

EDQM Webinar on N-Nitrosamines Impurities (21/01/2021)

N-nitrosamine impurities in medicinal products, Presentation by Cathie Vielle

Background & Regulatory Decisions - Useful information & urls links:

Background and regulatory decisions:

2018	2019	2020
<p>June: EU notified that an API manufacturer detected presence of NDMA in valsartan</p> <p>5 July: EC triggered a review in accordance with Article 31 of Directive 2001/83/EC to be carried out by EMA's Committee for Medicinal Products for Human Use (CHMP)</p> <p>20 September: the review extended to include medicines containing candesartan, irbesartan, losartan and olmesartan.</p> <p>Source: here</p>	<p>14 February: CHMP opinion on nitrosamine impurities in sartan containing a tetrazole group made public in an assessment report.</p> <p>2 April: EC's Implementing Decision concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations of medicinal products for human use which contain the active substances "candesartan", "irbesartan", "losartan", "olmesartan", "valsartan" => CHMP opinion rendered legally binding in EU & EEA member states</p> <p>Sept: start of Art. 5(3) of Regulation (EC) No 726/2004, whereby EMA's Executive Director can request a CHMP opinion – aim: to provide guidance to MAHs and manufacturers of medicines containing chemically synthesised APIs</p> <p>Source: here</p>	<p>9 July: publication of assessment report dated 25 June i.e. of CHMP opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 referral for nitrosamine impurities in human medicinal products CHMP opinion of 25 June 2020 ≠ European Commission's Decision of 2 April 2019</p> <p>Source: here </p> <p>13 Nov: EMA published a news announcing that "EMA's human medicines committee (CHMP) has aligned recommendations for limiting nitrosamine impurities in sartan medicines with recent recommendations it issued for other classes of medicines."</p> <p>Source: here</p>

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2018 Source:https://www.ema.europa.eu/en/documents/variation-report/sartans-article-31-referral-chmp-assessment-report_en.pdf

Assessment Report: https://www.ema.europa.eu/en/documents/variation-report/sartans-article-31-referral-chmp-assessment-report_en.pdf

2019 Source: https://ec.europa.eu/health/documents/community-register/2019/20190402144194/dec_144194_en.pdf

2020 Source: https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

Recommendations: https://www.ema.europa.eu/en/documents/referral/nitrosamine-impurities-final-outcome-art-53_en.pdf

2020 Source: <https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines>

Regulatory decisions - ctd:

2020

8 July: publication of assessment report dated 25 June i.e. of CHMP opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 referral for nitrosamine impurities in human medicinal products finalised. The Art. 5(3) had been triggered by the EMA Director in Sept. 2019.

These recommendations **apply to all medicines**. They include:

- developing additional guidance on:
 - the roles and responsibilities of companies involved in the manufacture of medicines;
 - controlling impurities;
 - good manufacturing practice (GMP);**
 - sampling and testing;
- improving communication with patients and healthcare professionals;
- expanding cooperation with international partners;
- further developing information technology systems.

✓ the control of the presence and risk of nitrosamine impurities shall be done at the **level of the medicinal product**

Publication of the outcome of a lessons learned exercise - *not entirely aligned with art. 5(3) opinion - (also triggered by the Art. 31 referral)* on the presence of nitrosamines in sartan medicines by the European medicines regulatory network: [Lessons learnt from presence of N-nitrosamine impurities in sartan medicines](#).

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Lessons Learnt Publication: https://www.ema.europa.eu/documents/report/lessons-learnt-presence-n-nitrosamine-impurities-sartan-medicines_en.pdf

N-nitrosamine impurities: CEP applications, Presentation by Ekaterina Nagdiyev

CHMP opinion on Article 5(3)

- Opinion published in June 2020, available on EMA website:
https://www.ema.europa.eu/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf
- EMA Q&As updated accordingly: [EMA Q&As](#)
- Risk of nitrosamine impurities:
 - Extended to biological products due to common risk factors (chemical reagents, packaging)
 - Exceptions for products indicated for advanced cancer (ICH S9 scope)
 - Deadlines for step 1 postponed
 - Root causes for the presence of nitrosamines:
 - APIs (route of synthesis, raw materials, degradation)
 - Interactions with finished product components (excipients, packaging)
 - GMP related aspects (cross-contaminations, recovered materials, etc)

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EMA Q&As: https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf