Reformulating the Future of Small Molecules

A special collection of recent stories exploring oral dose innovation, API stability, nitrosamine testing, and the evolving science of small molecule medicines

the Medicine Maker x Pfizer Kindeva

Green Propellants and the Future of Metered Dose Inhalers

The pressure is on to reduce the carbon footprint of respiratory drugs by using next-generation green propellants.

Addressing global climate change is pushing industries to re-evaluate their environmental footprint. The pharmaceutical sector is no different, with drug developers seeking to minimize the impact of their drug products on global warming. Metered dose inhalers (MDIs) have been a particular focus in recent years. While millions of patients depend on these devices, the traditional propellants have a global warming potential (GWP) far greater than carbon dioxide.

Global legislation is increasingly requiring companies to phase out standard propellants in favor of lower-GWP next-generation propellants (NGPs). For example, the 2016 Kigali Amendment to the Montreal Protocol mandates a 70 percent reduction in high-GWP hydrofluorocarbons (HFCs) by 2030. In line with its obligations as a signatory to this amendment, the EU has introduced F-Gas regulation with a target of an ambitious 95 percent HFC reduction by 2034. Comparable regulations are emerging in the US and the United Kingdom. This evolving regulatory landscape indicates that current MDI exemptions will likely be phased out, compelling pharmaceutical manufacturers to respond promptly.

Transitioning to alternative gases is also an economic imperative. Due to the introduction of the legislation discussed

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above, the supply of existing HFCs for MDIs is becoming constrained as their reduced usage makes their production less profitable, leading to significantly increased costs for MDI manufacturers. Furthermore, a mass transition of patients from MDIs to alternative devices, such as dry powder inhalers (DPIs) or soft mist inhalers (SMIs), could incur substantial additional expenses for healthcare systems, patients, and insurers. As just one example in the UK, studies suggest such a switch could cost the National Health Service an extra ~£12.7 million each year (~$17.2 million).

Leading pharmaceutical companies such as GSK, AstraZeneca, and Chiesi have already announced plans to launch NGP MDIs by 2025/2026, but the change must be managed carefully for the sake of patients. An unmanaged, widespread transition away from pressurized MDIs could inadvertently compromise patient adherence, and lead to an increase in disease exacerbations and hospitalizations. MDIs remain vital for numerous patients, particularly for fast-acting relief medications.

The challenges of next gen alternatives

While the consensus on greener propellants is clear, the transition presents significant complexities. Firstly, this transition demands substantial financial investment. Decarbonizing MDI platforms requires considerable capital for new research, establishing novel manufacturing facilities, and acquiring specialized equipment for handling NGPs.

Secondly, navigating the regulatory environment is complex and dynamic. Drug developers must rigorously demonstrate that new MDI products – and new formulation ingredients such as propellants – maintain equivalent efficacy and safety profiles compared to existing ones. This necessitates testing, performance validation, and knowledge into evolving regulations. Beyond technical specifics, patient-centric device design is also crucial. This involves developing inhalers that are easy to use, minimize side effects, provide rapid action, and deliver medication effectively to the lungs. Remaining current with evolving regulations is also vital to safeguard product approvals, and access to manufacturing facilities equipped for NGPs like HFA-152a and HFO-1234ze is necessary for efficient production of greener MDIs.

Thirdly, significant technical challenges arise in formulation development. Creating effective, stable, and patient-friendly MDI formulations with novel propellants can prove difficult. Key considerations include drug solubility within the new propellant, compatibility with inhaler components, and ensuring consistent patient usage. Achieving optimal aerosol performance for effective lung delivery demands specialized expertise.

Fourth, ensuring supply chain readiness is crucial. Establishing a reliable and scalable supply of NGPs and their associated components is vital. This requires close collaboration across a network of partners, from chemical companies to parts suppliers, to ensure operational continuity.

To successfully transition to NGP MDIs, companies need a comprehensive, well-planned strategy. This involves a complete understanding of aerosol dynamics, including how new propellants interact with drug formulations and how inhaler components release medication. It also means optimizing all elements simultaneously – the drug's formula, device parts, and manufacturing process – to ensure efficient scale-up.

In the coming years, innovative solutions will emerge, allowing patients to continue utilizing these essential devices while significantly reducing their environmental footprint.

This shift transcends mere regulatory compliance or cost savings; it is about establishing a pathway where essential medical treatments actively contribute to planetary health. As drug developers and manufacturers invest in new scientific advancements, the future of MDIs will depend on their ability to seamlessly integrate environmental responsibility with therapeutic excellence. The outlook is promising for MDIs that are truly future-proofed and sustainable, not just supporting patient health, but contributing to a cleaner, greener environment with every breath patients take.

Link
Online Article

Navigating Formulation Change in the EU

How to turn regulatory complexity into strategic strength

In an era defined by scientific innovation and global supply chain interdependence, one might expect formulation updates – often intended to improve stability, sustainability, or patient experience – to flow smoothly through regulatory systems. Yet in the European Union (EU), even modest formulation changes can trigger an unexpectedly intricate journey.

For every strength, in every market, and for every submission, what begins as a simple modification can quickly fragment into a series of national filings, each with its own interpretation and administrative nuance. For sponsors managing multi-country portfolios, navigating this patchwork of expectations is not simply a matter of regulatory inconvenience, but also a test of foresight, organization, and adaptability. The companies that succeed in Europe's complex regulatory landscape are those that treat change management not as a task to be endured, but as a discipline to be mastered.

The illusion of harmonization

Europe's regulatory framework is often celebrated for its harmonized structure, especially through centralized procedures and shared technical standards. But when it comes to lifecycle management, the harmony fades.

