JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Analytical Challenges in Ultra-Trace Quantitation of Nitrosamine Related Impurities within Complex Pharmaceutical Matrices

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Publication history: Received on 25th September 2025; Revised on 10th October 2025; Accepted on 12th October 2025

Article DOI: 10.69613/fdwf0x16

Abstract: The identification of mutagenic N-nitrosamine impurities in widely prescribed pharmaceuticals resulted in a major shift in drug safety assessment and quality control. While initial scrutiny is mostly on the small, volatile dialkyl nitrosamines, the investigation has inevitably expanded to Nitrosamine Drug Substance-Related Impurities (NDSRIs) complex, non-volatile structures formed by the nitrosation of the active pharmaceutical ingredient itself or its synthesis intermediates. Quantifying these impurities at ultra-trace levels, often in the nanogram per day range, presents a formidable analytical obstacle distinct from traditional impurity profiling. NDSRIs frequently lack commercial reference standards, exhibit complex isomeric profiles due to restricted rotation around the N-N bond, and possess physicochemical properties similar to the parent drug, complicating chromatographic separation. Moreover, the pharmaceutical matrix comprising various excipients and high concentrations of the active ingredient introduces significant ion suppression and matrix interference during mass spectrometric detection. A critical, often inevitable risk involves the in-situ formation of artifacts during sample preparation, potentially yielding false positives. This article evaluates the current state of analytical science regarding NDSRIs, focusing on the rigorous demands of sensitivity and selectivity required by regulatory bodies. It details the specific hurdles associated with sample extraction, the necessity of advanced mass spectrometry techniques like LC-HRMS, LC-MS/MS, and Ion Mobility Spectrometry for trace quantification, and the mitigation strategies employed to ensure method robustness. This review discusses about the generic screening methods as well as highly specific, optimized protocols essential for ensuring patient safety.

Keywords: NDSRIs; Ultra-trace analysis; LC-MS/MS; Matrix effects; Artifactual formation; Ion Mobility.

1. Introduction

The pharmaceutical industry has faced intense regulatory and scientific scrutiny following the 2018 discovery of N-nitrosodimethylamine (NDMA) in Valsartan, an event that triggered a global re-evaluation of impurity control strategies [1]. While the initial crisis involved simple, volatile nitrosamines originating from synthesis reagents and solvents, the scope of concern has widened significantly to encompass Nitrosamine Drug Substance-Related Impurities (NDSRIs). Unlike their smaller counterparts, NDSRIs share structural fragments with the Active Pharmaceutical Ingredient (API), typically resulting from the nitrosation of secondary or tertiary amine moieties within the drug molecule itself [2]. The formation of these impurities can occur during manufacturing, storage, or even within the drug product formulation due to reactions with nitrite impurities present in common excipients such as microcrystalline cellulose or crospovidone [3].

Regulatory agencies, including the FDA and EMA, have established Acceptable Intake (AI) limits based on carcinogenic potency, often requiring quantification at the parts-per-billion (ppb) level relative to the maximum daily dose [4]. These ultra-trace requirements necessitate analytical methods capable of exceptional sensitivity and selectivity. However, the structural complexity of NDSRIs renders traditional gas chromatography-mass spectrometry (GC-MS) workflows, which were suitable for volatile nitrosamines, largely ineffective due to the thermal instability and high molecular weight of these API-related compounds [5]. Consequently, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) or high-resolution mass spectrometry (LC-HRMS) has emerged as the gold standard for detection and quantitation [6]. Developing robust analytical methods for NDSRIs is fraught with difficulties. The presence of the API at concentrations six to nine orders of magnitude higher than the impurity creates a challenging dynamic range for detection systems. Moreover, the chemical environment of the solid dosage form contributes to a complex matrix that can interfere with ionization efficiency and extraction recovery [7]. This review discusses about the analytical challenges involved in analysis of NDSRIs, their unique physicochemical properties of these compounds and the rigorous methodologies required to overcome matrix interference and ensure accurate quantification.

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2. Physicochemical Properties of NDSRIs

The transition from analyzing small dialkyl nitrosamines to NDSRIs represents a leap in analytical difficulty, primarily driven by the structural intricacies of the target analytes. It is a prerequisite to understanding the physicochemical attributes of NDSRIs for successful method development.

