Pharmaceutical Technology®

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Nitrosamine Mitigation: A Path to Regulatory Compliance

Nitrosamine Impurities and Product Compliance

Risk to Resolution: Nitrosamine Mitigation

Nitrosamine Identification and Derisking Products

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Nitrosamine Impurities Deadline: Are Your Products Compliant?

By Jason Brown
Senior Manager
Analytical Sciences, R&D

Ensure FDA compliance after the new guidance released in August 2023 on nitrosamine contamination.

In August 2023, the FDA released its guidance on nitrosamine contamination, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs). This guidance set a November 1, 2023, deadline for risk assessment updates and an August 1, 2025, deadline for all drug manufacturers and market authorization holders to comply fully with the NDSRI limits set. This affects no small portion of the industry: about 30% of approved active pharmaceutical ingredients (APIs) are susceptible to nitrosamine formation. Thus, drug makers now are on the clock to correct issues that may arise with current commercial products. Issues with in-development APIs must be addressed before filing.

The FDA's guidance considers drug product manufacturers and Abbreviated New Drug Application (ANDA) holders just as responsible as NDA holders in terms of achieving/maintaining NDSRI limits. The FDA, European Medicines Agency (EMA), and Health Canada are fairly aligned on expectations—current limits are harmonized.

Among APIs at risk for forming NDSRIs, the FDA has specifically called out those containing secondary and dimethyl tertiary amines as most problematic. These functional groups can readily react with trace nitrite contamination present in the drug product to form NDSRI impurities.

While the new NDSRI guidance specifically applies to marketed products, drugmakers with products in development containing these high-risk functional groups would be well advised to assess and address risks proactively. This minimizes the risk of late-stage reformulation, added costs, and product launch delays.

INTERACTIVE BROCHURE

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In addition to compliance with the guidance's NDSRI limits, the FDA has mandated that each organization create and maintain a control strategy for each affected product.

To be effective and sustainable, a mitigation strategy should employ a multipronged approach; one cannot presume a single solution will address this problem. Potential strategies for vulnerable drug products include shelf-life reduction, investigating nitrite contribution from excipient suppliers, examining formulation processes, and introducing additives which mitigate the formation of nitrosamines.

A successful strategy will find a proper balance between all of these approaches. However, the use of nitrosamine mitigating additives is the only proactive solution that puts the developer in control … the other options are reactive or rely on the control of the supplier.

Adare Pharma Solutions: Unparalleled Experience in NDSRI Mitigation

Following outreach by the FDA in 2021 regarding an NDSRI susceptibility within a drug that Adare produces, our team of experts quickly changed their prioritization of nitrosamine mitigation. After correcting perceived risks with the product the FDA flagged, Adare began exploring the nitrosamine mitigation landscape, considering what could be done to reduce the risk of nitrosamine formation across the many APIs impacted in the industry.

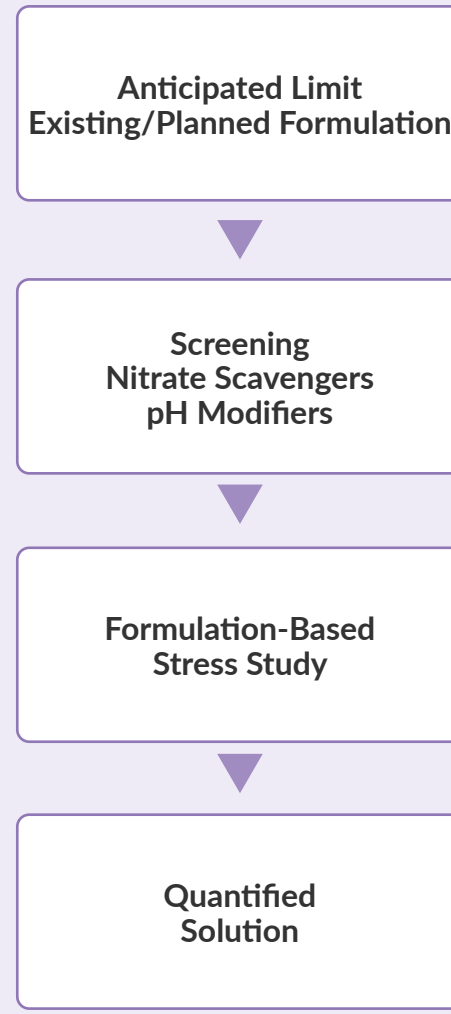
Because each API and drug product formulation is different, we knew that a one-size-fits-all additive strategy could not be applied. A solid state stress study that determined just the best overall additive in a controlled environment with a surrogate API would not be sufficient; the study would need to evaluate multiple additive types and concentrations using the API and formulation in question to provide developers the best fit for their product. (**FIGURE 1**). For some formulations and APIs, a pH modifier would be the answer. For others, it would be a nitrite scavenger. And for yet others, it would be both.

