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Hunt for nitrosamines in medicinal products

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Some time ago

19 September 2019
EMA/189634/2019

Information on nitrosamines for marketing authorisation holders

Request to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients

Step 1
Risk evaluation

Step 2
Confirmatory testing

Step 3
Changes to the marketing authorisation

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

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Nitrosamines

Nitrosating agent + amine

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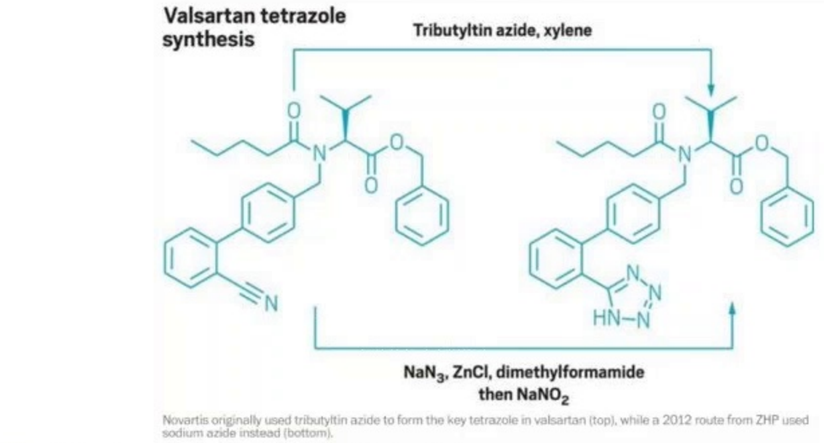
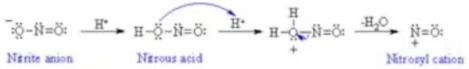
What has been learnt?

- Initial concerns relating to N Nitrosamines related to synthesis

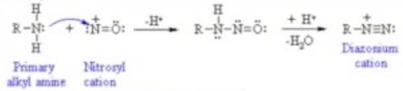


Novartis originally used tributyltin azide to form the key tetrazole in valsartan (top), while a 2012 route from ZHP used sodium azide instead (bottom).

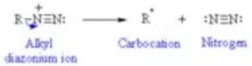
- The actual nitrosation reagent is the nitrosyl cation, NO^+ which is formed *in situ*:



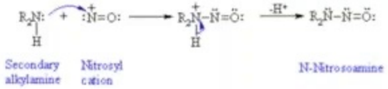
- The nature of the product depends on the nature of the initial amine
- **Primary alkyl or aryl amines** yield diazonium salts (hence the **diazotisation reaction**)



- Alkyl diazonium salts are very unstable and yield carbocation-derived products by loss of the very good leaving group, N_2:



- **Secondary alkyl or aryl amines** yield N-nitrosoamines:



FiercePharma

The FDA has opened a new front on its battle to clear the U.S. drug supply of blood pressure medicines of potentially carcinogenic impurities. It has cited Lantech Pharmaceuticals, which recovers solvents and makes API intermediates. (FDA)

The FDA upended the entire landscape for makers of sartan-based blood pressure medicines after finding some contained potential carcinogens. Now, the FDA is trying a new tack.

The FDA this month issued a warning letter to an Indian solvent recovery firm whose products may have contributed to some of the tainted drugs. The letter to Lantech Pharmaceuticals says its processing methods left open the chance for cross-contamination of solvents that contained the impurities known as N-Nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA).

"Given that your firm does not maintain logbooks or documentation demonstrating product use or cleaning associated with the use of these tanks, there is a potential for all products manufactured at your facility to contain nitrosamines through mix-ups or cross contamination," the warning letter says. It follows a March inspection at the facility in Ranastalam.

- Also related to contamination

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