POSITION PAPER

Aptar CSP Technologies

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

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 a development and validation plan for N-Sorb technology that can potentially meet and exceed regulatory expectations. This plan may allow pharmaceutical companies to confidently integrate N-Sorb into their products, assured of compliance with FDA nitrosamine impurity guidelines.

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.

Regulatory Strategy

To confirm suitability for specific drug applications, Aptar CSP applies a stepwise qualification approach:

Step 1 — Overall Migration Limit (OML) Compliance

- OML testing per EU Regulation No. 10/2011 has been completed on six primary N-Sorb variants
- All six passed with overall contamination below regulatory thresholds
- Statements of Compliance are available upon request for initial evaluations

Step 2 — Comprehensive Material Compliance

- Includes Specific Migration Limit (SML) and Non-Intentionally Added Substances (NIAS)
- USP <661> testing to meet U.S. pharmaceutical packaging standards
- *These tests will need to be performed for each form of N-Sorb product once they are qualified and for specific drug application. Compliance documentation will be provided as suitable.*

To support global regulatory filings, Aptar CSP compiles this data in a Drug Master File (DMF) on record with the FDA. Customers will receive a Letter of Authorization (LOA) for us in aNDA/NDA submissions, streamlining regulatory review.

FDA Regulatory Alignment

N-Sorb technology was accepted into the FDA Emerging Technology Program (ETP) in 2024. Since then, CSP has maintained active engagement with the Agency. The FDA has not raised any safety concerns regarding the materials used and has confirmed:

- EU 10/2011 compliance (OML, SML, NIAS) is suitable for demonstrating packaging safety per FDA's Container Closure Guidance;
- USP <661> testing is recommended for additional assurance.

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.

Supporing 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.