Even for products approved under centralized or mutual recognition procedures, post-approval variation requirements are rarely uniform. A single formulation update, perhaps intended to address an excipient shortage or improve product stability, could demand dozens of parallel submissions. Each national authority may apply different expectations on classification, documentation, or analytical comparability, and each strength must be treated as its own regulatory entity.

The outcome is a web of administrative complexity. A change deemed a Type IB variation (1) in one country might escalate to a Type II in another; one authority may seek a full comparability study, while another accepts a bridging justification. Sponsors find themselves managing multiple timelines and queries for what is, scientifically, a single change (2).

When small adjustments become strategic decisions

For global manufacturers, formulation changes are a fact of modern pharmaceutical operations. Changes in raw material sourcing, sustainability goals, and manufacturing efficiency initiatives can all require updates to a product's composition. In the EU, every minor variation (3) can become a strategic decision point: is it worth it?

A company introducing a slightly modified excipient to enhance shelf stability might face 30 individual filings across Europe, each requiring translation, local agent coordination, and data resubmission. For large portfolios, this burden compounds; for smaller companies, it can be prohibitive. Some simply postpone beneficial changes in Europe or maintain parallel formulations between regions, trading operational simplicity for regulatory pragmatism (4).

This tension between innovation and implementation reveals a deeper challenge: Europe's post-approval ecosystem was built for procedural rigor, not agility. As a result, incremental improvements that make medicines safer, easier to manufacture, or more sustainable can take months or years longer to reach patients.

Operational challenges beneath the surface

Behind the policy complexity lies an enormous operational toll. For regulatory and quality teams, managing formulation changes in Europe demands coordination across affiliates, manufacturing sites, and labeling teams.

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Among the most common friction points:

- Divergent interpretations: what constitutes a "minor" change is not universal. National agencies may apply different thresholds or data expectations.
- Asynchronous timelines: clock stops, administrative delays, and staggered approvals disrupt manufacturing and supply alignment.
- Labeling dependencies: even changes that do not alter product labeling may require bundling with other variations, delaying submission.
- Supply chain implications: staggered approvals mean batches with different specifications circulate concurrently, complicating serialization and quality oversight.exist for it?

In practice, these variables mean that a single modification can trigger months of cross-functional coordination. And because approvals arrive at different times, production planning becomes a moving target, forcing teams to balance compliance with supply continuity.

A system under pressure

The current regulatory model was not designed for the frequency or complexity of modern change control. Sustainability goals now demand reformulations that minimize environmental impact. Globalization of sourcing requires flexibility to respond to supply disruption. Digital manufacturing technologies are accelerating process optimization cycles.

Yet the system governing these post-approval changes remains largely manual and segmented. Each filing must be crafted, translated, and tracked individually. Each national assessment proceeds in isolation, with little mutual recognition of prior evaluations.

The result is systemic inertia at a moment when agility is most needed. Europe risks lagging behind in implementing quality improvements, not because its scientific standards are lacking, but because its procedural architecture has not evolved at the same pace as modern manufacturing.

Strategic planning as the differentiator

In this environment, the true differentiator is not regulatory knowledge alone, but rather strategic foresight. Sponsors that anticipate the complexity of EU lifecycle management can transform what seems like a constraint into a source of competitive advantage.

With that in mind, my five "top tips" for tackling formulation change from a strategic perspective are:

- **Invest in regulatory intelligence:** maintaining a centralized knowledge base of national requirements, agency behavior, and recent classification trends enables teams to predict where friction will arise. This intelligence turns variability into foresight.
- **Integrate change planning early:** regulatory, manufacturing, and supply chain functions must collaborate at the concept stage of any formulation adjustment. Early alignment allows submission sequencing that minimizes downtime and ensures manufacturing readiness when approvals land.
- **Centralize oversight and localize execution:** While each submission is national, a centralized regulatory command center ensures data consistency, message alignment, and synchronized timelines. This structure allows flexibility at the edges without losing control at the core.
- **Prioritize communication:** early engagement with agencies via scientific dialogue can clarify expectations, harmonize classification, and avoid costly rework.
- **Leverage digital tracking:** regulatory Information Management (RIM) systems and workflow platforms can bring visibility to hundreds of parallel submissions, providing dashboards for progress, bottlenecks, and dependencies in real time.

When approached in this way, managing formulation changes becomes less about endurance and more about orchestration as a test of operational maturity.

Link
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Bringing Stability to APIs Under Stress

Researchers develop new tool for evaluating API stability under various conditions.

An open-access framework has been developed with the goal of bringing consistency and structure to the way pharmaceutical researchers evaluate the stability of active pharmaceutical ingredients under stress. The Stability Toolkit for the Appraisal of Bio/Pharmaceuticals' Level of Endurance (STABLE), introduced by researchers from institutes in Egypt and Italy, provides a standardized approach to forced degradation testing through a scoring and visualization system that integrates five stress conditions.

"Traditional stability tests – such as real-time, accelerated, and forced degradation testing – often face challenges, including inconsistent interpretation and implementation across different regions and organizations," write the researchers. "STABLE addresses these challenges by providing a standardized and holistic approach to assessing drug stability across five key stress conditions: oxidative, thermal, acid-catalyzed hydrolysis, base-catalyzed hydrolysis, and photostability."

Forced degradation studies are typically conducted under acidic, basic, thermal, oxidative, and photolytic conditions. Regulatory documents such as ICH Q1A(R2), Q1B, and FDA and EMA guidelines outline recommended approaches to these studies, but tend to focus on procedural guidance rather than standardized scoring criteria. STABLE introduces a complementary, quantitative methodology that assigns numerical scores and visual indicators based on experimental data, allowing for easier comparison of results across compounds and laboratories.

