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Nitrosamines in Drug Substance and Drug Product-A Regulatory Challenge

Prasannakumar P Bhat, Balamuralidhara V*, Gowrav M P, Venkatesh M P

Pharmaceutical Regulatory Affairs Group, Dept. of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

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Abstract

Nitrosamine is the class of synthetic compound which is a potent genotoxic agent and considered as probable plausible human cancer-causing agents by the International Agency for Research on Cancer (IARC).N nitroso mixes are known as the potent carcinogenic and a global worry according to the various authorities and also from ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Before June 2018, the presence of nitrosamine in the drug substance and also product was not known, however in June 2018, USFDA identified the presence of Nitrosamine impurities in one of the API producers of valsartan which is recognized as NDMA (N-Nitroso dimethylamine). Valsartan is a medication which is utilized for the treatment of hypertension, cardiovascular breakdown and diabetic kidney damage. From that point forward, FDA has discovered that different kinds of nitrosamine mixes, e.g., N-Nitrosodiethylamine (NDEA), are available at unsuitable levels in APIs from various API makers of valsartan and different medications in the ARB class. (Angiotensin receptor blocker). Then the Regulatory Authorities has stepped forward for educating the health care professional, manufacturers and also public about the adverse effect(carcinogenic)of the NDMA and NDEA consumption.

*Corresponding Author

Name: Balamuralidhara V
Phone: +918971917777
Email: baligowda@jssuni.edu.in

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INTRODUCTION

Nitrosamines, or all the more accurately N-nitrosamines, allude to any particle containing the nitroso practical gathering. These particles are of concern in light of the fact that nitrosamine contamination are plausible human cancer-causing agents. In spite of the fact that they are likewise present in certain nourishments and drinking water supplies, their quality prescriptions is, in any case, thought about unsuitable.

Objective

1. To understand the nitrosamine impurities.
2. To understand how the impurities came to the drug.
3. To understand the limit set by the regulatory authorities for nitrosamine impurities and the prescribed test methods.
4. To know how the authorities handled the challenge and resolved them.
5. To have a view of the current status of the nitrosamine impurities in various drug substance and the drug product.

The structure showing NDMA and NDEA with impurities shown in figure Figures 1 and 2, (WHO, 2019).

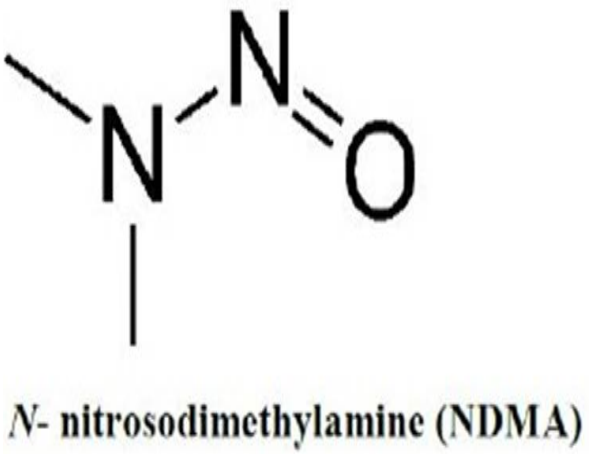

Figure 1: Structure showing NDMA Impurites

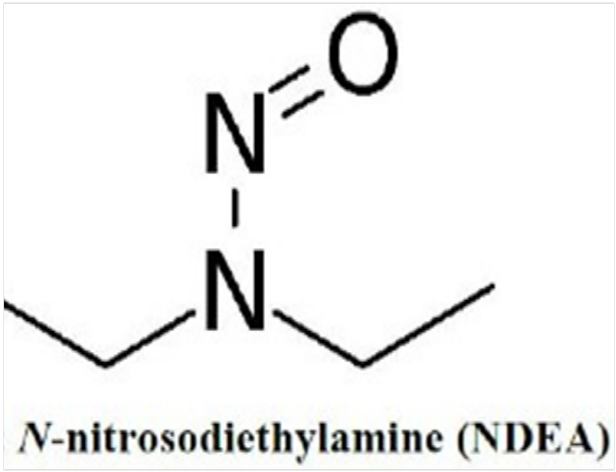

Figure 2: Structure showing NDEA impurities

Table 1, represents the NDMA limits and lot number tested from various companies (USFDA, 2019).

