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Nitrosamines: Authorities' Expectations and Typical Mistakes

by Sabine Paris, PhD

"Contaminants in medicinal products – focus on nitrosamines" was the title of an online training course organised by the German FORUM Institute on 12 November 2021. Four renowned experts from the authorities, industry and consulting shed light on all aspects of nitrosamines that play a role in the life cycle of a medicinal product: Regulatory requirements, development, responsibility of the manufacturer and suppliers as well as analytics and GMP supervision.

*Subscribers to the online knowledge portal **GMP Compliance Adviser** read the full report with the first update in 2022. This text is an excerpt on the activities of the GMP supervising authorities.*

Franz Schönfeld, PhD, GMP inspector at the District Government of Upper Franconia, presented the activities and expectations of his authority on the subject of nitrosamines.

He reported on the very first "nitrosamine case" in Germany in June 2018, which affected a pharmaceutical entrepreneur based in Northern Bavaria. In constant exchange with the German Federal Institute for Drugs and Medical Devices (BfArM) and the EMA, European and international measures were agreed and recommended (rejection of the affected batches of the finished medicinal product). In parallel, analytical investigations and toxicological assessments were carried out. The impurity was identified as nitroso-dimethylamine (NDMA). In early July 2018, all finished drug batches containing the active ingredient valsartan, which had been manufactured by Zhejiang Huahai Pharmaceuticals in China, were recalled across Europe. The Chinese active ingredient manufacturer was listed in 160 marketing authorisations.

"The challenge in chemical synthesis is isolating the active ingredient."

NDMA is formed during the synthesis of valsartan from the added reagents DMF and sodium nitrite at acidic pH values. Sodium nitrite is added to destroy the excess sodium azide (necessary for the synthesis of the tetrazole ring). This is called "quenching". The nitrite reacts with secondary amines (such as DMF) to form nitrosamines. To isolate the valsartan as nitrosamine-free as possible, the different polarity of the individual ingredients is exploited. After adding water and MTBE (methyl tert-butyl ether), two phases are formed. The non-polar phase with MTBE and valsartan is at the top. The polar phase with DMF and water is at the bottom. Here it is important to pay attention to a clean phase separation (no emulsion!).

The supervisory authorities expect the pharmaceutical manufacturer to carry out a structured and sound risk identification and analysis. Cause-effect diagrams and fault tree analyses can be used as tools. A risk analysis can be performed using FMEA, for example. The point is to evaluate the initial risk. How does the assessment change when risk-minimising measures are taken? But as long as the possible risk is not determined,

the worst case must be assumed.

The probability of occurrence of a nitrosamine contamination can only be reduced by changing the manufacturing process. The probability of detection increases only when a sufficiently sensitive and validated analytical method has been developed.

Good remedy: batch rejection

A suitable, temporary measure when identifying a possible risk is batch rejection. This is an internal company measure that does not leak to the outside and is also reversible. The rejection can be lifted again if further data and assessments do not confirm the risk.

The risk control measures must be agreed with the authorities. The risk control must be adapted in each case when new data/knowledge is available.

Typical errors

"The supplier qualification of active ingredient manufacturers is often only carried out superficially or audit reports of poor quality are purchased", Franz Schönfeld complains. However, the drug manufacturer is obliged to have detailed information on the manufacturing process of the active ingredient and to qualify and regularly audit its active ingredient manufacturer. This was also emphasised again by the EDQM in 2018. In practice, active pharmaceutical ingredients can actually only be obtained from manufacturers who disclose their manufacturing process to their customers and maintain a good exchange of information.

The more drug manufacturers actually look at active ingredient syn-theses in detail on site, the better the manufacturing processes will become.

The drug manufacturer should also take a closer look at the analytical method validation reports. Limit of detection (LoD) and limit of quantification (LoQ) may have been calculated incorrectly (e.g. wrong ranges chosen for the signal-to-noise ratio in order to obtain embellished figures).

The method may be validated on paper, but e.g. the recovery rate was still not determined. However, this is relevant, since a too low recovery rate can also simulate falsely low nitrosamine values. A change of the extraction agent can, for example, make a difference of 25% in the recovery and thus also in the analytical result.

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