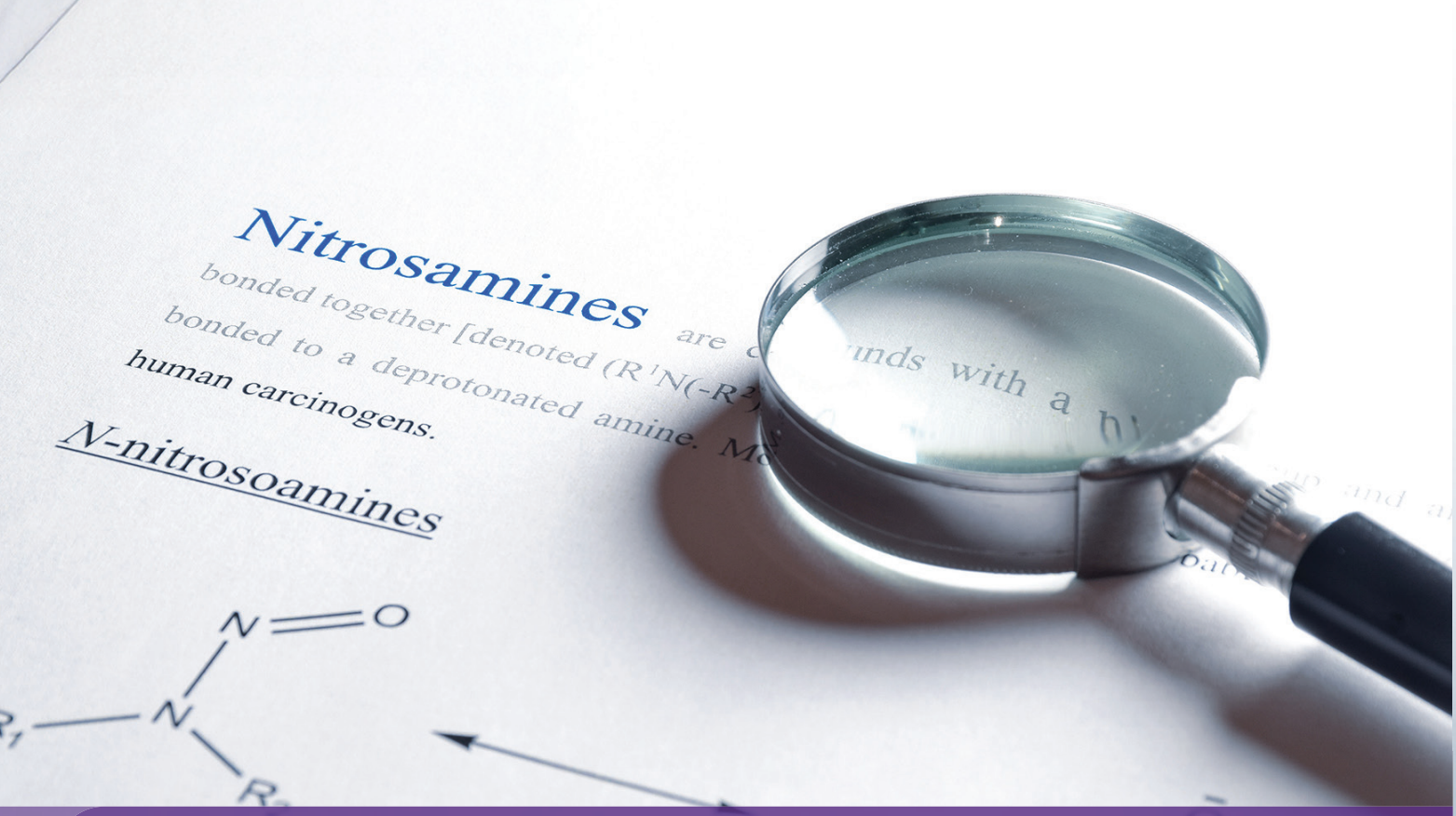

COMPLIANCE

Zero Hour for Nitrosamine Compliance

An analysis highlights regulatory consequences across the drug product life cycle

Viky Verna

Pharma and Medical Device Regulatory Affairs
Aptar CSP Technologies

The FDA deadline to meet nitrosamine control guidance is upon us. Here's a review of past nitrosamine-related regulatory actions — and lessons learned.

