

## N-SORB TECHNOLOGY FOR NITROSAMINE MITIGATION AND ENSURING GLOBAL REGULATORY COMPLIANCE

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### Introduction

Nitrosamine Drug Substance-Related Impurities (NDSRIs), which are probable human carcinogens, have been under increasing scrutiny by global regulatory authorities. These impurities have prompted recalls and stringent oversight due to their potential health risks. As regulations continue to evolve, drug manufacturers are now required to adopt comprehensive, proactive strategies to mitigate nitrosamine contamination in their products from all potential sources. Meanwhile, the FDA states in its website: “Another potential source of nitrosamine impurities that is not associated with a specific API is packaging.” To control this potential source, through its updated guidance *Control of Nitrosamine Impurities in Human Drugs* (Revision 2, September 2024), the FDA underscores the importance of incorporating packaging solutions into broader nitrosamine control strategies. Aptar CSP’s N-Sorb technology is designed to address this need by actively reducing and maintaining nitrosamine levels within regulatory limits, especially during drug storage and transport.

Accepted into the FDA’s Emerging Technology Program (ETP), N-Sorb represents a significant innovation in pharmaceutical packaging. This acceptance allows Aptar CSP to work directly with the FDA, ensuring the development and validation of the N-Sorb technology not only meets but exceeds regulatory expectations. Pharmaceutical companies can confidently integrate N-Sorb into their products, assured of compliance not just with FDA nitrosamine impurity guidelines but also those set by authorities such as the European Medicines Agency (EMA), Health Canada, and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan.

### Established Safety, Efficacy, and Regulatory Compliance

To demonstrate the safety and regulatory suitability of N-Sorb, Aptar CSP has taken critical steps aimed at satisfying global regulatory standards:

- **Use of GRAS Ingredients:** The active components of N-Sorb are classified as Generally Recognized as Safe (GRAS) in other intended use applications, which aligns with the FDA’s expectations for packaging materials used with drug products. This low risk selection provides a high level of confidence regarding the safety of N-Sorb in pharmaceutical applications, minimizing any regulatory hurdles related to safety concerns.
- **OML Testing:** N-Sorb has successfully passed overall migration limits (OML) testing, which provides the groundwork for demonstrating early indications that the material will not introduce harmful substances into drug products during storage. This initial success lays the foundation for further studies, which will support compliance with the EU’s packaging regulations, specifically Regulations 1935/2004, 450/2009, 2023/2006, and 10/2011, as amended. These upcoming studies will also confirm N-Sorb’s alignment with FDA packaging regulations, such as 21 CFR 177.1350, 177.1520, 182.1, and 182.2727, along with the FDA’s *Container Closure Systems for Packaging Human Drugs and Biologics Guidance* (July 1999). Additionally,

these studies are intended to meet the regulatory expectations of other jurisdictions, such as China, India, Japan, MERCOSUR, and South Korea.

- **Planned Compliance with USP <661>:** Aptar CSP is actively preparing to conduct studies in compliance with USP <661>, a key standard for pharmaceutical packaging materials. This standard, while not required for low-risk oral solid dose (OSD) products, sets a higher benchmark for packaging safety. By aiming for compliance with USP <661>, Aptar CSP seeks to provide an additional layer of regulatory assurance, which is particularly valuable for manufacturers submitting market authorization applications such as NDAs, ANDAs, and BLAs.
- **Proven Efficacy:** During discussions with the FDA, N-Sorb demonstrated a strong ability to adsorb a broad spectrum of nitrosamines and precursors such as nitrite and NOx species. This makes it a versatile solution applicable to various drug formulations that are susceptible to nitrosamine formation during manufacturing, storage, or distribution.

## Regulatory Confidence Backed by Proven Technology

Aptar CSP's N-Sorb technology is built upon a foundation of regulatory trust, supported by its proven 3-Phase Activ-Polymer™ platform, which has been used successfully in pharmaceutical packaging for many years. Drugs that have utilized this core technology are already approved and on the market. This extensive history provides further confidence that N-Sorb can be seamlessly integrated into pharmaceutical packaging solutions to address nitrosamine control, reinforcing its safety and efficacy profile.

In the context of regulatory submissions, N-Sorb offers significant advantages. For oral solid dose (OSD) products, which are generally categorized as low-risk, the FDA primarily requires compliance with food drug regulations. However, by conducting studies aligned with USP <661>, N-Sorb will provide an additional level of safety and assurance, exceeding baseline regulatory expectations. This will be particularly valuable for drug manufacturers submitting new or supplemental NDAs, ANDAs, BLAs, or CBE-30/PAS applications, where packaging integrity plays a key role in the overall risk management strategy.

## Current Results and Global Alignment

Initial data from ongoing testing efforts conducted as part of the ETP discussions have shown highly promising results. N-Sorb technology has the potential to reduce nitrosamine levels to below the Acceptable Intake (AI) limits set by the FDA and other global regulatory authorities, such as the EMA, Health Canada, and Japan's PMDA. These findings align with international regulatory expectations, demonstrating N-Sorb's broad applicability in addressing nitrosamine contamination across various jurisdictions.

