MAT JOURNALS

Journal of Advances in Pharmacy Practices
e-ISSN: 2582-4465
Volume 2 Issue 1

Nitrosamine Impurities in Drug Substances and Drug Products

Dr. Tabrez Shaikh[1*], Dr. Amit Gosar[2], Dr. Hussain Sayyed[3]
[1,2]Researcher, Indoco Research Centre, Analytical research & development, Navimumbai, Maharashtra, India
[1,3]Researcher, Sir Sayyed College, Department of Chemistry, Aurangabad, Maharashtra, India

INFO
Corresponding Author:
E-mail Id: **tabrezs@indoco.com*

DOI: *10.5281/zenodo.3629095*

Cite as:
Dr. Tabrez Shaikh, Dr. Amit Gosar, & Dr. Hussain Sayyed. (2020). Nitrosamine Impurities in Drug Substances and Drug Products. Journal of Advances in Pharmacy Practices (e-issn: 2582-4465), 2(1), 48–57. http://doi.org/10.5281/zenodo.3629095

ABSTRACT

Nitrosamine impurities are known to be mutagenic and carcinogenic, very small exposure of these impurities can lead to cancer. These impurities may be formed and get incorporated into drug substance or drug product through reagent, catalyst, solvent or raw materials used in the process of manufacturing. The various regulatory authority has published the press release or notice regarding the control of these impurities with the interim limit. Nitrosamine impurities can be avoided by taking precaution in the manufacturing of drug substance and drug products. Validated analytical methods are to be used to identify and quantify these impurities hence it needs highly sensitive instrument which can detect these impurities to the trace level at given interim limit. Liquid chromatography or Gas chromatography, along with mass detector is majorly used for their determination.

Keywords: *Classification, drug substances, drug product, impurities, nitrosamine and guidelines*

INTRODUCTION

Food and drug administration (FDA) and European Medicines Agency (EMA) in July 2018 announced that a carcinogenic impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are said to be present in generic drug substances and drug product, especially in angiotensin II receptor blockers (ARBs) or 'Sartans'class medicines which are used to treat patients with hypertension (high blood pressure) and heart failure (Fig.1). This announcement leads to voluntarily recall hundreds of batches of these generic versions by pharmaceutical distributor worldwide [1-3]. Further, the FDA and EMA investigation in year 2019 led to the detection of these Nitrosamine impurities in Pioglitazone used for the treatment of diabetes and Ranitidine an H2 (histamine-2) blocker used for the treatment of acidity of the stomach. Presently, low level of NDMA impurity found in Metformin also brought this drug under FDA and EMA investigations.

ICH M7 (R1) classifies Nitrosamine impurities as Class 1, which is known to be mutagenic and carcinogenic, based on

both rodent carcinogenicity and mutagenicity data. These Nitrosamine impurities impact the genetic material by means of mutations through chromosomal breaks, rearrangements, covalent binding or insertion into the DNA during replication. These changes in the genetic materials caused by the exposure to very low levels of Nitrosamine impurities can lead to cancer [4-6]. Thus, it is important to identify Nitrosamine impurities in drugs at very low levels to ensure safety to the public.