This is work that demands an experienced provider due to the steep barrier of entry in this still-emerging field. For example, the scientific literature on this topic has numerous gaps where the practical laboratory application of concepts is not always shown in the detail needed to apply to formulation development. Unlike providers with no history in NSDRIs, Adare's experience has given us the expertise to guide customers on creating a new formulation or reformulation that meets regulations.

Adare can provide the knowledge, sample analysis, and necessary instrumentation to customers who lack the in-house knowledge or instrumentation to mitigate their NDSRI-related risk, or who simply do not have the time and/or resources to dedicate to the task. The FDA has only granted two years for manufacturers, NDA holders, and ANDA holders to become compliant, so it's not ideal for a customer to spend a year of that time acquiring equipment and training staff, then tasking them with correcting out-of-compliance elements on a short deadline.

Adare's expertise helps remove that pressure. Our nitrosamine mitigation services empower customers to bring their products

FIGURE 1.



into compliance while allowing them to maintain control of the process at every step of the way.

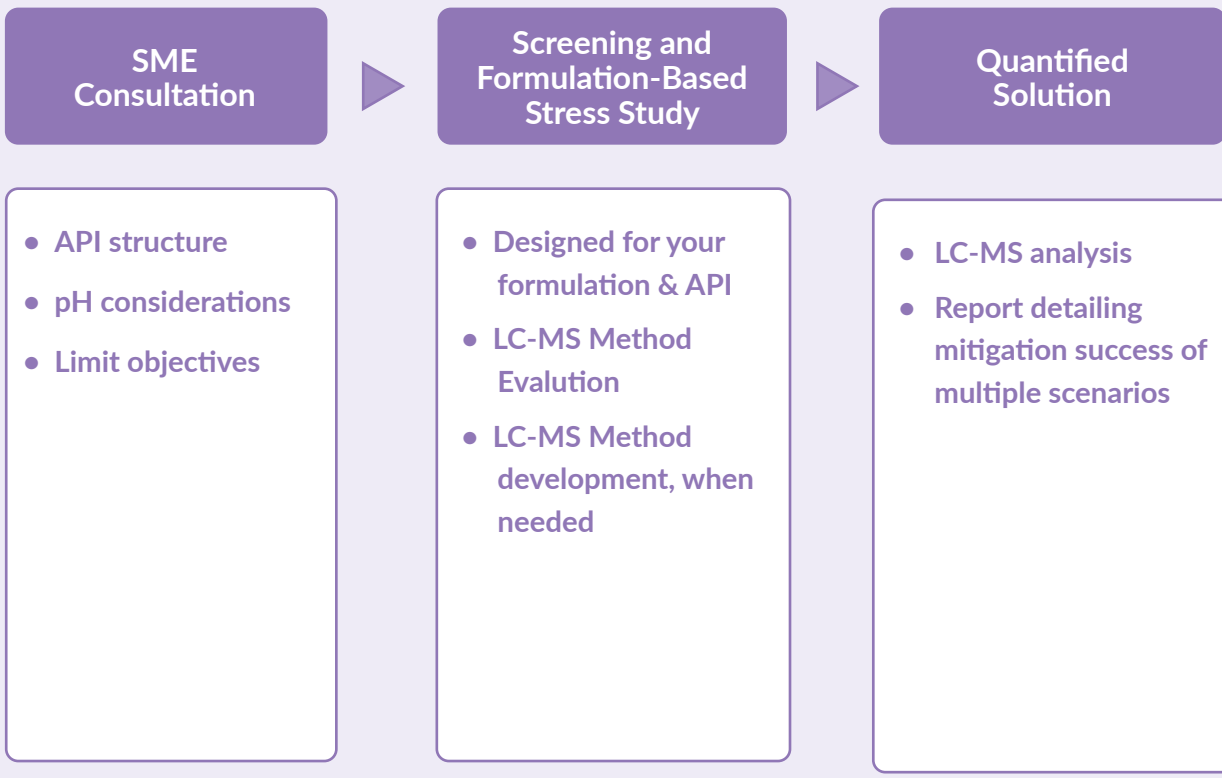
Adare's Comprehensive Nitrosamine Mitigation Process

