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Questions and answers on the 'Guideline on the limits of genotoxic impurities'

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Background

The aim of this question-and-answer document is to provide clarification and harmonisation of the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/QWP/251344/2006), published in 2006.



Questions and answers

Question 1. The guideline does not need to be applied retrospectively to authorised products unless there is a specific cause for concern. What might constitute "a cause-for-concern" in terms of application to currently marketed products?

If a manufacturing procedure for API remains essentially unchanged a re-evaluation with respect to the presence of potentially genotoxic impurities is generally not needed. However, new knowledge may indicate a previously unknown cause for concern. One example is the mesylate salt drug substances for which a few years ago, a concern regarding the potential for formation of genotoxic alkyl mesylates was raised. This concern resulted in the "Production Statement" requesting a specific evaluation of the potential for formation of these highly toxic products now included as part of the PhEur monographs for all the mesylates salts.

Question 2. The guideline indicates that it is necessary to reduce a known or suspected mutagenic impurity to as low as reasonably practicable (ALARP) even if the level is below the threshold of toxicological concern (TTC), i.e. in the decision tree ALARP considerations precede TTC considerations. If the level is already known to be below the TTC (which is a very conservative value), why is it necessary to reduce it even further? On a practical basis this would often involve developing analytical methods that have limits of quantitation around or below 1ppm level. The effort and resource this can take, and the possibility that it is not actually achievable, does not seem commensurate with the perceived risk.

If the level of a mutagenic impurity is below the threshold of toxicological concern (equivalent to a clinical dose $\leq 1.5 \mu\text{g/day}$) it is not necessary to apply ALARP considerations unless it is a structure of very high concern, e.g. N-nitroso, aflatoxins-like and azoxy-compounds.

Question 3. The guideline states: "When a potential impurity contains structural alerts, additional genotoxicity testing of the impurity, typically in a bacterial reverse mutation assay, should be considered."

i) If an impurity triggers a mutagenic structural alert, will a negative result in an Ames test on the impurity (conducted to regulatory acceptable standards) be sufficient to conclude that the compound is of no concern with respect to genotoxicity and no further 'qualification' studies will be required?

ii) Is the absence of a structural alert sufficient to show that the impurity is of no concern?

iii) Is it acceptable to control impurities with a structural alert by assuming they will be positive (without resorting to any testing) and ensuring the level remains below the appropriate TTC value?

i) Yes, a negative Ames test (conducted to regulatory acceptable standards) will overrule a structural alert and no further studies would be required providing the level remains below ICH Q3A/B limits.

ii) Yes, the absence of a structural alert based on a well-performed assessment (e.g. through application of commonly used QSAR assessment software such as DEREK or MCASE) will be sufficient to conclude that the impurity is of no concern with respect to genotoxicity and no further 'qualification' studies or justification will be required.

iii) Yes, genotoxicity testing is not obligatory when a potential genotoxic impurity is controlled at the TTC level, unless it belongs to a class of very potent genotoxic carcinogens (N-nitroso and azoxy compounds, or a aflatoxin-like compound).

Question 4. What would be an appropriate strategy to qualify a new impurity that arises during Phase III or with a commercial product? For example, would it be acceptable that a new unidentified impurity, discovered at the 0.05-0.09% range requires no action to be taken? Would an impurity discovered in the 0.10 to 0.15%, even if it triggers a structural alert, be fully qualified by testing the active ingredient containing this impurity in an Ames test?

In line with the ICH guideline, no action is generally required for a new unidentified impurity found at levels below the ICH identification threshold. When an impurity is found above the ICH identification threshold, but below the qualification threshold, and the structure gives rise to a structural alert, this can be negated by carrying out an Ames test on the active ingredient containing the impurity as long as the impurity is present at a minimum concentration of 250 µg/plate (estimated detection limit for most relevant mutagens in Ames test, see Kenyon et al., Reg Tox & Pharm, 2007, 75-86). If the structure cannot be elucidated, then no action is generally required. Above the ICH qualification threshold, then the ICH guidance should be followed.

Question 5. The guideline states that "A TTC value higher than 1.5 µg /day may be acceptable under certain conditions e.g. short-term exposure....". Is the CHMP in agreement with the principles of "staged TTC" dependent on the duration of clinical exposure, i.e. higher levels allowed for marketed drugs used to treat acute conditions, e.g. antibiotics. If 'yes', what levels would be acceptable?

TTC values for genotoxic impurities above 1.5 µg /day will be treated on a case-by-case basis. For short-duration treatments, the acceptability of higher levels will be in line with the principles outlined in the CHMP's answer to question 6.

Question 6. The wording of the guideline implies that it is intended to cover an issue not covered specifically by ICH Q3A/B guidelines. The scope of the ICH guidelines does not include clinical development prior to NDA or MAA submission. However, experience across a range of pharmaceutical companies indicates that some regulatory authorities are applying the genotoxic impurity guideline during clinical development. In case the scope should include application to clinical development, can the CHMP advise on how genotoxic impurities should be controlled during the development stage?

According to the scope of the guideline, it mainly applies to genotoxic impurities in "new active substances" which includes new active substances in both, MAA submissions as well as clinical trial applications. In fact, the CHMP Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in clinical trials (CHMP/QWP/185401/2004) states that "For impurities in IMPs, a justification that the product is safe for its intended use, considering the anticipated exposure of volunteers and patients, respectively, will be required.", and further on "a brief justification of the specifications and acceptance criteria for impurities should be provided based on safety and toxicity data."

