October 23, 2020

Submission of comments on 'ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - questions & answers, Step 2b'

(EMA/CHMP/ICH/321999/2020)

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received. When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
| EFPIA | The publication of the Q&A document is to be welcomed. However, there are some topics that are not addressed in sufficient detail and a number of questions raised by the stakeholder community that have not been answered completely. An update/revision process to the Q&A document should be considered to accommodate additional questions and clarifications. In particular, updates to ICH M7 or Q&A should occur based on emerging topics.  Although not captured in this version of the Q&As, given the ongoing discussion around nitrosamines and the very restrictive measures proposed by some agencies it is considered important and urgent to bring this discussion back to ICH M7 (Q&A). Application of ICH M7 to nitrosamine impurities with respect to acceptable intakes, use of SAR to determine acceptable intake, use of LTL approach, use of Option 4 controls are examples to be discussed and included.  Therefore, currently proposed measures deviate on an important number of aspects from principles laid down in the ICH M7 guideline. Hence it is important to have a data driven discussion on warranted measures which also align with ICH M7 where all parties involved can be present.  The term ‘TTC’ (i.e., 1.5 microgram/day) is inconsistently used across the Q&A and should be replaced with ‘acceptable limit (AL)’ or ‘acceptable intake (AI)’ to account for situations where a drug is not intended for lifetime (>10 years) administration.  Reference 2:” Carcinogenicity Potency Database (CPDB). [Online]. Available from: <URL:https://toxnet.nlm.nih.gov/cpdb/>” has been retired and is no longer available, please add either a curated database from LHASA <https://carcdb.lhasalimited.org/carcdb-frontend/>  or <https://files.toxplanet.com/cpdb/index.html> |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
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| Q1.1 | EFPIA | Proposed change:  Genotoxicity is an umbrella term which refers to the potential of a chemical to either directly or indirectly damage the genetic material of the cell. There are three main mechanisms of genotoxicity – mutagenicity, clastogenicity and aneugenicity. Mutagenic potential refers to the ability of a compound to induce point mutations (i.e., bacterial reverse mutation assay), while genotoxic potential refers to mutagenic, clastogenic (chemically induced damage or breakage of chromosomes) and aneugenic (chemically induced alteration in chromosome number) potential. ICH M7 focuses specifically on mutagenicity. |  |
| Q1.2 | EFPIA | In the context of ICH M7, (Quantitative) Structure-Activity Relationships ((Q)SAR) is considered an appropriate initial evaluation of mutagenic potential of an impurity at a daily dose of ≤ 1 mg. When a structural alert is identified, a follow-up in vitro evaluation (e.g., bacterial reverse mutation assay) could be conducted, or the impurity could be controlled by Threshold of Toxicological Concern (TTC). Negative results in either the (Q)SAR evaluation or the in vitro evaluation would classify the impurity under Class 5. The result of the bacterial reverse mutation assay overrules the (Q)SAR prediction. The presence of a “structural alert” using (Q)SAR prediction may be overruled by expert review (and not by visual inspection alone) and thus an impurity that carries a structural alert may nevertheless eventually be assigned Class 5 when expert review clearly negates the relevance of the respective alert.  With respect to non-mutagenic impurities the ICH Q3A & B reporting, identification and qualification limits continue to apply for drug substance and drug product in a phase dependent manner as defined in ICH M3. |  |
| Q1.3 | EFPIA | Reword: No. If an impurity is predicted to be negative in two appropriate (Q)SAR systems and is present at a level ≤1 mg/day, further genetic toxicity testing is not warranted. |  |
| Q1.4 | EFPIA | The original answer “In cases where the amount of impurity is >1 mg daily dose for chronic administration, regardless of the impurity classification, a minimum screen of genotoxicity studies (point mutation and chromosomal aberration) can be considered.” Could be misinterpreted as stated it contradicts the 0.05% ID limit for drugs > 2g in ICH Q3A.  In cases where the amount of impurity identified under ICH Q3A & B is >1 mg daily dose for chronic administration (> 6 months as defined by ICH E1), regardless of the impurity classification, a minimum screen of genotoxicity studies (point mutation and chromosomal aberration) can be considered. Note that ICH Q3A & B impurity identification limits for drugs > 2 g daily dose should be applied, unless there a chemistry rationale for lowering the identification threshold related to the presence of a potential mutagenic impurity (i.e. as stated in ICH Q3A & B - lower thresholds can be appropriate if the impurity is unusually toxic). |  |