USFDA first became aware of the NDMA and MDEA impurities present in valsartan in July 2018, also Medicine Regulatory Authorities got an awareness of the problem. Then various Regulatory authorities like USFDA, EMA, WHO and many more has taken serious action to battle the nitrosamine impurities reaching the public. More recently, nitrosamine impurities have been reported in pioglitazone and ranitidine containing products as well as Health Singapore Authority has recalled Three metformin medicines which had NDMA level which is above the internationally acceptable limits on December 2019 (FDA, 2019).

Table 2, represents, the metformin medicine recalled due to nitrosamine (Has, 2019).

The arrangement of nitrosamines is commonly just conceivable when optional or tertiary amines respond with nitrous corrosive. Nitrous corrosive itself is insecure however can be shaped in situ from nitrites (NO2) under corrosive conditions (WHO, 2019).

On account of the sartan mixes, most contain a tetrazole ring and the development of this tetrazole ring utilizes the utilization of sodium nitrite. Coincidently the solvents utilized either were amines or contained hints of amines, and this conceivable managed the watched NDMA and NDEA. The beginnings of NDMA content in bunches of ranitidine as of now stays indistinct. Regardless, during ongoing assessments, it was furthermore gathered that the probability for nitrosamine contamination content was more broad than basically the concurrent closeness of nitrites and amines in the association of the dynamic pharmaceutical fixing (API). Proof prescribes that wellsprings of nitrites or amines as coincidental contaminants of starting materials, reagents and solvents –,for instance, dimethylamine in the ordinary dissolvable dimethylformamide (DMF) – may similarly give conditions in which nitrosamines may outline. The remnant of nitrites or amines from coming about advances may moreover bear the expense of chances for course of action. Noticeably, contamination from outside sources has been perceived as a wellspring of nitrosamine content. In particular, sullying from the usage of reused materials and solvents that starting at now contain levels of nitrosamines. A referred to an instance of this incorporates the use of reused DMF, which is quenched with sodium nitrite to wreck remaining azide as a significant part of the recovery method. Materials and solvents can become cross-spoiled with nitrosamines or with contaminating impacts that could react downstream to shape nitrosamines if the equipment isn't agreeably cleaned between clients. Fundamentally, these additional segments, explicitly cross-sullying, are to moving degrees things obscure and may impact things that would some way or another or another not be depended upon to be in peril of nitrosamine advancement. These progressively broad concerns have induced the European Medicines Agency (EMA) to request that Marketing Authorisation Holders (MAHs) of all Finished Pharmaceutical Products (FPPs) direct risk evaluation to choose the peril of nitrosamine content (WHO, 2019).

NDMA and NDEA have a place with the supposed "companion of concern", which is a gathering of exceptionally strong mutagenic cancer-causing agents that have been grouped by the WHO's International Agency for Research on Cancer as most likely human cancer-causing agents. In spite of the strength of these polluting influences, there is as yet a generally safe that nitrosamine contaminations at the levels found could cause malignancy in people.