Each degradation pathway is evaluated using a set of predefined parameters. For example, acid-catalyzed and base-catalyzed hydrolysis are scored according to factors such as reagent concentration, exposure time, temperature, and the percentage of degradation observed. Similar matrices are used for thermal, oxidative, and photolytic conditions, with specific scoring frameworks detailed in the publication. The final result is a composite stability score and a color-coded pictogram that visually summarizes a compound's stability profile across the five stress conditions.

The paper says: "the inclusion of a STABLE pictogram provides an immediate visual summary of an API's degradation profile, highlighting specific vulnerabilities across the five stress conditions. This facilitates rapid interpretation and supports evidence-based decisions regarding formulation strategies and packaging requirements. For instance, APIs identified as photolabile may be prioritized for protection using amber glass containers, while thermally labile compounds may warrant controlled storage conditions."

However, the researchers have not developed STABLE to replace existing approaches. They emphasize: "STABLE metric should be viewed as a complementary tool…STABLE enhances the rigor and reproducibility of forced degradation studies by introducing a quantitative dimension that is currently absent from most regulatory frameworks."

The software tool supporting STABLE is freely available and open-source. According to the authors, the pictographic output can support decision-making during formulation development, packaging selection, and shelf-life prediction. They note, however, that STABLE assessments are primarily based on solution-phase stress testing, which may not always correlate with solid-state stability.

The STABLE software and full scoring system are available at: bit.ly/STABLE2025. The published paper is available here.

Link
Online Article

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Making the complex. Simple.

Pfizer-backed expertise. Specialized OSD technologies. Your complex challenges, solved.

A CMO for therapies that define legacies

Learn more about our oral solid dose manufacturing services.

The Truth About Softgels: Phthalate-Free, Powered by Glycerin and Sorbitol

Catalent offers clarification after recent discussions raised concerns around softgels, phthalates and potential health risks

By Stephen Tindal, Director, EU Scientific Advisory (Biopharmaceutics) at Catalent

There has been a recent suggestion that soft capsules (including soft gelatin capsules or soft gels including those made with starch/carrageenan), are a major source of phthalates and, as such, pose a potential health risk to consumers.

Recent information in news and social media platforms refer to a "2021 study that reported that the use of phthalate plasticizers was associated with a slightly higher risk of heart attacks." Since no definitive cause and effect was established by that study, some authors proceeded to provide supporting information of how phthalates have also been implicated in inflammation and/or plaque formation and that a potential major source of phthalates comes from "Medicine Capsules," particularly softgel capsules.

However, the suggestion that phthalates "are often used in softgel capsules" is not supported by any evidence in the article. Catalent is not aware of any such use from our own data or research of public domain information (that covers US/EU). Catalent can also confirm that no phthalates are used as shell plasticiser in any product manufactured by our company. In addition, public domain searching has not found any pharmaceutical softgel product that declares phthalates in the ingredient listing in the US or EU.

The original study where the link between urinary phthalate and early death was reported appeared in a peer reviewed journal on 15 May 2025. The study was mainly concerned with toxicity of high molecular weight phthalates (HMW) from plastics and especially those of di-2-ethylehexylphthalate (DEHP). The named high risk HMWs (DEHP, DiNP, DnOP) have molecular weights in the range 390-41.

Other phthalates are approved for use in drug products; for example, the FDA Inactive Ingredient Database (IID) lists diethyl phthalate, hypromellose phthalate and poly vinyl acetate phthalate. These have lower molecular weights (LMW) in the range 222-252. These are different phthalates to the ones named in the above study and are not mentioned as a risk for toxicity. The major applications are in tablets and powder filled capsules (usually in modified release coatings and solid dosage forms), so their use in "Medicine Capsules" (as stated in the article) is true, but it would be more accurate to state "Medicine Capsules and Tablets."

The same FDA IID does not list soft gel capsules as using phthalates, which is further supporting evidence to their not being used for this application, neither wholly, mostly, or partly. Furthermore, a 2019 study confirmed there was no association between consumption of fish oils (which are mostly taken in softgel form) and elevated urinary phthalate.

Softgel capsules do employ plasticisers in the shell. However, the plasticisers used are not phthalates and are almost exclusively from the polyol family (glycerine, sorbitol and related substances) as their performance is far superior. These materials have a long-standing safety record and are not associated with any increased risk of early death.

It is theoretically possible that there are softgel capsules (not made by Catalent) with a LMW phthalate-based coating applied to the outside of the shell in either in development or on the market. A shell coating would be much thinner than the softgel shell and would use a relative smaller quantity of plasticizer. We have not found any, and we estimate that these would likely form a very small portion of the total market. Consumers can find whether phthalates have been used in any product by reviewing the full list of excipients in the patient information leaflet provided with the drug, and even online.

In relation to over-the-counter (OTC) and vitamin/mineral supplements (VMS) softgel products, phthalate plasticizers are infrequently used and should not be presented as such. The only instances Catalent has been able to find are for softgels that are enteric coated, and it is possible that the coating might include a LMW phthalate. There are only a few of these products on the global market and none are manufactured by Catalent.

Consumers can verify the ingredients in any OTC/VMS product by checking the ingredient listing on the packaging.

Link
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Trends and Challenges in Nitrosamine Testing

As nitrosamine risks continue to reshape small-molecule development, five experts unpack the analytical, regulatory, and formulation challenges behind detecting – and controlling – these trace impurities.

