A viewpoint on the presence of *N*-nitrosodimethylamine (NDMA) impurity in certain generic samples of Valsartan

Srinivas Oruganti, PhD†

1. Background

The definition of 'quality generics' is an ever evolving phenomenon given the advancements in chemistry and process engineering as per QbD (Quality by Design) principles, coupled with advancements in the sensitivity of analytical methods and detection. Even in well-established generics ranging from antibiotics and drugs used for gastric, neuro- and cardiovascular indications, the quality paradigm has evolved over the past several years. A key requirement for a generic drug is the chemical and biopharmaceutical equivalence to the original drug developed by the innovator. In this context, great emphasis is laid on aspects such as chemical purity, potency, physico-chemical and solid-state properties which clearly have an impact on the disintegration time and dissolution rates. The need to have an identical property with the innovator drug becomes a mandatory requirement to launch a generic version. A high quality generic is essentially expected to meet all the parameters and therefore be considered as a safe yet cheaper alternate to the innovator drug. Interestingly, there is another important aspect of generic drugs that is being increasingly scrutinized by regulatory agencies world-wide with a clear intent to ensure quality medicines. The definition of quality in a generic drug can also be perceived as the absence of unwanted and unknown constituents in the drug product. A steady evolution in the technological advancements in chemistry, process engineering and analytical measurements and sensitivity and a deeper knowledge base in our understanding of GTIs etc have provided a microscopic lens to unearth certain constituents or impurities which were present in previously 'acceptable' generics.

An interesting example of such a discovery pertains to the contemporary news of Valsartan recalls. Valsartan **1**(Figure 1) - a non-peptide orally active angiotensin-II-receptor antagonist approved for use (FDA, 2002) either as a single agent or in combination with other active substances in the treatment of hypertension, heart attack and heart failure- was recently in the limelight due to specific circumstances surrounding the detection of *N*-nitrosodimethylamine (*NDMA*) in certain batches of the API.[1] The EU authorities were notified by Zhejiang Huahai Pharmaceutical - an API manufacturer based in China that supplies Valsartan for medicinal products authorized in the EU - that the presence of NDMA was detected in batches of valsartan manufactured at its site in Chuannan. Tests performed by the manufacturer on a random selection of API batches measured NDMA levels in the range between 3.4 ppm to 120 ppm, with an average of 66.5 ppm. NDMA is an *N*-nitroso compound and the presence of such levels of the impurity was bound to raise a particular concern. Specifically, *N*-nitroso compounds belong to the so-called "Cohort of Concern" - classes of chemicals that include other high potency genotoxic carcinogens like azoxy compounds. It has been estimated that more than 10% of chemicals that are a part of the Cohort of Concern would pose a cancer risk of >1 in 10^6 at an exposure even at the TTC value of 0.0025 µg/kg bw/day and are therefore specifically excluded from assessment *via* the TTC approach.[2]

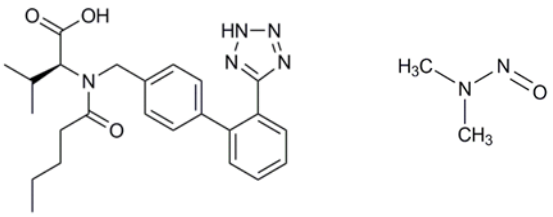


Figure 1. Chemical structures of Valsartan (*left*) and *N*-nitrosodimethylamine (*right*)

2. About *N*-nitrosodimethylamine (NDMA)

NDMA is a semi-volatile (b.p. 153 °C; v.p.1.080 kPa at 25°C) yellow, oily liquid that is produced in both industrial and natural processes. NDMA can be formed and released from diverse industrial sources, and may also be produced as an unintentional by-product of chlorination of wastewater and drinking water. NDMA exposure may occur through (a) ingesting food that contains nitrosamines (such as smoked or cured meats and fish) or alkylamines, which can cause NDMA to form in the stomach; (b) drinking contaminated water or malt beverages (such as beer and whiskey) that may contain low levels of nitrosamines formed during processing; (c) using toiletry and cosmetic products that contain NDMA; and (d) breathing or inhaling cigarette smoke. Workplace exposure can occur at tanneries, pesticide manufacturing plants and rubber and tire plants. The oral route is the primary human exposure pathway for NDMA.[3]

Classification of NDMA[4]	
American Conference of Governmental Industrial Hygienists (ACGIH)	**A3:** Animal carcinogen. "Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure."
International Agency for Research on Cancer (World Health Organization) (IARC)	**2A:** The agent (mixture) is probably carcinogenic to humans; there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.
National Toxicology Program (Health and Human Services Dept., Public Health Service, NIH/NIEHS) (NTP)	**2:** Reasonably anticipated to be carcinogens

†Dr. Srinivas Oruganti | Director, Dr. Reddy's Institute of Life Sciences & Head, Center for Process Research & Innovation ● soruganti@drils.org

