EFPIA position with respect to safety related aspects of EMA and Health Canada requests for N-nitrosamine evaluations

Medicinal Products Impurity Profiles and their Safety Assessment

Extensive sets of International (ICH) and regional guidelines have been defined to assure that the nonclinical and clinical safety and efficacy of medicinal products are well established during clinical development and use on the market. Manufacturing of chemically synthesized pharmaceuticals involves amongst others the use of (reactive) chemicals. Due to this process, residual presence of impurities cannot be totally avoided. However, as for the safety of the active drug substance itself, a series of ICH guidelines has been defined describing appropriate safe limits and risk assessment processes ensuring the safety of residual impurities.

N-nitrosamines within the context of the existing guidelines on impurity management

In a recent incident involving several sartan products two N-nitrosamines (in particular N-nitrosodimethylamine and N-nitrosodiethylamine, NDMA and NDEA respectively) were detected. Both compounds are considered mutagenic and are known rodent carcinogens. In the annexes to the EC that contained legally binding decisions regarding the involved sartans, initially temporary limits for these N-nitrosamines were defined that aligned with the ICH M7 guideline. However, the final limits defined for these N-nitrosamines were 3-100 fold lower that those previously and temporarily aligned with ICH M7, on the basis that N-nitrosamines belong to the "cohort of concern". With respect to the recent EMA request to MAH's to evaluate their complete portfolio of chemically synthesised drug products for the potential presence of N-nitrosamines, EFPIA would like to clarify its position regarding the approach to be taken regarding the assessment and control of DNA reactive (mutagenic) N-nitrosamine Impurities in pharmaceuticals to limit potential Carcinogenic risk.

N-nitrosamines and Cohort of Concern – implications

The Cohort of Concern was defined already long before the conception of the ICH M7. In their proposal for a pragmatic Threshold of Toxicological Concern (TTC) based risk assessment tool for substances present at low levels in the diet Kroes *et al*., (2004) defined the Cohort of Concern as 5 structural groups of which a significant fraction of their members may still be of a concern at the defined TTC level. N-nitrosamines were one of the groups included and this is reflected in ICH M7 which states the following in section 7.5:

"Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkylazoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline. Although the principles of this guideline can be used, a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for pharmaceutical development and marketed products."

Hence, and based on above statement, it is concluded that N-nitrosamines should be regarded and treated as any other mutagenic and (assumed) carcinogenic impurity, with the caveat that safety limits lower than the ICH M7 defined TTC based acceptable intakes may be required, given the high carcinogenic potency of some of the N-nitrosamines involved. In other words, N-nitrosamines, when proven (potentially) mutagenic, do not exert a mode of action or result in

another endpoint (carcinogenicity) that warrant a stricter approach as compared other potentially mutagenic substances. As mentioned before, given that some of the members of the N-nitrosamine group have been shown to be very potent rodent carcinogens they may require control to compound-specific Acceptable Intakes which are lower than the generic ICH M7 TTC of 1.5 mcg/day for lifetime exposures.

Based on the above concepts, EFPIA considers that the following principles (which are aligned with ICH M7 guideline) are applicable regarding the assessment and control of DNA reactive (mutagenic) N-nitrosamines impurities in pharmaceuticals to limit potential carcinogenic risk.