When did nitrosamines first enter your radar?

Kevin Parker: As a graduate student, I remember reading in science journals and seeing in the news that n-nitrosodimethylamine (NDMA) was found in batches of a major drug called Valsartan. While I wasn't in the pharmaceutical industry yet, my graduate research utilized mass spectrometry so I was interested in how nitrosamines would impact analytical chemists, as the extremely low levels allowed on a per-day basis require sensitive methodologies. In the years after the discovery of NDMA, conferences at Pittcon, ACS, and the American Society for Mass Spectrometry had a noticeable increase in the attention given to nitrosamines and the analytical challenges they pose.


Kevin Parker

Naiffer Romero: Nitrosamines entered my radar following the detection of Nitrosodimethylamine (NDMA), a probable human carcinogen in valsartan, a commonly-prescribed medication for hyper-tension, which triggered a global investigation of nitrosamines. This led to the discovery of nitrosamines in other pharmaceutical products like pioglitazone, ranitidine, nizatidine, and metformin, used to treat conditions ranging from heartburn to bacterial infections.

Jessica Hoskins: I first became aware of nitrosamines somewhere around 2018 or 2019. At the time I worked at a surfactant manufacturer, and some customers began to ask about the risk of small molecule nitrosamines or precursors in our products.

Jingyue Yang: Like Jessica, I first became aware of nitrosamines around 2018 when the FDA was notified that N-nitrosodimethylamine (NDMA) had been detected in valsartan drug products. Although nitrosamines had been extensively studied in fields like food and environmental science, this was the first significant instance of nitrosamine impurities being reported in pharmaceuticals, which quickly drew widespread attention.

At that time, our office was asked to develop analytical methods to quantify NDMA and other

"Detecting nitrosamines in pharmaceuticals presents several analytical challenges, including the need for trace-level analysis." – Naiffer Romero

small-molecule nitrosamines. Although I wasn't initially involved, I was later brought in to develop an LC-MS method to detect and quantitate those small molecule nitrosamines, which could be challenging for the GC-MS methodology used at the time.

We then developed our first LC-MS method, capable of analyzing six different nitrosamines in valsartan and losartan drug products. As nitrosamine issues in pharmaceutical products continued to expand and evolve, we applied the knowledge gained from these early efforts to develop a variety of methods for nitrosamine analysis.

Alan Thompson: At Almac Sciences, we have been developing mass spectrometric methods to detect and quantify genotoxic impurities at extremely low concentrations in both Active Pharmaceutical Ingredients (APIs) and formulated drug products for a number of years. Nitrosamines have been on our radar for a while, but the scope of our work was largely confined to the monitoring of upstream by-products identified during drug synthesis. As a result our methods were more geared towards ensuring that any nitrosamine by-products were adequately purged.


Naiffer Romero

They started to come to more prominence a few years back when nitrosamine impurities, including N-nitrosodimethylamine (NDMA), were detected in blood pressure medicines known as "sartans." This prompted the Committee for Medicinal Products for Human Use (CHMP) to ask marketing authorisation holders to review all chemical and biological human medicines for the presence of nitrosamines and to test products at risk following guidelines issued by the European Medicines Agency (EMA). Since then multiple products have been identified as potential sources of nitrosamines; notably in drug products, where interaction between API and excipient components can increase the probability of their formation.

Are they dangerous?

Jingyue Yang: Nitrosamines are classified as possible or probable carcinogens, but not all nitrosamines carry the same level of risk. Probable carcinogens such as NDEA are assigned an acceptable intake of 26.5 ng/day due to their high potency, while others have lower potencies and may be controlled at the threshold of toxicological concern (1500 ng/day).

Naiffer Romero: I'd add that according to the International Agency for Research on Cancer (IARC), some nitrosamine impurities are identified as probable or possible human carcinogens that may cause harm to patients in cases where acceptable intake (AI) levels are too high, or exposure is sustained over a long period of time. While exposure to nitrosamines can be dangerous, we have come to learn that not all nitrosamines carry the same risk level.

Alan Thompson: There is substantial documented evidence of the carcinogenic and mutagenic properties of these compounds. The wide range of human exposure sources such as food, drugs and cosmetics in addition to occupational sources such as cutting oils and hydraulic fluids, coupled with the presence of endogenous precursors within the digestive system, has prompted

the necessity for regulatory action and the search for evermore sensitive methods of analysis.

Guidance for industry regarding the recommended acceptable intake limits for Nitrosamine Drug Substance Related Impurities (NDSRIs) have been issued by the Food and Drug Administration (FDA), and is graded based on the carcinogenic potency category of the nitrosamine compounds in question. The potency of the nitrosamine is dependent on the structure of the compound and can range from an acceptable intake (AI) of 26.5ng/day for Category 1 to 1500 ng/day for Category 5.

What are the main types of nitrosamines?

Kevin Parker: Within n-nitrosamines two classes of molecules arise. One subset is derived from common amine building blocks such as dimethylamine, diethylamine, diisopropylamine, etc. The n-nitrosamines formed from these common secondary amines make up what is dubbed the "cohort of concern": a group of seven n-nitrosamines which all have stringent daily limits assigned to them as low as 26.5 ng/day. The other group of n-nitrosamines are formed by reactions of APIs or other related compounds along the synthetic route, forming what's known as "n-nitrosamine drug substance related impurities" (NDSRIs). NDSRIs have varying control limits based on the potential carcinogenicity associated with their structure.