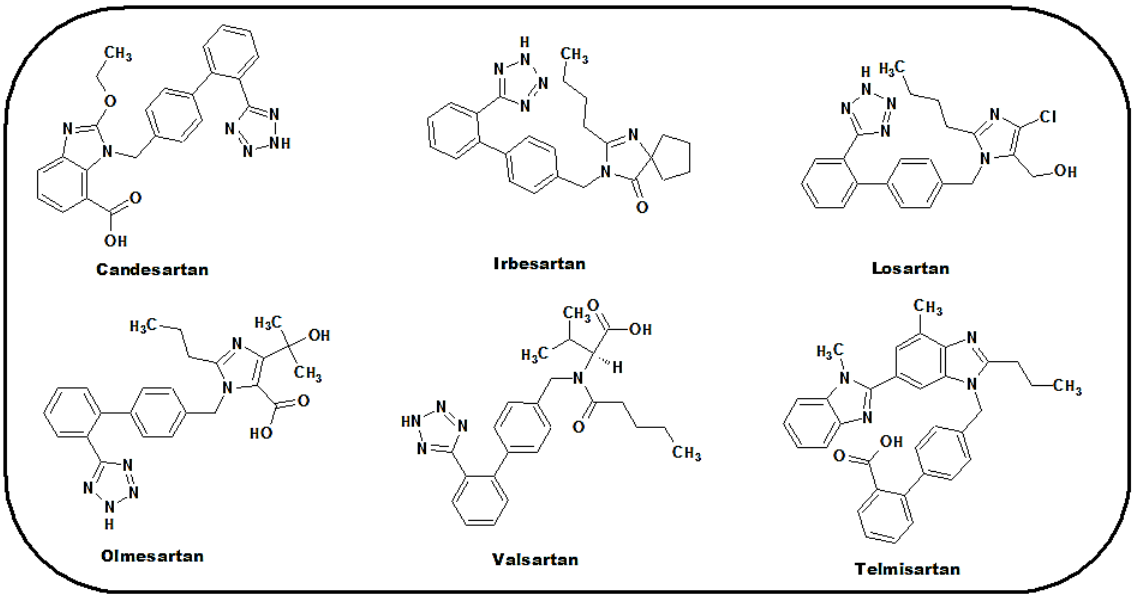

Figure 1: *Structure of sartans drug.*

SOURCES OF NITROSAMINE IMPURITIES

Nitrosamine impurities can get incorporated into the drug substance and drug product basically through process formation, direct introduction, degradation or cross-contamination. Manufacturing of drug substances involves raw material, intermediates, solvents, chemicals and reagents [7-9]. Through these stages, if this impurity is formed or present it may get incorporated and carried forwarded to drug product as shown in (Fig.2).

