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POSITION PAPER

NDMA, NDEA and Impact on Pharmaceuticals

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Agenda

- Executive Summary
- The ARBs – Sartans story
- Metformin – recall of extended release product
- Ranitidine – root cause and *in vivo* formation
- The chemistry of nitrosamine formation
- Sidvim's position

Executive Summary

This position paper attempts to analyse the current situation with respect to the NDMA, NDEA and other related impurities that have been detected at unacceptable levels in certain sartans, ranitidine, nizatidine and metformin tablets.

The presence of NDMA has been known for a very long time – it is present in water and certain foods as well. However it is only recently that higher levels have been detected in some products.

NDMA and NDEA belong to the so-called "cohort of concern", which is a group of highly potent mutagenic carcinogens that have been classified by the WHO's International Agency for Research on Cancer (IARC) as probable human carcinogens. Despite the potency of these impurities, there is still a very low risk that nitrosamine impurities at the levels found in natural sources could cause cancer in humans. However, it is a matter of grave concern if these are formed in pharmaceutical products at unacceptably high levels.

It is observed in the case of sartans that the root cause was successfully identified and changes in the manufacturing process could eliminate the presence of these impurities. The current stand is to test each batch and release the same for human consumption only if it meets the limits specified by the regulatory agency.

In the case of ranitidine, nizatidine and metformin- the root cause is as yet not assigned- and hence the only alternative is to take these products off the shelves so as to avoid human exposure to these impurities. This situation may change in the future if resolved.

Executive Summary (contd.)

The Indian Scenario: DCGI has issued notification that manufacturers must test and ensure compliance of the products to meet the current nitrosamine levels for all products sold in India.

- The additional testing required by DCGI for these products involves expensive instruments and further reduces the margins for the manufacturers. Also the analytical testing methods are different for each of these products. Outsourcing these tests to external labs is one option that may be used. However it may be difficult to enforce compliance unless alternative cost effective methods are developed.
- In December 2019, the sartan market in India was worth approximately Rs. 5,069 crore, while the ranitidine market was worth approximately Rs. 662 crore, according to data from AIOCD Pharmasofttech AWACS. Glenmark Pharma's Telma was the market leader among sartans, followed by Mankind Pharma's Telmikind and USV's Tazloc. Among ranitidine brands, Cadila Pharma's Aciloc was the market leader, followed by GSK's Zinetac and J B Chemicals & Pharmaceuticals' Rantac.

The following presentation attempts to analyse the present status and offer some insights on the future.

Ref.: Express Pharma Pulse

Sartan containing dosage forms

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What did the FDA find in the generic sartans?

- Beginning in Summer 2018, FDA learned and reported that some **generic versions** of the angiotensin II receptor blocker (ARB) medicines contain nitrosamine impurities that **don't meet** the agency's **safety standards**.
- Valsartan, losartan, irbesartan and other "-sartan" drugs are a class of medicines known as angiotensin II receptor blocker (ARBs) used to treat high blood pressure and heart failure.
- Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA), and N-Nitrosodiethylamine (NDEA), are probable human carcinogens (a substance that could cause cancer), and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) is a potential human carcinogen.
- Nitrosamines are known environmental contaminants and found in water and foods, including meats, dairy products and vegetables.
- The presence of these nitrosamine impurities in ARB medicines was unexpected. FDA's ongoing effort has determined that these impurities may be generated when specific chemicals and reaction conditions are present in the manufacturing process of the drug's API, and may also result from the reuse of materials, such as solvents.

Ref.: US FDA Website

FDA's current stand is to test and release only those products with acceptable levels

Valsartan products are used to treat chronic conditions such as high blood pressure and congestive heart failure. On July 13, 2018, FDA announced a recall of valsartan tablets because of the potential for certain products to contain an impurity, N-nitrosodimethylamine (NDMA).

- This impurity is classified as a probable human carcinogen and is believed to have been introduced into the finished products **as a result of the manufacturing process**.
- Subsequently, an additional nitrosamine, N-nitrosodiethylamine (NDEA), has also been detected in some valsartan products. N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), and NNitrosodibutylamine (NDBA), and N-Nitrosomethyl-4-amino-butyric acid (NMBA) have also been flagged as potential nitrosamine impurities.
- **Not all** valsartan, losartan, and irbesartan-containing medications are affected and being recalled.
- **Not all** lots of valsartan, irbesartan, and losartan from a manufacturer involved in a recall are affected and being recalled. FDA has posted a list of currently available ARBs and the status of their assessment of those medications.
- All products need to be tested for levels of impurities – and released only if it meets the specification.

