ALMAC
Partnering to Advance Human Health

Almac's Integrated Nitrosamine Impurity Solutions

Introduction

N-nitrosamines (N-nitroso derivatives of amines) are regarded as highly problematic impurities in drug substances because many are potent genotoxic agents and probable human carcinogens. They can form during manufacturing or storage when a nitrosating agent (such as nitrite or nitrous acid) reacts with a susceptible amine in the active ingredient, excipients, or packaging.



The presence of even trace levels of nitrosamines in medicines became a prominent concern in 2018, when N-nitrosodimethylamine (NDMA) was found in certain blood-pressure drugs, triggering widespread recalls and intense regulatory scrutiny worldwide. As a result, health authorities such as the FDA and EMA have set strict guidelines requiring manufacturers to assess and minimise nitrosamine risks, keeping these impurities at very low levels to protect patient safety and drug quality. Almac can control, measure and identify sources of N-nitrosamine impurities throughout the production process and product life cycle.

Case study- Mitigating N-Nitrosamine drug substance related impurity (NDSRI) formation

During a client engagement, Almac conducted a comprehensive risk assessment and identified the potential for N-nitrosamine drug substance related impurity (NDSRI) formation originating from the active pharmaceutical ingredient (API) during drug product (DP) manufacturing and subsequent storage.

The API was produced in our GMP-certified facility and subsequently formulated into the drug product at our site in Craigavon, Northern Ireland.

The risk assessment revealed that one of the excipients used in the formulation could contain a nitrosating agent, specifically sodium nitrite. This has the potential to react with the API either during or following the DP manufacturing process to generate a NDSRI.

What we can do for you!

Almac has expertise and 20 years' experience in developing and validating methods for genotoxic impurities in both API and DP applications. Using advanced LC-MS and GC-MS instruments and tailored extraction techniques, methods can be customised to suit the sample matrix. The recent introduction of Orbi-Trap LC-MS has resulted in further improvements in specificity and sensitivity with quantitation limits of as low as 50ppb.

We can:

- Initially assess for presence of a N-nitrosamine impurity.
- Develop and validate the method to quantify N-nitrosamines in API or DP.
- Identify, synthesise and qualify N-nitrosamine impurity reference standards.

Contact us:

Global HQ
+44 (0) 28 3833 2200

US HQ
+1 (215) 660 8500

Ireland
+353 90 646 0200

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