| Q2.1 | EFPIA | For the 2.1 Question and Answer, "semi-synthetic" should only refer to the drug substance and not the drug product. Reword the Question and Answer for clarity. Question: Are semi-synthetic drug substances and their corresponding drug products included in the scope…  Answer: The following compounds used in the manufacturing process of semi-synthetic drug substances and their corresponding drug products should be considered… |  |
| Q3.1 | EFPIA | Please add:  Whilst out of scope of ICH M7, a known non mutagenic carcinogen would be considered as ICH M7 class 5 but would require control to the appropriate ADI for that material. |  |
| Q4.1 | EFPIA | Suggestion to change:  Any increase in dose of the active pharmaceutical ingredient (API) that would increase any mutagenic and potential mutagenic impurity (class 1/2) to levels above the acceptable limits is considered significant (see Tables 2 and 3 and the addendum).    In such cases a re-evaluation of the mutagenic impurity limits is recommended |  |
| Q6.2 | EFPIA | An out of domain or non-coverage result from one of the two (Q)SAR models requires additional assessment in order to classify the compound as a Class 5.  Given that the relationship between chemical structure and DNA reactivity is well understood, it is unlikely that a structure with mutagenic potential would be associated with an out of domain result. However, expert review can provide reassurance in assignment of such impurities to class 5.  Expert review may include one or a combination of the following [Amberg et. al., 2019]:  1. Comparison to structurally similar analogs for which bacterial reverse mutation assay data are available (read-across approach)  2. Expert review of the chemical structure to determine if there is potential for the chemical to react with DNA.  3. (Q)SAR output from an additional validated model (see Question 6.1) of the same methodology (i.e., expert rule-based or statistical) that generates a prediction that is within its applicability domain |  |
| Q6.3 | EFPIA | N/A |  |
| Q6.4 | EFPIA | If an impurity is positive in the Ames test, and levels of the impurity cannot be controlled at an appropriate acceptable limit, it is recommended to conduct an in vivo follow-up test with mutagenic endpoint (mutagenicity). The other follow-up tests outlined in Note 3 are also acceptable when scientific rationale is provided to support their use.  For any of the above tests, adequate exposure should be demonstrated in line with ICH S2. |  |
| Q7.1 | EFPIA | Please re-discuss if the term “clearly” is needed |  |
| Q7.2 | EFPIA | *In vivo* gene mutation assays are currently not validated to directly assess cancer risk because the endpoint is mutation and not carcinogenicity  Results from these tests could identify mode of action and/or direct further testing strategy to complement the available data for a weight of evidence approach ie. data from a well-conducted in vivo mutation assay could be utilized in a weight of evidence to justify a limit higher than the TTC on a case-by-case basis. Justification for the point of departure utilized in calculating a safe level, as well as uncertainty factors or safety margins would need to be provided.” |  |
| Q7.3 | EFPIA | The LTL approach can be applied to compounds with exposure limits based on a compound/class specific AI (Section 7.2.2). This LTL approach is not directly applicable to PDEs as they are derived by a different methodology (Section 7.2.2), however higher levels of exposure for short-term exposure (30 days or less) are outside of scope of ICH M7 but may be considered acceptable on a case by case basis using the principles defined in ICH Q3C & D. |  |
| Q7.4 | EFPIA | Clarification needed as the lifetime duration is for drugs intended for HIV treatment. HIV drugs for cure and pre-exposure prophylaxis (PrEP) may have different treatment regimens and should be considered separately. Also need to clarify that this applies to HIV-treatment drugs at the marketing phase.  Pleased Revise the following:  “For regulatory submissions 18 months after the date:” into For **HIV treatment-related** regulatory submissions ….”.  Also, change the 1st bullet point to “applications for marketing of new drug substances and new drug products”.  Finally add the following sentence to the end of the response “Drugs intended for PrEP should be considered under the appropriate LTL duration category.”  In addition, real world data should be used as supportive data in general to assess the effectiveness of such therapies in terms of longer survival more thoroughly. |  |