1. The principles in ICH M7 regarding Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions are applicable in the specific case of N-nitrosamines (see Section 6 of the ICH M7 guideline).
2. The focus of the assessments should be on DNA reactive N-nitrosamines that are positive in the bacterial reverse mutation assay (see Note 2 of the ICH M7 guideline). The bacterial reverse mutation assay is recognized to be an appropriate test for the detection of N-nitrosamines (OECD 471, ICH S2R). The sponsor should ensure that the bacterial reverse mutation assay is appropriately designed for the detection of the potential mutagenicity of an N-nitrosamine compound (i.e. standard bacterial strains with a consideration of appropriate test vehicle, pre-incubation protocols and appropriate metabolic activation as per OECD 471).
3. In the case of an identified DNA reactive N-nitrosamine *with* robust rodent carcinogenicity data, safety limits based on the compound-specific Acceptable Intake will be used to define an acceptable limit in final drug product. This could include derivation of an Acceptable Intake based on a conservative linear extrapolation from the TD50 from the CPDB database or if the data is available the $BMDL_{10}$ modelling approach (see Note 4 of the ICH M7 guideline). Both modelling approaches can provide acceptable intakes for mutagenic carcinogenic N-nitrosamines e.g. the acceptable intake for NDMA via linear extrapolation from the TD50 for a 50 kg person is 96 ng/day whereas the Acceptable Intake for NDMA via the $BMDL_{10}$ modelling approach (which is considered to represent a more wholistic estimate of risk as it addresses uncertainties in the predicted Acceptable Intakes) is 145 - 215 ng/day [EMA/217823/2019]. It is the responsibility of the MAH to justify the modelling approach and the robustness of the available carcinogenicity data when deriving an Acceptable Intake for a specific N-nitrosamine.
4. In the case of an identified DNA reactive N-nitrosamine *without* robust rodent carcinogenicity data, safety limits based on compound-specific Acceptable Intakes derived from carcinogenicity data on closely related structures should be used (e.g. class-related limits for N-nitrosopiperidines, N-nitrosopiperazines and N-nitrosomorpholines to define an acceptable limit in final drug product - see section 7.5 of the ICH M7 guideline).
5. In the case of an identified DNA reactive N-nitrosamine where compound-specific Acceptable Intakes cannot be derived by these approaches, safety limits based on a conservative lifetime Acceptable Intake for any N-nitrosamine of 44 ng/day could be used to define an interim acceptable limit in final drug product. This conservative interim limit is based on a linear extrapolation from a TD50 value of 0.044 mg/kg/day (the 5th percentile of the distribution of rodent TD50's for the N-nitrosamines in the CPDB database) to a theoretical cancer risk of 10^{-5} which is the accepted lifetime risk level used in ICH M7. This Acceptable Intake for any N-nitrosamine of 44 ng/day is based on the principles discussed in Kroes *et al.,* (2004) and is proposed as a pragmatic interim value until a further scientifically rigid assessment of N-

nitrosamine mutagenicity and carcinogenicity has been conducted as part of an ICH M7 addendum.

6. Where applicable, Acceptable Intakes may be adjusted for "Less-Than-Lifetime" exposure (see section 7.2 and Note 6 of the ICH M7 guideline) using the same principles that are applicable for any mutagenic carcinogen (regardless of potency). For class 1 N-nitrosamines, the "Less-Than-Lifetime" acceptable intakes would be based on an adjustment of lifetime acceptable intake using the "Less-Than-Lifetime" safety factors defined in ICH M7 (i.e. for treatment durations of < 1 month, >1 – 12 months, >1 – 10 years and >10 years to lifetime - the lifetime Acceptable Intake would be increased by a factor of approximately 80, 13.3, 6.7 and 1 respectively. These are the same safety factors applicable for any potential or known mutagenic carcinogen e.g. 120 mcg/day ÷ 1.5 mcg/day = 80 - as defined in ICH M7). For, class 2 and class 3 N-nitrosamines (of unknown carcinogenic potential) "Less-Than-Lifetime" Acceptable Intakes using these same principles could be applied to the proposed conservative lifetime Acceptable Intake for any N-nitrosamine of 44 ng/day and would be the subject of an ICH M7 addendum.
7. Where applicable, for impurities specified on the drug substance specification, Acceptable Intakes for multiple mutagenic impurities should follow the principles of ICH M7 (e.g. when there are two Class 2 or Class 3 impurities, individual limits would apply, whereas for three or more Class 2 or Class 3 impurities multiple impurity limits would apply. In contrast, Class 1 Impurities with compound-specific or class-related acceptable intake limits would not be included in the total limits of Class 2 and Class 3 impurities (see section 7.4 of ICH M7).
8. These above safety approaches are also applicable to all patient populations based upon the conservative nature of the risk approaches being applied (see section 7.5 of the ICH M7 guideline).
9. The maximum allowable limit for a DNA reactive N-nitrosamine in final drug product will be defined as per ICH M7 (i.e. the Acceptable Intake divided by the applicable maximum daily dose).

Given the broad scope of the Health Authority requests (i.e. including any N-nitrosamine), EFPIA considers it important to stress that the ICH M7 hazard identification and risk assessment framework is applied. Control strategy approaches for nitrosamines should follow the general principles proven successful for all other mutagenic impurities as detailed in ICH M7 Section 8. Based on the above and to clarify on an international level EFPIA would welcome some specific Q&As to be added to the ICH M7(R1) guideline which is currently under revision. In addition, in order to provide a globally acceptable limit based on the appropriate safety considerations, it is recommended a series of Compound-Specific Acceptable Intakes for the more commonly encountered N-nitrosamines are added as an appendix to the ICH M7 guideline.

References

ICH M7(R1) Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk https://www.ich.org/index.html

Kroes *et al.,* (2004) Food and Chemical Toxicology, 42, 65–83.

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