FUTURE-PROOFING PARENTERAL PACKAGING AGAINST NITROSAMINES

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DATWYLER

INTRODUCTION

During the last five years, industry regulators, including the US Food and Drug Administration (FDA), have been forced to look closely at the contamination risk of nitrosamines – organic compounds that are commonly found in foods and water but that could have carcinogenic properties in high concentrations. The discovery of large quantities of nitrosamines in many drugs has led to a high number of product recalls, and has raised the possibility of costly lawsuits for pharma companies.

In this paper, we will look at why the issue of nitrosamine contamination has emerged since 2018, what causes of contamination have been identified, how regulators and the pharmaceutical industry have responded, and how parenteral packaging can be adapted to minimise the risk.

Recalls are a normal part of pharmacovigilance processes.

RISK FACTORS AND RECALLS

Nitrosamine contamination has led to many high-profile drug recalls in recent years, including popular medications for hypertension, heartburn and diabetes. In fact, Morgan Stanley estimates that the recall of an over-the-counter heartburn medication, once the best-selling drug in history – may cost its marketing authorisation (MA) holders between $10.5bn and $45bn in trial judgments.

Overall, there have been more than 250 nitrosamine-related drug recalls since 2018, with tens of thousands of lawsuits yet to be filed.

One article published by the Journal of Pharmaceutical Sciences reviewed the APIs and drug impurities of 12,000 small molecule drugs to identify their potential to form nitrosamines under the relevant conditions. The data revealed that 40.4% of the analysed APIs and 29.6% of the API impurities were potential nitrosamine precursors, meaning many more recalls could make the list.

There is still debate over the level of risk that nitrosamines pose to health. According to the FDA, some nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, though people taking drugs containing NDMA at or below the acceptable intake limits every day for 70 years are not expected to have an increased risk of cancer.

The Journal of Medicinal Chemistry, in its Critical Analysis of Drug Product Recalls due to Nitrosamine Impurities, notes that recalls, which are a normal part of stringent pharmacovigilance processes, are justified due to the genotoxic and carcinogenic potential of N-nitrosamines compounds, which raise serious safety concerns.

In September 2020, the FDA set a clear intent to ensure the control of nitrosamines in pharmaceutical products. At the time, its database showed that more than 1400 product lots had been recalled due to N-nitrosamine exceeding the acceptable limit.

EXPOSING THE NITROSAMINE RISK: HOW DID WE GET HERE?

There is no shortage of nitrosamines in the environment. They are formed in the air, as they are a by-product of combustion processes, and in trace amounts in water due to biological processes. They find their way into food products through the reaction of nitrite with nitrosatable amines in meat, fish, and other products at higher temperatures.

Many regulators had already set safe limits for nitrosamines in foods and, in some cases, drinking water. The pharmaceutical industry's drug recall problem emerged in 2018 from routine testing for the benefit versus risk balance of certain blood pressure medicines. During the course of that testing, the FDA and European Medicine Agency (EMA) observed nitrosamines levels that were high compared to the existing guidelines on acceptable limits.

Both agencies found similar results in their routine testing, as did some drug manufacturers, and when nitrosamine levels were seen to exceed the guidelines on daily intake limits in Valsartan, an angiotensin II receptor blocker used to treat heart failure and hypertension, all drugs in the sartans class were investigated. Subsequently, nitrosamines were found in some diabetic and heartburn treatments.

According to the National Institutes of Health in the US, many nitrosamines are potent carcinogens, with more than 30 listed under California's Proposition 65, which requires businesses to provide warnings to state residents about significant exposures to chemicals that cause cancer, birth defects or other reproductive harm.

NDMA, NDEA, N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitrosomethyl-n-alkylamine (NMA), and 12 other carcinogenic NMAs are identified as risk factors by the National Institutes of Health, as they exhibit common genotoxic and tumorigenic activities in animal studies. Its conclusion is that nitrosamine contamination in drugs for long-term use can increase cancer risks and pose a serious concern to public health.

Nitrosamine	AI Limit (ng/day)
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Table 1. Acceptable Intake Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products (source: FDA)

A SWIFT REGULATORY RESPONSE

The discovery of nitrosamines in some types of drug product led regulators to conduct a detailed analysis of the impurities in infected APIs and drug treatments. Conducting a thorough risk assessment of all relevant products, while simultaneously ensuring a consistent supply of drug products to patients, was a major challenge for both regulators and the pharmaceutical industry.