***Drinking water and groundwater guidelines for NDMA in various U.S. states*[3]**

State	Guideline(µg/L)	State	Guideline(µg/L)
Alabama	0.0013	Mississippi	0.00131
Alaska	0.017	New Jersey	0.0007
California	0.003	North Carolina	0.0007
Colorado	0.00069	Pennsylvania	0.0014
Delaware	0.001	Texas	0.018
Florida	0.0007	Washington	0.000858
Indiana	0.0049	West Virginia	0.0013
Massachusetts	0.01	1 µg/L = 1 ppb	

3. Probable source of NDMA in Valsartan

In the CHMP list of questions[1] released by European Medical Agency, it has been indicated that "*NDMA appears to be generated during the formation of the tetrazole ring by reaction of dimethylamine (which may be present as an impurity or degradant in the solvent dimethylformamide (DMF) and sodium nitrite under acidic conditions (where nitrous acid is formed). It can also not be excluded that other N-nitrosamines could be generated with other solvents or under other specific reaction conditions where other amines are present*". While the particulars of the manufacturing process were not disclosed, the use of sodium nitrite in acidic milieu during the tetrazole formation step can be reconciled to in one of the two ways:

(a) to quench the excess sodium azide left unreacted from the reaction with methyl *N*-valeryl-*N*-[(2'-cyanobiphenyl-4-yl)methyl]-L-valinate[5]

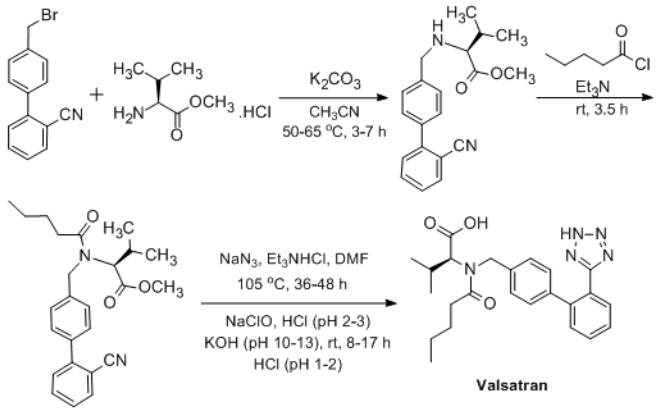
$$2NaN_3+2HNO_2 = 3N_2+2NO+2NaOH$$

(b) to eventuate tetrazole ring formation upon reacting with the aminoamidine obtained by reacting hydrazine with methyl *N*-valeryl-*N*-[(2'-cyanobiphenyl-4-yl)methyl]-L-valinate

$$R–CN + N_2H_4 \rightarrow R–C(=NH)NHNH_2$$

$$R–C(=NH)NHNH_2 + HNO_2 \rightarrow R–Tetrazole.$$

One of the synthetic routes to **1** that avoids the use of sodium nitrite for destroying excess NaN_3 and thus prevents NDMA formation has been shown below in Scheme 1.[6] In addition, tetrazole construction with such azide source as Bu_3SnN_3 which



Scheme 1. Synthesis of Valsartan **1** (use of NaOCl for quenching excess NaN_3)

can be solubilized in non-protic solvents (*e.g.*xylene and toluene) can potentially avert the formation of NDMA by not having the requirement to employ DMF as the solvent. However, in such a case, strict control of possible tin impurity in the final API is of paramount importance. [7,8] Among the various other Sartans, the possibility of NMDA generation in Losartan cannot be ruled out if NaN_3/DMF conditions are used for the tetrazole construction. [9]

4. Methods for detection and quantification of NDMA impurity

The following methods have been employed for detection and quantification of NDMA impurities (Figure 2):[3]

(a) Capillary column gas chromatography (GC) and chemical ionization tandem mass spectroscopy (MS)
(b) GC and a nitrogen-phosphorus detector (NPD)
(c) Isotope dilution, GC and MS
(d) Liquid chromatography tandem MS (LC/MS/MS)

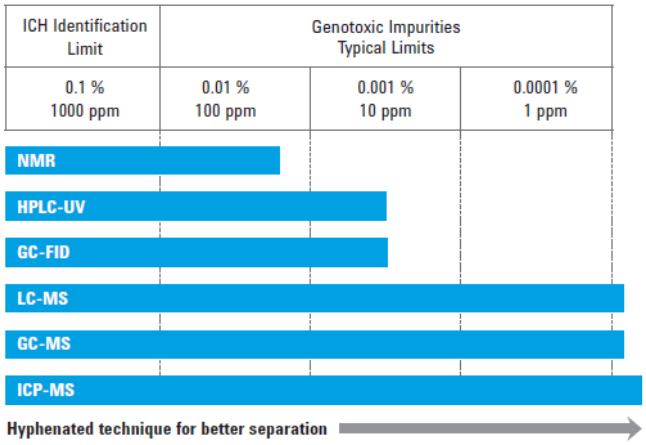


Figure 2. Lower detection levels of genotoxic impurities require more sophisticated analytical techniques for quantification [taken from *Genotoxic impurities in pharmaceutical products: Regulations and Analysis* (Agilent Technologies)]