Nitrosamines emerged as a significant public health concern in mid-2018, when the FDA and other global regulatory authorities detected N-nitrosodimethylamine (NDMA), a probable human carcinogen, in batches of valsartan — an angiotensin II receptor blocker (ARB) used for hypertension and heart failure. Since then, regulatory agencies have demonstrated a strong commitment to protecting patients by establishing clear guidelines and expectations related to nitrosamine risk control.

In the U.S., the FDA issued multiple guidance documents to inform industry stakeholders of these evolving expectations. Notably, these include the Guidance on Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August 2023) and the revised Guidance on Control of Nitrosamine Impurities in Human Drugs (September 2024, Revision 2). These documents initially culminated in a critical compliance deadline — August 2025 — for manufacturers to meet defined nitrosamine control requirements. On June 23, 2025, the

FDA clarified that companies employing mitigation strategies that require a longer implementation timeline must provide at least a progress update by the deadline.

Alongside these regulatory publications, the FDA has taken numerous enforcement actions against noncompliant firms. These include Form FDA 483 observations, warning letters, product recalls, clinical holds, and issuance of complete response letters (CRLs) due to inadequate nitrosamine controls.

To illustrate the seriousness of the August 2025 deadline, the regulatory team at Aptar CSP Technologies conducted a detailed review of publicly available FDA enforcement data and regulatory announcements from 2018 through 2025. This analysis highlights significant regulatory consequences across various stages of the product life cycle — from pre-approval submissions to post-marketing surveillance — and offers insight into lessons learned from enforcement trends.

Before Drug Products Entered the Market

Past Regulatory Actions Taken

1. Complete response letters: CRLs are formal FDA notifications indicating that a drug application cannot be approved in its current form due to the inadequacy or unacceptability of the data provided in the drug application submitted for review. While there is not an official database that lists the CRLs, at least three major cases were found in the public domain. These three cases of CRLs were issued recently (in 2023-2024) for the following:

- Nitrosamine impurities exceeding acceptable limits. Some cases required additional testing including additional stability data and/or repeat-dose studies on animals, especially if a reformulation was considered.
- Insufficient nitrosamine testing or risk assessments. The FDA requested risk assessments according to ICHQ3D, M7(R2) and related FDA guidance documents.
- CMC (chemistry, manufacturing and controls) deficiencies. For example, one of the companies was asked to submit further nitrosamine impurity data per the updated draft guidance issued after NDA submission. For this case, one of the release testing facilities needed to be reinspected.

The consequences faced by the sponsor of these applications included delays in market approval, clinical trial holds, and rework of application data.

2. Refuse to file (RTF): An RTF letter is issued by the FDA when a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is deemed incomplete or fails to meet regulatory submission standards. While no publicly disclosed RTF letters to date have cited nitrosamine concerns as the sole justification, the growing emphasis on nitrosamine control suggests this could become a more common basis for rejection. Applications that lack adequate risk assessments or fail to include a control strategy for nitrosamine impurities, may be subject to RTF action, delaying entry into formal review and approval timelines.

3. Clinical holds: Although not always easily traceable in FDA databases, several clinical trial delays have been publicly linked to nitrosamine-related issues. Based on industry reporting and Aptar CSP's internal research, at least three clinical programs for critical drugs (e.g. cancer) have experienced clinical holds.

The first case was raised in 2021 after the first FDA guidance publication, and the other two cases were triggered more recently in 2024. For one case, the sponsor needed to implement manufacturing adjustments to comply with regulatory expectations. For another, there were nitrosamines found in produced batches. For the third case, a full risk assessment was needed to assure compliance before proceeding to the next clinical trial phase.

FDA Guidance Expectations

To avoid the regulatory consequences outlined above, the FDA has clearly articulated expectations that vary depending on the stage of the product life cycle.

For drug products under development (pre-submission), companies must proactively assess and control nitrosamine risks before submitting INDs, NDAs or ANDAs. Applications submitted without documented nitrosamine control strategies may be found deficient, leading to an RTF or CRL preventing approval.

For drug products with submitted applications (post-submission), applicants who have already filed submissions without addressing nitrosamine risks are expected to amend their applications accordingly. This includes submitting supplemental data or responses to FDA information requests. Several CRLs have already been issued for this reason. Similarly, products authorized for clinical trials may face clinical holds if updated nitrosamine assessments are not provided.

Approved Drug Products

Past Regulatory Actions Taken

1. 483 observations and warning letters: FDA Form 483 observations are a list of potential violations of the FDA 21 Code of Federal Regulations (CFR), observed during an inspection, that can be issued to a company. Warning letters (WLs) are official letters sent to inspected companies where the potential violations are confirmed. A WL is a formal enforcement action requiring response and corrective action.