"Most of the health authorities, especially the EMA and FDA, acted in a very fast and, I would say, exemplary way to address this issue," remarks Tabassam Sharif, Regulatory Affairs Manager at Datwyler, which designs and manufactures elastomer components for syringes, cartridges, and vials. "They conducted studies testing various products and issued a number of guidelines for the pharma industry, for healthcare professionals, and also for patients."

The authorities gave a timeline to MA holders to conduct a risk assessment study of potential nitrosamines on all of the authorised, already marketed products in a phased manner.

The EMA finalised a review under Article 5(3) of Regulation (EC) No 726/2004 in June 2020 to provide guidance to MA holders on how to avoid the presence of nitrosamine impurities in human medicines.

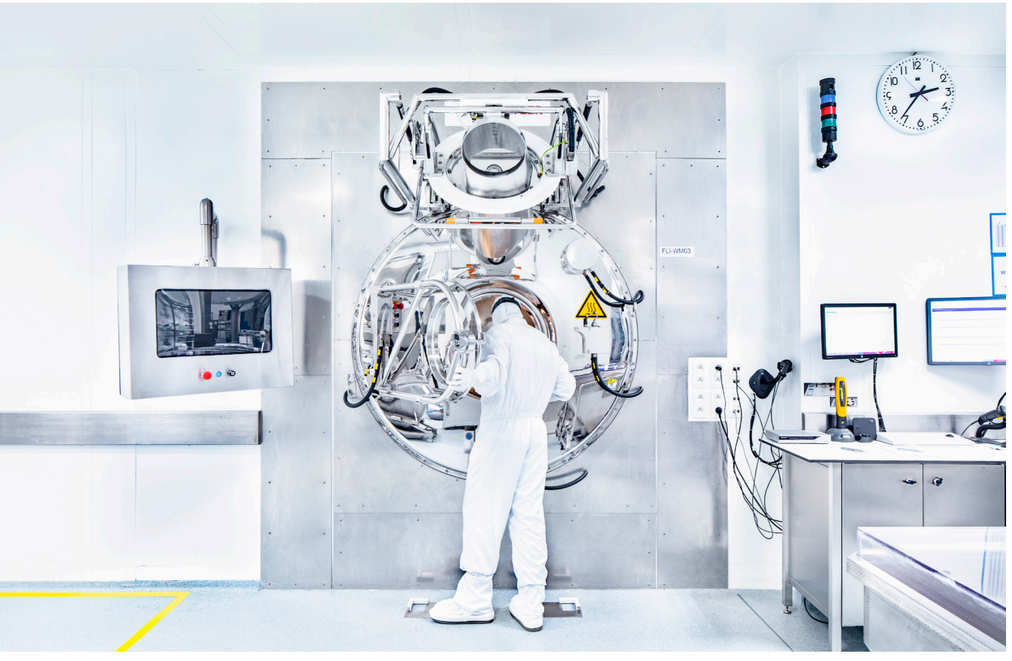
The EMA's Committee for Medicinal Products for Human Use (CHMP) requested MA holders to review all chemical and biological human medicines for the possible presence of nitrosamines and test products at risk.

Companies are required to have appropriate control strategies to prevent or limit the presence of these impurities and, where necessary, to improve their manufacturing processes. The authorities have been praised for providing a clear process for risk assessment, and risk mitigation strategies were outlined in line with the level of risk. If a low level of risk was identified, then confirmation testing over a certain time period would be required, as well as updating of existing registration dossiers with the recent studies on nitrosamines.

"All these types of activities were covered in a phased manner," adds Sharif. "Regulators and the pharma industry worked well together. APIs were mostly on the high risk end of nitrosamine formation."

In addition to regulatory guidelines issued by different authorities, Pharmacopeia also took action. The European Pharmacopoeia published a specific chapter, Nitrosamines in Active Substances, where potential nitrosamines were listed, as well as how they can be tested and what the possible sources are. Similarly, the US Pharmacopeia published a chapter on Nitrosamines Impurities.

"They completed the process in a very short time," continues Sharif. "As the authorities are now quite sensitive about this nitrosamine issue, the industry has now included this risk assessment as a routine development step during the early stage of development of every drug product. That's the main step they have taken. They are also routinely conducting stability studies, in which they are also testing nitrosamines. So that's a change on the industry side."