Our multi-pronged approach to nitrosamine mitigation helps identify the best additive(s) for a customer's API and formulation, and it can be used on both commercial and in-development products.

The first step is a conversation with the customer to evaluate their API and existing formulation, which will inform the study structure. For example, modifying bulk pH or adding nitrite scavengers may be effective ways to suppress NDSRI formation, but these same changes may accelerate standard degradation pathways. This "magic bullet" thinking is a common problem with providers who don't have Adare's experience with NSDRIs. After any change to the formulation, both the API and the formulation must be reevaluated holistically, paying careful attention to the microenvironment created for the API.

Following this discussion, we utilize a liquid chromatography-mass spectrometry (LC-MS)

FIGURE 2.



method to begin screening modifiers and additives. A control is used to deliberately form nitrosamine, then we analyze how each additive and amount impacts nitrosamine levels in the compound at various levels and combinations (for example, a pH modifier and a nitrite scavenger together).

We take these learnings from the lab studies and determine a range of viable options for the customers. These chosen additives are then used in a formulation based solid state stress study that reveals how much nitrosamine formed in the original vs modified formulations during the study.

The results of our testing and a range of mitigation options are provided in a comprehensive final report to the customer, with the advantages and disadvantages of each approach clearly articulated. This allows the customer to make a decision based specifically on the needs of their formulation (**FIGURE 2**). The customer stays in control of their product's future every step of the way; we empower them to make knowledgeable decisions about the viable options, but the ultimate decision is always theirs.

The FDA's guidance sets acceptable limits for nitrosamine impurities and enforces implementation of a control strategy, holding both applicants and manufacturers accountable together. Adare's work directly informs a customer's response to the requirement for a control strategy that keeps the product within the acceptance limits.

Regain Control of Your Product With Adare Pharma Solutions

Working with a company like Adare that's experienced in nitrosamine mitigation is crucial to quickly solving NDSRI-related challenges and meeting the FDA's August 2025 deadline. Time is running out … if your product is susceptible to nitrosamine contamination, it's vital to act quickly.

Our nitrosamine mitigation experts can provide you with informed and quantifiable options, then help you prioritize the options that best meet your needs. We can help you find the right path forward and resolve your nitrosamine issues quickly and efficiently.

Jason Brown *brings a wealth of knowledge and practical experience to his role as Senior Analytical Sciences Manager at Adare Pharma Solutions, where he serves the role of global nitrosamine subject matter expert. He has led Adare's innovative approaches to understanding nitrosamine formation, measurement, and mitigation to ensure regulatory compliance internally and for our customers. With a deep-rooted understanding of cGMP, ISO17025, and ISO9001 standards, Jason has skillfully managed numerous investigations, including Out of Specification (OOS), Out of Control (OOC), Corrective and Preventive Actions (CAPA), and Root Cause Analyses. Before joining Adare, he served organizations including Q Laboratories, Fujimi Corporation, Hydration Technology Innovations, and W. R. Grace & Co. Jason has a BS in Chemistry from George Fox University.*

NITROSAMINE IMPURITIES: ARE YOU COMPLIANT?

GUIDANCE ON NITROSAMINE HAS BEEN ISSUED | DEADLINES ARE APPROACHING




Adare Pharma Solutions has expertise in mitigating the presence of nitrosamine that very few other CDMOs can claim. As a proactive outsourcing partner, we've been controlling nitrosamines in our own products for nearly two years, and we can employ the same mitigation processes to develop the best long-term control strategies for your product.