Jingyue Yang: I'd add that nitrosamines can form in pharmaceuticals through manufacturing processes that involve certain solvents, reagents, or contaminated materials (or from leaching through packaging). Many of these nitrosamines have been extensively studied in other industries. On the other hand, NDSRIs are nitrosamines formed from drug substances or their related impurities that contain vulnerable nitrogen atoms within their molecular structure.

What are the main analytical challenges involved in detecting nitrosamines?

Kevin Parker: As with any ultra-low level quantitation experiment, the inherent issue that is always present regards concentration. With sub ppm levels required for almost all analysis, it is necessary to push the instruments to the edge of their capabilities. Often mass spectrometry is used for low-level quantitation, with plenty of examples using both high resolution hybrid instruments and triple quadrupole mass analyzers. The sensitivity observed with modern triple quadrupole mass spectrometers mean they are usually the most ideal instruments to use for ultra-low-level quantitation.

With n-nitrosamines being such a ubiquitous topic in the field of analytical chemistry, there are a lot of manufacturer notes and methods published to use as starting points for analysis. However, these methods often don't consider sample matrices – which can complicate things. Drug products often contain compounds that are not well ionized during mass spectrometry, and can therefore cause significant losses in sensitivity through ionization suppression.

Another challenge in n-nitrosamine analysis comes when differentiating between n-nitrosamines and other isobaric compounds which share a similar neutral loss. It is here where chromatography comes into play and method development is key. Ensuring that you have n-nitrosamine specifically (as opposed to c- or o-nitrosamines) is a requirement for any triple quadrupole method which relies on the neutral loss of NO for detection.

While less common, there are quite a few methods published which use gas phase chromatography for smaller n-nitrosamines such as NDMA, NDEA, NDIPA, etc.

Jingyue Yang: In my opinion, sample preparation and matrix effect are the main analytical challenges in detecting and quantitating nitrosamines. Getting NDSRI reference standards also can be challenging for us, but I'm not sure whether that should be counted too!

In the pharmaceutical industry, liquid chromatography coupled with mass spectrometry (LC-MS), including LC-MS/MS and LC-HRMS, is the most commonly used technique for nitrosamine detection.

Alan Thompson: I agree, the most common techniques in the pharmaceutical industry are GC-MS and LC-MS, as well as HPLC-UV. The eventual technique used is decided by a number of factors including solubility, volatility, workup procedure and required limit of detection or quantitation.

The main challenge we have experienced in detecting nitrosamines thus far is ensuring we can achieve adequate method sensitivity. However, sensitivity is dependent on the solubility of the API in question. Using a more concentrated sample increases the possibility

Trends and Challenges in Nitrosamine Testing

"As an analytical scientist, you'd prefer to develop your method with a limit of quantification below the acceptable intake limit – but sometimes this can be challenging to achieve." – Jessica Hoskins

of reaching low detection and quantitation limits, but risks increasing the content of excipients in formulated drug product samples, potentially hindering the extraction process or suppressing the mass spectrometer signal.

When developing methods, we always try to ensure that excipients and the API are chromatographically resolved as much as possible from the nitrosamine under investigation. This is particularly important for the API since it often has a similar mass to the nitrosamine derived from it, resulting in adduct ions or isotopic interference from the API being captured by the nitrosamine MRM transition. We also try to ensure that only the nitrosamine is diverted to the MS source, to minimize the potential build-up of API or excipient on the source, which can lead to diminishing recovery as the run progresses.

Previously, we have used internal standards (IS) in sample preparations as a way of correcting nitrosamine recovery. Isotopically labeled standards are often not commercially available, however, which means Almac would have to synthesize these. Nitrosamines generated from related API impurities can be used as internal standards, however it needs to be ensured that they too are also resolved from the API and excipients and enters the MS at a similar time to the nitrosamine under investigation.


Jessica Hoskins

Jessica Hoskins: One of the main challenges faced by the pharmaceutical industry is reaching the necessary limit of detection for NDSRIs. Compound specific acceptable intake levels set by regulatory agencies can be as low as 18 ng/day. The absolute detection limit needed analytically therefore depends on the combination of the potential maximum daily dosage (MDD) of the drug, the practical concentration you can prepare the drug product sample solution and the percentage of that drug product that is API. For example, with a MDD of 1 g per day, a moderate API drug load (15 percent of drug product by weight), and a prepared drug product sample concentration of 100 mg/mL (15 mg/mL on API basis), an acceptable intake limit of 26.5 ng/day translates to a 0.4 ng/mL method limit. As an analytical scientist, you'd prefer to develop your method with a limit of quantification (LOQ) below the acceptable intake limit – but sometimes this can be challenging to achieve!

Since drug product matrices can be quite complex, sample preparation and chromatography are key parameters to achieve the necessary LOQ (in addition to mass spectrometry optimization, of course). For example, asymmetric N-nitrosamines exist in two stable rotameric forms, which can be separated chromatographically. Some excipients are not UV active and do not ionize well in MS, and yet may still interfere with the MS signal of a nitrosamine analyte if coeluting from the column.

Naiffer Romero: Detecting nitrosamines in pharmaceuticals presents several analytical challenges, including the need for trace-level analysis, as others have mentioned – nitrosamine analysis requires detection at very low levels, often in the parts-per-billion (ppb) range, requiring highly sensitive analytical methods. Specificity is another challenge, as the potential for false-positive

identification due to background contamination or co-eluting compounds necessitates the use of highly specific detection techniques. Additionally, artifact formation during analysis requires careful method optimization, and in some cases the use of inhibitors can prevent unintended nitrosamine formation. Recovery poses yet another hurdle, as matrix interference and differences in solubilities make it challenging to achieve accurate recovery of nitrosamines when spiked in drug products.