2.1. E/Z Isomerism and Rotamers

A defining characteristic of the N-nitroso functionality is the partial double-bond character of the N-N bond, resulting from resonance delocalization of the lone pair of electrons on the amine nitrogen onto the oxygen of the nitroso group [8]. This electronic distribution creates a barrier to rotation, typically in the range of 23 kcal/mol, leading to the existence of distinct E (Entgegen) and Z (Zusammen) conformers, also referred to as rotamers. For small, symmetrical nitrosamines like NDMA, this isomerism is rapid and often analytically irrelevant at ambient temperatures. However, for bulky NDSRIs, the steric hindrance introduced by the API scaffold stabilizes these rotamers, preventing rapid interconversion and allowing them to separate chromatographically [9].

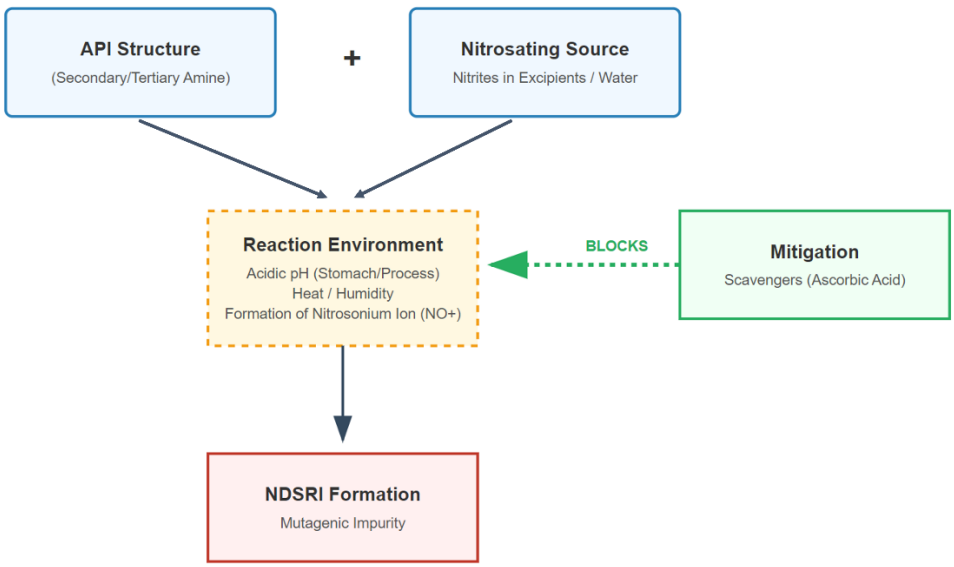

Figure 1. Mechanism of NDSRI Formation & Mitigation

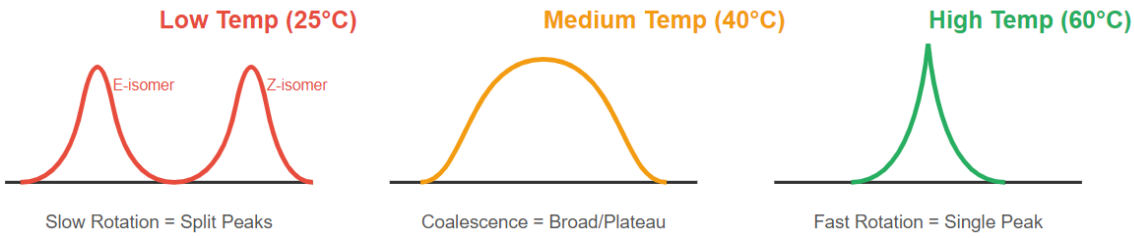

Figure 2. Impact of Temperature on Rotamer Separation

In a standard Reversed-Phase Liquid Chromatography (RPLC) separation, an NDSRI may manifest as a single broadened peak, a doublet, or two completely resolved peaks depending on the thermodynamics of the rotation relative to the chromatographic timescale. This phenomenon complicates integration and quantification significantly. If the isomers are fully resolved, they must be rigorously summed to determine total impurity content, assuming the detector response factor is identical for both conformers. However, if they are partially resolved (coalescing), accurate integration becomes subjective and prone to variability [10]. Elevating the column temperature can sometimes coalesce these peaks by accelerating the interconversion rate, effectively overcoming the rotational energy barrier. Yet, this approach introduces a risk of thermal degradation for labile NDSRIs, necessitating a careful thermodynamic balance between peak shape improvement and analyte stability.

