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

In 2018, N-nitrosamine impurities 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, e.g. the EMA Information notice to MAHs of September 2019 and the WHO information note of December 2019.

More recently, the WHO Prequalification Unit published a note informing that it will be contacting finished products applicants and API Master File holders to request that a risk assessment is undertaken to evaluate the potential for the presence of nitrosamine impurities for the concerned APIs and products.

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, in order to protect public health.

1) 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 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.

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.

2) 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.

3) Risk evaluations for drug products require adequate time because the understanding of risk factors is evolving

Information already published by NRAs (e.g. the Sartans exercise), has shown that impurities were either not found, or present at very low levels. It is acknowledged also that the area of higher risk would be associated with the API. Thus, the R&D-based industry is initially focusing its risk evaluation on the synthetic APIs.

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.

The ICH M7 Guideline, which outlines recommendations for assessment and control of mutagenic impurities that reside, or are reasonably expected to reside, in a final drug substance or product, provides appropriate general guidance for this exercise. A revision of the ICH M7 GL could specifically address how its principles should be applied to the assessment and control of certain cohort of concern impurities such as N-nitrosamines.

The confirmatory testing steps that may follow as a result of the above risk evaluation should only be conducted on representative products where a significant risk has been identified. This is critical to guarantee an optimum use of often limited analytical resources, especially in the current COVID-19 pandemic situation.

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

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 in an internationally-harmonized manner, based on scientific evidence.