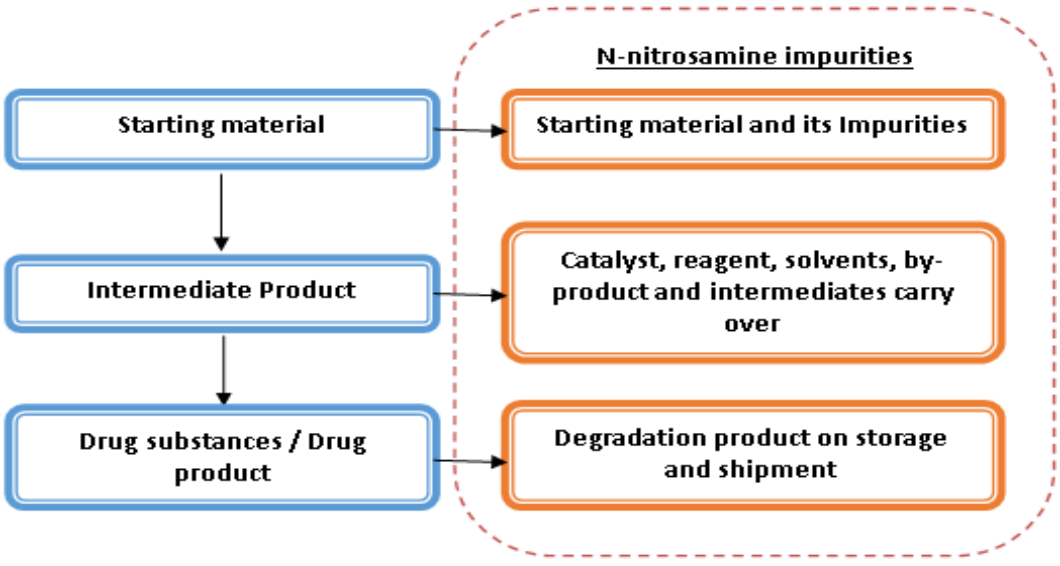

Figure 2: *Sources of Nitrosamine impurities.*

1. Primary, secondary, tertiary amines or quaternary ammonium salts along with nitrosating agents such as Sodium nitrite are considered to be precursors for the generation of Nitrosamines impurities. Similarly, carbamate, amides and N-alkyl amides if nitrosated may form Nitrosamine impurities. The extent of Nitrosamine impurity formation depends mainly on the type of reagent, their structure and the concentration of the nitrosating agent. Secondary amines are considered to be more reactive (Fig.3).
2. Recovered solvents and catalysts used in the process may cause a risk for Nitrosamine formation. As these solvents or catalysts are treated with sodium nitrite or nitric acid in order to destroy residual azide which may lead to the formation of Nitrosamine impurities.
3. Contaminated starting material or raw material supplied by the vendor may introduce the Nitrosamine impurities in drug substance or drug product.
4. Cross-contamination between different manufacturing processes and products on the same production line may lead to contamination of Nitrosamine impurities. A process where nitrosating reagents are not used may still be contaminated through the presence of nitrite in the water used in the manufacturing process.
5. Trace amount of these impurities may be formed due to decomposition of solvent or other materials used in the synthesis of drug substances. Similarly, by-products formed in the drug synthesis process may get be carried forward to the drug substances as Nitrosamine impurities. Solvents such as Dimethylformamide, Dimethylacetamide (DMF) or Diethylacetamide (DEA) may form potential NDMA and NDEA impurities (Fig.3).
6. Use of certain packaging materials for finished product may for Nitrosamine impurities. According to one hypothesis the packing material lidding foil containing nitrocellulose, printing primer may react with amines in printing ink to form Nitrosamines impurities, which may get transferred to the drug product.

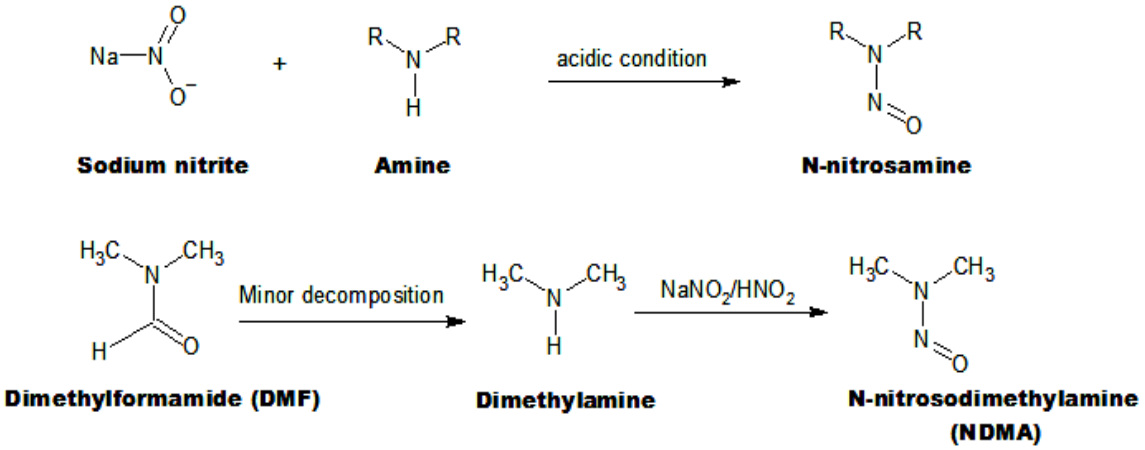

Figure 3: *Formation of Nitrosamine impurities.*

Experts suggest that the NDMA impurity in Valsartan could have come from sodium nitrite, which is used to expel remaining sodium azide reagent. Under the acidic condition, nitrite ion forms nitrous acid, which then could react with trace amounts of dimethylamine, a degradation product of the solvent Dimethylformamide (DMF). Fig. 3

shows the formation of impurities in drug synthesis. Some of the secondary amine and their corresponding Nitrosamine impurities formed are tabulated below in Table-1.