The health authorities provided a clear risk assessment process.

There is a well-known link between certain types of rubber and nitrosamines.

IDENTIFIED SOURCES OF NITROSAMINE CONTAMINATION

In its advice to MA holders, the EMA noted that it had identified the major causes of nitrosamine formation and contamination:

- Use of sodium nitrite ($NaNO_2$), or other nitrosating agents, in the presence of secondary, tertiary amines or quaternary ammonium salts within the same or different process steps
- Use of sodium nitrite ($NaNO_2$), or other nitrosating agents, in combination with reagents, solvents and catalysts, which are susceptible to degradation to secondary or tertiary amines, within the same or different process steps
- Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts)
- Use of recovered materials (e.g. solvents, reagents and catalysts), including recovery outsourced to third parties who are not aware of the content of the materials they are processing and routine recovery processes carried out in non-dedicated equipment
- Use of contaminated starting materials and intermediates supplied by vendors that use processes or raw materials which may allow nitrosamine formation
- Cross-contamination due to different processes run on the same line and due to operator-related errors such as inadequate phase separations
- Degradation processes of starting materials, intermediates and drug substances, including those induced by inherent reactivity in combination with carry-over of sodium nitrite ($NaNO_2$), or other nitrosating agents
- Use of certain packaging materials. Nitrosamine contamination has been observed by one MA holder in a finished product stored in blister packaging. The MA holder has hypothesised that the lidding foil containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines, which would be transferred to the product under certain packaging process conditions

"There are a number of pathways by which nitrosamines can be introduced into or generated as impurities in the pharmaceutical drug products," notes Sharif. "Packaging can also be a potential source – container closure systems, nitrocellulose blister in the packaging and the storage conditions of the drugs are all potential sources."

For the packaging part of the risk profile, caused by reactions of residual amine impurities with nitrosating sources in excipients of primary packaging, or reactions of nitrosating sources in the drug formulation with amines in the packaging, there are relatively simple steps that can be taken.

"There is indeed a link between rubber and nitrosamines which dates back a very long time," says Tine Hardeman, Manager of Material Development at Datwyler. "In certain rubber types, accelerators are used. If you have a specific type of elastomer, such as polyisoprene, and you want to cure it with sulphur then you often need to add an accelerator because otherwise the reaction is too slow."

"Most of those accelerators are not so healthy to start with," she adds. "They already bring some health concerns in themselves, but they also have the very important downside that after the reaction they generate secondary amines, which are a source of potential nitrosamine formation."

The good news is that this nitrosamine risk is mainly linked with older formulations of rubber. Now, most pharmaceutical rubber is halobutyl-based rather than polyisoprene. Halobutyl is more reactive and does not require an accelerator in the curing process.

"If you don't use accelerators, you can eliminate this source of secondary amines," states Hardeman.

CONCLUSION

While regulators and pharma companies continue to monitor the risk of contamination and better understand the carcinogenic properties of nitrosamines, one potential risk factor – parenteral packaging – can be eliminated relatively simply. Datwyler's award-winning sustainability work is helping the global pharmaceutical market transform into a greener, more environmentally friendly industry, and its sealing solutions are already designed to reduce the likelihood of nitrosamine contamination. The company has been manufacturing nitrosamine-free halobutyl compounds for primary packaging for decades.

"From the elastomeric closure part, in most cases we're already on the safe side, because the rubber used in pharmaceutical applications largely consists of very clean rubber, not using any accelerators," says Hardeman. "There are a few exceptions out there, with some very old legacy compounds, but with our pharmaceutical elastomeric closures you should not worry about nitrosamine risk."

For pharma applications with long-term contact with drugs – such as stoppers for vials, plungers for prefilled syringes, and combiseal material – halobutyl rubber is already the primary substance used. In the medical segment, where contact with drugs is minimal (for example, injection sites or needle sleeves), polyisoprene compounds are still in use, as the additional elasticity provided by the material is required. While the transition to cleaner compounds will be slower in this space due to the lower risk profile of medical applications, device manufacturers are also starting to feel the pressure to move to nitrosamine-free compounds. In these instances, Datwyler promotes the use of formulations that are cured in different ways without using nitrosamine-generating accelerators.

Halobutyl rubber is used for applications that have long-term contact with the drug.

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