The CHMP agrees with the use of a staged TTC concept during clinical development.

The acceptable limits for daily intake of genotoxic impurities are 5, 10, 20, and 60µg/day for a duration of exposure of 6-12 months, 3-6 months, 1-3 months, and less than 1 month, respectively. For a single dose an intake of up to 120 µg is acceptable. Compared to the proposal of a staged TTC in the Mueller et al (Reg Tox & Pharm, 2006, 44, 198–211) paper these values incorporate a dose rate correction factor of 2 to account for deviations from the linear extrapolation model.

	Duration of exposure				
	Single dose	≤1 month	≤3 months	≤6 months	≤12 months
Allowable daily intake	120 µg	60 µg	20 µg	10 µg	5 µg

Question 7. The guideline text implies that the indicated TTC value of 1.5 µg /day is a level that can be applied to each individual genotoxic impurity in a drug substance. Could this be confirmed?

When more than one genotoxic impurity is present in the drug substance, the TTC value of 1.5 µg/day can be applied to each individual impurity only if the impurities are structurally unrelated.

In case of structural similarity, it can be assumed that the impurities act by the same genotoxic mode of action and have the same molecular target. and thus might exert effects in an additive manner. In such a situation, a limitation of the sum of the genotoxic impurities at 1.5 µg/day is recommended. This might be practically not achievable with reasonable efforts in particular when the maximum daily dose is very high and thus may demand application of lower group limits. Justifications should be made on a case-by-case basis taking into consideration issues such as:

- Maximum daily dose of the active substance;
- Therapeutic indication;
- Step of the synthesis at which the genotoxic impurity(ies) arise;
- Capability of the manufacturing process (purification steps) to eliminate these impurities;
- Capability of the analytical procedure to control these impurities.

In cases where routine use of more powerful detection methods would be difficult, one could consider using such methods during development or testing of the first commercial batches, in order to demonstrate that the actual values are sufficiently below the TTC. In such a case, skip testing could be considered instead of routine testing, providing that the Competent Authorities, based on a risk assessment, consider the approach as acceptable.

Question 8. The European Pharmacopoeia Commission Policy for dealing with potentially genotoxic impurities was issued in March 2008. This policy is to be applied during elaboration and revision of pharmacopoeial monographs. It provides very pragmatic guidance on how the CHMP guideline can be applied to active substances described in existing monographs. Can the same principles, as outlined within this policy, apply to established drug substances, which do not have pharmacopoeial monographs?

Yes. For active substances included in medicinal products authorized by the competent authorities before implementation of the CHMP guideline, the specifications as described in the dossier for marketing authorization should be followed. Action is needed only where there is study data demonstrating genotoxicity of the impurity. The existence of structural alerts alone is considered insufficient to trigger follow-up measures unless it is a structure of very high concern, e.g. N-nitroso, aflatoxins-like and azoxy-compounds. If a new synthetic route is used that may give rise to different potentially genotoxic impurities or to higher levels of previously recognized potentially genotoxic impurities then the situation should be discussed with the competent authority.

Question 9. What is a reasonable policy for setting specifications for potentially genotoxic impurities which are theoretical or actual impurities in a drug substance manufacturing process?

Different possible scenarios can be identified and the applicable policies to be applied for each of them are described below:

Example 1 – A potential genotoxic impurity

The definition for a potential genotoxic impurity is derived from the definition for "Potential impurity": an impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the (new) drug substance (ICH Q3A, Glossary).

If a potential genotoxic impurity is just a theoretical impurity i.e. based on theoretical considerations but not found in practice as demonstrated by studies during development of the manufacture, the impurity does not need to be included in the drug substance specification.

Example 2 – A (potentially) genotoxic impurity actually formed or introduced prior to the final step of the synthesis

If a (potentially) genotoxic impurity is formed or introduced in a step before the final synthesis step, it is considered possible to not include this impurity in the drug substance specification if it is controlled by a suitable limit in a synthesis intermediate and if it is unambiguously demonstrated by analysis results (use of spiking experiments are encouraged) that presence of this impurity does not exceed 30 % of the limit, derived either from TTC or otherwise defined acceptable limit etc, in the drug substance. If these conditions are not fulfilled, this impurity has to be included in the drug substance specification and the test has to be carried out on a routine basis.

Should a genotoxic impurity not be controlled at the intermediate stage, then the scenario of example 3 applies.

Example 3 - A (potentially) genotoxic impurity is formed or introduced in the last synthesis step

If a (potentially) genotoxic impurity is formed or introduced in the final synthesis step, it should be included in the specifications. However, it is considered possible to apply skip testing if the level of the impurity does not exceed 30 % of the limit, derived from either TTC or otherwise defined acceptable limit etc, in the drug substance. Data should be presented for at least 6 consecutive pilot scale or 3

consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is needed.

The following definitions apply:

Genotoxic impurity: an impurity that has been demonstrated to be genotoxic in an appropriate genotoxicity test model, e.g. bacterial gene mutation (Ames) test.

Potentially genotoxic impurity: an impurity that shows (a) structural alert(s) for genotoxicity but that has not been tested in an experimental test model. Here potentially relates to genotoxicity, not to the presence or absence of this impurity.

References

M.O. Kenyon, J.R. Cheung, K.L. Dobo, W.W. Ku: An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. Reg Tox & Pharm, 2007, 75-86.