Table 1: *Amines and corresponding Nitrosamine impurities.*

Amines	Corresponding Nitrosamine impurities
Dimethylamine	N-nitrosodimethylamine (NDMA)
Diethylamine	N-nitrosodiethylamine (NDEA)
Dipropylamine	N-nitrosodipropylamine (NDPA)
Diisopropylamine	N-nitrosodiisopropylamine (NDIPA)
Dibutylamine	N-nitrosodibutylamine (NDBA)
Ethylmethylamine	N-nitrosomethylethylamine (NMEA)
4-(methylamino)butanoic acid	N-nitroso-N-methyl-4-aminobutyric acid (NMBA)

REGULATORY PERSPECTIVE

Food Drug Administration (FDA)

In June 2018, FDA was informed by one of valsartan drug substances manufacture about the presence of an impurity, identified as N-Nitrosodimethylamine (NDMA). Further investigation by the FDA found out that other Nitrosamine impurities, e.g., N-Nitrosodiethylamine (NDEA) were also present at unacceptable levels in drug substances from multiple drug substances manufacturer of valsartan and other drugs in the ARB class. As there was no acceptable limit in the specification for Nitrosamines, as an initial measure, the FDA published "interim acceptable limits" for these Nitrosamine impurities in ARB drugs. Drug substances and drug product exceeding these limit levels were recommended to recall the drug product from the market. The FDA advised that drug product manufacturers, that they should test the samples of each drug product batch or drug substances lot used for the drug product manufacture for the US market to determine whether it has contain a detectable amount of Nitrosamine impurities. FDA has also published validated methods to detect and quantify NDMA and NDEA impurities in all ARB drug substances and some drug products [10].

European Medicines Agency (EMA)

EMA first initiated Nitrosamine impurities investigation in July, 2018 and found out that sartan-containing medicines are contaminated with Nitrosamine impurities, which leads to recall of several drug products and come under review by the European Union (EU), thus it set strict new manufacturing requirements for these medicines.

Earlier in January, 2019 the EMA recommended that companies making sartan medicines review their manufacturing processes so that Nitrosamine impurities cannot be formed. Companies were given a transition period to make necessary changes during which strict temporary limits on levels of these impurities were applied. After this period companies will have to demonstrate that their sartan products have a safe level for these impurities before they can be used in the EU. The EMA noted that in the vast majority of sartan medicines, impurities were either not found or were present at very low levels. The EMAs Committee for Medicinal Products for Human Use (CHMP) will provide guidance on avoiding the presence of Nitrosamine impurities to marketing authorization holders, which they should consider alongside their knowledge of the manufacturing processes of their products [11].

Other Regulatory Agency

Therapeutic Goods Administration (TGA) of Australia made advice in a public notice that it has introduced requirements for

sponsors of 'sartan' blood pressure medicines to take measures to avoid the presence of Nitrosamine impurities in medicines and implement rigorous testing of their medicines to identify the presence of any Nitrosamine impurities. The TGA provides a two year transition period (2019-2021) to allow sponsors to review and if necessary make changes to their manufacturing processes and to implement adequate testing methods. During the transition period sponsors must inform the TGA if they identify the presence of Nitrosamine compounds in their medicines. Changes to manufacturing processes and/or controls if needed should be lodged as a 'category 3' request under section 9D (3) of the Therapeutic Goods Act 1989 (the Act). The TGA Laboratories has adapted a publically available US-FDA test method. Health Canada continues to hold manufacturers responsible for the safety and effectiveness of drugs sold on the Canadian market and has taken several actions to mitigate the risk to Canadian. Health Canada continues to work closely with international regulatory partners including the FDA and the EMA to share information and coordinate efforts on inspections, risk assessments and public communications. Health Canada has provided a method that has been developed to detect and quantify the Nitrosamine impurities NDMA and NDEA in angiotensin II receptor blockers (ARBs) [12-13].

LIMITS AND ACCEPTABLE INTAKE

Nitrosamine impurities are classified as Class-1 impurities as per ICH guidelines due to its known carcinogenicity and mutagenicity. For the calculation of its limit, the median toxic dose TD50 (Shows toxicity in 50% cases) is used. The TD50 is the well-accepted by ICH M7 (R1) for the calculation of the acceptable excess risk to calculate acceptable intake (AI) for mutagenic and carcinogenic impurities and it is a well-recognized international standard.

