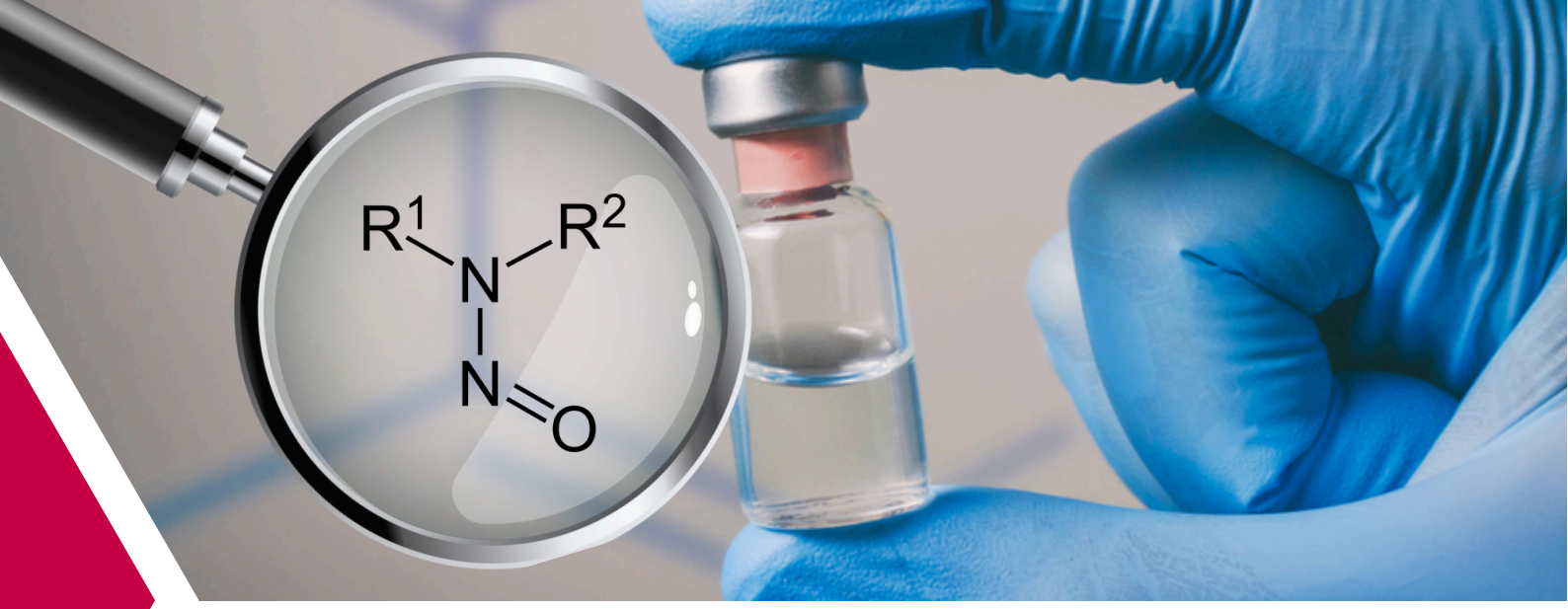


The Risk of Nitrosamine Impurities in Biologics

What Biopharma Developers Need to Know

Nitrosamine impurities are highly toxic compounds, known for their potential to damage DNA and increase the risk of cancer, even in trace amounts. Regulatory agencies across the globe, including the FDA and EMA, have raised alarms after detecting these impurities in several drug products, resulting in the recall of widely used pharmaceuticals like valsartan, ranitidine, and metformin. While much of the focus has been on small molecule drugs, the landscape is shifting — and biologics are not exempt from this scrutiny.

A Growing Concern for Biologics

The risk of nitrosamine contamination in biologics may seem low at first glance, due to the high-water purity used for the manufacturing, formulation and storage conditions which are unfavorable to the formation of nitrosamines, and effective purification procedures.

However, as biologics become more complex and incorporate synthetically derived components, the potential for nitrosamine formation and introduction increases. In these cases, the risk mirrors that of small-molecule drugs, as chemically produced components and intermediates can harbor the same vulnerabilities to nitrosamine impurities. Additionally, the packaging materials used in biologic products, such as elastomeric vial stoppers and other components in container closure systems, have been shown to contribute to nitrosamine formation which can leach into the final product.