REGAIN CONTROL OF YOUR PRODUCT WITH NITROCLEARx

- Receive real-world mitigation support ... from start to finish
- Find the right balance between all effective approaches
- Evaluate a range of potential strategies that put you back in charge
- Make informed decisions on the solution that meets your needs
- Evolve your strategy as your final formulation develops

LET OUR EXPERTS CREATE A QUANTIFIED MITIGATION STRATEGY DEVELOPED SPECIFICALLY FOR YOUR MOLECULE YOUR FORMULATION, AND YOUR MICROENVIRONMENT

SCREENING STUDY
A thorough examination of nitrosamine formation vectors and potential additives

SOLID STATE STRESS STUDY
In-depth formulation-based investigation of additive candidates

FINAL REPORT
Quantified results with multiple solution pathways and expert recommendations

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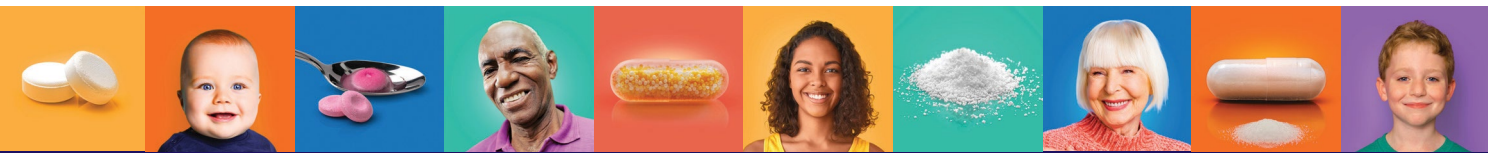
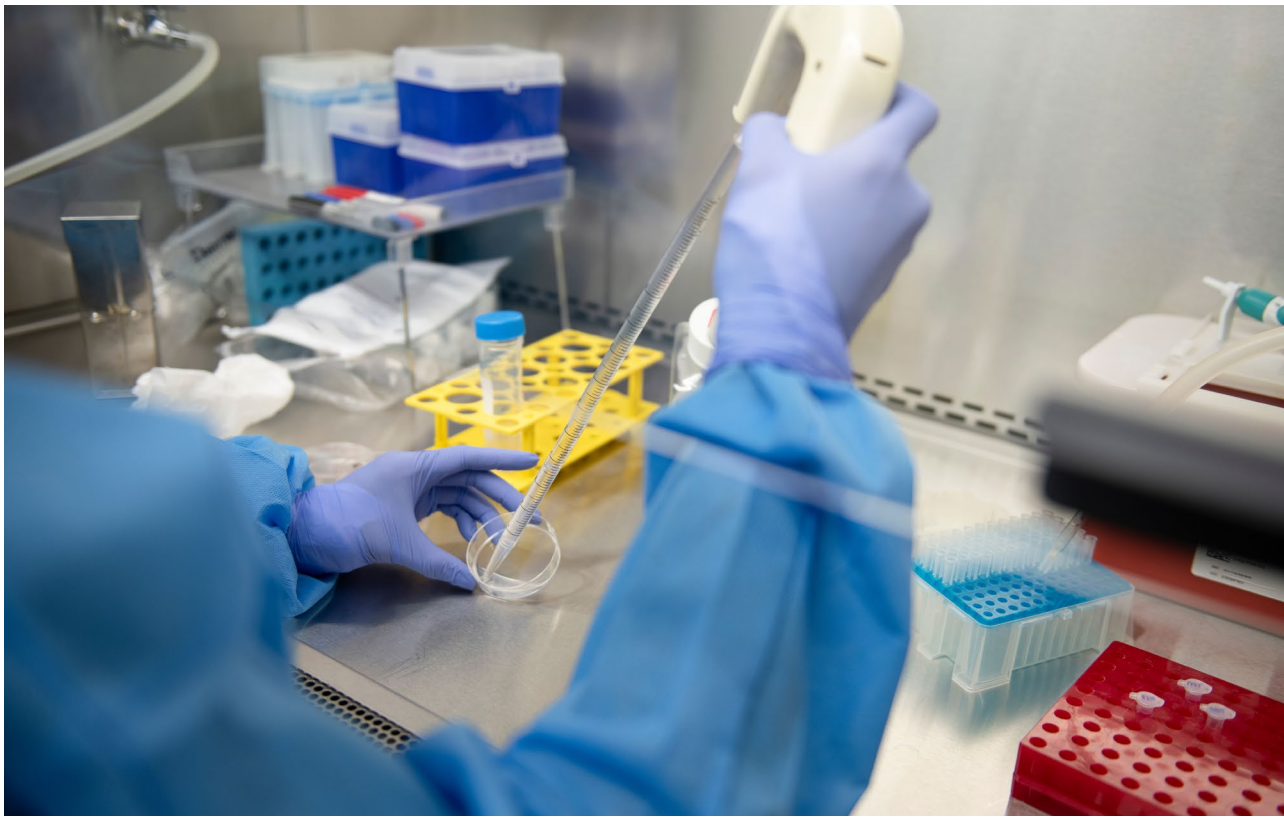