Table 1. Comparison of Conventional Nitrosamines and NDSRIs

Feature	Small Dialkyl Nitrosamines (e.g., NDMA, NDEA)	Nitrosamine Drug Substance-Related Impurities (NDSRIs)
Origin	Synthesis reagents, solvents, water	Nitrosation of the API or intermediates
Molecular Weight	Low (< 150 Da)	High (Similar to API)
Volatility	Volatile / Semi-volatile	Non-volatile
Chromatography	GC-MS or LC-MS	LC-MS/MS or LC-HRMS (GC unsuitable due to thermal instability)
Isomerism	Rapid interconversion (single peak)	Restricted rotation (often distinct E/Z isomers)
Reference Standards	Readily available	Custom synthesis required; often unavailable

2.2. Polarity and Solubility

NDSRIs typically retain the core hydrophobic skeleton of the parent API, meaning their solubility (logP) and polarity profiles closely mirror that of the drug substance. This similarity poses a significant challenge during the separation of the impurity from the bulk API [11]. In techniques such as Solid Phase Extraction (SPE) or Liquid-Liquid Extraction (LLE), finding a solvent system that selectively extracts the trace impurity while rejecting the abundant API is often chemically impossible due to the lack of orthogonal functional groups. Consequently, the analytical instrument must tolerate high matrix loads, or the method must rely on extreme chromatographic selectivity to separate the huge API signal from the minute impurity response to prevent source saturation and isobaric interference.

3. Challenges in Sample Preparation and Extraction

Sample preparation is one of the most critical source of error in the ultra-trace analysis of NDSRIs. The objective is twofold: to extract the analyte quantitatively from a complex solid matrix and to prevent the artificial generation of nitrosamines during the process.

3.1. Artifact Formation During Analysis

One of the most insidious challenges in nitrosamine analysis is the potential for in situ formation of the impurity during sample preparation. If the API contains a susceptible secondary amine and the excipients (or solvents) contain trace nitrites, the conditions used for extraction can catalyze the nitrosation reaction [12]. Acidic diluents, often used to ensure API solubility, can protonate nitrite to form nitrous acid, a potent nitrosating agent. This leads to false-positive results or artificially inflated quantitative values, which can have severe commercial consequences including unnecessary batch rejections.

Table 2. Potential Sources of Nitrite in Common Pharmaceutical Excipients

Excipient Class	Examples	Typical Nitrite Levels (ppm)
Disintegrants	Crospovidone, Sodium Starch Glycolate	0.5 – 10.0
Fillers/Binders	Microcrystalline Cellulose (MCC)	0.01 – 1.5
Lubricants	Magnesium Stearate	< 0.5
Glidants	Colloidal Silicon Dioxide	< 0.1
Capsule Shells	Gelatin, HPMC	Varies significantly

To mitigate this, analytical chemists must employ robust inhibition strategies. The addition of scavengers such as sulfamic acid or ascorbic acid to the extraction solvent is a common practice. These agents react rapidly with free nitrite, effectively removing the nitrosating source before it can interact with the API [13]. However, the validation of these inhibition steps is complex. It requires demonstrating that the scavenger is effective under the specific extraction conditions (time, temperature, pH) without degrading the native NDSRI or suppressing the signal in the mass spectrometer. For instance, high concentrations of ascorbic acid can lead to severe ion suppression in electrospray ionization sources.

3.2. Matrix Interference and Extraction Efficiency

Solid oral dosage forms contain binders, fillers, lubricants, and disintegrants that can interfere with extraction. Polymeric binders, such as hypromellose or povidone, can encapsulate the API and its impurities, requiring aggressive sonication or mechanical shaking

to ensure complete release [14]. However, excessive mechanical stress can generate localized heat, promoting the degradation of thermally labile NDSRIs. Furthermore, insoluble excipients must be removed via filtration or centrifugation. The choice of filter membrane is non-trivial; certain materials, particularly nylon, have been known to adsorb specific nitrosamines via hydrogen bonding, leading to low recovery [15]. Conversely, some filter housings may leach contaminants that interfere with trace detection.

Development of a suitable diluent involves a delicate trade-off. The diluent must dissolve the NDSRI completely but ideally precipitate or limit the solubility of the matrix components. Given the structural similarity between the NDSRI and the API, achieving solubility discrimination is rarely feasible. Therefore, the extract injected into the LC-MS/MS system is typically "dirty," containing high loads of API and solubilized excipients. This necessitates the use of divert valves to send the high-concentration API elution to waste, protecting the mass spectrometer source from contamination, provided the NDSRI and API are chromatographically resolved [16].