Ref.: US FDA Website

Novartis Valsartan did not have the impurity NDMA

- Valsartan was patented by Novartis Pharmaceuticals in 1996 in the US market and sold under the name Diovan. The product was genericised in the USA in 2012. Valsartan alone and in combination with other drugs is sold by many players in the US market today- more than 20 ANDA approvals for valsartan and its combinations are currently listed in the Orange Book.
- Valsartan manufactured by Novartis does not contain NDMA – the reason for the same is that the route of synthesis followed by Novartis differs from that used by many other manufacturers. Zhejiang Hua Hai followed a specific route of synthesis using N,N-dimethylformamide, which likely lead to the formation of NDMA as impurity.
- The presence of another carcinogen, *N*-nitroso-*N*-methyl-4-aminobutyric acid (**NMBA**), was found in lots of losartan potassium.
- A solvent dimethylformamide (DMF) was used in the synthesis of valsartan made by several companies and is classified by the World Health Organization as a probable carcinogen.

Ref.: US FDA Website

How did the impurity get formed?

- One hypothesis is that - the impurity was probably produced in a key tetrazole-forming step in the synthesis.
- Basis a 2014 issued patent it is seen that ZHP (Zhejiang Hua Hai Pharmaceutical) has an improved method for forming the tetrazole ring of valsartan. For this key step, ZHP uses sodium azide, which leads to higher yields compared with the original patented route from Novartis that uses tributyltin azide. It is important to note that - ZHP implemented their updated process for supplying product synthesized by the new process to the US in 2012 after it was approved by relevant regulatory agencies including the FDA.
- This reagent switch made by ZHP requires chemists to get rid of excess sodium azide by adding sodium nitrite, which under acidic conditions can form nitrous acid. Nitrous acid likely reacted with small amounts of dimethylamine to produce NDMA. Dimethylamine is a degradation product of the solvent used in the reaction, dimethylformamide.
- The synthetic origins of the NDEA impurity, however, is still unclear. It is suggested that it could have formed through a similar chemical route involving diethylformamide as a solvent instead of dimethylformamide.

Ref.: Chemical and Engineering News

Limits have been set by FDA for NDMA, NDEA and NMBA

Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

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	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
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

- The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure
-

** These values are based on a drug's maximum daily dose as reflected in the drug label
*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

Ref.: US FDA Website

Risk estimate is low and alternatives are available to ARBs

April 2019- Janet Woodcocks message on ARBs

- The FDA calculated that if you took the very highest dose of one of the affected medicines over four years, and you took the medicine that was the most contaminated, the risk is an additional **one case in 8,000 people**. To put this in context, currently one out of every three people in the U.S. will experience cancer in their lifetimes. Here's the reality for all of us.
- We're exposed to these nitrosamines every day in small amounts in our food, our water, and our soil. For example, low levels of nitrosamines are present in smoked foods like bacon and grilled and processed meats. They also occur naturally in fresh vegetables and water.
- The risk estimate is a worst-case scenario, and in fact no one would have been exposed to that much nitrosamine from ARBs, because most batches of the drugs contained much lower levels. Nitrosamines are allowed in our food and water supply in small amounts, and we seldom give it much thought. But, they shouldn't be in our drug supply, and the FDA is going to make sure that they are removed completely from any drug that you might take.
- FDA and companies continue to test medicines to make sure none of these medicines contain the nitrosamines.

Ref.: US FDA Website

Alternate Drugs that can be used in the treatment of hypertension - in place of ARBs

Class	MOA	Examples
Diuretics	Increase urine output & decrease fluid volume	Hydrochlorothiazide, furosemide
Beta adrenergic receptor blockers	Decrease the heart rate & myocardial contractility, reducing cardiac output	Propranolol, metoprolol
Alpha adrenergic receptor blocker	Alpha 1 blockers: inhibit sympathetic activation in arterioles, causing vasodilation	Prazosin, terazosin
Centrally acting sympatholytics	Alpha 2 agonists: decrease sympathetic impulses from the CNS to the heart & arterioles, causing vasodilation	Clonidine, methyldopa
Calcium channel blockers	Block calcium ion channels in arterial smooth muscle, causing vasodilation	Verapamil, diltiazem, nifedipine, amlodipine
ACE inhibitors	Block formation of angiotensin II, causing vasodilation & block aldosterone secretion, decreasing fluid volume	Captopril, enalapril
Angiotensin Receptor Blockers	Prevent angiotensin II from reaching its receptors, causing vasodilation	Telmisartan, Olmesartan
Direct Vasodilators	Act on the smooth muscle of arterioles, causing vasodilation	Hydralazine, minoxidil sodium
Direct Renin Inhibitor	Lowers blood pressure by decreasing renin activity, and angiotensin I and II levels.	Aliskiren

The treatment of hypertension involves the use of many different drug classes.