The TD50 value reported for NDMA is 0.096 mg/kg/day for the most sensitive species rat [5].

The extrapolation to the excess risk level for cancer is calculated by linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD50 by 50,000 (50% or 0.5 x 100,000). For NDMA this translates into a dose of 1.92 ng/kg/day. For a person with a bodyweight of 50 kg, this would result in an AI level of 96 ng/day (50 x 1.92 ng). Similarly, for NDEA, it comes out to be 26.5 ng/day. Following ICH M7 (R1) guideline, FDA has calculated limit for NDMA and NDEA impurities in various sartans drug as tabulated below in Table 2. Through this procedure, the limit for Nitrosamine impurities in any drug substance or drug product can be calculated. FDA and EMA have made clear that these are interim limits [14-15].

Table 2: *Limit for NDMA & NDEA in sartans drugs.*

Active substance (max daily dose)	**NDMA**		**NDEA**	
	AI ng/day	**Limit (ppm)**	**AI ng/day**	**Limit (ppm)**
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)		0.320		0.088
Losartan (150 mg)		0.640		0.177
Olmesartan (40 mg)		2.400		0.663
Valsartan (320 mg)		0.300		0.082

REVIEW OF THE MANUFACTURING PROCESS

The European Medicines Agency (EMA) has issued templates for marketing authorization holders to use when filing results of product testing for Nitrosamine contamination. The following steps are required by the manufacturer to control the assessment of Nitrosamine in human medicinal products [16].

Step I. Risk evaluation

The marketing authorisation holder along with drug substance and drug product manufacturer should perform a risk evaluation of Nitrosamine as per ICH Q9 and ICH M7 guidelines within six months (Notice publication 26 September, 2019). The risk evaluation should be conducted in a priority manner i.e. the highest probability of contamination should be evaluated first. Authorities must be informed about the evaluation results. If a risk of potential contamination has been detected, the marketing authorisation holder should proceed to go to step 2 as below.

Step II. Confirmatory testing

After risk evaluation, confirmatory testing activity should start immediately. A product with high-risk must analytically be tested first as soon as possible for Nitrosamine impurities using validated methods having appropriately sensitive. Similarly, confirmatory testing of all the concerned drug product should be concluded at the latest within three years of the publication of the notification or otherwise justified. If Nitrosamine is detected, the competent authorities are to be informed immediately, irrespective of the amount detected.

Step III. Changes to the marketing authorisation

Changes to the marketing authorisation such as a change in the manufacturing process of a drug substance or drug product specifications are to be applied in a timely manner. If there is a risk to public health the competent authorities must be informed immediately. All steps must be completed within three years in a prioritised manner.

AVOIDING NITROSAMINE CONTAMINATION

All amine along with nitrosating agents are considered to be antecedent in the generation of Nitrosamines impurities in the drug substance or drug products. Thus, the following precautions may lead to minimize these impurities in human medicinal products [17].

1) Nitrosamines impurities are formed when nitrites or other nitrosating agents react with the secondary or tertiary amine or quaternary ammonium salts are used within the same or different steps of the manufacturing process of drug substances. Thus avoiding the use of these reagents can prevent Nitrosamine impurity formation.
2) Many of Nitrosamine impurities get purged out with the solvent. If these solvents are recovered and reused, there may be a chance of reintroduction of these impurities in the drug synthesis process. Therefore, use of recovered solvent should be avoided in the manufacturing process. Similarly, recovered catalyst may contaminate the drug with Nitrosamine impurities if reused.
3) Contaminated raw material, intermediate and reagents used in drug substance manufacturing are also the potential source of Nitrosamine impurities. The degradation product of raw materials and intermediate on storage in the presence of traces of nitrites may lead to the formation of Nitrosamine impurities. Hence, these materials should be properly stored and tested for Nitrosamine impurities.
4) Equipment used for the manufacturing

of drugs substances may be cross-contaminated with Nitrosamine impurities due to previous products. Equipment should be properly cleaned and checked for contamination.