These Form 483 and WL issuances may lead to other regulatory actions such as import alerts, product recalls, clinical holds, or refusal to approve applications.

Between 2020 and 2025, the FDA significantly increased the number of Form 483 and warning letters issued related to nitrosamine risk management. Based on Aptar CSP's internal review of publicly available enforcement documents, at least 10 FDA Form 483 inspection observations and seven WLs have cited failures to adequately control or evaluate nitrosamine impurities. These findings often reflect gaps in risk assessments, control strategies, or documentation of mitigation efforts. In many cases, the observations directly referenced the FDA guidance document for the lack of nitrosamine testing, insufficient supplier qualification for at-risk ingredients, or inadequate impurity trending and analysis during stability studies.

Furthermore, the FDA frequently cited companies for releasing products without demonstrating that nitrosamine levels were within acceptable intake (AI) limits, and for not adequately investigating the root causes of unexpected nitrosamine findings. In some cases, companies were also criticized for failing to submit field alert reports (FARs) in a timely manner after detecting nitrosamines in commercial batches.

2. Recalls and market withdrawals: From 2018 through 2025, the FDA has overseen more than 40 drug product recalls linked to nitrosamine contamination or risk of nitrosamine formation. The first nitrosamine-related recalls occurred in 2018, when 10 products were suddenly recalled from the U.S. market. After no recalls in 2019, only one in 2020, and one more in 2021, there was a spike with 10 recalls in 2022, six in 2023, and 15 recalls in 2024. By April 2025, eight products had already been recalled for the year.

These recalls span a wide range of dosage forms and therapeutic categories, including oral solid dose products such as ARBs (e.g., valsartan, losartan), ranitidine, rifampin, metformin, duloxetine, varenicline, and several generic antihypertensives and antidepressants. Nitrosamine species such as NDMA, NDEA, NMBA, NTTP, and various nitrosamine drug substance-related impurities (NDSRIs) were identified across these recalls. In several cases, the root cause was traced back to raw material contamination, degradation during storage, or nitrosamine migration from packaging components.

Aptar CSP's internal research has identified over 25 distinct manufacturers or distributors involved in recalls due to confirmed or potential nitrosamine presence. Among these, repeat recalls affecting multiple batches or strengths of the same product were common, suggesting systemic issues in impurity control strategies. Some recalls involved more than 100,000 bottles, indicating broad distribution before detection. In addition, the FDA has classified many of these events as Class II recalls, highlighting the concern for potential, but not immediate, risk to patient health. However, a number of Class I recalls were also initiated, including for drugs like ranitidine and certain ARBs, reflecting high-priority public health risks.

For many of the recalls, market withdrawal was enforced due to the patient risks associated with the level of nitrosamines, such as for ranitidine. In other cases, partial recalls were sufficient, especially if a drug shortage could put patients at risk. For example, the FDA allowed rifampin, rifapentine, and the medicine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP) to remain in the market above the acceptable intake limit of 0.1 parts per million (ppm) and at or below 20 ppm, until the manufacturer can reduce or eliminate the impurity.

Notably, in several 2022–2025 recalls, the root causes of nitrosamine formation extended beyond APIs and excipients. FDA investigators and company assessments increasingly identified packaging-related contributors, such as nitrosating agents from adhesives, colorants, or secondary amine-based materials in blister films and bottle liners. An increase of recall notifications was also noted for multiple other regulatory authorities and jurisdictions such as EMA, Health Canada, MHRA (UK), ANVISA (Brazil), Namibia, Korea, Singapore and PMDA (Japan).

3. FDA import alerts and refusals: The FDA employs import alerts as a regulatory tool to prevent violative products from entering the U.S. These alerts enable detention without physical examination (DWPE) or import refusals of products that appear to violate FDA requirements (adulterated or misbranded), including those related to the presence of nitrosamine impurities. Import alerts are designed to mitigate public health risks by proactively stopping the importation of unsafe or non-compliant products at the border.

Although nitrosamine-related import alerts are not always explicitly listed in the FDA's publicly searchable databases, enforcement actions suggest that at least one product was placed under Import Alert 66-40 in 2018 due to nitrosamine contamination concerns. Furthermore, even when a specific finished drug product is not explicitly named on an import alert, it may still be subject to detention if it contains an API that originates from a manufacturer currently listed under DWPE for nitrosamine violations.