5. Methods for removal of NDMA impurity

NDMA is not removable by air stripping, activated carbon adsorption, reverse osmosis or biodegradation.[10] It is degraded extremely slowly by ozone. Potential technologies that have been employed for water treatment are UV irradiation, UV plus hydrogen peroxide (UV/H_2O_2), granular activated charcoal (using Fenton's reagent), combined adsorption and microwave irradiation (Cu-ZSM-5 Zeolites) and resin (*e.g.* Ambersorb 572) adsorption. The principal by-products of UV photolysis of NDMA are dimethylamine (DMA) and nitrite. When UV/H_2O_2 is applied, nitrate is the major degradation product and the concentration of DMA is significantly lower than with direct photolysis. The usage of granular activated charcoal mainly leads to nitrate or nitrogen gas, monomethylamine and formaldehyde as by-products. It was interesting to note the absence of by-products formation when zeolites were employed.[10,11] In the present context of NDMA tainted Valsartan, a potentially viable method of NDMA removal will entail converting the impure API into its insoluble barium salt

†Dr. Srinivas Oruganti | Director, Dr. Reddy's Institute of Life Sciences & Head, Center for Process Research & Innovation ● soruganti@drils.org

by treatment with aqueous $Ba(OH)_2$ and treating the filtered salt with aqueous HCl to regenerate the API.[12] Another approach one could consider is the process modification for the synthesis of Valsartan which could potentially eliminate the NDMA source.

[1] EMA release; CHMP List of questions (EMA/CHMP/467845/2018; dated 16 July 2018).

[2] (a) EFSA (European Food Safety Authority) and WHO (World Health Organization), 2016. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree. *EFSA Supporting Publication* 2016; 13(3):EN-1006, 50 pp. (b) Risk assessment of members in the Cohort of Concern requires compound-specific toxicity data.

[3] (a) Technical Fact Sheet – N-Nitroso-dimethylamine (NDMA); November 2017. Available at: https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf. (b) Concise International Chemical Assessment Document 38: *N*-Nitrosodimethylamine. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad38.pdf

[4] Known and Suspected Human Carcinogens: Carcinogens Reference List. Available at: https://www.ehs.uci.edu/programs/sop_library/CARCIN.pdf

[5] Zupancic, Silvo. *Improved process for preparing Valsartan*. WO 2011/124655 A1; Oct 13, 2011.

[6] Li, Hongwu; Yang, Hejun; Guo, Yongzheng; Jiang, Dong; Xiao, Jun; Guo, Hongju; Xu, Yongping. *Method for preparing Valsartan*. CN 103554049 B; Mar 23, 2016.

[7] Padi, Pratap Reddy; Bollikonda, Satya Narayana; Jasty, Ananda Mohan; Yasareni, Suma Latha; Parmar, Vishal Dayaram. *Process for preparing Valsartan*. US 7659406 B2; Feb 9, 2010.

[8] Chinta, Raveendra Reddy; Nangi, Gangadhara Bhima Shankar; Nayini, Mahendar Reddy; Yallapa, Somappa Somannavar; Budidet, Shankar Reddy; Aminul, Islam; Meenakshisunderam, Sivakumaran. *An improved process for preparation of Valsartan*. US 8981109 B2; Mar 17, 2015.

[9] Vardanyan, Ruben; Hruby, Victor. *Synthesis of best seller drugs*. Academic Press, 2016, pp 329-356.

[10] N-Nitrosodimethylamine in drinking-water - World Health Organization. Available at: www.who.int/water_sanitation_health/dwq/chemicals/ndma2ndadd.pdf.

[11] Alaba, Peter Adeniyi; Sani, Yahaya Muhammad; Olupinla, Sunday Felix; Wan Daud, Wan Mohd.; Mohammed, Isah Yakub; Enweremadu, Christopher C.; Ayodele, Olubunmi O. Toward N-nitrosamines free water: Formation, prevention, and removal. *Critical Reviews in Environmental Science and Technology*, **2017**, *47*, 2448-2489.

[12] .N, Senthil Kumar; Reddy, Shankar B.; Sinha, Brajesh Kumar; Mukkanti, Kagga; Dandala, Ramesh. New and Improved Manufacturing Process for Valsartan. *Organic Process Research & Development*, **2009**, *13*, 1185-1189.

†Dr. Srinivas Oruganti | Director, Dr. Reddy's Institute of Life Sciences & Head, Center for Process Research & Innovation ● soruganti@drils.org