As companies started to undergo "confirmatory testing," they found how critical the quality of the reference material is to guarantee accuracy in their testing results.

Can you give us an overview of the regulatory environment for nitrosamines?

Kevin Parker: Regulators around the world such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidelines and limits around the control of n-nitrosamines in drug products. These often include guidelines and regulations concerning testing and detection of n-nitrosamines, determination of acceptable limits, reporting and recalling pharmaceutical products and issuing guidance documents on how to control for n-nitrosamines.

Jingyue Yang: International regulatory agencies have actively collaborated to address nitrosamine impurities in pharmaceutical products since the issue first emerged. Various workshops and training sessions have been held by regulatory authorities to explain policies, as well as to gather insights and feedback from stakeholders. In a relatively short period, multiple agencies have released guidance documents. Over the past four years, the FDA has issued and revised guidance documents for industries reflecting the latest developments. Overall, regulatory agencies worldwide view nitrosamine impurities as a significant quality and safety concern and have dedicated substantial resources to developing proactive regulatory strategies as a result.

Alan Thompson: Agreed, Jingyue. Procedure EMA/369136/2020 (Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products, issued on June 2020) by the EMA gives an in-depth overview on all aspects of nitrosamines; from root cause of nitrosamine formation through to considerations for the development of quantitative methods, and calculation risk for exposed patients in case of detection of N-Nitrosamines in medicinal products. Further to this, EMA/409815/2020 Rev.16 (issued in July 2023) details questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. This includes an update to the limits which apply for nitrosamines in medicinal products.

Recommended Acceptable Intake (AI) Limits for NDSRIs, issued by the FDA in August 2023 contains a useful flowchart which can be used to predict the carcinogenic potency of an NDSRI, and subsequently identify an associated recommended AI limit and potency category. The calculation of AI assumes a daily administration of the maximum daily dose of the medicinal product, and is based on the approach outlined in the ICH M7(R1) guideline in addition to the principles related to the toxicological evaluation in the assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

Jessica Hoskins: At this point in time, I'd sum up the regulatory environment as continually evolving. As the analytical experts in the lab, we must be familiar with the regulatory environment and work closely with other areas of the organization to make sure we are developing methods to appropriately assess the risk of nitrosamine formation. As a large company focused on product quality and safety for patients, we have internal resources to help us keep up to date with the changing regulatory environment. USP's Nitrosamines Exchange forum is also a good resource as a scientist to keep up with the latest developments.

Naiffer Romero: Agreed, and as the regulatory landscape and guidelines continue to evolve, several key changes have emerged to address nitrosamine impurities. In accordance with regulatory guidelines, pharmaceutical companies now perform risk assessments for chemically synthesized drug products to identify potential nitrosamine impurities. This necessitates the prioritizing of investigations into nitrosamine risks through comprehensive risk assessments for all the components and processes involved in the manufacturing of a drug product. If a

"Over the past four years, the FDA has issued and revised guidance documents for industries reflecting the latest developments." –Jingyue Yang

risk is identified, companies should develop and validate sensitive and specific methods for nitrosamine analysis in accordance with regulatory guidelines to confirm their presence and potentially report levels exceeding the limit of quantitation (LOQ). Supplier qualification has become critical, helping to ensure that raw material and excipient suppliers have appropriate controls to minimize nitrosamine risks. Robust change control procedures must be implemented to evaluate the impact of any changes on nitrosamine risk. Regulatory agencies have also established acceptable intake (AI) limits for common nitrosamines or provided interim limits when necessary, as others have mentioned.

Any advice for ensuring compliance with nitrosamine regulations?

Jingyue Yang: The FDA's publication of the RAIL Guidance (Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)) in August 2023 and the Nitrosamine Guidance (Control of Nitrosamine Impurities in Human Drugs) (updated in September 2024) have provided significant clarity regarding the recommended acceptable intake limits for various nitrosamines (see here). These guidelines enable the evaluation of recommended acceptable intake limits for a wide range of nitrosamines, offering clear benchmarks for method sensitivity requirements.


Jingyue Yang

Where provided, manufacturers are encouraged to adopt FDA recommended AI limits. For products marketed in the US, however, alternative approaches can be used if they satisfy the requirements of the applicable statutes and regulations.

What future trends do you foresee in the field of nitrosamine analysis and regulation?

Alan Thompson: The discovery of nitrosamines in "sartans" prompted a wide-ranging review of existing medicinal products, whereby numerous compounds were identified as potential compounds for nitrosamine formation. Whilst this formation is often facilitated by the presence of nitrites present in drug excipients, it can often be compounded by environmental factors, given the presence of nitrites in water and the extensive use of nitrites as preservatives within the food industry.

In addition to this, many of the new nitrosamine compounds identified are generated from related APIs, and therefore toxicological data on them can be quite limited. However, greater regulatory harmonization between different bodies, including a focus on validation acceptance criteria, would certainly add another level of control to what is a fast-emerging field of pharmaceutical, environmental and food science.

Jessica Hoskins: I couldn't agree more, greater harmonization is always welcome!

