ChemWerth

GENOTOXIC AND NITROSAMINE IMPURITY

SITUATION

Recent, unexpected findings of nitrosamine impurities in drugs such as angiotensin II receptor blockers, ranitidine, nizatidine and metformin have raised RED FLAGS at the FDA. Additional scrutiny is being applied to APIs, given the potential carcinogenic nature of nitrosamines.

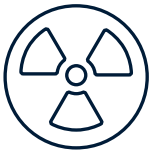
The term nitrosamine describes a class of compounds having the chemical structure of a nitroso group bonded to an amine. The compounds can form by a nitrosating reaction between amines (secondary, tertiary or quaternary amines) and nitrous acid (nitrite salts under acidic conditions). These are considered a more potent category of genotoxic impurities.

PROBLEM

General root causes for nitrosamines in APIs are possible in the presence of secondary, tertiary or quaternary amines and nitrite salts under acidic conditions. Nitrite salts may form nitrous acid, which can then react with an amine to form a nitrosamine. Nitrite salts can also carry over into subsequent steps, potentially forming nitrosamines later in the process. In addition, amines may be present in the manufacturing process either via being part of the API or by being intentionally added as reagents or catalysts.

But that's not all ... contamination of vendor supplied raw materials can be a source of nitrosamines, as can recovered solvents, catalysts and reagents. The quenching process in the main reaction mixture can also generate nitrosamines.

And let's not overlook the possibility that the source of the problem could be in a lack of manufacturing process optimization and controls.



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IMPLICATIONS

To comply with the recent FDA nitrosamines guideline published in September 2020, a nitrosamine impurity risk assessment for all APIs is required to be completed. Although the FDA nitrosamine guideline only refers to the nitrosamine risk as being from chemically synthesized APIs, the recent EMEA nitrosamine guidelines further expanded it to include fermentation APIs.

If a nitrosamine(s) needs (need) to be listed for the drug master file specifications and/or the manufacturing process is revised to reduce or eliminate nitrosamines, then a submission of an amendment to the DMF is required.

RECOMMENDATIONS

ChemWerth recommends that suppliers and manufacturers take our lead and proactively perform genotoxic and nitrosamine impurity risk assessments for all APIs.

ChemWerth has implemented procedures with our API manufacturers to conduct nitrosamine impurity risk assessments; following up these assessments with appropriate actions to reduce, prevent or control nitrosamines in the Active Pharmaceutical Ingredient.

If a risk of nitrosamines is identified, confirmatory testing of three batches should be conducted using appropriately sensitive/validated methods. ChemWerth works with our API manufacturers to identify the root cause for the formation of the nitrosamine(s) and determine if the process can be optimized to reduce these impurities below the acceptable limits.

ChemWerth recommends that API manufacturers optimize the manufacturing process for APIs during the development of the route of synthesis in order to minimize the formation of nitrosamines. API manufacturers should follow the principles outlined in ICH Q11 Development and Manufacture of Drug Substances.

If a nitrosamine is detected above the LOQ, the API supplier should work with the manufacturer to develop a strategy to ensure the nitrosamine level remains within the Acceptable Intake Limit (AI). In this case, an appropriate release specification should be set and tested with an appropriately validated method for each batch release.

If the nitrosamine impurity risk assessment determines there is no potential for nitrosamines, there is no need to perform additional testing.

ChemWerth recommends that suppliers and manufacturers take our lead and **proactively perform genotoxic and nitrosamine impurity risk assessments for all APIs.**

If a risk of nitrosamines is identified, **confirmatory testing of three batches should be conducted using appropriately sensitive/validated methods.**

To conduct your own nitrosamine risk assessment, email us at sales@chemwerth.com for a copy of our Nitrosamine Risk Assessment Questionnaire

REFERENCES

M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018).

Control of Nitrosamine Impurities in Human Drugs (Feb 2021).

European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5 (3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines (Feb 2021).

Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (January 2020).

There is simply no substitute for experience.
Trust your ANDA to an expert.

CHEMWERTH