These have different modes of action.

Many a times anti-hypertensives are prescribed as combination products as well.

Angiotensin Receptor Blockers - Market Impact

Total Exports – volume and value

Molecule	Q1 2020 Volume (Kg)	Q1 2019	Q1 2020 Value (USD)	Q1 2019
Telmisartan	21,572	H	3,522,066	H
Valsartan	99,918	L	27,363,207	L
Losartan	188,758	L	22,421,704	L
Irbesartan	54,271	L	8,350,533	L

L: 2019 value was lower
H: 2019 value was higher

US FDA, EMA and other regulatory agencies posted testing requirements and procedures to be followed.

The pharma industry made **necessary changes to the manufacturing process** and adopted the new testing standards.

The market is unlikely to be impacted in the long run.

Ref.: Import Export Database

Metformin Dosage Forms

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The background to the Metformin recalls

Metformin is an oral antidiabetic that helps control blood sugar levels. It is the first line medication for the treatment of Type II diabetes mellitus, especially in people who are overweight.

When can a patient not take metformin?

- Metformin is contraindicated in patients with factors that predispose to lactic acidosis. The predisposing factors are: A renal function damaged, concomitant liver disease or excessive alcohol intake, unstable or acute heart failure and personal history of lactic acidosis.
- It is very important to advise patients with eGFR 30-60 mL/min to stop taking metformin if they develop any condition associated with dehydration, sepsis or hypoxemia. Also metformin should be stopped prior to intravenous iodinated contrast.

In May 2020:

- The U.S. Food and Drug Administration has **recommended recalls** of certain metformin products that may contain the impurity N-nitrosodimethylamine (NDMA) above the acceptable intake limit.
- FDA has further advised that patients taking recalled metformin should continue taking it until a doctor or pharmacist gives them a replacement or a different treatment option. It could be dangerous for patients with type 2 diabetes to stop taking their metformin without first talking to their health care professional.

Ref.: World J Diabetes

Metformin products reveal the presence of NDMA across different brands on testing

- In March 2020, Valisure filed a citizen petition with the FDA after it found high levels of NDMA in certain batches of metformin. The citizen petition described Valisure's testing protocols that improved the accuracy of its testing and requested the agency recall the contaminated metformin. On May 27, 2020, the FDA announced it had found high levels of NDMA in **some versions of metformin**. The agency said it would be in contact with the manufacturers of the contaminated batches to determine the appropriate next steps.
- It is important to note that the presence of NDMA in metformin products may be primarily due to **contamination during manufacturing** as opposed to a fundamental instability of the drug molecule, which is the case with ranitidine.

Ref.: FDA Citizens Petition Valisure

What are the options available to replace Metformin in Type II diabetes mellitus?

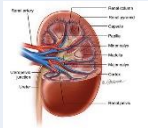
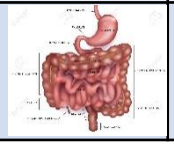
- In the Consensus of ADA/EASD 2015 sulfonylureas and glinides appear as an alternative to metformin when metformin is contraindicated or not tolerated, and they represent an alternate treatment option in double and triple therapy, whereas in the Consensus of the American Association of Clinical Endocrinologist (AACE) 2016, sulfonylureas and glinides appear as the last alternative both in monotherapy and combined treatment.
- There are many other drugs that can be used to treat Type 2 Diabetes Mellitus – however metformin is by far the oldest and likely the most cost effective.

It is important to note that as per the current analysis by the US FDA – NDMA has been found only in the extended release versions.

- The agency is also **asking all manufacturers of extended release versions of metformin** to evaluate their risk of excessive NDMA and to test at-risk product before each batch is released onto the U.S. market. If testing shows NDMA above the acceptable intake limit, the manufacturer must inform the agency and should not release the batch to the U.S. market.
- FDA's testing has shown elevated levels of NDMA in some extended release (ER) metformin formulation but **not in the immediate release (IR) formulation or in the active pharmaceutical ingredient**.

