There is a current focus by the FDA on nitrosamine impurities as these have been found in some angiotensin II receptor blocker (ARB) medicines, such as valsartan, and more recently in histamine-2 receptor blocker medicines, such as ranitidine. Robust analysis to determine if these impurities are present and at what levels is critical to ensure these potentially harmful impurities do not enter the market in the future.

Impurity risk
Nitrosamine impurities found in some angiotensin II receptor blocker and histamine II receptor blocker medicines, have been the driver for recent product recalls. Laboratory studies have concluded that these impurities are classified as probable human carcinogens. They are believed to have been introduced into the finished products during the manufacturing process, although they are not expected to cause harm when ingested in very low levels. In recent years unacceptable quantities of nitrosamine impurities have been detected in some medicines and have become the subject of focus for regulatory agencies. In 2018, N-nitrosodimethylamine (NDMA) and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) were detected in a number of blood pressure medicines, such as valsartan, leading to a recall of several products and an EU review, which set strict new manufacturing requirements for these medicines. In 2019, NDMA was detected in some batches of ranitidine, a H2 receptor blocker used to treat acid reflux, resulting in product recalls and initiating further regulatory review. Other nitrosamine impurities, N-nitrosodipropylamine (NDIPA), and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) are also considered impurity risks and robust analytical testing methods are required to ensure that drugs and drug products are safe for consumption now and in the future.

In response to these impurity concerns the FDA Office for Testing and Research (OTR) has established suitable analytical methods to determine levels of these nitrosamine impurities and establish interim acceptance limits. The methods include GC/MS Headspace Chromatography-mass spectrometry (GC-MS), Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS), and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS).

Intertek also offers an Ultra-Performance Liquid Chromatography Low Resolution Tandem Mass Spectrometry (UPLC – LR/MS/MS) method for the rapid detection of several nitrosamine impurities. Additionally, in September 2019, the EMA began a review under Article 5(3) of Regulation (EC) No 726/2004 to provide guidance to marketing authorisation holders on how to avoid the presence of nitrosamine impurities in human medicines. As part of this review, the CHMP has requested marketing authorisation holders for human medicines to conduct a risk evaluation to identify products at risk of N-nitrosamine formation or (cross-)contamination and report the outcome by 26 March 2020.

Meeting your nitrosamine challenges
We can help you to meet the FDA and EMA requirements for product testing and risk evaluation through our tailored nitrosamine analysis services to detect and quantify nitrosamine impurities. Intertek has established the FDA methods within our GMP laboratory services to assist clients in performing the required method validations where the data can be used to support regulatory submissions or quality assessment of the API or drug product.

Our services include:
- Method Development & Validation
- Impurities Analysis – for nitrosamine and other carcinogenic or genotoxic impurities
- Toxicology Risk Assessments

Figure 1: Chromatogram of NDMA/NDEA working standard. Peak A) NDMA and peak B) NDEA, equivalent to 150ppb and 300ppb respectively relative to a 350mg sample.
NITROSAMINE IMPURITY ANALYSIS (NDMA, NDEA, NDIPA AND NMBA) IN MEDICINES

GC-MS Headspace Method for Detection of NDMA in Valsartan Drug Substance and Drug Products

In 2018, the FDA announced a recall of Valsartan tablets (an angiotensin II receptor blocker used to treat high blood pressure) because of the potential for certain products to contain NDMA. A second impurity was subsequently reported, N-Nitrosodiethylamine (NDEA). The OTR developed a gas chromatography-mass spectrometry (GC/MS) headspace method to detect and quantify the presence of NDMA (Limit of Detection (LOD) 5ng/g, and Limit of Quantitation (LOQ) 100ng/g) or NDEA (LOD 20ng/g, LOQ 50ng/g) in drug substance samples (Figure 1).

Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine Drug Substance and Drug Product

As GC based methods had been observed to elevate NDMA levels in tested materials an alternative method was developed by the FDA which prevents the degradation of ranitidine and the subsequent formation of NDMA. In September 2019, a liquid chromatography method using high resolution mass spectrometry (LC-HRMS) to measure NDMA levels in ranitidine drug substance and drug product was published, with LOD 10ng/g, lower LOQ 33ng/g and upper LOQ 3333ng/g.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product

This liquid chromatography FDA method is based on a triple-quadrupole mass spectrometry platform. It is an alternative or confirmatory method for the detection of NDMA in ranitidine drug substance and drug products. The triple quadrupole platform is more widely available than the LC-HRMS platform previously shared by the FDA.

A Rapid Detection Approach

Ultra-Performance Liquid Chromatography, Low Resolution Tandem Mass Spectrometry (UPLC-LRMS/MS) method for the determination of NDMA, NDEA, NMBA and NDIPA in valsartan drug substance.

Intertek have also developed an alternative approach using UPLC-LRMS/MS. This method allows for the rapid detection and quantitation of several nitrosamine impurities, NDMA, NDEA, NMBA and NDIPA, with LOD 5ng/g, lower LOQ 15ng/g and upper LOQ 75ng/g. This is an ideal approach for a rapid initial screen for the common nitrosamine impurities to aid and accelerate your risk assessment. Once optimized for your APIs or drug products, we can validate the method if required.

Toxicological risk assessment

In addition to experienced pharmaceutical impurity analysis, we can support with toxicological risk assessments. Our experienced consultants conduct risk assessments to address the impact associated with exposure to residual solvents, process impurities, extractables & leachables, elemental impurities (ICH Q3D) and other substances that may find their way into a pharmaceutical product.

Total Quality Assurance

Intertek’s network of GMP compliant laboratories provide compliant data to support regulatory requirements or product development activities of our global clients. Bringing quality and safety to life, we help you bring your product to market quickly, responsibly, and economically, ensuring Total Quality Assurance.

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