Table 1: The NDMA limits and lot number tested from various companies

Company	Products	Lot Tested	NDMA level ppm	NDMA level mcg
Sanofi Pharmaceutical	OTC Ranitidine 150mg	19E413M	0.07-2.38	0.01-0.36
		19D554		
		19A432U		
		19C540		
		19D431I		
		19D442N		
		19D423M		
		19D464M		
Sanofi Pharmaceutical	OTC Ranitidine 75mg	18L012U	0.10-0.55	0.01-0.04
		9A003U		
		19B006M		
		18M025M		
		18N023U		
		19B005N		
		19A002U		
		18N026U		
Cardinal Health	OTC Ranitidine 150mg	9FE2953	1.02	0.15
Watson	Rx Nizatidine 150mg	350798M	0.05	0.01
Watson	Rx Nizatidine 300mg	1333973A	0.04	0.01
Strides Shasun Ltd	Rx Nizatidine 150mg	7704758A	0.11	0.02
Strides Shasun Ltd	Rx Nizatidine 300mg	7704022A	0.09	0.03
Novitium	Rx Ranitidine 300mg	S18038B	2.85	0.86
Dr. Reddy's	Rx Ranitidine 300mg	C805265	0.68	0.20
Strides Shasun Ltd	Rx Ranitidine 300mg	7702255A	0.11	0.03
Sandoz	Rx Ranitidine 300mg	HU2207	0.82	0.25
Strides Shasun Ltd	Rx Ranitidine 300mg	7704537A	0.02	0.00
Aurobindo	Rx Ranitidine 300mg	RA3019001-A	1.86	0.56
Ajanta Pharma USA Inc	Rx Ranitidine 300mg	PA1229B	0.23	0.07
Silarx Pharma	Ranitidine 150mg Syrup	3652081-02661	1.37	0.20
Pharma Associates	Ranitidine 150mg Syrup	BE00, BF75	0.03-0.07	0.004-0.012
		BF77, BF78		
		BDFF, COAC		
Amneal Pharmaceuticals	Ranitidine 300mg	AR181795A	0.52-2.17	0.16-0.65
		AR190878A		
		AR190876A		
		AR191177A		
		HB05819		
		HB06119		
		HL08718		
Sanofi Pharmaceutical	Ranitidine 150mg	19D570	0.08-2.17	0.01-0.33
		19D428U		
		19E408M		

Table 2: List of recalled metformin medicines due to nitrosamines

	Product name	Batch Recalled	Local supplier
1	Glucient XR Tablet 500mg	One batch 2881382	Glorious Dexa Singapore
2	Meijumet Prolonged Release Tablet 750mg	All batches	Pharmazen Medicals Pte Ltd
3	Meijumet Prolonged Release Tablet 1000mg	All batches	Pharmazen Medicals Pte Ltd

Table 3: Limits given by USFDA for the NDEA and NDMA impurities

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day) *	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day) *	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day) *	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96***
Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	0.32
Olmesartan	80	96	1.2	26.5	0.33	96	1.2
Eprosartan	800	96	0.12	26.5	0.033	96	0.12
Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

Table 4: Regulation laid by the European Union for the limit of NDMA and NDEA

	NDMA		NDEA	
Active substance (max daily dose)	Maximum daily intake	Unit(ppm)	Maximum daily intake(ng)	Unit(ppm)
Candesartan(32mg)	96.0	3.000	26.5	0.820
Irbesartan(300mg)	96.0	0.320	26.5	0.088
Losartan(150mg)	96.0	0.640	26.5	0.177
Oimesartan(40mg)	96.0	2.400	26.5	0.663
Valsartan(320mg)	96.0	0.300	26.5	0.082

Just constrained polluting influence explicit danger information is accessible for NDMA and NDEA. In light of this data between time, worthy admissions for these particular pollutions have been embraced by most significant controllers, as demonstrated in the table. Because of their auxiliary closeness, NDIPA, NEIPA, and NMBA are considered by universal controllers to show a toxicological profile like NDMA and NDEA. For a nitrosamine debasement that is excluded, the standards as laid out in 'ICH's M7(R1)' guidelines are prescribed to be utilized to decide a worthy intake. At any rate, one nitrosamine sample of valsartan demonstrated to be Ames test negative (USFDA, 2019).

Figure 3, shows the symbols of various regulatory authorities across the world.Table 3, represents, Limits given by USFDA for NDEA and NDMA impurities (USFDA, 2019).