Ref.: World J Diabetes

The different treatment options for Type II Diabetes Mellitus are listed below

Class	MOA	Examples
Biguanides	Reduces hepatic glucose output, lowers fasting glucose 	Metformin
Sulfonylureas	Bind to their receptor found on the surface of beta-cells, triggering insulin release in a glucose-independent manner 	Gliclazide, glipizide
DPP4 	Dipeptidyl peptidase-4 -bind to the DPP-4 active site, inhibiting the inactivation of glucagon-like peptide-1 (GLP-1), thereby increasing its availability	Saxagliptin, Sitagliptin
TZD - PPAR gamma agonist	Thiazolidinediones or glitazones. Lower blood glucose levels through insulin sensitisation. Act by activating **PPARs** (peroxisome proliferator-activated receptors) - specific for **PPARγ**	Rosiglitazone, pioglitazone
GLP 1 RA	GLP-1 receptor agonist -stimulate beta-cell insulin release and slow gastric emptying [Glucagon like peptide-1] 	Exenatide, Liraglutide
SGLT2 	Sodium-glucose co-transporter2 : Act by blocking the SGLT2 protein involved in reabsorption of glucose from the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels	Canagliflozin, Dapagliflozin
Alpha glucosidase inhibitor	Slow down the digestion of starch, slows intestinal carbohydrate absorption and reduces post-prandial blood glucose level excursions. 	Acarbose

It is too early to see if Metformin volumes are impacted

Total Exports – volume and value

Molecule	Q1 2020 Volume (Kg)	Q1 2019	Q1 2020 Value (USD)	Q1 2019
Metformin	5,912,467	L	23,815,666	H

L: 2019 value was lower
H: 2019 value was higher

For metformin exports in Q1 2019, the price per Kg was higher, leading to higher revenues

Based on the Import Export data for 2020 the volumes do not appear to be impacted. However it is still too early to predict the impact of the presence of NDMA on future volumes.

It is important to note that only specific dosage forms- i.e. extended release tablets- have been asked to be recalled by FDA. However, the Valisure Citizens petition reveals that NMDA presence may be seen in the immediate release products as well.

There is likely to be need for further investigation on root cause before appropriate measures to safeguard patients can be put in place. A temporary drop in sales volume may be likely.

Ref.: Import Export Database

Ranitidine Dosage Forms

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Ranitidine has NDMA- however the other H2 blockers and PPIs tested by FDA were free of the impurity

- Thus far (as of November 1, 2019), the FDA and industry testing of medicines in the histamine-2 (H2) blocker and proton pump inhibitor (PPI) classes has identified NDMA only in ranitidine and nizatidine. The FDA says its tests of samples of alternatives, such as Pepcid (famotidine), Tagamet (cimetidine), Nexium (esomeprazole), Prevacid (lansoprazole) and Prilosec (omeprazole) show no NDMA impurities in these medicines.
- NDMA can also be formed through natural processes. Ranitidine, the active ingredient in Zantac, has a **molecular structure that makes it susceptible to naturally creating NDMA once it is ingested**. Specifically, the ranitidine compound contains the two elements that are required to form NDMA: nitrite ("N") and dimethylamine ("DMA"). The presence of both nitrite and dimethylamine in ranitidine's chemical structure renders it highly capable of producing NDMA under the right conditions.

Ref.: US FDA Website & Golderberg Law

How is NDMA formed from Ranitidine?

- A recent independent study conducted by Valisure Online Pharmacy sought to understand how capable ranitidine was of naturally producing NDMA.
- During the testing, Valisure simulated the conditions that ranitidine is exposed to in the human stomach to see how the ranitidine would react; namely, they mixed ranitidine with the gastric fluid and sodium nitrites that stimulate the digestion process.
- They found that when the **ranitidine interacts with the gastric fluid and sodium nitrites found in the stomach**, **high amounts of NDMA are produced**. In fact, when exposed to the simulated stomach conditions, the ranitidine produced approximately 304,500 nanograms (ng) of NDMA per tablet.
- This is an alarming amount of NDMA, considering the FDA-approved acceptable amount of NDMA intake is **96 ng per day**.
- Therefore it is seen that NDMA is not only found in ranitidine products on storage under normal conditions– it may likely be formed *in vivo* due to interactions with gastric fluids as well.

Ref.: US FDA Citizens Petition of Valisure

Valisure's Citizen Petition gives additional *in vitro* data that supports NDMA formation

- Valisure tested ranitidine tablets by themselves and in conditions simulating the human stomach. Industry standard "Simulated Gastric Fluid" ("SGF" 50 mM potassium chloride, 85 mM hydrochloric acid adjusted to pH 1.2 with 1.25 g pepsin per liter) and "Simulated Intestinal Fluid" ("SIF" 50 mM potassium chloride, 50 mM potassium phosphate monobasic adjusted to pH 6.8 with hydrochloric acid and sodium hydroxide) was used alone and in combination with various concentrations of nitrite, which is commonly ingested in foods like processed meats and is elevated in the stomach by antacid drugs.

- These more biologically relevant tests were done in 100mL reaction volumes with one 150 mg tablet of ranitidine for each test that was allowed to react for one hour. 1mL of solution from each experiment was analyzed using the low temperature GC/MS method**. The results of Valisure's tests on ranitidine tablets in biologically relevant conditions demonstrate significant NDMA formation under simulated gastric conditions with nitrite present.**

- NDMA formation in the stomach has been a concern for many years and specifically ranitidine has been implicated as a cause of NDMA formation by multiple research groups including those at Stanford University.