FDA Guidance Expectations

To avoid these regulatory consequences, the FDA has clearly defined expectations for manufacturers in its updated guidance on nitrosamine impurities.

Manufacturers are expected to have completed risk assessments and, where risks are identified, validated testing

and mitigation controls. Additionally, any test result that exceeds the AI limits must be reported to the FDA. Failure to comply with these expectations may result in enforcement actions including 483 observations, warning letters, recalls or import alerts.

Consequences of Enforcement Actions

The FDA's enforcement actions in response to nitrosamine-related violations since 2018 have triggered wide-ranging regulatory and commercial consequences for pharmaceutical manufacturers. In many cases, a single inspection triggered a chain of consequences. For example, an initial 483 observation can escalate to a warning letter, followed by product recalls and even import refusals. Companies affected have been required to conduct extensive risk assessments, revise control strategies, and in some cases, change manufacturing processes, introduce additional manufacturing control, reformulate, or repackage drug products to address nitrosamine contamination risks. Especially when it comes to nitrosamines, the FDA often published advisory notes and press releases on its website highlighting enforcement actions taken against companies because of nitrosamine contaminations. Since these actions often become public, the reputation of the companies can be affected.

These compliance actions also come with considerable financial and operational burdens, as well as development and production delays. Companies may need to invest in new equipment, validate updated manufacturing processes, and initiate new R&D programs to support reformulations or mitigation technologies, all of which can significantly add to compliance costs. In some instances, production lines must be paused, with losses reaching millions of dollars per day, compounded by the costs of rejected or recalled batches. In the development pipeline, several clinical trials have been paused due to nitrosamine findings, resulting in delays in drug approvals and potential disruptions to patient access. These delays can also trigger investor concerns, leading to a loss of funding or company devaluation, particularly for innovative drug and generics firms dependent on time-sensitive development milestones.

Post-Deadline Expectations

The FDA's timeline for nitrosamine-related compliance was not arbitrary. It reflects what the agency considers to be a reasonable period for manufacturers to conduct comprehensive risk assessments and perform confirmatory testing to verify if results exceed acceptable limits. By now, manufacturers must have identified effective mitigation measures, determined the expected timeline for implementation, and reported the progress status to the FDA. The rationale is grounded in public health protection: patients continue to be exposed to potential carcinogenic impurities and any delay in mitigation puts vulnerable populations at unnecessary risk.

When considering the regulatory enforcement actions, which have gradually increased in recent years, an even greater increase in clinical holds, CRLs, warning letters, and recalls can be expected, until the industry gets the opportunity to catch up with the regulatory expectations. To meet these expectations, companies will need to not only implement new product development and manufacturing approaches and strategies that specifically mitigate nitrosamine contamination; they will also need to ensure they generate the associated risk assessment documentation and confirmation testing evidence to address potential auditor requests during inspections, as well as support new drug applications and supplements.

FDA Updates: Packaging as Mitigation

An important update to the Nitrosamine Guidance (Version 2 – September 2024) is the FDA's inclusion of packaging solutions as part of acceptable nitrosamine mitigation strategies. In conjunction with this revision release, the FDA also updated its website to indicate that certain nitrosamine impurities might be best addressed through a replacement of packaging.

While the agency has not formally stated an expedited review pathway for such technologies, there is growing evidence, including from FDA meetings and case reviews, that mitigation strategies involving packaging may be reviewed and approved more rapidly, especially when they can be directly tied to preventing nitrosamine formation in high-risk drug products.

In fact, the FDA has admitted one such technology into its Emerging Technology Program, which helps promote the adoption of innovative approaches to pharmaceutical product design and manufacturing.

For new drug applications, the FDA expects sponsors to provide stability data in accordance with ICH guidelines, including both six-month accelerated and 12-month long-term real-time studies. For marketed products, the FDA confirmed that utilizing novel active packaging technologies as a nitrosamine control measure typically requires a prior approval supplement (PAS), though in lower-risk cases a combination of three months' accelerated and supportive long-term data may be sufficient. With broader experience, reporting pathways such as CBE-30 may be acceptable in the future.

To support these regulatory pathways, technical, performance, and safety data related to new packaging technologies must be generated for inclusion into the drug master file (DMF #14789). These efforts aim to build FDA confidence in the robustness of active packaging-centric nitrosamine mitigation solutions, and provide pharmaceutical sponsors with a clear, compliant framework to integrate them into their nitrosamine mitigation strategies.