Kevin Parker: The future of nitrosamine analysis in pharmaceutical products will always involve proper risk assessments, testing for nitrosamines, and robust regulatory guidance. However, I think future development will focus on the prevention of nitrosamine formation all together. Using scavengers that can remove the building blocks or inhibitors that stop the

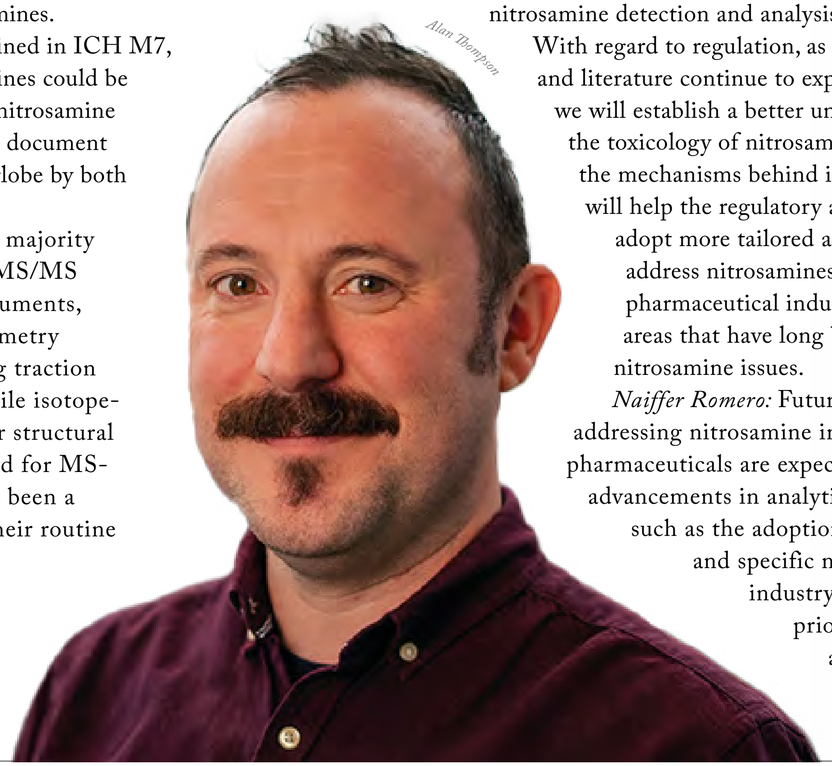
Trends and Challenges in Nitrosamine Testing

chemical reactions required for nitrosamine formation, the control strategies surrounding nitrosamines will become more robust. Further understanding of the formation of nitrosamines in solid state drug products will only enhance the industry's ability to prevent and control nitrosamines.

Similar to the guidance outlined in ICH M7, a future approach to nitrosamines could be used in which the limit of all nitrosamine impurities are captured in one document that is distributed across the globe by both regulators and industries.

Jingyue Yang: Although the majority of analyses still rely on LC-MS/MS using triple quadrupole instruments, high resolution mass spectrometry (HRMS) is gradually gaining traction in the field. Additionally, while isotope-labeled internal standards (or structural analogs) are the gold standard for MS-based quantitation, there has been a noticeable shift away from their routine use as more recent methods utilize external standards without isotope labeling.

Looking forward, I hope to see advancements in LC-MS technology and methodology that enables the direct identification of any nitrosamine species in a sample without prior knowledge (a non-targeted analysis). Such capabilities would significantly enhance the scope and efficiency of nitrosamine detection and analysis.


Alan Thompson

With regard to regulation, as ongoing studies and literature continue to expand, I believe we will establish a better understanding of the toxicology of nitrosamines, as well as the mechanisms behind it. This progress will help the regulatory agencies to adopt more tailored approaches to address nitrosamines not only in the pharmaceutical industry, but also in the areas that have long been exposed to nitrosamine issues.

Naiffer Romero: Future trends in addressing nitrosamine impurities in pharmaceuticals are expected to include advancements in analytical techniques, such as the adoption of more sensitive and specific methods. The industry is likely to prioritize prevention and mitigation strategies, including the careful selection of raw materials, optimization of manufacturing processes, and the addition of antioxidants or pH modifiers to drug formulations to minimize the risk of nitrosamine formation.

Increased collaboration and data sharing between regulatory agencies, industry, and researchers are anticipated to enhance the understanding and control the formation of nitrosamine impurities. Additionally, identifying new sources of nitrosamines remains a critical focus, as emerging reports highlight previously unrecognized sources that must be understood and mitigated.

To support manufacturers, USP offers resources including documentary standards and a wide range of reference materials which include official USP Reference Standards and Pharmaceutical Analytical Impurities (PAI) – all of which are valuable tools for impurity detection and control. USP also facilitates the Nitrosamines Exchange, a virtual knowledge-sharing community with over 5,000 scientific members who discuss best practices and share resources related to nitrosamine impurities. Heightened regulatory scrutiny and public awareness have driven a proactive industry approach, focusing on the development of sensitive analytical methods, robust risk assessments, and preventive measures to ensure pharmaceutical safety and quality. Continuous improvement and close collaboration with suppliers and strict control of materials will be essential to effectively address the challenges posed by nitrosamine contamination.

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The Golden Age of Drug Discovery

Sitting down with Insmed's Tom Heightman, we discuss new technologies for drug discovery and the promise of human genome sequencing data.

Insmed recently opened a new R&D facility in Cambridge, UK. The 17,000 square foot facility will focus on synthetic rescue for serious diseases. Overseeing the facility is Tom Heightman, Senior Vice President of Research at Insmed. We sat down with him to discuss trends in drug discovery and the power of genetics.

What are the most exciting trends that you're seeing in drug discovery?

There's so much going on that it's hard to know where to start. At the highest level, I think the sheer amount of data scientists have access to is transforming everything. We now have access to millions of human genome sequences to help us understand health and disease. Our ability to image processes in human cells and model disease is remarkable. Tools like AlphaFold allow us to predict protein structures with incredible accuracy, opening the door to in silico drug design.

