13 October 2020
EMA/538158/2020

Overview of comments received on ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - questions & answers (EMA/CHMP/ICH/321999/2020)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Gilead Sciences International Ltd
2	Laurus Labs Limited, India
3	Sanofi
4	Medicines for Europe
5	Swissmedic
6	LEO Pharma A/S

Please note that comments will be sent to the **ICH M7(R2) Maintenance EWG/IWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments – overview

Stakeholder no.	General comment (if any)
1	The Q&A document provided many clarifying aspects of ICH M7 which is well needed. We were disappointed in Question 7.2 as there has been a lot of scientific advancement in the use of *in vivo* mutagenicity data to derive compound-specific limits, contradicts text in ICH M7(R1), and is critical toxicological process for providing limits higher than the TTC in lieu of a carcinogenicity study. Hernandez et al., 2011 found that dose-response data from in vivo genotoxicity studies can be used to predict carcinogenic outcomes (Hernandez et al. 2011, *Environ Mol Mutagen*. 52(7):518-28). The science of dose response *in vivo* mutation data has advanced over the years with the shift away from being pure hazard identification studies and to be used for limit setting (Heflich et al., 2020. Environ Mol Mutagen. 61(1):34-41.; Johnson et al., 2014 *Environ Mol Mutagen*. 55(8):609-23.). Finally, Section 7.2 contradicts the original text of ICH M7(R1) where it states "Results in the appropriate in vivo assay may support setting compound specific impurity limits" (Section 6). Also, in Section 7.2.2 it discusses how to derive limits for impurities that exhibit a practical threshold, even for "DNA-reactive compounds". We recognize that there is more science and examples required to develop methodology for developing compound-specific limits. However, Question 7.2 will create high regulatory hurdles which will prevent future use of dose-response information from in vivo studies. We propose deleting Question 7.2.
4	Medicines for Europe welcomes the publication of the Q&A document related to ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, this will further clarify any doubts and align on the expectations. Some comments on the Q&A document have been raised by our members and presented below.
5	The Q&A is considered very useful and provides clarity on identified issues raised during the application of ICH M7.

2. Specific comments on text

Question no.	Stakeholder no.	Comment and rationale; proposed changes
Q 1.1	3	**Comments:** Note 1 provides general guidance on the relationship of ICH M7 with ICH Q3A and Q3B. The use of both "mutagenic potential" and "genotoxic potential" in Note 1 is confusing. Are these terms considered interchangeable? **Proposed change:** No. The terms "mutagenic potential" and "genotoxic potential" are not interchangeable. Mutagenic potential refers to the ability of a compound to induce point mutations (i.e., bacterial reverse mutation assay), while genotoxic potential refers to both mutagenic and clastogenic potential. ICH M7 focuses specifically on mutagenic~~ity~~ impurities with potential carcinogenic risk.
Q 1.1	4	**Comments:** After Q&A 1.1 clearly explaining that the focus in the ICH M7 is on mutagenicity, the term used in Q&A 1.3 is "genetic toxicity testing" and not "mutagenic toxicity testing". Does this mean that an impurity that is above the ICH Q3A/Q3B qualification threshold but has no (Q)SAR alerts and is found at less than 1 mg/day, there is no need for the Ames test or chromosomal aberrations? This is not clear, because the ICH Q3A and Q3B guidelines tell us that in order to qualify an impurity at a level above the qualification threshold you should test for mutagenicity (in the Ames test) and clastogenicity (in the chromosomal aberrations assay) in addition to general toxicity studies (one species, usually 14 to 90 days).
Q 1.1	5	**Comments:** It reads *Mutagenic potential refers to the ability of a compound to induce point mutations (i.e., bacterial reverse mutation assay), [..]* – sentence appears not to be complete, according to the glossary in the guideline (definition of a mutagenic impuritiy), the "i.e." is actually an "e.g." – please clarify. **Proposed change:** Add words in bold: *Mutagenic potential refers to the ability of a compound to induce point mutations (i.e., **in a** bacterial reverse mutation assay), [..]*
Q 1.2	5	**Comments:** It reads: *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).*