On June 19, a U.S manufacture of valsartan, Prinston Pharmaceuticals Inc., asked the Centre for Drug Evaluation and Research (CDER)which is part of the FDA on its products manufactured by Zhejiang Huahai Pharmaceutical Co. (ZHP) containing valsartan Active Pharmaceutical Ingredient (API). Prinston informed CDER that they had stopped making valsartan items because ZHP identified contamination in the Active Pharmaceutical Ingredient. When the FDA started an investigation, they found out that the other regulatory authorities are also taking actions for the NDEA and NDMA impurities for the drug valsartan and ranitidine drug. The Major authorities were Health Canada, European Medicine Agency, Central drug standard Control Organization. USFDA, European Medicines Agency, European Directorate for the Quality of Medicines, Regulatory Operations and Regions Branch and Therapeutic Products Directorate of Health Canada, and

Figure 3: Various regulatory Authorities

the Pharmaceuticals and Medical Devices Agency in Japan had closely worked on the steps to be taken for the impurities. They had exchanged their information on the drug, their results of an analysis on the drug (USFDA, 2018).

Informing patients and the public as well as health care providers was the priority. FDA has provided a path for manufacturers to distribute risk assessments that can be used by manufacturers to determine the proximity of genotoxic emissions. This is a course that has been accepted by the two controllers and industry globally. In order to carry out the risk assessment for any genotoxic degradation, it must be accepted by the manufacturing process. FDA initiated the process of inspecting the manufacturing sites across the world for the impurities and cGMP and made the review of the manufacturers record pertaining the tests and the methods carried out during the impurities. Based on the FDA's analysis of the manufacturing process, it has testing all the products which come under the angiotensin receptor blocker to determine if it contains nitrosamine impurities because steps involved in the synthesis of other ARB might be similar to the valsartan. On November 1, 2019, CDER has said that Ranitidine is safe and NDMA levels found in this drug is the same as that of the levels which are found in the meat (USFDA, 2018)

In the European Union (EU), following an Article 31 audit of sartans in danger of containing nitrosamine debasements (those containing a tetrazole ring),9 makers were approached to survey and make changes to their assembling procedures to limit nitrosamine pollutions to the degree for all intents and purposes conceivable. A progress time of two years has been permitted to roll out these improvements. During this progress period, between time constraints as sketched out in table 1 are being applied to items. Groups of items surpassing these cut-off points for an individual polluting influence, or clusters containing both NDMA and NDEA are not permitted in the EU. Amendments are being made to the European Pharmacopeia to the medication substances monographs for the sartan arrangement to incorporate testing for nitrosamines. Furthermore, the general monograph for APIs (General monograph 2034) is under update and will likewise incorporate proper tests. Because of these measures, numerous sartan items were briefly reviewed from the EU showcase. Many have now come back to showcase; in any case, EU guidance to patients was not to stop their medications except if they have been encouraged to do as such by their drug specialist or specialist. Along these lines, the USFDA attempted to recognize and review medications with levels above interval adequate cut-off points. The USFDA distributes a rundown of ARB items and their status regarding nitrosamine content. Like the EMA, the USFDA accentuated that the dangers, (for example, stroke) of unexpectedly suspending these medications far exceed the okay connected with proceeding with the drugs with these

contaminations. All the more as of late degrees of the contamination NDMA has been distinguished in clumps of ranitidine and nizatidine items. Ranitidine medications are utilized broadly to decrease the creation of stomach corrosive in patients with conditions, for example, indigestion and stomach ulcers. They are accessible over-the-counter and on a solution. Administrative office responses have shifted. Some individual European national controllers, just as Swiss medic and Health Canada, took prudent steps to either review or suspend dispersion of all ranitidine items until the examination of clumps showed NDMA was underneath satisfactory levels. The EMA is presently assessing accessible information to evaluate whether patients utilizing ranitidine are at any hazard from NDMA. Different specialists, for example, the USFDA, have mentioned an intentional review of items just if test results show levels of NDMA over the interval levels.12 The USFDA has confirmed that the degrees of NDMA saw in most ranitidine and nizatidine items are like levels expected on the off chance that you ate basic nourishments like flame-broiled or smoked meats. Many companies have initiated voluntary recalls of their ranitidine products as preventative measures. As a general measure, the EMA has requested that the MAHs of all FPPs evaluate the possibility of nitrosamines being present in all products containing chemically-synthesize active ingredients. Although nitrosamines are not expected to form during the manufacture of the vast majority of medicines, the possibility of cross-contamination or unintentional introduction of amines and nitrites has prompted the request for companies to undertake this precautionary review. These reviews are expected to be broad in scope and to consider all aspects of the manufacturing process including Finished Pharmaceutical Product manufacture. The EMA has requested that MAHs complete this review within 6 months (EMA, 2019)

