LABORATORY SERVICES

CHROMAK RESEARCH INC

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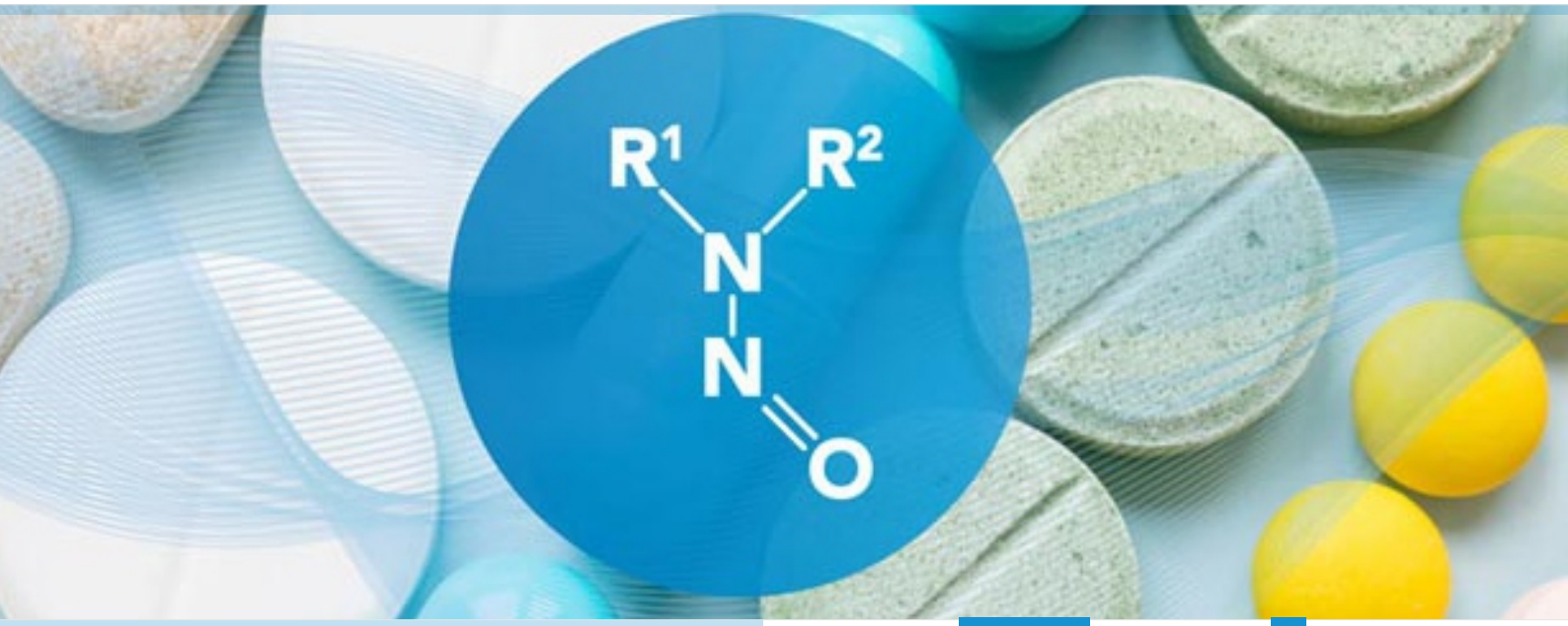

NITROSAMINES IMPURITIES

Nitrosamine impurities became a focus for authorities in July 2018, when they announced a recall of angiotensin II receptor blocker (ARB) medicines, known as “sartans”, due to being a probable human carcinogen N-nitrosodimethylamine (NDMA). Since then, more cases of drug substance and drug product batches contaminated with Nitrosamines came to be known, recalls and further reviews are being carried out by several national authorities in US, Canada, Switzerland and Singapore. Chromak Research use GC-MS method to determine the presence of NDMA, NDEA, NDIPA, NEIPA and NDBA according to the methodology developed and approved by the FDA. Our scientists also utilizes LC-MS & GC-MS to determine the amount of NDMA in DRUG substances and Drug product to ICH Q2 (R1), with LOD 0.375 ng/mL and LOQ 1.25 ng/mL level. Our scientist can assist you in performing the necessary method validations to support your product throughout the regulatory submissions process or for quality assessment of your products.

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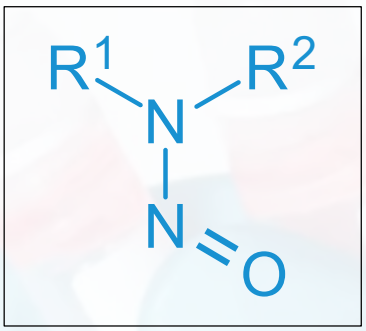
What are nitrosamines?



Nitrosamines are a family of carcinogens impurities which are formed by the reaction of secondary amines, amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents with the nitrogen in the +3 state. Nitrosamines are classified by the ICH M7 (R1) Guideline as Class 1 impurities, "known mutagenic carcinogens".

Most probable root causes for presence of nitrosamines for all products

- Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).
- Use of contaminated starting materials and intermediates by nitrosamine
- Use of sodium nitrite (NaNO2), or other nitrosating agents.
- Use of recovered materials (e.g. solvents, reagents and catalysts).
- Cross-contaminations.
- Degradation processes of starting materials, intermediates and drug substances.

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Laboratories are fully equipped with standard laboratory equipment and state of the art analytical instrumentation including ICP-MS, LC-MS, GC-MS, HPLC, GC with Headspace, TLC, UV, IR, Polarimeter, Refractometer, muffle furnace, vacuum ovens, stability chambers and Amino Acid Analyzer.