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A REVIEW OF PAST REGULATORY ACTIONS TRIGGERED BY NITROSAMINES:

LESSONS LEARNED TO COMPLY WITH FDA NITROSAMINE CONTROL GUIDANCE BY THE AUGUST 2025 DEADLINE

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 non-compliant 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 lifecycle — from pre-approval submissions to post-marketing surveillance — and offers insight into lessons learned from enforcement trends.

1. Before Drug Products Entered the Market (Pre-approval)

a. Past Regulatory Actions Taken

i. Complete Response Letters (CRLs)

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 Complete Response Letters, 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.

ii. Refuse to File (RTF)

A Refuse to File (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.

iii. 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 case, there were nitrosamines found in produced batches. For the 3rd case, a full risk assessment was needed to assure compliance before proceeding to the next clinical trial phase.

b. FDA Guidance Expectations

To avoid the regulatory consequences outlined above, including CRLs, RTFs, and clinical holds, the FDA has clearly articulated expectations that vary depending on the stage of the product lifecycle:

i. 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.

ii. 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.

2. For Approved Drug Products (Post-approval)

a. Past Regulatory Actions Taken

i. 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. The FDA 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 Warning Letter 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 Warning Letters 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.

ii. 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 (1) product recall in 2020, and one (1) in 2021, there was a spike with 10 recalls in 2022, 6 in 2023, and 15 recalls in 2024. By April 2025, 8 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, PMDA (Japan), etc.

iii. FDA Import Alert and Import Refusals

The FDA employs Import Alerts as a regulatory tool to prevent violative products from entering the United States. 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 active pharmaceutical ingredient (API) that originates from a manufacturer currently listed under DWPE for nitrosamine violations.

b. FDA Guidance Expectations

To avoid the regulatory consequences previously described, such as Form 483 observations, Warning Letters, recalls, or import alerts, 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.
- Any test result that exceeds the AI limits must be reported to the FDA no later than August 1, 2025.
- 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 re-package 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 and adding significantly 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.

Why the August 2025 Deadline Matters

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 the specified August deadline, manufacturers must have identified effective mitigation measures, determined the expected timeline for implementation, and reported the progress status to the FDA. Despite the extension of this timeline for the implementation of nitrosamine controls, the FDA reiterated the importance of the August deadline. 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.

Expectations After the August Deadline

When considering the regulatory enforcement actions, which have gradually increased in recent years, we expect to see an even greater increase in Clinical Holds, CRLs, Warning Letters, and recalls 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 to support new drug applications and supplements.

FDA Website 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 Aptar CSP's N-Sorb technology into their Emerging Technology Program, which helps promote the adoption of innovative approaches to pharmaceutical product design and manufacturing.

Aptar CSP Discussions with the FDA Emerging Technology Team (ETT)

As part of its participation in the FDA's Emerging Technology Program (ETP), Aptar CSP has actively collaborated with the Agency to align on regulatory expectations for its N-Sorb technology, an innovative active packaging based solution for mitigating nitrosamine risk. For new drug applications (NDAs), 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 Agency confirmed that the addition of N-Sorb 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, Aptar CSP continues to generate technical, performance, and safety data to be included in its Drug Master File (DMF #14789). These efforts aim to build FDA confidence in the technology's robustness and provide pharmaceutical sponsors with a clear, compliant framework to integrate N-Sorb into their nitrosamine mitigation strategies.

Summary Conclusion: Lessons from Enforcement — A Proactive Compliance Approach

The regulatory landscape surrounding nitrosamine control is rapidly evolving, and the consequences of non-compliance are already well-documented. As detailed in this report, numerous pharmaceutical companies have faced clinical trial holds, application delays, Warning Letters, and product recalls due to unacceptable nitrosamine levels or insufficient mitigation strategies. These enforcement actions have affected both marketed and investigational products, disrupting patient access, triggering financial and operational setbacks, and harming sponsor credibility.

With the August 1, 2025 compliance deadline approaching, the FDA has made its expectations clear: manufacturers must complete risk assessments, provide progress updates on the implementation of nitrosamine control strategies, and report any findings that exceed acceptable intake (AI) limits. Based on enforcement trends, regulatory scrutiny is expected to intensify following the deadline. To avoid potential sanctions, manufacturers should act now to finalize testing, mitigation planning, and documentation to demonstrate readiness when the FDA begins requesting evidence of compliance.

References

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