- Valisure identified a **possible enzymatic mechanism via dimethylarginine dimethylaminohydrolase ("DDAH") for the liberation of ranitidine's DMA group** which can occur in other tissues and organs separate from the stomach. Liberated DMA could lead to the formation of NDMA when exposed to nitrite present on the ranitidine molecule, nitrite freely circulating in the body, or other potential pathways particularly in weak acidic conditions such as that in the kidney or bladder.

Ref.: US FDA Citizens Petition of Valisure

Studies on Ranitidine by Stanford University confirm the formation of NDMA *in vivo*

One study was completed and published in 2016 by Professor William Mitch and his team at Stanford University. The study showed that healthy individuals, both male and female, that took Zantac 150 mg tablets produced **roughly 400 times elevated amounts of NDMA in their urine** (over 40,000 nanograms) in the proceeding **24 hours after ingestion**. These results alone are extremely alarming, given NDMA has been implicated as an etiological agent for bladder cancer, however, the implications could be significantly worse given that NDMA is known to be heavily absorbed by the body instead of being excreted into urine. Relevant excerpts from this study are shown below:

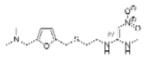
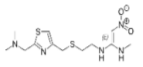
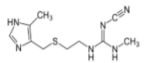
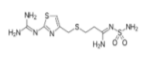
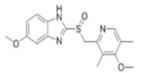
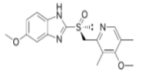
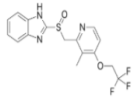
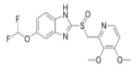
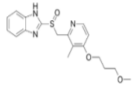
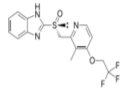
- Summary findings of study: "Following ranitidine intake, the urinary NDMA excreted over 24 h increased 400-folds from 110 to 47,600 ng, while total N-nitrosamines increased 5-folds. NDMA excretion rates after ranitidine intake equaled or exceeded those observed previously in patients with schistosomiasis, a disease wherein N-nitrosamines are implicated as the etiological agents for bladder cancer."

- Regarding urinary NDMA likely being a small fraction of total NDMA exposure in the body: "While urinary N-nitrosamine concentrations may more directly reflect systemic exposure, it is important to note that such estimates are conservative. Actual systemic NDMA exposure is likely much higher than that eliminated in urine, as previous studies have indicated a high metabolic conversion rate of NDMA (i.e. >99.9%) and therefore its low renal clearance (i.e. only ~0.05% excreted in urine)."

Ref.: US FDA Citizens Petition of Valisure

Alternatives to Ranitidine – not containing NDMA – are available

- Analysis of NDMA levels across common antacid medications.

Scientific Name (Tablets tested)	Brand (Lot#)	Structure	NDMA per tablet (ng)	Attachment B Data Reference #
Ranitidine (1x 150 mg tablet)	Zantac (7702406A)		2,978,551	18
Nizatidine (1x 150 mg capsule)	Axid (1290625A)		41,693	19
Cimetidine (1X 200 mg tablet)	Tagamet (9AE2576)		Not Detected	20
Famotidine (2x 40 mg tablets)	Pepcid (1805012732)		Not Detected	21
Omeprazole (2x 40 mg capsule)	Prilosec (19182878)		Not Detected	22
Esomeprazole (2x 40 mg capsule)	Nexium (C806922)		Not Detected	23
Lansoprazole (3x 30 mg capsule)	Prevacid (C807365)		Not Detected	24
Pantoprazole (2x 40 mg tablets)	Protonix (PAN18101)		Not Detected	25
Rabeprazole (4x 20 mg capsules)	AcipHex (BY33E009)		Not Detected	26
Dexlansoprazole (2x 60 mg capsule)	Dexilant (A27540)		Not Detected	27