The Council of Europe had also taken the measures and reviewed Site Master File and Marketing Authorization Applications by EU authorities. Sampling and testing of API and Medical Products. They also conducted GMP inspection and decision has taken on contaminated products which are in the market. Update of the Ph. Eur monographs for sartans with tetrazole ring and Development, validation of a general method that may be used as a reference has been initiated. The decision has taken that the solvents are being used which is free of nitrosamine impurities and manufacturing processes can be changed (EDQM, 2019).

CDSCO also has taken action on ranitidine impurities-it has ordered its officials to check for the nitrosamine impurities (The Indian Express, 2018).

Test Methods

The low levels at which the nitrosamine impurities occur creates challenges for testing. To assist in the testing of samples the USFDA has published several test methods that may be considered when determining nitrosamine content in the API or FPP. The USFDA has recommended the use of an LC-HRMS method when testing ranitidine due to the lower temperate conditions of the method; higher temperature conditions of some test methods may cause the sample to generate NDMA. Similarly, the Official Medicines Control Laboratories (OMCLs) Network of the Council of Europe has also published several methods that may be used when testing for nitrosamines

The following are the methods used for determining nitrosamine in valsartan shown in Figure 4. (EDQM, 2019), Table 4 represent the regulation laid by European union for limits of NDMA and NDEA (EMA, 2019).

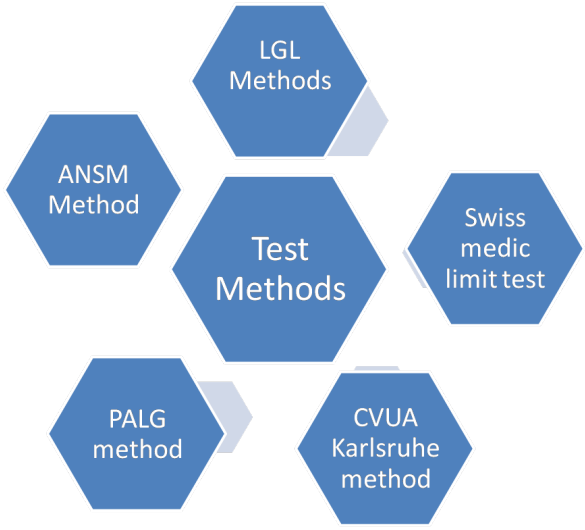

Figure 4: Various methods of determining nitrosamine in valsartan

LGL Method

It's an LC-MS/MS method (AB SciexQtrap) a qualitative assurance method for NMBA for determining losartan drugs impurity.

Figure 5, shows the GC-MS and LC-MS/MS methods used for the analysis of NDMA and NDEA

1. Swiss surgeon limit test

It is for Nitrosamine assurance by LC-MS/MS (valsartan,Olmesartan and candesartan).

