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EDITORIAL

Carcinogenic Impurities in Generic Sartans: An Issue of Authorities' Control or a Problem with Generics?

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Abstract

The recent flood tide of recalls of sartan generics due to carcinogenic impurities has brought to the forefront the issue of the safety and efficacy of generic drugs. Several of these issues are discussed in this editorial. ***Rhythmos 2019;14(2):23-26.***

Key Words: hypertension; sartans; angiotensin receptor blockers; generics; drug excipients; carcinogens; drug recalls

Abbreviations: NDEA = N-nitrosodiethylamine; NDMA = N-nitrosodimethylamine; NMBA = N-Nitroso-N-methyl-4-aminobutyric acid

Angiotensin-receptor blockers (ARBs) or sartans are among the most widely used medicines for hypertension and heart failure. A lot of commotion has been raised recently over the problem of successive global recalls of several generic preparations of ARBs ("sartans") because of carcinogenic impurities (three substances discovered to date: NDMA, NDEA and NMBA; see discussion below) detected initially in valsartan products by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) which issued recall orders, while other authorities followed closely with similar recalls. [1, 2] If one resorts to Wikipedia (https://en.wikipedia.org/wiki/Valsartan), one will find the following excerpt about this serious health problem:

"On July 6, 2018, the EMA recalled certain batches of valsartan and valsartan/HCT film-coated tablets distributed in 22 countries in Europe, plus Canada.[26] Zhejiang Huahai Pharmaceutical Co. (ZHP) in Linhai, China manufactured the bulk ingredient contaminated by N-nitrosodimethylamine (NDMA), a carcinogen. The active pharmaceutical ingredient was subsequently imported by a number of generic drug-makers, including Novartis, and marketed in Europe and Asia under their subsidiary Sandoz labeling, and in the UK by Dexcel Pharma Ltd and Accord Healthcare.[26] In Canada, the recall involves 5 companies and a class action suit has been

initiated by a private law firm.[27][28] Authorities believe the degree of contamination is negligible, and advise those taking the drug to consult a doctor and not to cease taking the medication abruptly. On July 12, 2018, The National Agency of Drug and Food Control (NA-DFC or Badan POM Indonesia) announced voluntary recalls for two products containing valsartan produced by Actavis Indonesia and Dipa Pharmalab Intersains.[29] On July 13, 2018, the FDA announced voluntary recalls of certain supplies of valsartan and valsartan/hydrochlorothiazide in the U.S. distributed by Solco Healthcare LLC, Major Pharmaceuticals, and Teva Pharmaceutical Industries.[30] Hong Kong's Department of Health initiated a similar recall.[31] On August 2, 2018, the FDA published two lengthy, updated lists, classifying hundreds of specific U.S. products containing valsartan into those included versus excluded from the recall.[32] A week later, the FDA cited 2 more drugmakers, Zhejiang Tianyu Pharmaceuticals of China and Hetero Labs Limited of India, as additional sources of the contaminated valsartan ingredient.[33] In September the FDA announced that retesting of all valsartan supplies had found a second carcinogenic impurity, N-nitrosodiethylamine (NDEA), in the recalled products made by ZHP in China and marketed in the U.S. under the Torrent Pharmaceuticals (India) brand.[34] According to a 2018 Reuters analysis of national medicines agencies' records, more than 50 companies around the world have recalled valsartan mono-preparations or combination products manufactured from the tainted valsartan ingredient. The contamination has likely been present since 2012 when the manufacturing process was changed and approved by EDQM and FDA authorities. Based on inspections in late 2018, both agencies have suspended the Chinese and Indian manufacturers' certificates of suitability for the supply of valsartan in the EU and the US.[35] Although the brand name Diovan was recalled due to the presence of the contaminant NDMA, not all forms of valsartan are recalled or contaminated.[36]"

N-nitroso-dimethyl-amine (NDMA) is an organic chemical that forms in both industrial and natural processes, and has been used to make liquid rocket fuel, softeners, and lubricants.[2] NDMA is a known animal carcinogen. The US Environmental Protection Agency found a link between NDMA and liver cancer, but NDMA exposure may also be associated with bladder, renal, pancreatic, intestinal, colon, and stomach cancers. The presence of this impurity in generic sartan preparations was attributed to changes in the manufacturing process of the active substance effected since 2012.[3] The impurity was found incidentally while performing tests other than routine batch-release specification assessments.

Unfortunately, this calamity was not limited to generic valsartan preparations and two more sartans, irbesartan and losartan, were found to be plagued by the same impurities. Thus, the recall was subsequently expanded to these other sartan products as impurities were detected in the irbesartan API (active pharmaceutical ingredient) produced by India's Aurobindo and in losartan products made using an API from China's ZHP. Thus, the presence of carcinogenic and mutagenic impurities in the ARB drugs containing tetrazole ring has led to worldwide product recalls.[1] This huge health problems points to a gap in current pharmaceutical industry practice that escaped Drug controlling authorities' attention.

Recently, to appease the public's concern over this widespread problem, the FDA published a list of 40 "safe" sartan generics free of carcinogen impurities (www.fda.gov/Drugs/DrugSafety/ucm634620.htm). Furthermore, the FDA has added a site with Qs&As on this story, i.e. about impurities found in certain generic ARB products (https://www.fda.gov/Drugs/DrugSafety/ucm626122.htm). On 1/2/2019, the EMA issued a directive for manufacturers regarding the allowed NDEA or NDMA impurities in their products (< 0.03 parts per million) and called them to review their manufacturing processes to avoid presence of nitrosamine impurities, allowing them a 2-year transition period to comply (https://www.ema.europa.eu/en/news/sartan-medicines-companies-review-manufacturing-processes-avoid-presence-nitrosamine-impurities).