## Leveraging N-Sorb for FDA Compliance

Given the FDA's three-step mitigation strategy—risk assessment, confirmatory testing, and implementation of control measures—drug manufacturers should consider incorporating N-Sorb as a key component of their nitrosamine risk management strategy. Here's how:

- **Risk Management Documentation:** Integrating N-Sorb into risk assessments allows drug manufacturers to clearly document its role in reducing nitrosamine levels in packaging. These assessments should

include supporting data from comprehensive testing and validation studies that demonstrate N-Sorb's efficacy in controlling nitrosamine impurities. This provides a robust foundation for regulatory filings, ensuring that packaging solutions are fully aligned with risk mitigation strategies. Aptar CSP can support the drafting of the Risk Management Documentation.

- **Regulatory Documentation:** Aptar CSP will provide all necessary regulatory documentation, including Letters of Authorization (LOA) to access data from our Drug Master File (DMF) and eCTD-ready sections. In addition, drug manufacturers must generate product-specific test results tailored to their final packaging configurations. This will typically involve compatibility and stability studies to ensure the long-term effectiveness of N-Sorb in reducing nitrosamine contamination for the specific drug product.
- **Meetings with FDA:** To ensure regulatory compliance, Aptar CSP recommends collaborating closely with drug manufacturers early in the development process to strategize the steps outlined in the FDA guidance. As each product may face different challenges, we strongly encourage initiating early discussions with the FDA and/or regulatory authorities. Presenting detailed plans to regulators at an early stage helps ensure alignment with their expectations and prevents potential delays during the approval process.
- **FDA Submission:** When preparing submissions for FDA approval, manufacturers should include comprehensive evidence of N-Sorb's effectiveness as part of their overall nitrosamine control strategy. Aptar CSP's active engagement with the FDA through the Emerging Technology Program (ETP) helps streamline the regulatory process, reducing the burden on manufacturers and enabling smoother, faster approval pathways.

## Continued Collaboration and Final Data Requirements

While robust evidence has been generated to support N-Sorb's effectiveness, regulatory authorities, including the FDA, will expect final stability data. This includes:

- **Extractables and Leachables Studies:** These studies ensure no harmful substances migrate from the packaging into the drug product during storage over its intended shelf life.
- **Final Packaging Configuration Testing:** Stability and compatibility studies in the final packaging configuration will be necessary to confirm the long-term protection N-Sorb provides against nitrosamine formation.

Drug manufacturers incorporating N-Sorb into their packaging solutions will be well-positioned to comply with the FDA's nitrosamine guidance. By doing so, they will proactively address regulatory expectations and protect their products from contamination risks.

## Supporting Regulatory Compliance Through Expertise

As part of the FDA's ETP, Aptar CSP is uniquely positioned to assist pharmaceutical companies in navigating the complex regulatory landscape surrounding nitrosamine control. With a long history of regulatory compliance, including multiple approved drugs already on the market, Aptar CSP provides expert guidance on nitrosamine control documentation. We are committed to supporting manufacturers through successful regulatory submissions and ensuring compliance with evolving global requirements.

## Conclusion

The regulatory landscape around nitrosamines continues to evolve, presenting both challenges and opportunities for drug manufacturers. By incorporating Aptar CSP's N-Sorb technology into their packaging solutions, companies can meet global regulatory expectations while ensuring the safety and integrity of their products. As we continue to work closely with the FDA and other regulatory authorities, we remain committed to providing the data, guidance, and support necessary for manufacturers to achieve compliance with nitrosamine control regulations.

For further details on how N-Sorb can be integrated into your nitrosamine risk management strategy, please contact our team.

## Global Regulatory Reporting - Timeline Expectations

The FDA has set deadlines for risk assessments, confirmatory testing, and mitigation strategies, along with regulatory reporting requirements. And when it comes to a “nitrosamine impurity [that] may be best addressed through replacement of packaging... FDA may recommend a shorter implementation timeline...”

**Table 4: Recommended Implementation Timelines**

(Updated: 9/4/2024)

Nitrosamine Impurity	Performing Risk Assessment	Confirmatory Testing	Submission of Required Changes
Small Molecule Nitrosamines	March 31, 2021	When a risk is identified	October 1, 2023
NDSRIs	November 1, 2023	When a risk is identified	August 1, 2025

Several other regulatory authorities, including the European Medicines Agency (EMA), Health Canada, and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, have issued specific timeline dependent expectations for drug manufacturers regarding nitrosamine control, similar to the FDA's requirements. The final deadline for Step 3 variations for chemical medicinal products was October 2023, which required submitting the variations to implement corrective measures based on earlier risk assessments. Like the EMA, Japan (PMDA) and several other jurisdictions, including South Korea, China, and MERCOSUR countries expect companies to implement corrective actions and provide a control strategy for reducing nitrosamine levels within the 2023-2025 window.