When you bring all these developments together into the interdisciplinary toolkit we use to understand biology and translate that understanding into drug design, it really feels like we're in a golden age of science. I've been in the industry for 27 years, and one of the great things about this field is that it keeps you forever young. Technology is always moving forward, and we're constantly integrating new techniques and fresh thinking into what we do. It's an exciting journey, and I wouldn't change a moment of it.

And what about exciting new technology launches?

Gene sequencing is one that stands out immediately. The first human genome was sequenced just over 20 years ago at enormous expense, and now, even here in the UK with the UK Biobank, we have access to more than half a million human genomes. This is an incredibly powerful dataset. CRISPR gene editing is another key area. It's a hugely powerful technology that is game changing.

In chemistry, we face the challenge of making the molecules we design and then testing them. Here, too, there have been incredible advances, particularly in organic synthesis using visible light photo-redox techniques. We can now create complex molecules that might have once required a 12-step synthesis and more than a month to make in a fraction of the time. In some cases, they enable us to make molecules that we simply couldn't produce before.

It's no good having AlphaFold and AI design the perfect molecule if you can't then make and test it. The ability to actually synthesize those designs is an essential link in the chain – and it's advancing very rapidly.

Is solubility still a big problem in the industry?

The onus is on drug designers to create brilliant molecules that not only engage their target in human cells, but have developable properties. We can now apply design approaches to a range of parameters, including solubility.

The Golden Age of Drug Discovery

One cutting-edge area of science I haven't mentioned yet is the analysis of small-molecule crystal structures and the use of AI to predict crystal lattices – and therefore solubility. This means we can design for solubility during the optimization process. This ties back to what I said earlier about it being a golden age of science. I have seen projects in the past that struggled with solubility, but formulation technology is advancing rapidly too, offering clever ways to overcome those challenges.

What is Insmed working on at the moment?

We already have a strong clinical pipeline in respiratory disease. Now, across our four research sites in the US and the UK – New Jersey, New Hampshire, San Diego, and Cambridge – we're expanding into a range of other therapeutic areas.

In Cambridge, we have a particular focus on CNS diseases, especially neurodegenerative disorders. What's powerful about our global research organization is that the company has brought together teams with expertise in different areas and modalities. This means we can draw on strengths across small molecules, oligonucleotides, biologics, and even gene therapy to select the most appropriate modality – or combination of modalities – for each specific case.

Our approach is to focus on target discovery. We start by unravelling the biology of a disease that has been poorly studied. As we build a better understanding of that biology and identify how we might manipulate it for therapeutic benefit, we consider the entire cellular chain: from the gene in the DNA, through expression into RNA, translation of that

The Golden Age of Drug Discovery

"When you bring together human genetics, AI, advanced imaging, and modern chemistry, it really feels like we're in a golden age of science."

RNA into protein, and the protein's life cycle in the cell.

Having access to multiple modalities means we can intervene at any point along that chain. It allows us to determine which approach produces the strongest effect on the biology, and which is best tolerated.

What influenced the recent decision to invest in Cambridge?

With three sites already in the US, looking beyond the country was a great way to access diverse thinking and alternative approaches. Cambridge is a truly powerful biomedical ecosystem. It brings together a world-leading ancient university, multiple academic institutes, a major hospital that continues to expand, and a thriving biotech and pharma hub. Together, these elements create an intellectual powerhouse that fosters diverse perspectives.

Specifically, Insmed was interested in synthetic rescue with a genetics-focused target discovery platform. That platform was the brainchild of Cambridge professor Sir Steve Jackson, who founded Adrestia, which Insmed acquired in 2023. Adrestia had developed the platform, begun assembling a world-class team of drug hunters, and the science underway there was highly complementary to Insmed's own research. There was also an exceptional cultural fit. The Cambridge team shares the same core values as the wider Insmed organisation: a commitment to patients, a spirit of collaboration, and a "How can I help?" mindset.

What aspects of the new facility are you most excited by?

We've brought together, under one roof, expertise in three key areas: cutting-edge cell biology and imaging, chemistry and drug design, and computational biology and data science. These are all stitched together with powerful integrative informatics. That level of integration is something I'm genuinely thrilled about.

Each of these core areas is also underpinned by some remarkable new technology and equipment. I have to mention our investment in the cell imaging and microscopy suite! There's a real beauty to certain aspects of medical science and biology, and cell imaging is one of them. To be able to take a neuron from a patient-derived cell in the brain, image it, and watch – in almost real time – what's going right and what's going wrong, is extraordinary. To be able to then apply a drug molecule we hope will improve those processes, and actually see the changes happening inside the cell on a screen, is hugely compelling.

What can you tell us about Insmed's current focus areas and plans for the future?

We have a focus on serious and rare diseases with unmet needs. We have a strong respiratory franchise and clinical pipeline. We're also expanding our focus into CNS, neurodegeneration, and neuromuscular diseases.

The unmet need is enormous. There are more than 7,000 known rare diseases, and it's estimated that one in 17 people will have a rare disease of some kind. More than 95 percent of those conditions currently have no treatment.

Although the numbers are sobering, there's a hope. Advances in human genetics are revealing the underlying causes of many of these diseases. We're seeing more initiatives to carry out genetic testing, which helps us understand what's gone wrong in each case. This, in turn, allows the scientific community to apply new techniques and approaches to tackle them.

What other big industry trends are you keeping an eye on?

I may sound like a broken record, but the impact of human genetics and genomics on understanding health and disease is only going to get bigger. This isn't just about drug design; it's about how healthcare providers start integrating genetic data into diagnostic processes. This creates an ecosystem that's highly favourable for companies like ours when we want to bring forward new medicines.

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