From Risk to Resolution: A Groundbreaking Approach to Nitrosamine Mitigation

When the FDA reached out to Adare Pharma Solutions regarding potential nitrosamine formation in a beta blocker, our experts quickly developed an effective in-depth process to mitigate impurities in all commercial products.

The issue of nitrosamine contamination in pharmaceutical products has become the significant concern within the industry, due to the potential carcinogenic risks posed by these impurities. The U.S. Food and Drug Administration (FDA) has been proactive in addressing this issue, issuing warnings about the risks associated with Nitrosamine Drug Substance-Related Impurities (NDSRIs). The concern first gained widespread attention in 2018 with the discovery of nitrosamine impurities in Valsartan, a widely used antihypertensive medication. Since then, over 250 distinct nitrosamines have been identified in various drug products.

The Challenge

The FDA's guidance places equal responsibility on drug product

manufacturers, Abbreviated New Drug Application (ANDA) holders, and New Drug Application (NDA) holders to achieve or maintain NDSRI limits. In 2021, Adare Pharma Solutions was contacted by the FDA regarding potential NDSRI formation in one of our commercial products—a beta blocker. Beta blockers, falling within the group of secondary and dimethyl tertiary amine APIs, are particularly susceptible to nitrosation.

WEBINAR

Nitrosamine Impurities Deadline: Are Your Products Compliant?

The challenge was compounded by the fact that alternative approaches to mitigating nitrosamine formation—such as modifying formulation processes, minimizing nitrite contributions from excipients, or reducing shelf life—were unlikely to be effective. These methods alone would not adequately address the risk of NDSRI formation in our beta blocker product. As a result, we needed to devise an innovative solution to mitigate this risk and ensure compliance with FDA guidelines while maintaining the product's efficacy and safety.

The Process

Working closely in collaboration, our experts developed a comprehensive nitrosamine screening process to address the potential NDSRI formation in its beta blocker product. This process employs a multi-pronged approach to nitrosamine mitigation, identifying the best additives for a customer's API and formulation.

API/Microenvironment Study

The first step in our process involved evaluating the API and existing formulation holistically. This detailed analysis of the API and the microenvironment created for it allowed our scientists to identify potential mitigating compounds and inhibitors specific to this API and formulation. The insights from this analysis guided the design of the solid-state stress study, ensuring it was tailored to the unique properties and challenges of our product.

Solid State Study

Next, we conducted a lab-based solid-state stress study to simulate real-world conditions in a controlled environment. Our exactingly detailed setup enabled us to replicate nitrosamine formation typically seen over months or years within a six to eight-week timeline. Our experts ran several concurrent experiments and tested multiple modalities of nitrosamine inhibition, identifying a range of effective mitigation options.

Unlike liquid-state studies, which can lead to incorrect findings due to different reaction mechanisms, our solid-state study revealed distinct and accurate insights into the formulation's behavior. By maintaining realistic nitrite and inhibitor ratios, we ensured that our conclusions were practical and avoided unnecessary formulation changes that could affect the medication's efficacy.

LC-MS Analysis

Throughout the API/Microenvironment and solid state studies, we employed liquid chromatography-mass spectrometry (LC-MS) to analyze the impact of various additive levels and combinations on nitrosamine formation. This method provided precise and reliable data, enabling us to refine our approach continuously.

The experiments demonstrated that a one-size-fits-all additive strategy could not be applied. A multi-faceted approach would be necessary to effectively minimize nitrosation and ensure compliance with FDA guidelines, both now and in the future.

Using the results of our comprehensive lab studies and analyses, our experts evaluated various pH modifiers and nitrite scavengers in our beta blocker, meticulously examining multiple concentrations and combinations to identify the optimal solution for nitrosamine mitigation.