3.3. Limitations of SPE and LLE

While traditional sample cleanup techniques like Solid Phase Extraction (SPE) are valuable for enriching trace analytes, their applicability to NDSRIs is limited by the lack of specific functional differences between the impurity and the parent drug. Most SPE sorbents that retain the NDSRI (e.g., HLB or C18) will also retain the API, leading to column overloading and breakthrough [17]. Consequently, many validated methods rely on "dilute-and-shoot" approaches or simple protein precipitation workflows, placing the burden of selectivity entirely on the chromatographic separation and the mass spectrometric detection.

4. Chromatographic Separation

Achieving adequate chromatographic resolution is paramount in NDSRI analysis, not only to separate isomeric forms but to isolate the trace impurity from the overwhelming API signal.

4.1. Stationary Phase Selection

Traditional C18 stationary phases, while versatile, often struggle to separate NDSRIs from the parent API due to their similar hydrophobicity and retention mechanisms. To address this, column chemistries utilizing alternative selectivity mechanisms have gained prominence. Phenyl-hexyl, biphenyl, and fluorophenyl phases employ pi-pi interactions and shape selectivity, which are particularly effective for resolving positional isomers and rotamers typical of NDSRIs [18]. These phases can often separate the NDSRI from the API even when C18 columns fail, enabling the effective use of divert valves to discard the API fraction. The unique interaction of the nitroso group electrons with the pi-system of the stationary phase offers a lever for selectivity that alkyl phases lack.

Table 3. Stationary Phase Selectivity for NDSRIs

Stationary Phase	Selectivity Mechanism	Practical Use Case
C18 (Octadecyl)	Hydrophobic interaction	General screening; often insufficient for API/NDSRI separation.
Phenyl-Hexyl	π-π interactions, Shape selectivity	Separating aromatic NDSRIs from API; Rotamer separation.
Biphenyl	Enhanced π-π interactions	Resolving structural isomers and polarizable compounds.
PFP (Pentafluorophenyl)	Dipole-dipole, H-bonding, π-π	Halogenated compounds; separating positional isomers.
HILIC	Hydrophilic partitioning	Very polar NDSRIs (uncommon) or orthogonal 2D-LC separation.

4.2. Mobile Phase Optimization

The pH of the mobile phase plays a critical role in peak symmetry and retention. Since many NDSRIs are neutral or weakly basic, pH modification can be used to manipulate the ionization state of the interfering API, potentially altering its retention time away from the neutral nitrosamine [19]. However, the choice of modifiers is constrained by MS compatibility; volatile buffers like ammonium formate or ammonium acetate are required. While acidic conditions (using formic acid or difluoroacetic acid) are generally preferred to enhance ionization efficiency in positive ESI mode, careful optimization is necessary to prevent on-column degradation of labile nitrosamines, specifically those prone to acid-catalyzed denitrosation.

4.3. Multidimensional Chromatography (2D-LC)

When single-dimension chromatography fails to provide sufficient resolution or matrix removal, Two-Dimensional Liquid Chromatography (2D-LC) offers a powerful alternative. In a heart-cutting 2D-LC configuration, the fraction containing the NDSRI is collected from the first column and transferred to a second column with orthogonal selectivity (e.g., C18 followed by HILIC or Phenyl) [20]. This technique allows the vast majority of the API and matrix to be discarded in the first dimension, while the second dimension provides a clean separation of the target impurity. While instrumentally complex, 2D-LC provides the ultimate solution for detecting NDSRIs co-eluting with the parent drug.

5. Detection Using Mass Spectrometry

Mass spectrometry serves as the detector of choice for NDSRIs, with Triple Quadrupole (QqQ) and High-Resolution Mass Spectrometry (HRMS) systems dominating the landscape.

5.1. Ionization and Suppression

Electrospray Ionization (ESI) is the most common interface, yet it is highly susceptible to ion suppression caused by co-eluting matrix components or the API itself [21]. When the API elutes, it can consume the available charge in the ESI droplet, effectively "blinding" the detector to the co-eluting NDSRI. Atmospheric Pressure Chemical Ionization (APCI) is an alternative that is less prone to matrix effects and suitable for neutral compounds, utilizing gas-phase ion-molecule reactions rather than liquid-phase charge ejection. However, APCI requires thermal stability that some labile NDSRIs may lack. Therefore, ensuring chromatographic separation of the API from the NDSRI is often more critical than the choice of source.