Ref.: US FDA Citizens Petition of Valisure

Alternative safer treatment regimens to Ranitidine are widely used and marketed

Class	MOA	Examples
Gastric antacids	Partially neutralize gastric acid and inhibit pepsin (a proteolytic enzyme) activity both directly and by increasing pH, thus protecting the stomach mucosa. These agents must be taken frequently to maintain increased pH in the stomach.	Milk of magnesia (magnesium hydroxide)
H_2 receptor antagonists	Act specifically to competitively block the H_2 histamine receptors of parietal cells. They inhibit both basal and stimulated gastric acid secretion.	Cimetidine, Famotidine
Proton pump inhibitors	Inhibit the proton (H^+-K^+–ATPase) pump of the parietal cells in the stomach, thus inhibiting gastric acid (HCl) secretion into the lumen of the stomach.	Omeprazole, Lansoprazole, Rabeprazole
Mucosal Protective Agents	Thought to accelerate the healing of duodenal ulcers by forming a protective barrier over the ulcer base. It forms an ulcer-adherent complex with the proteinaceous exudate at the ulcer site. It is also thought to protect ulcers from pepsin.	Sucralfate
Prostaglandins	Promote protective mucus secretion from epithelial cells in the stomach and inhibit gastric acid secretion for gastric parietal cells.	Misoprostol
Drugs to eradicate *Helicobacter pylori*	Therapies (PPI with antibiotics) to reduce mucosal cell inflammation & destruction caused by *H. pylori* in the gastric epithelium	PPI + antibiotics

Ranitidine status in India is to monitor the impurities – but product recalls have not been instituted yet

- DCGI status: Sep 2019: DCGI asked manufacturers of Ranitidine API & formulations to verify their products and take appropriate measures to ensure patient safety after news of ranitidine contamination came in picture.
- Dr. V.G. Somani Drugs Controller General (India) said in a notification to all zonal / sub zonal offices of CDSCO that, "It has been reported that some ranitidine medicines, contain a nitrosamine impurity called N-nitrosodimethylamine (NDMA) at low levels. The NDMA has been classified by International Agency for Research on Cancer (IARC) as probably carcinogenic to humans."

Ref.: Pharmatutor.org

Ranitidine & PPI's import export data does not reveal a dip as yet

Total Exports – volume and value

Molecule	Q1 2020 Volume (Kg)	Q1 2019	Q1 2020 Value (USD)	Q1 2019
Ranitidine	197,975	H	4,820,566	H
Famotidine	69,776	L	5,148,334	L
Omeprazole	1,227,941	H	27,783,694	H
Pantoprazole	162,900	L	23,286,053	L

L: 2019 value was lower
H: 2019 value was higher

For Omeprazole exports in Q1 2019, the differences are too small to be significant

The import export data for 2020 does not reveal any drastic dip in the case of ranitidine as yet. However, many countries have already started banning its usage. The important aspect to note here is the **lack of root cause being identified** and the ability to be formed both *in vitro* and *in vivo*. Hence it is unlikely that NDMA levels will be controlled easily.

It is likely that unless root cause is identified and safeguards in terms of new processes and dosage forms are put in place to control NDMA formation within safe levels- this molecule will may not be able to continue in the market for long.

Ref.: Import Export Database

Chemistry behind the development of nitrosamine impurities

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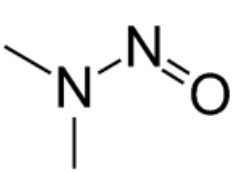
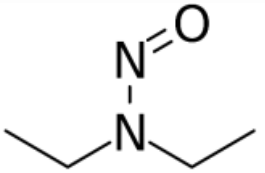
Nitrosoamines NDMA (N-nitrosodimethylamine) and NDEA (N-nitrosodiethylamine)

Why has NDMA become a buzz word?

- NDMA and NDEA are members of N-nitrosamines found in APIs, FDFs, food, beer, cured meats, rubber products, tobacco smokes and even in drinking water.
- There is a growing concern regarding the health effects associated with exposure to nitrosamines because of their potential carcinogenicity.
- In November 2019 WHO set limit for Nitrosoamines.



N- nitrosodimethylamine (NDMA)



N-nitrosodiethylamine (NDEA)

1989
µg/L levels of NDMA observed in Canada

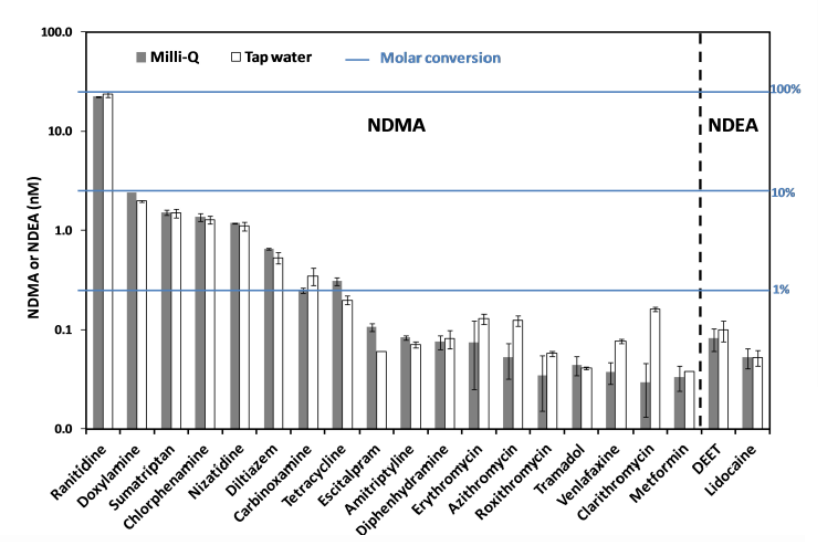
1998
NDMA found in water in US

2010
Health Canada issued guideline for NDMA in water 100 ng/Lit

2019
WHO set limit for NDMA
96 ng/Day

Study of Nitrosamine formation in various Drug Products, under specified conditions

What studies and reviews reveal about Nitrosamine formation potential, for selected Drug Products under specified conditions?