During this process, we prioritized realistic nitrite and inhibitor ratios, ensuring practical conclusions and avoiding unnecessary formulation changes that could compromise the medication's efficacy.

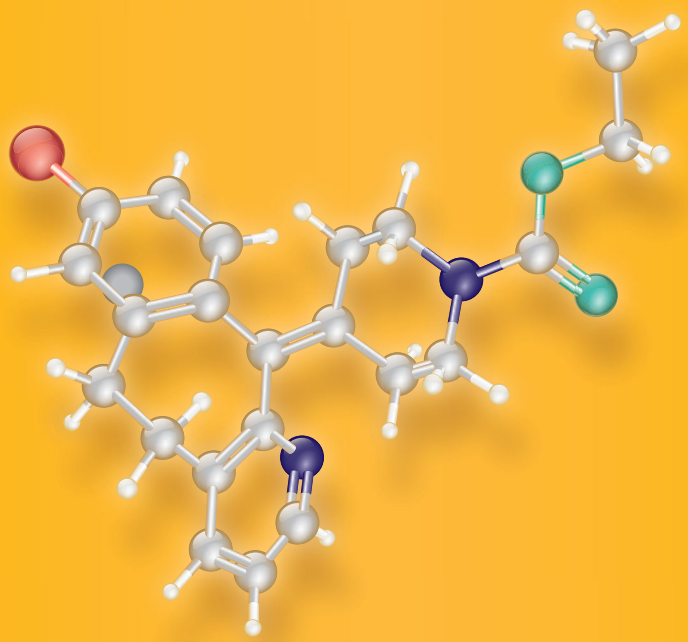
The Result

Our nitrosamine mitigation process successfully determined multiple paths to bring our product into full compliance with FDA limits, demonstrating quantifiable results: a reduction of NDSRI formation in our product by up to 84%.

The effective multi-pronged approach that we developed is now being offered to customers for any commercial or in-development products at risk of nitrosiation. Our scientists identify the best additive(s) for a customer's API and formulation, then provide them with informed and quantifiable options to resolve their nitrosamine issues quickly and efficiently.

Adare Pharma Solutions can develop the best long-term control strategies for your product, providing quantified mitigation options specifically designed to minimize nitrosamine formation without compromising its efficacy. If your product is susceptible to nitrosamine contamination, contact Adare today to speak to a nitrosamine mitigation expert.

DO YOU NEED A CDMO THAT CAN DEVELOP THIS



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A New Framework for Identifying Nitrosamine Risks and Efficiently Derisking Products

A clear standard for identifying APIs susceptible to NDSRI formation has remained elusive – until now. Adare's team of nitrosamine experts have developed a straightforward framework that simplifies the identification of at-risk APIs.

By Jason Brown
Senior Manager
Analytical Sciences, R&D

Since the release of the FDA's guidance on Nitrosamine Drug Substance-Related Impurities (NDSRIs), the pharmaceutical industry has been diligently attempting to identify at-risk APIs, update risk assessments, and devise control strategies for both commercial and in-development products. But despite the numerous papers, software tools, and expert opinions generated from these efforts, there is no clear-cut definition of APIs susceptible to nitrosiation.

Seeking to Clarify Risk Assessments

While the FDA's guidance identifies 250 APIs, it was not their intent to provide a comprehensive list of all APIs at risk. This has left pharmaceutical companies and experts to navigate this challenge independently. Companies must still meticulously review their products to identify any additional at-risk substances.

This lack of a clear-cut definition from regulators has created significant uncertainty within the industry. Despite agreement on toxicity and limit setting, there is no consensus among industry experts on which functional groups significantly increase or decrease the risk of nitrosamine formation.

PODCAST

Navigating Nitrosamine Impurities with Jason Brown

For example, a 2022 article by Srinivasan and Lambert argues that nitrosamides should not be treated similarly to nitrosamines; although this hypothesis is widely adopted, it remains a topic of debate.

When our team at Adare Pharma Solutions was tasked with evaluating our portfolio of over 65 commercial products, as well as numerous products in development, we initially faced the same paralysis that has affected the industry: How does one apply rules that are still ill-defined?