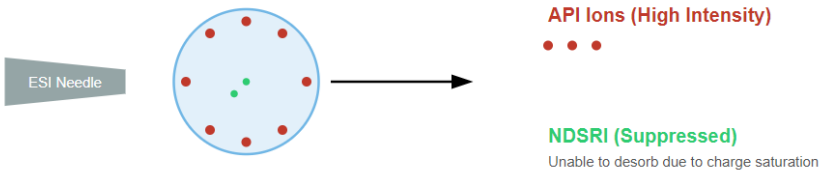

Figure 3. Mechanism of Ion Suppression in ESI

5.2. MRM Transition

In Triple Quadrupole systems, quantification is performed using Multiple Reaction Monitoring (MRM). The selection of transitions is challenging; the characteristic loss of the nitroso group (M+H → M+H-30, loss of NO) or the hydroxyl radical (M+H → M+H-17, loss of OH) are common fragmentation pathways but are often non-specific [22]. Relying on these generic transitions can lead to high baseline noise and interference from isobaric background ions. Method development must prioritize unique product ions derived from the drug-specific backbone of the NDSRI to ensure specificity, even if these transitions are less intense. In cases where the loss of NO is the only viable transition, analysts must rely on relative retention time and ion ratios to confirm identity.

5.3. High-Resolution Mass Spectrometry (HRMS)

High-Resolution Mass Spectrometry (HRMS), utilizing Orbitrap or Q-TOF technology, is indispensable during the early stages of method development and for confirmation. Its ability to determine accurate mass within sub-ppm error ranges allows analysts to distinguish the target NDSRI from isobaric interferences that would otherwise yield false positives in a low-resolution QqQ method [23]. HRMS is also critical for elucidating the structure of unknown peaks that may arise during stress testing or stability studies, providing elemental composition data that aids in identifying the mechanism of formation.

5.4. Ion Mobility Spectrometry (IMS)

A recent advancement in the analysis of challenging NDSRIs is the application of Ion Mobility Spectrometry (IMS), including Differential Mobility Spectrometry (DMS) or FAIMS. IMS adds a dimension of separation orthogonal to chromatography and mass-to-charge ratio, separating ions based on their collisional cross-section (size and shape) in the gas phase [24]. This technique is particularly valuable for separating protomers, isomers, or isobaric interferences that co-elute chromatographically and have identical

mass spectra. By filtering out the background noise and interferences in the drift tube, IMS can significantly improve signal-to-noise ratios and lower limits of quantitation (LOQ).