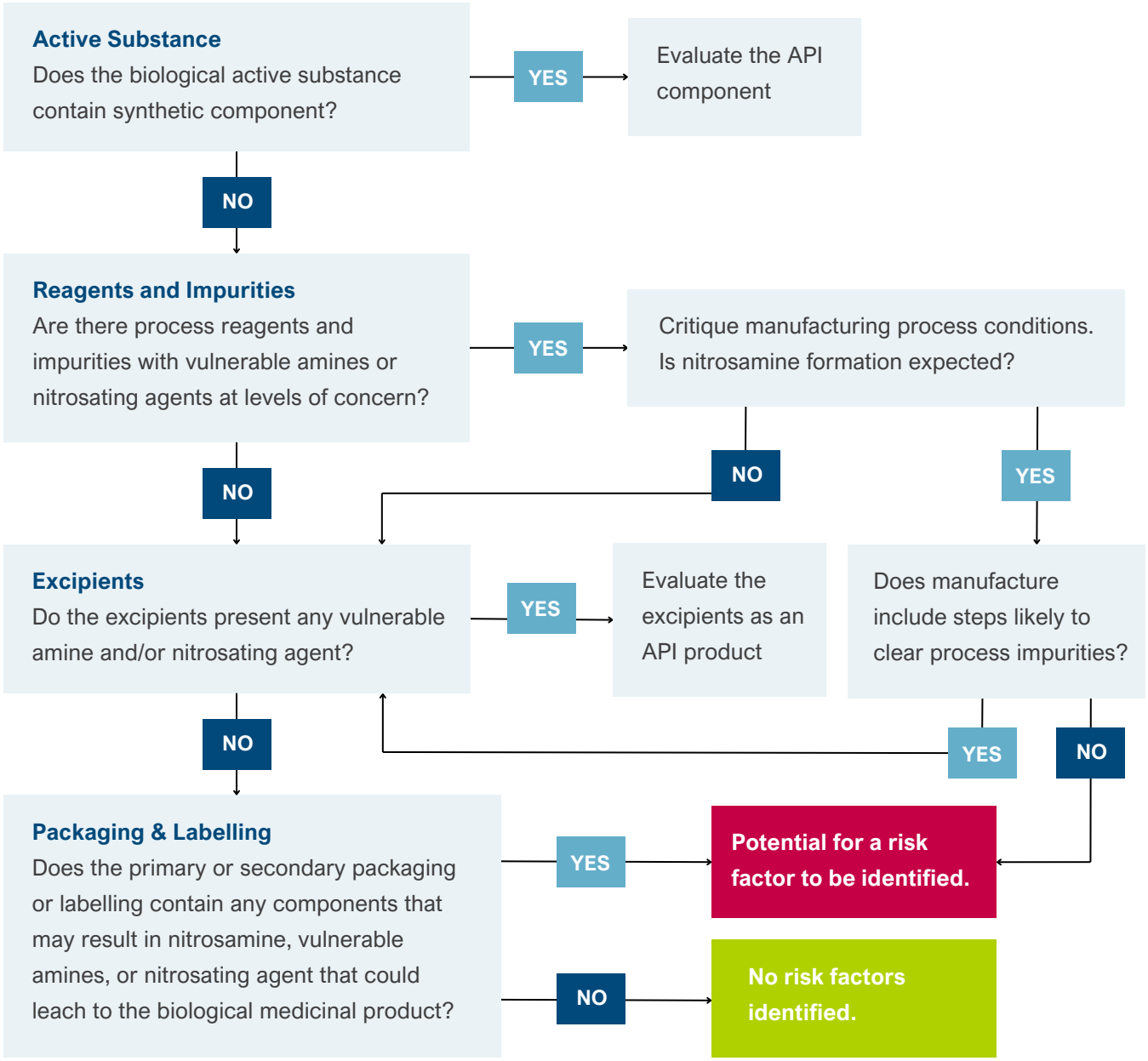
Regulatory Response: Biologics in the Spotlight

In 2020, the EMA extended its nitrosamine risk assessment guidance to biologics, signaling the start of heightened regulatory expectations for this class of therapeutics. Health Canada, Swissmedic, and ANVISA have since followed suit, urging biologics manufacturers to adopt rigorous risk assessments and implement sensitive detection methods. The use of advanced techniques like gas chromatography-mass spectrometry (GC-MS/MS) and liquid chromatography-mass spectrometry (LC-MS/MS) is recommended for identifying and quantifying nitrosamines, with regulatory bodies expecting quantification limits to meet strict thresholds.

Where the Risk Lies for Biologics

Although biologics have not faced market withdrawals due to nitrosamine contamination so far, the diversity in biologic molecular types, production methods, and supply chains introduces various risk factors for nitrosation. Ongoing vigilance, robust risk assessments (see framework below, adapted from the European Federation of Pharmaceutical Industries and Associations - EFPIA 2020), and cutting-edge detection methodologies are essential to safeguard patient safety and ensure compliance with evolving regulatory expectations.

Solvias is committed to helping biologics manufacturers navigate these challenges. We offer comprehensive nitrosamine risk assessments tailored to biologics and other complex therapeutic modalities. By combining our scientific expertise with state-of-the-art analytical technologies, we can help you stay ahead of regulatory requirements and ensure the purity and safety of your products.



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