- Not only Ranitidine, many Drug Products lead to NDMA/NDEA.

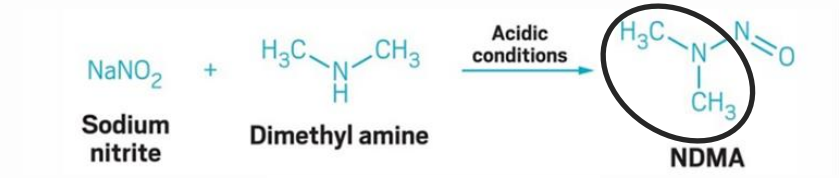
- Ranitidine, the first pharmaceutical which drew attention as a potential NDMA precursor with a high conversion rate upon chloramination (*Schmidt et al., 2006*).

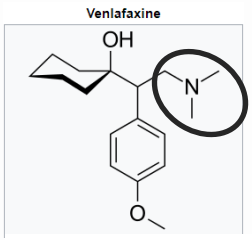
Comparisons with literature (Common conditions: pH = 7.0 ± 0.1, NH_2Cl = 28.4 mg/L, PPCPs = 25 nM, room temperature)

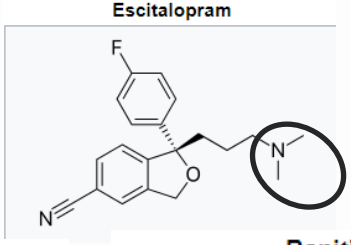
Compound	*Schmidt et al., 2006 (Drinking water, 7d)*		*Present data (Milli-Q® water, 24h)*		*Present data (Tap water, 24h)*	
	NDMA (ng/L)	Molar conversion	NDMA (ng/L)	Molar conversion	NDMA (ng/L)	Molar conversion
Ranitidine	1200	62.9 %	1665 ± 6	89.9 ± 0.3 %	1744 ± 82	94.2 ± 4.4 %
Nizatidine	91	4.9 %	88.0 ± 1.3	4.8 ± 0.1 %	82.7 ± 6.9	4.5 ± 0.4 %
Tetracycline	23	1.2 %	23.0 ± 1.6	1.2 ± 0.1 %	14.9 ± 1.0	0.8 ± 0.1 %

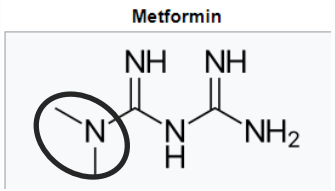
NDMA/NDEA Genotoxic impurities : What is common in Drug Products tested positive for NDMA?

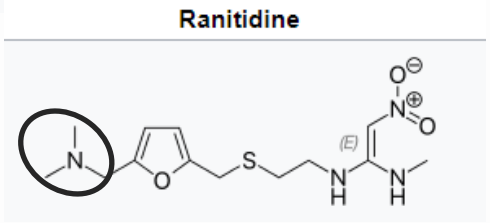
Who is responsible for NDMA? Structure? Process?











- Wherever there is a dimethyl/diethyl amine (DMA/DEA) group in API or wherever there is use of DMA/DEA, either in process or its derivative is used as an intermediate/reagent, it could encounter nitrites & there would be possibility of generation of NDMA/NDEA.
- Instrumentation is going to become more advanced to be able to detect these impurities in future.
- NDMA and NDEA belong to group of highly potent mutagenic carcinogens.

Analytical methods and tools of determination of NDMA

How one could detect NDMA?

- **GC/MS Headspace Chromatography Mass Spectrometry Approach** : This method is for ARBs (sartans).
- **Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine DS & DP :** FDA observed method for testing ARBs for nitrosamine impurities is not suitable for testing ranitidine because heating the sample generates NDMA. A LC-HRMS method was subsequently developed by the FDA to measure the levels of NDMA in ranitidine.
- **Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine DS & DP:** This method is a liquid chromatography-tandem MS (LC-MS/MS) method for the determination of NDMA in ranitidine drug substance and drug product. This triple-quad platform is more widely available than the LC-HRMS platform.
- **Rapid Detection Approach: Ultra-Performance Liquid Chromatography, Low Resolution Tandem Mass Spectrometry (UPLC- LR/MS/MS).**

There are many modern analytical tools. Technology is improving day by day to help patients stay away form NDMA. It is up to suppliers to invest in these technologies and ensure quality of the products.