Finding a Pattern Between Susceptible APIs

In our quest for clarity, we embarked on an extensive research effort. This led to identification of characteristics distinguishing APIs that are susceptible to NDSRI formation from those that are not. This was not merely an academic pursuit; the financial implications of nitrosamine mitigation are significant. Each derisked API and associated product can save approximately $100,000 in LC-MS method development, validation, and confirmatory testing alone.

Our team leveraged FDA guidance to meticulously analyze its database of identified APIs, focusing on the structures and functional groups of each API and the resulting nitrosamines.

Adare brought numerous hypotheses and questions to the investigation, aiming to either confirm or refute our assumptions.

In the end, we identified three straightforward questions that determine if an API is susceptible to nitrosiation.

The Adare Nitrosamine Formation Framework: Three Simple Questions for Your Drug

Does the API Contain Secondary and Dimethyl Tertiary Amines?

The recent FDA guidance specifically highlights secondary and dimethyl tertiary

amines as structures of concern for nitrosamine formation. No other API alert structures were identified. Notably, primary amines, quaternary amines, and other forms of tertiary amines were not flagged as risks. The instability and reactivity of primary amines likely contribute to their exclusion, while steric hindrances primarily drive exclusion of other amines.

The FDA has shown no actionable concern for APIs that do not contain secondary or dimethyl tertiary amines. However, if your API does contain these amines, regulators may still consider your product a risk; proceed to the next question for further evaluation. Not all secondary and dimethyl tertiary amine-containing APIs will necessarily form nitrosamine impurities. The next two questions are designed to help narrow down whether it is truly at risk.

Is the Amine Group Found in a Hybridized Orbit?

Among other factors, hybridized orbits provide stability, reducing the probability and speed of reactions that could lead to nitrosamine formation. Hybridized orbits are easily identified when the amine group of interest is double-bonded to an alpha-carbon. This configuration stabilizes the amine group, thereby lowering the likelihood of reaction.

If your API's amine group is part of any hybridized orbit, its susceptibility to forming nitrosamine impurities is significantly reduced. If the amine group is not in a hybridized orbit, proceed to the next question to further evaluate the risk of nitrosamine formation.

Is the Amine Group Immediately Adjacent to a Carbonyl Group?

Amines immediately adjacent to a carbonyl group, carboxamides, are not included in the FDA's data set of materials identified as at risk. This exclusion is likely due to the electron-withdrawing properties of carbonyl groups, which significantly decrease the rate of reaction. The presence of a carbonyl group adjacent to the amine of interest reduces its reactivity to such an extent that no API with this configuration has been identified by the FDA as being a concern for forming nitrosamines.

By evaluating your API using these three questions, you can determine whether nitrosiation is a concern in accordance with criteria the FDA has used to identify at-risk products. This straightforward framework simplifies the process of identifying and mitigating potential impurities, facilitating compliance with regulatory guidelines.

The Adare Nitrosamine Formation Framework in Action

Before completing this research and defining our framework, the Adare team was asked to evaluate acetaminophen for potential nitrosamine formation. Despite its well-characterized structural stability and the expected low risk, we needed to conduct thorough due diligence requiring over 2 weeks of analysis.

Our experiments confirmed what we suspected: that nitrosamine formation did not occur and was not realistically possible. However, now that this simple framework exists, weeks of lab work are no longer necessary for similar products. The assessment can be reduced to a simple paper exercise by asking three questions of the API.

Applying the framework to our domestic portfolio of 65+ products enabled Adare Pharma Solutions to narrow down the number of products needing further evaluation to just 11. This strategic approach realized a significant cost saving of $1.9 million.

The Path Forward

Further work is needed by regulatory bodies to refine and clarify expectations surrounding nitrosamine risk assessments. Unclear guidelines currently lead to inconsistent responses and uncertainty within the industry. As more data becomes available, these rules will almost certainly evolve, hopefully leading to increased clarity that will benefit both regulators and the pharmaceutical industry.

But until then, this framework can aid researchers, reduce costs, and protect patients. With this clear and straightforward method for identifying at-risk APIs, researchers can focus their efforts more

efficiently. The cost savings realized allow companies to allocate resources more effectively, ultimately speeding up the development process. Most importantly, by ensuring that potentially harmful nitrosamines are identified and mitigated, our framework plays a vital role in safeguarding patient health and maintaining trust in pharmaceutical products.

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