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Letter to the Editor

Carcinogen tainted generic drugs: a matter of concern

Sir,

The burden of non-communicable diseases is progressively on a rise across the globe with India contributing to a substantial quantum.[1] Nearly 63% of total deaths in India are due to non-communicable diseases, of which 27% are due to cardiovascular diseases (CVDs). High blood pressure is among the most important risk factors for CVDs. Data (from 1950 to 2014) on hypertension in the Indian populace, revealed a high overall prevalence of 29.8% (95% CI 26.7-33.0), showing a constant rise and a marked increase in urban (33.8%) population than in rural (27.6%).[2] With the increasing prevalence of hypertension, the drug market for antihypertensive drugs in India has taken a gigantic leap over recent years. Based on a large nationally representative dataset for the private pharmaceutical market which was collected by IQVIA (one of the largest healthcare data science company companies) reports that Indian hypertension drug market grew at a compound annual growth rate (CAGR) of 6.9% from the year 2016-2018, with a total of 21,066 million anti-hypertensive pills sold in the year 2018 at a value of 87.36 billion. A total of 182 different antihypertensive drugs were sold in India in 2018, out of which 134 were fixed-dose single-pill combinations (SPCs). Two drug SPCs had the largest number of permutations and combinations (>105) those that were sold under 1000 brands and generic preparations by several manufacturers.[3]

In June 2018, an active pharmaceutical ingredient (API) manufacturer in China notified European authorities about the undetected purity, N-nitrosodimethylamine (NDMA, also known as dimethyl-nitrosamine) in the valsartan API, manufactured at its site in Chuannan. NDMA is a known genotoxic and carcinogenic agent in animals and a single dose of less than a milligram can mutate mice cells and stimulate tumours.[4] It is classified as class 2A carcinogen (probably carcinogenic) in humans by the International agency for research on cancer (IARC, WHO) and 2 grams can kill a person in days.[5] On demanding an investigation report on the root cause of the presence of NDMA, the manufacturer indicated that NDMA is formed at the tetrazole ring-forming step in the valsartan API manufacturing process (including quenching of remaining azide with nitrous acid). In July 2018 United States (US) Food and Drug Administration (FDA) announced the presence of NDMA in valsartan and started overseeing the recall of drugs from three pharmaceutical companies, who bought their active ingredient for valsartan from Zhejiang Huahai Pharmaceutical Co. Ltd. The recall has been expanded 51 times to include two more related antihypertensives viz. irbesartan and losartan. Some of the contaminated batches of valsartan contain much as 17 micrograms of NDMA in a single pill.[6] Angiotensin-receptor-blockers (ARBs) has been recalled in the United Kingdom in June and August by the medicines and healthcare products regulatory agency (MHRA), which also confirmed three possible azido contaminants in cardiac medicines. Other European nations like France, Switzerland and Ireland have also recalled ARBs containing azido impurities. Similarly in Canada, irbesartan-containing products were withdrawn in June 2021 due to high levels of azido impurities.[6] Not just low- and middle-income countries, almost 90% of all medications prescribed in the US and around 50% in India are generics because they are a cost-effective alternative. The generic companies get approval based on the evidence of average bioequivalence in drug absorption with that of the innovator drug by conducting bioavailability/bioequivalence (BA/BE) studies. If two drug products are shown to be bioequivalent, it is assumed that they will generally reach the same therapeutic effect or are therapeutically equivalent. With the safety and efficacy data of the innovator being in place, the regulatory scrutiny is far too less, right from the start. Further, with the US holding around 42% of manufacturing sites of the world saw a 7% dip in the domestic drug quality surveillance inspections by FDA in the financial year 2019 as compared to 2018.[7] As of 2020, 13% of foreign manufacturers were reported to have never had an inspection since doing business with the US. Another 17% have not been inspected for over five years.[8] To add to the misery, the effect of the pa pandemic continues to put inspections on hold. One of the manufacturing facilities in the region of Sangareddy, India, is amongst the ten sites registered with the FDA for the manufacture of medicines. It was last inspected in 2018 and scored the lowest agency's rating. Similarly in November 2019, a well-known MNC's valsartan API manufacturing unit in Andhra Pradesh was issued a warning letter by the US FDA.

Many other manufacturers recalled 40 batches of ARBs in May 2020, the figure has now dramatically increased to 49 batches of specific losartan tablets. To our dismay, the representative from the parent firm only released a statement that the active component was manufactured by some other company which cannot be identified. NDMA is not the only concern, many other manufacturers reported that DIPNA (NDIPA, NDIA) and EIPNA (NEIPA/NIEA) can also potentially be formed during the generation of valsartan due to the use of N, N-diisopropyl ethyl-N-ethylamine (DIPEA), a tertiary amine, in the synthesis of

valsartan. European authorities authorized and limit the daily intake of valsartan (320 mg) and maximum concentration for DIPNA, EIPNA, and the corresponding concentration of NDEA to 26.5 ng/day and 0.08 ppm, respectively. April 2020 also witnessed the recall of NDMA-tainted zantac and other generic ranitidine, used for the treatment of heartburn from the market. Value, an independent testing facility, in September 2019 filed a citizen petition after tipping off regulators to NDMA in their medicine.[10] They discovered that ranitidine is the active component in zantac, and convert to NDMA over time or when kept at raised temperatures. It was not just ranitidine, metformin a commonly used diabetic medication was also recalled for containing NDMA or similar compounds. Pfizer in July 2021 did a voluntary nationwide recall of twelve lots of varenicline, a smoking cessation medication due to the presence of nitrosamine (N-nitroso-varenicline), above the established acceptable daily intake (ADI) level.[11] Another pharmaceutical company Macleod's found nitrosamines called 1-methyl-4-nitosopiperazine (MNP) and 1-cyclopentyl-4-nitrosopiperazine (CPNP) in the tuberculosis drugs rifampicin and rifapentine. Elevated levels of MNP was found both in rifampicin and rifapentine, but in rifampicin, these levels were found above the acceptable intake level of 0.16 ppm while Rifapentine samples had another nitrosamine called 1-cyclopentyl-4-nitrosopiperazine (CPNP) at levels above the acceptable intake limit of 0.1 ppm.[12]

It is thus imperative that we rise to the cause and be vigilant because this crisis could be like peeling an onion. More the regulatory agencies take a closer look into the generic brands; more names might join the queue. This is not the end; this might just be the beginning.

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