| Q7.5 | EFPIA | N/A |  |
| Q8.1 | EFPIA | The employment of the 1% of TTC value is an expansion of the current scope of ICH M7, since it puts a stronger emphasis on analytical testing data in the final drug substance. Excerpt from M7: *A control strategy that relies on process controls in lieu of analytical testing can be appropriate if the process chemistry and process parameters that impact levels of mutagenic impurities are understood and the risk of an impurity residing in the final drug substance above the acceptable limit is determined to be negligible. In many cases justification of this control approach based on scientific principles alone is sufficient.*  The answer also currently contradicts answer to Q8.2, which asks for ‘*More detailed information on the calculation is expected when the predicted level of the impurity in the drug substance approaches the TTC*.’  If the 1% is maintained TTC should be replaced by AI. Additionally, a reference to the Barber 2017 paper similar to Q8.2 is considered helpful.  Consider modifying the answer in the following ways:  Option A (removal of 1%, and reference to Barber paper): Use of Option 4 **(Barber et al 2017)** is appropriate when a mutagenic impurity is demonstrated to have a negligible risk of being present in the final drug substance. The risk assessment can be based on scientific principles alone...  Option B (clarification that both calculation and analytical data are acceptable, and reference to Barber paper): Use of Option 4 (**Barber et al 2017**) is appropriate when a mutagenic impurity is demonstrated to have a negligible risk of being present in the final drug substance (e.g., 1% of **AI, verified via data or science-based evaluation or calculation**). The risk assessment can be based on scientific principles alone...  Option C (changed wording to predicted and include reference to Barber paper): Use of Option 4 (**Barber et al 2017**) is appropriate when a mutagenic impurity is ~~demonstrated~~ **predicted** to have a negligible risk of being present in the final drug substance (e.g., 1% of **AI**). The risk assessment can be based on scientific principles alone.... |  |
| Q8.2 | EFPIA | N/A |  |
| Q8.3 | EFPIA | Reword the first sentence of the answer to question 8.3 for consistency with the original ICH M7 text. There is widespread misunderstanding of the meaning of the term "potential mutagenic impurity" across industry. Some define "potential mutagenic impurity" as "may be present" and others define "potential mutagenic impurity" as "may be mutagenic". It would be helpful to not use the phrase "potential mutagenic impurities" in the Q&A.  The appropriateness of the use of Option 4 will depend on more situations than what is described, especially for “less reactive” impurities. For instance, there will be cases where the TTC is high and where data has been generated supporting an Option 4. Equally, there will be instances where Option 4 for “reactive” materials is appropriately justified without experimental data when the purge prediction is substantiated by some data.  Proposal for the answer: For potential mutagenic impurities (class 1, 2 or 3) introduced or generated in the last synthetic step, given the proximity to the final product, Option 1 is the preferred control strategy. However, Option 2, 3 and 4 control strategies may be possible when appropriately justified. The control strategy may be influenced by the presence of a subsequent recrystallisation step, a highly effective purification operation (e.g., chromatography), the reactivity (e.g. highly reactive reagents such as thionyl chloride) and physical characteristics of the impurity (e.g. low boiling point such as methyl chloride) and the availability of data (analytical data or substantiation of the purge arguments). In most cases, the justification of an Option 4 control strategy solely based on prediction is not considered sufficient unless a detailed justification is presented for a very large predicted purge ratio (> 1000-fold). |  |
| Q8.4 | EFPIA | While position of the EWG is understood by experts it does not immediately appear to follow a science and risk-based logic. Consider modifying the response to better explain why skip-testing is permissible for Option 1, but non permissible for Options 2 and 3. |  |