5) The drug substances manufacturer should test and check the carryover of Nitrosamine impurities in various intermediate stages and if it is present, it should be controlled with the proper limit.
6) The manufacturer should modify the process to purge out amines, nitrites and Nitrosamine impurities at various stages. Control strategies should be implemented to detect and control Nitrosamine impurities in intermediate or drug substances.

Overall, it can be concluded that Nitrosamines in finished products can be very effectively controlled by selecting the synthesis path which minimizes the formation of these impurities and also observing implementing strict GMP requirements such as cleaning of equipments and control of the recovery process for solvents may also lead to remove and limit the Nitrosamine impurities in drug substance and drug product.

ANALYTICAL METHODS

The development of analytical methods to determine Nitrosamines impurities is the challenging task due to very low levels of impurities present in the complex matrices. The developed methods also need to be validated to conform to GMP requirements. Several methods have been published by the FDA to cover NDMA and NDEA in different 'sartans'. The EMA has indicated the extension of measures to include more Nitrosamines.

Other regulatory authorities (Canada, Switzerland and Singapore) have adopted their own measures and published analytical methods. Most of the methods used for testing of Nitrosamines in drug substance and drug product utilize the chromatographic techniques such as reversed-phase liquid chromatography (LC) or gas chromatography (GC) combined with various detectors such as mass spectrometry (MS), Ultraviolet spectrophotometry (UV) or nitrogen chemiluminescence (NCD) etc. [18-20].

European network of Official Medicines Control Laboratories (OMCLs) has developed methods for the testing of specific Nitrosamines in sartans on the basis of different analytical principles. The Irish OMCL in the Public Analyst's Laboratory in Galway (PALG), the French OMCL at the ANSM site in Montpellier, the Chemisches and Veterinär-Untersuchungsamt (CVUA) Karlsruhe as well as the LGL Bayern established analytical methods for quantification of Nitrosamine on behalf of the network. Additionally, the U.S. FDA, Health Canada and Swissmedic have published methods for the simultaneous determination of Nitrosamine. Some of these methods are tabulated below in Table-3.

Table 3: *Published analytical methods for testing Nitrosamine impurities.*

Method	Technique	Ionisation	Impurity	Sample
FDA	GC-MS (DI)	Triple quad	NDMA, NDEA,	Valsartan (DS and DP)
	GC-HS-MS	Quadrupole	NDMA, NDEA	
	LC-MS/MS	HR / Triple Quad	NDMA	Ranatidine (DS and DP)
PALG	GC-HS-MS	Single Quad	NDMA	Sartans (DS and DP)
ANSM	HPLC-UV	Not applicable	NDMA, NDEA	Sartans (DS and DP)
CVUA	UPLC-MS/MS	APCI	NDMA, NDEA	Sartans (DS and DP)
Health Canada	GC-MS/MS	EI	NDMA, NDEA	Sartans (DS and DP)
Swissmedic	GC-MS	EI	NDMA, NDEA	Sartans (DS and DP)
LGL	GC-HS-MS	EI/CI	NDMA, NDEA	Sartans (DS)
	LC-MS/MS	Q-trap	NDMA, NDEA	Sartans (DS and DP)

These published testing methods serve as a starting point for the development and validation of analytical methods, appropriate for other drug substance and drug products. The FDA says that these methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product or if the results are used in a regulatory submission.

Gas Chromatography

Gas chromatography along with mass spectrometry (GC-MS) is the most frequently employed technique for the determination of Nitrosamines with lower molecular weight. The majority of recent publications employ GC-MS, GC–MS/MS or GC-HS-MS technique due to its high selectivity and low detection limit. The FDA has developed and validated a combined GC-HS-MS method for the simultaneous evaluation of four Nitrosamine impurities in Valsartan drug substance and drug products, these impurities are N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodiisopropylamine (NDIPA), and N-nitrosoethylisopropylamine (NEIPA). This method meets all the requirements of current regulations with sensitivity and repeatability and exceed the expected requirements of the control limits. GC-TEA (Thermal energy analyser) also provides high selectivity for Nitrosamines. The high molecular weight Nitrosamines are rather labile molecules and it is impossible to determine by GC.

