APIC

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Subject: Letter of intent for collaboration between API manufacturers[1] and MAHs regarding Nitrosamine Drug Substance Related Impurities (NDSRIs) acceptable limits in APIs

With this letter, we, APIC, would like to express awareness about the issue regarding limits for Nitrosamine Drug Substance Related Impurities (NDSRIs) applicable for final medicinal drug products and willingness to support MAH(s) with supplying APIs with appropriate levels of nitrosamine impurities in order to ensure the availability of safe medicines of the required quality.

Background: Assessment report of the *CHMP's Article 5(3) of Regulation (EC) No 726/2004* opinion on nitrosamine impurities in human medicinal products (EMA/369136/2020)[2] and associated *Question and answer document* (EMA/409815/2020)[3] provide general guidance and recommendations to mitigate and prevent the presence of nitrosamines in human medicinal products. In this context "*all MAHs/Applicants of human medicinal products should work with the manufacturers of their Active Pharmaceutical Ingredients (APIs) and finished products (FPs) in order to ensure that the presence of nitrosamine impurities in their medicinal products is mitigated as much as possible and controlled at or below a limit defined based on ICH M7(R2) principles for substances of the "cohort of concern".*"

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[1] In this document API manufacturers refer to API producers in Europe represented by APIC.

[2] Assessment report, Procedure under **Article 5(3)** of Regulation EC (No) 726/2004, Nitrosamine impurities in human medicinal products. EMA/369136/2020, 25 June 2020, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

[3] Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. **EMA/409815/2020.** Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation revision 19_QA10_Oct23 (europa.eu)

Since the beginning of the nitrosamine issue, it is evident that the main focus has shifted from small molecular weight nitrosamines to NDSRIs. In particular, a significant risk of nitrosamine impurities formation from APIs (or their related impurities) containing a vulnerable amine has been identified during finished product formulation and/or storage due to the presence of trace nitrites. In addition, NDSRIs are also being detected in the API(s). Therefore, APIC is aware that if nitrosamine impurity is potentially formed during API and final product manufacturing processes and stability, acceptable limits in API are required to be lower than those published in the current guidelines[2], as these limits apply for nitrosamines in final medicinal product. Therefore, suitability of acceptable limits for NDSRI(s) in API(s) due to the potential increase/formation of the nitrosamine(s) in final medicinal product should be evaluated on a case-by-case basis, as it depends on the drug product and its process. In this context, APIC expresses intention and willingness to collaborate with MAH(s) for defining product specific controls regarding NDSRIs for a given API supplied by API manufacturer. With this, APIC supports MAH(s) to ensure the quality, safety and efficacy of their medicines and in complying with the Nitrosamines guidance outlined by the EU Network.

Please note that this letter is not official binding, all details would need to be further discussed and aligned between API manufacturer and MAH.

Sincerely,

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