Columnists writing about this sartan contamination story indicate "So we're going to have to think about the way that synthetic routes in the generic API business are monitored" (https://blogs.sciencemag.org/pipeline/archives/2019/01/04/the-sartan-contamination-story). Unfortunately, the story does not seem to come to a close soon, as more recalls continue to be issued, either

voluntarily by manufacturers or when detected by Authorities, reflected in the title "Another Day, Another ARB, Another Contaminant" recently posted when a third carcinogenic nitrosamine impurity, N-Nitroso-N-methyl-4-aminobutyric acid (NMBA), was discovered in sartan generics (losartan lots) (https://www.medpagetoday.com/cardiology/hypertension/78320). As per the information about this impurity that one can find in PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/61445-55-4#section=Biological-Test-Results), studies have shown that NMBA is a known animal carcinogen as it can cause cancer in rats such as bladder cancers, which renders it a potential human carcinogen. What will happen next in this saga of sartan recalls remains to be seen. For sure, this has been an overly costly oversight on part of regulatory Authorities with an ongoing impact (https://pharma.nridigital.com/ pharma_feb19/a_costly_oversight_the_ongoing_impact_of_the_valsartan_recall).

In the end, the question arises whether the problem is with the Authorities' control over the manufacturers or it is a problem inherent to the manufacturing process of the generic drugs. In the case of sartans, carcinogenic impurities came from multiple API manufacturers (Table 1) that synthesize related sartan molecules and then sell them to companies that make the final tablets that reach consumers (https://pubs.acs.org/doi/10.1021/cen-09708-scicon1). The four API manufacturers that produced the impure sartans are Zhejiang Huahai Pharmaceutical (ZHP) based in China and Hetero Labs, Mylan Laboratories, and Aurobindo Pharma, all based in India. First, ZHP was forced to disclose the presence of the NDMA impurity after receiving a complaint from a drug company customer in June 2018 about an unidentified impurity in valsartan API that the customer received from ZHP. Meanwhile, the FDA's scientists estimate that patients had been taking the generic drugs from the recalled batches for 4 years before they were actually recalled; and by ingesting the carcinogenic impurity continuously for 4 years, a new cancer case may arise among 8000 recipients.

Generic drugs are widely used worldwide to decrease pharmaceutical expenditures for patients and payers. [3] All relevant properties of the active ingredient in a given generic should be identical with those of the original brand-name drug. However, drug excipients may differ greatly. To ensure pharmacokinetic similarity between the generic and the branded medicine, generics should undergo comparative bioavailability and bioequivalence studies in humans before being licensed. Several issues and concerns regarding the reliability of this process have been voiced, [4] while the FDA has recognized the problems related to the initial regulations about this process and changed them in 2004. [5] Some of us remember the major problem that emerged with the initial introduction of a generic formulation of the classical quinidine gluconate drug available as "Quinaglute" in the US, when our patients who were previously controlled on the branded drug were returning with arrhythmia recurrences to find out that the only reason for this was a recent switch to the generic formulation.

Table 1. Recallled Sartan Generics, Detected Carcinogenic Impurities and Companies Involved

Sartans	*Valsartan, Irbesartan, Losartan*
Carcinogenic Impurities	*NDMA, NDEA, NMBA*
Companies	*Zhejiang Huahai Pharmaceutical Co. (ZHP), Linhai, China*
	Novartis, Switzerland
	Sandoz, Germany
	Mylan Laboratories, US
	Dexcel Pharma Ltd, UK
	Accord Healthcare, UK
	Actavis, UK & Indonesia
	Dipa Pharmalab Intersains, Indonesia
	Zhejiang Tianyu Pharmaceuticals, China
	Hetero Labs Limited /Camber, India
	Torrent (AvKare, Legacy) Pharmaceuticals, India
	Aurobindo Pharma, India & US
	Solco Healthcare LLC / Prinston Pharmaceutical Inc, US
	Major Pharmaceuticals, US
	Teva Pharmaceutical Industries, Israel & US
	Pro Doc, Laval, QC, Canada
	Pfizer, US & Japan
	Camber Pharmaceuticals, US
	ScieGen Pharmaceuticals (GSMS), Singapore

NDEA = N-nitrosodiethylamine; NDMA = N-nitrosodimethylamine; NMBA = N-Nitroso-N-methyl-4-aminobutyric acid

Further to the problems related to generics, there is the issue of *pseudogenerics or authorized generics*, considered to be "exact copies" of the brand-name drug, for which, health authorities do not require in vivo comparative bioavailability tests to license them. Pseudogenerics or authorized generics are commonly marketed by brand-name manufacturers to maintain market share after loss of market exclusivity. [6] Some have even proposed comparisons to be conducted of authorized generic products to other generic drug products to serve as useful routine assessments of the performance of the generics relative to brand-name products in real-world settings. [6] However, there are still problems even with this type of generics; in two of these pseudogenerics, carcinogenic impurities (NDMA) were detected and led to their recall; these were NDMA-contaminated generic valsartan formulations manufactured in Canada by Sandoz Valsartan and Pro Doc. [3]

In ***conclusion***, the saga of sartan recalls due to carcinogenic impurities detected in a large number of tainted sartan products continues and brings about the issue of reliability of the industry of generics with problems identified in the manufacturing process and the steps and measures taken, or their lack thereof, by the Regulatory Authorities in controlling this process and ensuring the safety and efficacy of the generic medicines.

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