Liquid Chromatography

LC technique offers a faster alternative to the traditional GC-MS methods. The use of high-resolution accurate mass spectrometry helps to obtain good selectivity for the detection of both GC-detectable and GC-undetectable compounds along with thermally stable and unstable Nitrosamines. The FDA has observed that the GC-MS method for testing ARBs of Nitrosamine impurities is not suitable for testing ranitidine because heating the sample generates NDMA. An LC-HRMS method was subsequently developed by the FDA to measure the levels of NDMA in ranitidine drug substance and drug product following ICH Q2 (R1). The limit of detection (LOD) is 0.011ppm, limit of quantitation (LOQ) is 0.033 and the range of the method is 0.033 – 3.33ppm. In addition, several methods using liquid chromatography-mass spectrometry (LC-MS) or LC-MS/MS have been reported in the scientific literatures. However, only a few studies have reported for NDMA analysis using conventional high-performance liquid chromatography (HPLC), especially in the drugs. HPLC is the most popular technique for quality control of APIs and products in routine analysis and it is preferable if NDMA impurity is simultaneously detected with drug substances by a single HPLC analysis. Thus, it is important to develop a fast and simple analytical method for NDMA in drugs by using HPLC.

ANALYTICAL METHOD DEVELOPMENT

The basic task for the development of an analytical method for Nitrosamine impurities is to develop the method which can detect these impurities at very trace levels and well below the TTC. Various advanced and sophisticated techniques should be employed for their detection. The developed analytical method should have less variability by conducting a series of controlled experiments thus to make quality and safe drug products. As global regulatory, requirements have gone more stringent and analytical methods for global products must be able to meet all the regulatory requirements. Method development is a continuous process where the goal is to consistently improve the quality of the product [21].

ANALYTICAL METHOD VALIDATION

A very general definition of validation is establishing documented evidence which provides a high degree of assurance that a specific procedure, process, equipment, activity or system will consistently produce a product meeting its predetermined specifications and quality attributes. Validation is an important feature after the development of any analytical method because it is closely related to the quality of the results. All analytical methods, whether qualitative or quantitative are required to be validated. The degree of validation varies for the type of method and its application. For several years now method validation studies, guidelines and procedures have focused mainly on quantitative methods of analysis. Validation is an imperative activity in the process of impurities profiling where the developed analytical method used for the determination of genotoxic impurities in drug substances is validated in order to establish that the method is suitable for its aimed purpose. The analytical methods are validated with specificity, linearity, precision, accuracy, ruggedness, robustness and forced degradation parameters in accordance with ICH Harmonized Tripartite Guidelines [22-23].

CONCLUSION

Highly mutagenic and carcinogenic Nitrosamine impurities need to limit it to the acceptable limit in drug substances and drug products. Potential sources of Nitrosamine impurities such as raw material, reagent, catalyst, solvents and cross-contamination used in manufacture should be identified to control it in drug substances. Medicine regulatory authorities such as FDA, EMA, TGA and Health Canada have published several public notices to guide the manufacturer to control and limit these impurities to acceptable intake levels. Regulatory authorities have also issued the templates for marketing authorities to assess the Nitrosamine impurities in human medicinal products. Nitrosamine impurity formation can be avoided by selecting proper reagent, catalyst and solvents in the manufacturing of drug substances. The analytical method used for the determination and quantification of Nitrosamine impurities is by GC or LC using mass spectroscopy. These methods should be well developed and validated as per ICH guidelines to determine these impurities upto very low levels.