| Q8.5 | EFPIA | The answer appears to rule out periodic verification testing. Additionally, it appears viable per ICH M7 to change the control strategy through a post marketing variation. This should be recognized in the response.  Proposed changes to answer:  ~~No.~~ Batch data alone demonstrating that a potential mutagenic impurity is consistently <30% TTC is not sufficient to justify no testing of that impurity **but periodic testing of Option 1 controls may be appropriate per 8.4**.. Options 1, 2, and 3 should test either at release or upstream in the process. However, if there is negligible risk of the impurity to be present in the drug substance, an Option 4 control strategy may be considered with appropriate justification. See question 8.1 and 8.2 for recommendations on supporting an Option 4 control strategy. **A post-approval change in the control strategy from Options 1, 2 or 3 to Option 4 may be considered through a variation.** |  |
| Q8.6 | EFPIA | The current text is too restrictive. During process development, purge studies may be conducted before finalization of the commercial manufacturing process, using process conditions emulating those of the final process.    Proposed change:  Lab scale experiments are typically sufficient when generating measured purge factors or when defining in-process control points. These studies should employ conditions representative of the final process described in the application and should (…) |  |
| Q9.1 | EFPIA | NA |  |
| Q9.2 | EFPIA | Some impurities are not controlled by TTC there the following editorial change is request.  In the following paragraph a change should be made:  The maximum daily dose, acceptable limit (i.e. TTC, AI, PDE), and proposed duration of treatment can also be noted.  For marketing applications, the answer notes that in Module 4, (Q)SAR reports should be included to support the risk assessment and control strategy. In M7(R1), this did not seem to be required, but rather “results and description of in silico (Q)SAR systems used, and as appropriate, supporting information to arrive at the overall conclusion for Class 4 and 5 impurities.”  We suggest clarifying whether this is a new requirement that Q(SAR) reports need to be included for all predictions, or if an in silico report is included to support the overall conclusion, that it should be included in Module 4.  Listing of all class 4 and 5 impurities in the 3.2.S.3.2 ICH M7 hazard assessment table can be excessive, especially in clinical development where frequent changes in impurities occur.  Propose to modify text to request listing class 1-3 in QSAR table and providing a link to e.g. (Q)SAR report for class 4 and 5 in Module 4 ? It would be helpful that the table in 3.2.S.3.2 includes only class 1-3. A statement would be given that all other impurities were negative in the (Q)SAR prediction using system x (version 1) and system y (version 2) or negative Ames data are available.  The following advice is included on where to include information on mutagenic impurities in the Quality section of the dossier. ‘In Module 3, the ICH M7 risk assessment and control strategy should be provided in detail. This type of information is often placed in section 3.2.S.3.2 Impurities; however, it is sometimes placed in other CTD locations per ICH M4Q guidance. A table summary of the ICH M7 hazard assessment and ICH M7 impurity control strategy is recommended to improve clarity.’ In order to allow efficient and effective management of a dossier throughout the product lifecycle for a product with global reach, inclusion of ‘control strategy’ information in a ‘descriptive’ module such as S.3.2 is unwise. Locating ‘control strategy’ information in other modules such as S.2.3 or S.4.5 is generally a better strategy. A more general reference to the ICH M4Q Q&A document where the location of impurity information is discussed in more detail would be helpful in this Q&A document.  Proposed change (if any):  ‘In Module 3, the ICH M7 risk assessment and control strategy should be provided in detail. Impurity information should be provided in CTD locations as per ICH M4Q and ICH M4Q Q&A document guidance (See section 3 ‘Associated information located in different sections’) eg. S.3.2 and S.4.5 etc. A table summary of the ICH M7 hazard assessment and ICH M7 impurity control strategy is recommended to improve clarity.’  Referencing specific sections to submit information and the need for hyperlinks is overly prescriptive. Suggest to replace request for hyperlinks with cross-reference. |  |

Please add more rows if needed.