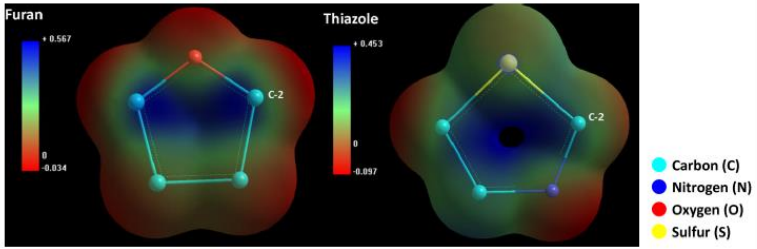
NDMA daily dosage and Limits and reasons for different levels of conversions to NDMA

What are the permissible limits of NDMA?

Active substance (max daily dose)	Max. daily intake (ng)	Limit (ppm)
Candesartan (32 mg)	96	3.00
Irbesartan (300 mg)	96	0.32
Losartan (150 mg)	96	0.64
Olmesartan (40 mg)	96	2.40
Valsartan (320 mg)	96	0.30
Nizatidine (300 mg)	96	0.32
Metformin ER (2000 mg)	96	0.05
Metformin IR (2550 mg)	96	0.04

Why there is difference in level of formation of NDMA?

- Chemistry plays very important role. For example:
- The furan ring of ranitidine has a symmetric structure and the C2 site is electrophilic due to oxygen, whereas, C2 site on the thiazole ring of nizatidine is nucleophilic because of the combined effects of nitrogen & sulphur.
- Hence, higher NDMA conversion from ranitidine than that from nizatidine.



What was the reason for the FDA action against ranitidine and what could happen next?

Why USFDA has specifically taken action against ranitidine and why other DS are treated differently?

Non assignable cause

- There is no answer today as to why NDMA develops in Ranitidine. Whether it degrades over a period of time? Whether it comes from the process? Whether it forms in the body? Nobody knows the answer, making it a "non-assignable cause".
- This could be more risky than valsartan, since in valsartan the cause of formation of NDMA impurity is known and measures have been taken by the manufacturers.
- USFDA , EDQM have taken actions against ranitidine.

What next?

DCGI has adapted wait and watch approach

- Product is in Indian market for decades.
- Studies on Indian populations are not reported in literature.
- DCGI perhaps would wait for more data on local population.

Root cause of NDMA in ranitidine is not known. Risky?

- Could it be controlled in FDF, below detectable levels?
- Answer is yes. With the help of modern analytical tools.

Options for suppliers

- US and EMEA have taken views. DCGI would assess the situation.
- Use this time to assign root cause for NDMA in Ranitidine.
- Proactively, reduce shelf life till analysis is complete.
- Generate data (design clinical studies) and submit to DCGI with risk benefit analysis without compromising patient safety.

Sidvim's Position

The impurity is a definite matter of concern from the patient safety perspective! The ability to detect impurities will improve with time as analytical instrumentation becomes more and more advanced. Therefore it is likely that many more of the older drugs will be subjected to such scrutiny going forward- and that new inventions will build safeguards at the discovery and development stage itself.

- The safety aspects in case of the generic sartans appear to have been **resolved** with both regulatory authorities and industry working closely together for the same. Necessary changes in API processes and additional testing to limit the NDMA, NDEA levels have been incorporated. The generic players have also executed a quick turnaround in adopting the new requirements.
- In the case on Metformin- the silver lining is the absence of the impurity in the API itself – as seen in the current status of testing. Hence, it argues that the formation of the impurity is at the finished dose manufacturing stage. The **identification of the root cause** is likely only a matter of time, experimentation and development of a suitable testing methodology. Once this is done safeguards can be put in place as needed. In our opinion therefore may not have a long term market impact and is likely to get resolved.
- The case of ranitidine is much more grave in the fact that the impurity is getting formed *in vivo* as well as *in vitro*. No root cause for *in vitro* formation of the impurities has been identified as yet. The Stanford *in vivo* study in humans after oral dosing reveals urinary levels that are inordinately high. Hence this would be a matter of concern even going forward. The prognosis for this molecule appears to be dark in our opinion and it will likely be eliminated from the market - unless ways and means to circumvent both *in vivo* and *in vitro* formation of the impurity are established and patient safety is not compromised.

Thank You!

We welcome questions! For more information please contact:

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