REFERENCES

1. Antonis Manolis (April 26, 2019), "Carcinogenic Impurities in Generic Sartans: An Issue of Authorities' Control or a Problem with Generics", *Rhythmos*; Volume 14, Issue 2, pp.23-26. DOI: 10.1021/cen-09708.
2. FDA Press Release (July, 2018), "FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity," *APHA*.
3. EMA Press Release (September 21, 2018), "Valsartan: Review of Impurities Extended to Other Sartan Medicines," *EMA*, Available at https://www.ema.europa.eu.
4. Jennifer L. Caulfield (1997), "*The chemistry of nitric oxide-induced deamination and cross-linking of DNA",* (Doctoral dissertation), *Massachusetts Institute of Technology*, pp. 1-153.
5. R. Nilsson (July, 2011), "The molecular basis for induction of human cancers by tobacco specific nitrosamines", *Regulatory Toxicology and Pharmacology*, Volume 60, Issue 2, pp. 268-80. Available at https://doi.org/10.1016/j.yrtph.2011.02.014.
6. Lijinsky W. Andrews AW. (October, 1983), "The superiority of hamster liver microsomal fraction for activating nitrosamines to mutagens in Salmonella typhimurium", *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. Volume

111, Issue 2, pp.135-144. DOI: 10.1016/0027-5107(83)90058-1.
7. Aloka Srinivasan (2019), "Proactive Evaluation of Possible Genotoxic Impurities during the Early Stages of Drug Development", http://www.pharmtech.com.
8. G. Subba Rao (1980), "N-Nitrosarnines from drugs and nitrite: potential source of chemical carcinogens in humans", *Pharmacy International*, Volume 1, pp. 187-190.
9. "Information on nitrosamines for marketing authorization holders", *European Medicines Agency*, pp. 1-10, EMA/CHMP/428592/2019 Rev. 2.
10. U. S. Food and Drug Administration update (Jan 25, 2019), "Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues", https://www.fda.gov.
11. European Medicines Agency (Dec 2019), Questions and answers on "Information on nitrosamines for marketing authorization holders", EMA/CHMP/428592/2019 Rev. 2 https://www.ema.europa.eu.
12. Therapeutic Goods Administration (TGA) (2019), "N-nitroso compounds in 'sartan' blood pressure medicines", Available at https://www.tga.gov.au/node/881814.
13. Health Canada (2019), "Impurities found in certain angiotensin II receptor blocker (ARB) products, also known as sartans".
14. U. S. Food and Drug Administration (February, 2019), "FDA update table of interim limits for nitrosamine impurities in ARBs", from https://www.fda.gov.
15. European Medicines Agency (2019), "Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines", EMA/351053/2019 rev. 1.
16. European Medicines Agency (2019), "Information on nitrosamines for marketing authorization holders", https://www.ema.europa.eu, EMA/189634/2019.
17. European Medicines Agency (2019), "EMA advises companies on steps to take to avoid nitrosamines in human medicines", https://www.ema.europa.eu, EMA/511347/2019.
18. Agnes Shanley, FDA Press Release (August, 2018), "FDA Announces Preliminary GC/MS Headspace Method".
19. EDQM Press Release, "OMCLs Release Three Methods for Determination of NDMA in Sartans," https://www.ema.europa.eu.
20. Parr MK, Joseph JF (2019), "NDMA impurity in valsartan and other pharmaceutical products: Analytical methods for the determination of N-nitrosamines", *J. of pharma. and biomedical analysis*. Volume 164, pp.536-49, Available at https://doi.org/10.1016/j.jpba.2018.11.010.
21. Mingjiang Sun, David Q. Liu, Alireza S. Kord (2010), "A Systematic Method Development Strategy for Determination of Pharmaceutical Genotoxic Impurities", *Organic Process Research & Development*. Volume 14, Issue 4, pp.977-985, Available at https://doi.org/10.1021/op100089p.
22. Hussain, S., Gosar, A., & Shaikh, T. (2018). Impurity profiling in pharmaceuticals: a review. *World J Pharm Res*, Volume 7, Issue 9, pp. 305-320.
23. Chang Chau Chan, Lee Y.C, Harman Lam, Xui Ming Zhang (2004), "Analytical method validation and instrument performance verification", *John Wiley and Sons*. Pp. 320, ISBN: 978-0-471-25953-4