The NDMA Story: Lessons Learned from a Global Pharmaceutical Challenge

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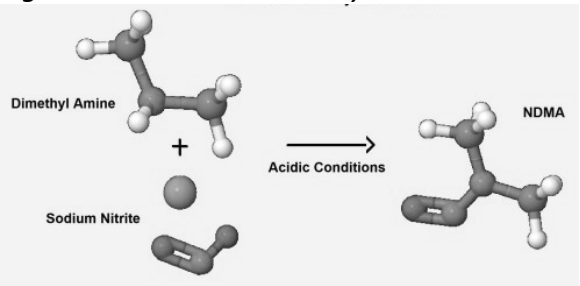
Nitrosamine impurities such as N-nitrosodimethylamine (NDMA) were identified in drug products like Valsartan, Losartan, Irbesartan, Ranitidine (OTC) etc [1], well above the established limits. To contextualize patient population risk, for every 8,000 individuals taking the highest recommended dose of Valsartan daily for four years during the period of contamination, one additional cancer case would be expected [2]. The issues affected brand [3] and generic drug products alike and affected high-volume medications that had been in widespread use for years. Pharmaceutical organizations, and regulators were involved in identifying the risk. In the case of Ranitidine, it was an independent pharmacy verification using gas chromatography-mass spectrometry that revealed a pronounced 74 m/z peak, indicating elevated NDMA levels.

Initially, nitrosamine formation was believed to be limited to specific synthesis pathways, such as those used in tetrazole ring containing sartans. However, evolving evidence has demonstrated that NDMA and other nitrosamines can be formed under certain conditions and in the presence of specific solvents, reagents, and raw materials [Figure 1]. The impurities can also be carried over during the manufacturing process when using specific equipment or some reagents. An interesting case is of Valsartan, where a process optimization initially hailed as a technological advancement (WO/2011/124655) was later identified as the root cause of elevated NDMA levels [4]. While the change enabled cost efficiencies and market competitiveness, it also inadvertently led to a significant public health issue, the full extent of which became apparent only later. The incident underscore the necessity of revisiting long-standing assumptions and highlight the importance of robust control strategies in both API and finished dosage form manufacturing.

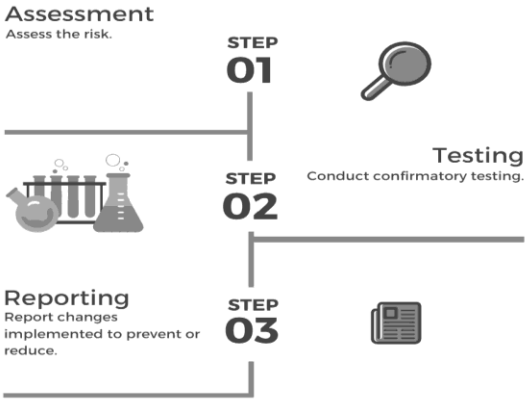
Figure 1: Potential NDMA Synthetic Route



According to ICH M7 (R2) [5], Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, N-Nitrosamines are compounds of concern due to their mutagenic carcinogenic effect. Regulatory bodies, including the U.S. FDA, now require that manufacturers take comprehensive steps to prevent or eliminate nitrosamine contamination [6, 7, 8]. The most recent US FDA guidance, Control of Nitrosamine Impurities in Human Drugs (Rev. 2, September 2024) [9], urges manufacturers to conduct comprehensive risk assessments in collaboration with API suppliers. These evaluations should account not only for synthesis pathways but also for degradation mechanisms that may generate nitrosamines during manufacturing or storage [Figure 2]. The updated guidance places additional focus on Nitrosamine Drug Substance-

Related Impurities (NDSRIs), emphasizing the need for specific risk assessments and control strategies tailored to each API. Despite the challenges, the pharmaceutical industry particularly the generics sector which represents approximately 90% of global drug volume [10] responded swiftly. The rapid alignment with regulatory expectations following the findings exemplifies the industry's agility and commitment to patient safety.

Figure 2: The Three Steps



The nitrosamine recalls are a reminder to the industry that prioritizing lean manufacturing efficiency over science can pose serious risks to patient safety if not evaluated comprehensively. Despite the drug product recalls, pharmaceutical organizations may not be penalized this time for the years of patient poisonings on the grounds that they were unintentional. However, any future negligence is unlikely to be viewed with the same leniency. It should be noted that a court has already issued a seven-year prison sentence in a case involving intentional NDMA poisoning that occurred over a period of less than one year [11]. In comparison, the ramifications of exposing millions of patients to carcinogenic contaminants over several years could be exponentially more severe, both financially and reputationally. Given these realities, finished drug product manufacturers are likely to pursue more rigorous contractual agreements with their API manufacturers, clearly defining risk sharing mechanisms. From a regulatory standpoint, it is impractical to monitor every change across the thousands of registered Drug Master Files (DMFs). The onus, therefore, lies with API manufacturers to conduct thorough internal evaluations. It is essential to perform and thoroughly document science-based risk assessments, transparently communicate relevant changes to formulators, strengthen analytical capabilities, and involve independent subject matter experts prior to approving and implementing any modifications. Bulk drug manufacturers have a major responsibility in ensuring patient critical APIs supplied to the market are safe.

References:

1) *US FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan):* https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
2) *US FDA Laboratory analysis of valsartan products:* https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products
3) *Zantac's Original Maker Halts Shipping on Carcinogen Concern:* Https://Www.Bloomberg.Com/News/Articles/2019-09-25/Zantac-S-Original-Maker-Halts-Distribution-On-Carcinogen-Concern
4) *WIPO Improved Process for Preparing Valsartan:* https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011124655
5) *ICH M7(R2) Assessment And Control Of Dna Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk:* https://database.ich.org/sites/default/files/ICH_M7%28R2%29_Guideline_Step4_2023_0216_0.pdf
6) *US FDA Information about Nitrosamine Impurities in Medications:* https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications
7) *European Medicines Agency (EMA) Nitrosamine impurities:* https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines/nitrosamine-impurities
8) *Health Canada Nitrosamine impurities in medications- Overview:* https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html
9) *US FDA Control of Nitrosamine Impurities in Human Drugs:* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs
10) *AAM The U.S. Generic & Biosimilar Medicines Savings Report:* https://accessiblemeds.org/wp-content/uploads/2025/01/AAM-2024-Generic-Biosimilar-Medicines-Savings-Report.pdf
11) *Queen's student faces prison after trying to poison his roommate with tainted baked goods:* https://www.theglobeandmail.com/canada/article-victim-of-alleged-queens-university-poisoning-testifies-against/