2. PALG method

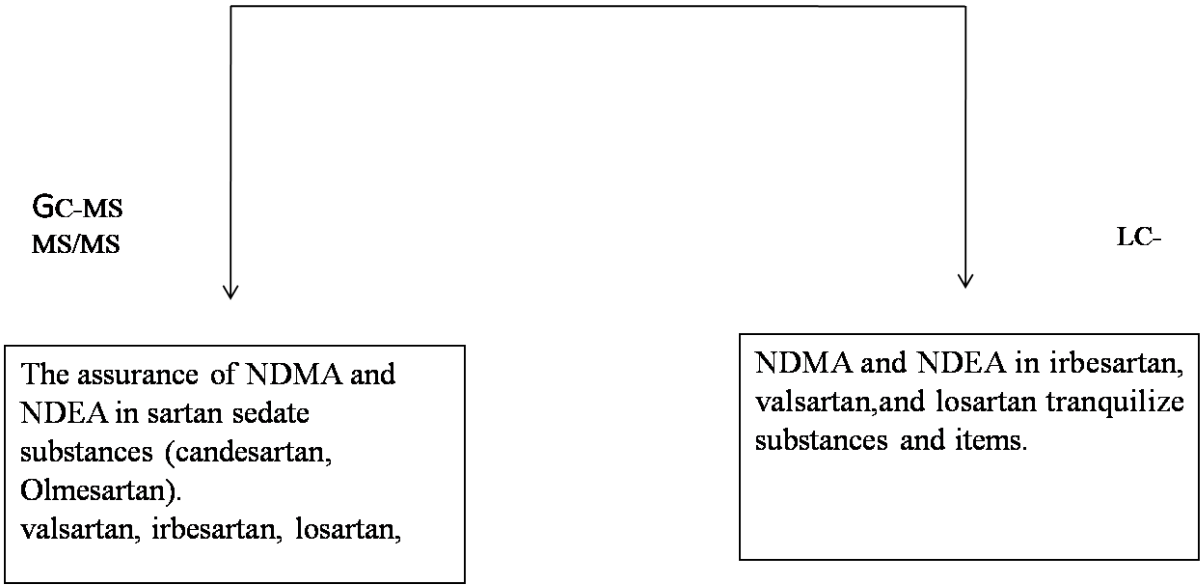

Figure 5: Methods foranalysis of NDMA and NDEA

Headspace GC-MS (single quad) and appropriate to the assurance of NDMA in sedate substances and relating powdered tablets of the sartan gathering.

3. ANSM technique

Depends on HPLC-UV and material to the assurance of NDMA in tranquilize substance and comparing powdered tablets of valsartan.

Methods for determining nitrosamine in ranitidine:

4. The German OMCL

A GC-MS screening strategy for NDMA in ranitidine sedate substances.

5. UHPLC-APCI-MS/MS

Permits assurance of NDMA in ranitidine sedate substances and medication items (USFDA, 2019).

Discussion

Information to patients

1. USFDA has not recalled all the ranitidine and valsartan drugs marketed in US
2. It has not recommended to stop taking these medicines at this movement
3. Consumers taking OTC ranitidine could consider utilizing other OTC items endorsed for their condition (USFDA, 2019).

Health care professionals should know the following

Several medications are approved as ranitidine for the same or related uses. Health care professionals should talk to patients who are concerned about ranitidine about other treatment options.

If recalled samples of ranitidine is present, it should not be given to patients.

The FDA continues to test ranitidine products from multiple manufacturers and assess the potential impact of ranitidine on patients. In addition, the FDA has recently published a test method that regulators and industry can use to detect impurities of nitrosamine in ranitidine. FDA requested manufacturers of ranitidine to perform laboratory tests to analyse NDMA levels in ranitidine.

On the basis of the results of this ongoing investigation, the FDA will take appropriate action. Some manufacturers have chosen to stop ranitidine distribution as a precautionary measure while the NDMA impurity is being investigated by the FDA and other international regulators.

Consumers and health care professionals should report any adverse reactions with ranitidine to the FDA's MedWatch program to help the agency better understand the scope of the problem (USFDA, 2019).

CONCLUSIONS

The Regulatory authorities have worked in collaboration for the betterment of the society and also, they laid down the limits to be permitted for the impurities. They have also laid down the rules and constantly for handling the drug substance and drug products. They also Valsartan made a strong effort for reaching to the public and health care professionals. The challenge was to set out the rules and limits and various authorities across the globe have done the job perfectly. The limits set are 0.09% microgram or 0.32ppm of NDMA per day is consid-

ered safe for daily intake. This is based on the 2018 ICH guidelines M7(R1). There will be a probability of 1/100000 cancer occurrence. If the NDMA limits found above safe limit then the drug has to be withdrawn from the market. On December 4 Health Singapore Authority has withdrawn 'metformin' drug from the market and cancer risk from an additional 6-month exposure is estimated to be less than 0.00002%.and it is working on it. From all these cases we can observe the challenges faced by Regulatory Authorities in day to day life.

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