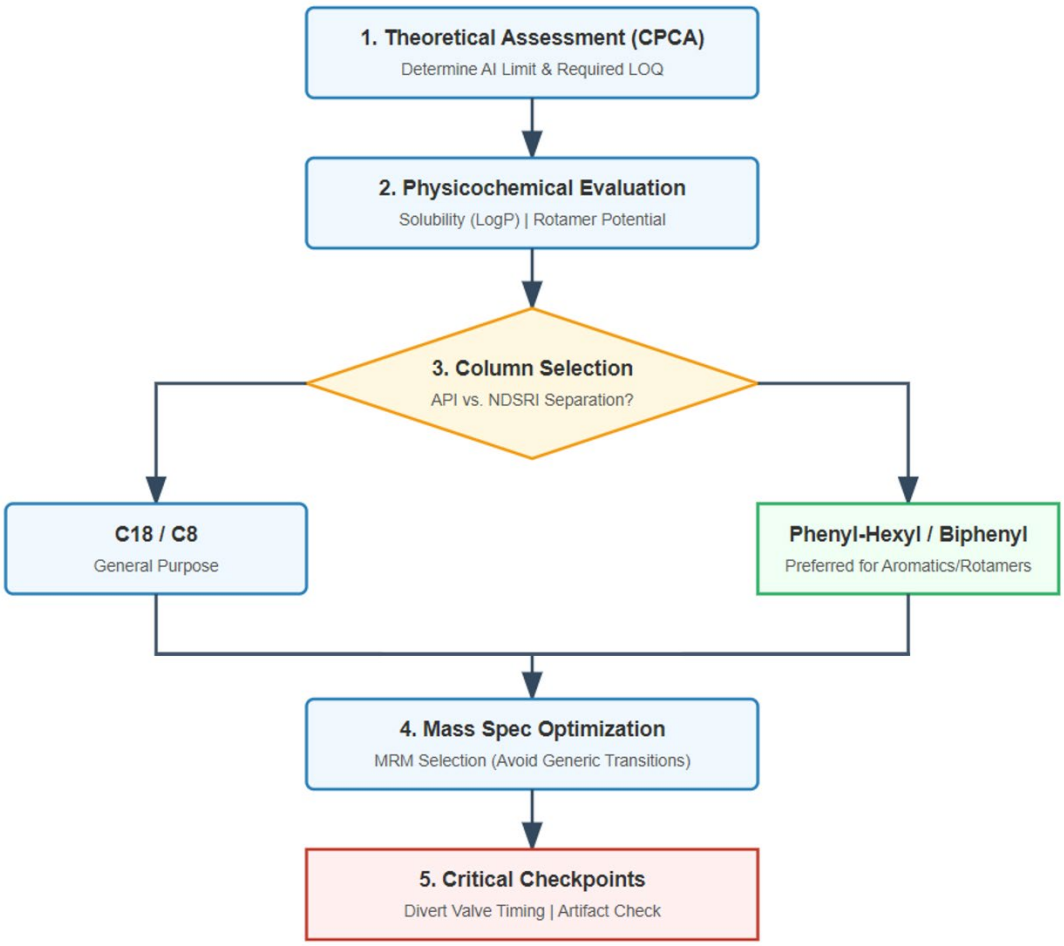

Figure 4. Systematic Method Development

6. Regulatory Guidelines

The regulatory guidelines for NDSRIs are evolving rapidly, moving from broad precautionary measures to specific, science-based control strategies.

6.1. The CPCA Guidelines

To address the sheer volume of potential NDSRIs, regulators have adopted the Carcinogenic Potency Categorization Approach (CPCA) [25].

Table 4. Carcinogenic Potency Categorization Approach (CPCA) Categories

CPCA Category	Potency Score	Acceptable Intake (AI) Limit (ng/day)	Characteristics
1	< 0	26.5	Highly potent; No detoxifying features.
2	0	100	Moderate potency.
3	1	400	Weak detoxifying features present.
4	2-3	1500	Strong detoxifying features (e.g., bulky groups).
5	≥ 4	1500	Very low potency; Steric hindrance.

This predictive framework assigns a potency score to an NDSRI based on its structural features specifically the substitution pattern at the alpha-carbons, the presence of electron-withdrawing groups, and steric bulk. Based on this score, NDSRIs are categorized into five potency classes, with Acceptable Intake (AI) limits ranging from a stringent 26.5 ng/day (Class 1) to a more lenient 1500 ng/day (Class 5). This tiered approach allows manufacturers to prioritize resources on the highest-risk compounds and defines the required sensitivity of the analytical method.

6.2. Analytical Requirements

Regulatory bodies expect methods to be fully validated according to ICH Q2 guidelines, with strict criteria for linearity, accuracy, and precision at the limit of quantitation (LOQ) [26]. The LOQ must typically be at or below 50% of the AI limit. Given the low AI limits for potent NDSRIs (e.g., 26.5 ng/day), this often translates to detecting impurities at <0.03 ppm relative to the API, pushing modern LC-MS/MS instrumentation to its physical limits. Furthermore, control strategies are increasingly relying on the "skip testing" approach (ICH M7 Option 2 or 3) if process capability can be demonstrated, which places an even higher burden on the accuracy and reliability of the initial data generation

Table 5. Typical Method Validation Criteria for NDSRIs at Trace Levels

Parameter	Acceptance Criteria (Typical)
Specificity	No interference from blank/placebo at retention time of NDSRI.
Linearity	$R^2 \geq 0.990$ from LOQ to 120% of limit.
Accuracy (Recovery)	70% – 130% at LOQ level; 80% – 120% at higher levels.
Precision (Repeatability)	RSD ≤ 20% at LOQ; RSD ≤ 10% at higher levels.
Sensitivity (LOQ)	S/N ≥ 10; Must be ≤ 50% of the AI limit (e.g., ≤ 0.015 ppm).
Solution Stability	Change in response ≤ 10% over study duration (essential for artifact check).

7. Conclusion

The quantitation of NDSRIs in complex pharmaceutical matrices represents one of the most significant analytical challenges in contemporary drug development. It requires a departure from generic impurity profiling toward highly specialized, ultra-sensitive methodologies. The successful analysis of these compounds demands a holistic understanding of their unique physicochemical properties, including rotameric behavior and solubility profiles. It necessitates rigorous sample preparation strategies that inhibit artifactual formation while ensuring high recovery. Furthermore, the reliance on advanced LC-MS/MS, HRMS, and emerging technologies like Ion Mobility highlights the critical need for selectivity in both separation and detection. As regulatory frameworks like the CPCA continue to mature, the analytical community must remain agile, developing robust control strategies that ensure the safety of pharmaceutical products without compromising their availability to patients.

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