

## **Nitrosamines: Swissmedic Guidance Requires New GMP/API Focus**

[Andreas Balsiger Betts](#)

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Nitrosamines are chemical compounds used in the production of most rubber products, as well as some pesticides and cosmetics. They are abundant in cigarette smoke and can also be found in beer and food preserved with nitrites, such as fish, meat and cheese products. Nitrosamines are known to cause cancer in mammals, and it is widely suspected that they are carcinogenic for humans.

In mid 2018, national competent authorities (NCAs) around the globe learned about the contamination of Valsartan with a certain type of nitrosamine. Valsartan is an active pharmaceutical ingredient (API) belonging to the group of sartans, or angiotensin II receptor blockers, and used in certain antihypertensive drugs produced by a Chinese API manufacturer.

Until August 2018, Swissmedic, the Swiss agency for therapeutic products, discovered contaminated Valsartan in batches of 10 different medicinal products with a Swiss marketing authorization. As a consequence, Swissmedic recalled the concerned products, tested all other medicinal products containing Valsartan and requested that samples of all future batches be submitted to Swissmedic's laboratory to be tested before being put on the market.

Not long after, in November 2018, NCAs became aware that in addition to Valsartan, other sartans supplied by API manufacturers were contaminated with new types of nitrosamines. This led to another series of precautionary measures, such as requesting that marketing authorization holders (MAHs) re-evaluate the quality assessment of their products in order to guarantee their compliance with good manufacturing practices (GMPs) and fixing limits for nitrosamines in medicinal products. In Switzerland, these limits are provisional until the end of 2020. As of January 1, 2021, APIs used in medicinal products will have to be free of nitrosamines.

In its guidance, published on November 15, 2019, Swissmedic reminds MAHs that it is their responsibility to ensure that their medicinal products are manufactured in accordance with GMP. Furthermore, Swissmedic — following closely the HMS' guidance but setting tighter timeframes — requests that MAHs take the following preventative measures:

- Risk assessments: MAHs are required to perform a risk assessment for all their products containing synthetic APIs until May 15, 2020 (i.e., 10 days earlier as demanded by the HMA). Related templates are provided by the HMA.
- Testing: Within two years after the publication of Swissmedic's guidance (November 15, 2021, almost a year earlier than requested by the HMA), the MAHs

have to test all their medicinal products that have been identified as having a risk of nitrosamine contamination, using officially certified methods of testing. For products whose risk is high, the confirmatory testing has to be performed immediately.

- **Application for variations:** For concerned medicinal products, the MAHs have to initiate the necessary adaptations (e.g., changes in the manufacturing process or in the specifications of the API) and submit applications for variations of the product. This last step has to be taken within a “reasonable period of time.”