APIC
ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

APIC
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02 August 2024

Subject: APIC position on Nitrosamine Drug Substance Related Impurities (NDSRIs) and vulnerable amine impurities acceptable limits in APIs

We, APIC, would like to express awareness regarding Nitrosamine Drug Substance Related Impurities (NDSRIs) that might also be formed during final product manufacturing processes and/or storage. Consequently, acceptable limits for NDSRIs in APIs might need to be set lower than those published in the current nitrosamine guidelines in order that drug product manufacturers are able to meet acceptable intake (AI) levels in their final medicinal products. Furthermore, APIC is aware that vulnerable amine impurities (nitrosamine precursors) in APIs, or where the API itself represents a vulnerable amine, could be potentially converted to the corresponding NDSRIs during final product manufacturing processes and/or storage. Therefore, the acceptable levels for vulnerable amine impurities in APIs, which are set in line with ICH Q3A/compendial monograph, are sometimes not acceptable from the perspective of corresponding NDSRI formation at drug product level.

In this context, APIC expresses intention and willingness to collaborate with MAH(s) to support specific limits for NDSRIs and vulnerable amine impurities in API suitable for medicinal product. Nevertheless, APIC expects that the levels of NDSRIs/vulnerable amine impurities, which are stricter as per current guidelines (i.e. nitrosamine guidelines, ICH Q3A, PhEur monograph), are determined on a case by case basis, considering API process capability and the risk from drug product process itself, and are justified by reliable and comprehensive scientifically based risk assessment, supported by other supportive studies/data, if needed (for example, but not limited to, reactivity/vulnerability of vulnerable amine, conversion, stability). Furthermore, APIC is of the opinion that tightening of the limits per default (including where not justified/needed) would be too much of a burden for the API manufacturer and too strict limits/requirements might lead to API shortages.

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 abovementioned APIC position is not officially binding, all details would need to be further discussed and aligned between API manufacturer and MAH.

Yours sincerely,

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