in APIs and/or drug products.

Industry believes that all the above will be more successfully achieved where reporting expectations and timelines are harmonised across NRAs.

2. The potential formation of N-Nitrosamines impurities is a complex and global concern that needs a proportionate and aligned global response that takes into account of the current, ever-evolving scientific knowledge

The chemistry of nitrosamine formation is complex, and it is important to continue to share knowledge between industry and NRAs to ensure accurate information is gathered on the risks of their presence in medicines, and to the patients taking them. A common understanding is best achieved on an aligned global basis in order to protect patients worldwide as quickly and efficiently as possible, and by industry and regulators 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 NRAs and industry could be helpful to support this global approach (such information could include: root causes, analytical methods and results etc...).

Since this exercise was initiated in 2019, significant progress has been made demonstrating the low risk associated with traces of nitrite in water during API manufacturing and that this can be controlled through adequate purge¹. With regard to excipients, the potential for the formation of nitrosamines by reactions between low levels of nitrosating agents (e.g. nitrite) in excipients and the API, during manufacture and storage of the drug product, is not yet fully understood, and continues to be investigated further. In addition, the potential for formation of very low levels of nitrosamines during certain packaging operations has been reported, but the impact still needs further investigation. Thus, 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.

Furthermore, specific considerations should be given to products classes out of scope of the ICH M7 Guideline, such as those intended for advanced cancer, which fall under the scope of the ICH S9, and should thus be controlled according to ICH Q3A(R2) and ICH Q3B(R2), as specified in the ICH S9 Q&A document. If the active substance itself is mutagenic or clastogenic at therapeutic concentrations, nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH M7(R1).

Some NRAs have also extended the scope of the risk evaluations to include all biological medicinal products, although it is recognised that there is a very low risk of nitrosamines impurities being present in such products. Similarly, vaccines, which are biologically-derived products, fall within the scope of risk evaluations for biological products. As with other biologic products, there is a very low risk of nitrosamine impurities being present in vaccines, and the infrequent dosing regimens for vaccines would considerably lower cumulative exposure to any nitrosamine impurities that might be present. Therefore, risk management will focus on specific formulations involving synthetically derived excipients or adjuvants.

IFPMA recommends that any revision of regulatory standards and guidelines that may be necessary to address this issue and protect public health should be science-driven and harmonized globally. This includes the revision of the ICH M7 Guideline, with scientific and technical input from industry and regulators, to specifically address how its principles should be applied to the assessment and control of certain cohort of concern impurities such as N-nitrosamines.

¹ Potential for the Formation of N-Nitrosamines during the Manufacture of Active Pharmaceutical Ingredients: An Assessment of the Risk Posed by Trace Nitrite in Water - <https://pubs.acs.org/doi/full/10.1021/acs.oprd.0c00224>

3. Control strategy, including Confirmatory Testing considerations

The control strategy for nitrosamine impurities should be based on the scientific understanding of the manufacturing process of drug substance and drug products, and the properties of the input materials for these processes. Industry considers that it is important to distinguish confirmatory testing from control strategies intended to avoid or reduce presence of nitrosamines in medicinal products.

Industry understands that 'confirmatory testing' is only conducted to confirm the presence of nitrosamines in the drug product, where the conditions and/or probability of potential levels exceed an appropriate safety threshold. 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. The validation of such methods must be fit-for-purpose and may not need to meet all traditional criteria such as described in ICH Q2[2].

Where confirmatory testing has to be performed on the drug product, it should be conducted on an appropriate number of batches. Judicious use of resources to conduct confirmatory testing, both human and equipment, is necessary and may require testing of representative samples (e.g. using matrixing or other approaches) rather than those from a particular country

With regard to the remediation of manufacturing processes, where these may be needed, industry believes that current GMPs (cGMP) for Drug Substance and Drug Products are suitable and do not need to be changed. Thus, and to support the application of existing requirements, IFPMA and its members recommend that cGMP best practices to address N-nitrosamines impurities be supported by aligned communications from industry associations and inspectorates.

Patients' safety remains IFPMA members utmost priority, and IFPMA supports its member companies' commitment to perform risk evaluations for the formation of nitrosamine impurities. IFPMA acknowledges and highlights also that significant industry resources have had to be redistributed to address the global COVID-19 crisis.

IFPMA believes that the risks for the formation of nitrosamine impurities can be addressed through application of the current regulations and guidelines, and supports strengthening of these guidelines, including ICH M7, in an internationally-harmonized manner, based on scientific evidence.

^[2] ICH Q2: Validation of Analytical Procedures: Text and Methodology