Nitrosamine contamination policy for APIs

N-Nitrosamines are a class of substances of concern to international regulators and the pharmaceutical industry. This is because many nitrosamines are highly potent mutagenic agents that have been classified as probable human carcinogens.

The potential for the presence of nitrosamines was first highlighted in 2018, in conjunction with the angiotensin-II receptor blocker valsartan. Since that time, it has become clear that there exist multiple paths by which nitrosamine contamination may occur. These include, for example: carry-over from primary and secondary synthetic pathways; side-reactions with the solvents and reagents used; side-reactions with contaminants within the solvents and reagents used; degradation; and cross-contamination from recycled materials. This list is not exhaustive, but illustrates the complexities of ensuring pharmaceuticals are nitrosamine free. It also highlights the difficulty in pre-supposing a particular active pharmaceutical ingredient (API) should be free of nitrosamine contamination based on its chemical structure.

For this reason, in April 2020 PQT/MED, in line with other international regulators, called for manufacturers to undertake a risk evaluation of all APIs currently submitted to PQT/MED (please refer to https://extranet.who.int/pqweb/news/manufacturers-conduct-risk-assessments).

In line with international practice this approach involved a three-step process.

- Step 1: Risk Evaluation for the potential presence of nitrosamines.
- Step 2: Confirmatory Testing if a potential risk was identified.
- Step 3: Updates to the relevant authority regarding mitigation strategy, if the presence was confirmed.

As a logical extension of this request, any new APIMF procedure applications, or new API Prequalification applications submitted since 1 January 2021 are expected to include a completed nitrosamine risk assessment report and to have incorporated any relevant information within the relevant subsections of the module 3.

In addition, since changes to the preparation or storage of an API may affect the potential for the presence of nitrosamines, PQT/MED also expects that manufacturers have considered what effect the changes proposed have had on the potential for nitrosamine contamination. In this respect, the API Amendment Guidance has been recently revised to include this.

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