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Short communication

Root causes for presence of nitrosamine impurities in active pharmaceutical substances and finished pharmaceutical products

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Introduction

Nitrosamines, such as NDMA (*N*-nitrosodimethylamine), NDEA (*N*-nitrosodiethylamine) and NMBA (*N*-nitroso-*N*-methyl-4-aminobutyric acid), are organic compounds containing the nitroso functional group. According to ICH M7 (R1), nitrosamines are identified as a "cohort of concern" or Class 1 impurities (known mutagenic carcinogens). The International Agency for Cancer Research (IARC) categorized nitrosamines as "probably carcinogenic to humans" (2A-group) (ICH M7 (R1), 2018).

Detection of nitrosamines impurities in valsartan, in July 2018, actualized the possible presence of these impurities in other active substances and finished pharmaceutical products (EMA, 2018). The presence of nitrosamines impurities has also been found in other Angiotensin II receptor blocker (ARB) active pharmaceutical ingredients, containing a tetrazole ring in their structure such as losartan and irbesartan. More recently, *N*-nitrosodimethylamine have been identified in certain histamine-2-blockers (ranitidine, nizatidine) and in an antihyperglycemic medication metformin. Since then, more active substances and medicinal product batches contaminated with nitrosamines have been recalled (EMA, 2019).

Root causes for presence of nitrosamine impurities

After the recall of numerous batches of sartans and ranitidine, the question is: what are the main routes of N-nitrosamine contamination of active substances and finished products? The first route is the use of contaminated starting material in the manufacturing process, such as solvents, reagents, catalysts as well as recycled materials. The second source of contamination is formation of nitrosamine impurities during manufacturing process from an intermediate or from the active ingredient itself (EMA, 2020). Theoretically, the formation of nitrosamine impurities in pharmaceuticals is possible to occur when a precursor amine coexists with a nitrosating agent under suitable conditions for the reaction of nitrosation, such as acidic conditions for nitrite.

The tetrazole ring appear to be of key importance for desired angiotensin receptor antagonist effects of sartans at the molecular level and is present in five of eight sartans that have been widely marketed. The process of tetrazole ring formation at the very end of the synthesis has been proposed to be the root of nitrosamines contamination of sartans. The synthesis of the tetrazole ring involves the reaction of nitrile with organic azides, most commonly tributyltin azide (Bu_3SnN_3), sodium azide (NaN_3) and trimethyltin azide (Me_3SnN_3) (Baumann et al., 2011).

In case of valsartan, data show that its tetrazole ring was formed using Bu_3SnN_3 as the azide source and *N,N*-dimethylformamide (DMF) as a solvent, the other necessary factor that contributed to valsartan contamination with nitrosamines. Due to their human toxicity potential, more amount of azides remaining after the formation of the tetrazole ring was quenched with nitrite under acidic conditions. Dimethylamine as a secondary amine present either as an impurity or as a possible degradation product of DMF, reacts with nitrite and serves as a amine source for *N*-nitrosidimethylamine

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(NDMA), the first nitrosamine that led to valsartan recalls (Snodin and Elder, 2019). Similarly, the presence of NDEA and NMBA in valsartan is the result of a reaction of nitrites with TEA (triethylamine), or NMP (*N*-methyl-2-pyrrolidone), respectively. The synthetic pathways of losartan, irbesartan and candesartan also rely on azide-nitrile reaction to form tetrazole ring and thus are exposed to the same risk factors for nitrosamine contamination (EMA, 2020).

While in sartans nitrosamines are formed by chemical reaction during the synthesis of the active substance, as a result of the application of azide in combination with an unsuitable solvent choice, the situation with ranitidine is more complex. Ranitidine molecule is very unstable and contains both a nitrile and a dimethylamine, which combination leads to formation of *N*-nitrosodimethylamine. A potentially concerning possibility is the increasing level of NDMA in ranitidine over time, when the tablets are stored at temperatures higher than room temperature (White, 2020).

Conclusion

Knowing their mutagenic and carcinogenic effects, the presence of nitrosamines in active pharmaceutical ingredients must be limited. All this implies the need primarily for identifying the main reasons for contamination with these impurities and then developing the appropriate methods for their detection and quantification. Medicine regulatory authorities are taking steps to solve this problem, but also we need to highly improve our knowledge in this area and prevent future human exposure with these impurities through medicines.

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