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		In the guideline it reads: *To follow up on a relevant structural alert (Class 3 in Table 1), either adequate control* *measures could be applied or a bacterial mutagenicity assay with the impurity alone can be conducted.* Please clarify if there are any additional options for the in vitro evaluation and add them or re-word to be more specific.
Q 1.3	5	**Comments:** Is use of the word "recommended" in the question appropriate? The short answer "No" implies that further testing is not recommended, although you seem to rather mean "not warranted/necessary". **Proposed change:** Either replace the word "recommended" in the question by "necessary/warranted" or delete the "No." in the answer.
Q 1.4	4	**Comments:** Q&A 1.4 clarifies the situation where even if the impurity is a Class 4 or Class 5, if it is present at above 1 mg/day, you are compelled to perform an Ames test and a chromosomal aberrations assay in order to complete the qualification. The question that arises here, is what is the rationale behind requiring the Ames test in such a situation? If the entire basis of classifying impurities in the ICH M7 guideline is based on (Q)SAR analysis, and an impurity can be classified as being non-mutagenic, then why does this classification not prevail also when the level exceeds 1 mg/day?
Q 1.4	5	**Comments:** The wording "can be considered" in the answer is very vague. I understand that the respective text in the M7 guidance document is also vague (Note 1: "In cases where the amount of the impurity exceeds 1 mg daily dose for chronic administration, evaluation of genotoxic potential as recommended in ICH Q3A/B could be considered."). However, is such a vague wording appropriate for a guidance document? **Proposed change:** Consider using a more strict wording.
Q 2	3	**Comments:** Scope of the Guideline **Proposed change:** ***To add in the Q&A:*** What is agency expectation in terms of assessing acceptable cancer risk level for this new indication? In Nitrosamine,

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		biologicals and/or vaccines has been added in the scope. For M7, clarify if this will be part of drug product in scope.
Q 3.2	4	**"No. Mutagens that are demonstrated to be non-carcinogenic in appropriate and well-conducted animal bioassays will be treated similarly to Class 5 impurities."** **Comments:** Does this mean that they can be categorised as class 5 and treated as non-mutagenic or just treated as non-mutagenic but remaining class 2?
Q 6.1	5	**Comments:** What are the expectations regarding: *The model should be evaluated and shown to be **sufficiently predictive** of bacterial reverse mutagenicity. Standard validation techniques that should be used are recall, cross-validation, and external validation. **Evidence** that the model has not been over-fit should also be provided.* *For any system developed in house or not commonly used, …* How do you define "not commonly used"? **Comment 1:** The sentence *"For any system developed in house or not commonly used, to demonstrate how each model follows these principles and to understand how a (Q)SAR model was developed and validated, submission of the OECD (Q)SAR Model Reporting Format* *(QMRF) [OECD QRMF, 2017] for each model used should accompany each regulatory submission"* is difficult to understand. **Proposed change:** Split the sentence and refer to the respective (Q)SAR model for which additional information should be available, e.g.: *For any (Q)SAR model developed in-house or not commonly used, information about the development and validation should be included in the regulatory submission dossier. For documentation of this information, the OECD (Q)SAR Model Reporting Format (QMRF) [OECD QMRF, 2017] should be used.* **Comment 2:** Is the harmonized template of JRC and EU the same of the referenced OECD QMRF 2017? Please clarify or in the case that it is the same, some details could be deleted: **Proposed change:** ~~A harmonized template for~~ The QMRF ~~was developed by the Joint Research Centre (JRC) and EU Member State authorities. This template~~ summarizes

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		and reports key information on (Q)SAR models, including the results of any validation studies as well as provides supplementary information on applicability of the model to a given chemical.
Q 6.2	5	**Comment 1:** In the second paragraph of the answer, it reads: *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.* Does this also apply for statistical-based models? It is not really clear what is meant here. **Proposed change:** Reconsider wording of this paragraph (is it necessary at all?). **Comment 2:** In the third paragraph of the answer, it reads: *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*. Is the reference of the prediction to the applicability domain correct? To my understanding, the applicability domain refers to the chemical properties. **Comment 3:** In the first paragraph of the answer, it reads: *Additional assessment is warranted.* Does it mean that an expert review is sufficient or is an *in vitro* evaluation necessary? Consider rewording, which could also allow deletion of paragraph 2 as questioned under Comment 1. **Proposed change:** *An expert review is warranted*.
Q 6.3	4	**"If an impurity tests negative in an Ames assay, it is considered a Class 5 impurity. Addressing positive results in a clastogenicity assay is out of scope of ICH M7."** **Comments:** Where does the mouse lymphoma assay sit in this scheme? The mouse lymphoma can detect mutagens but also detects clastogenic activity and is easily confounded.

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Q 6.3	5	**Comment 1:** The terms "Ames study" and "Ames assay" are not consistent with the wording in the previous Q&As and the M7 guideline ("bacterial reverse mutation assay"). **Proposed change:** Use consistently "bacterial reverse mutation assay" throughout the document (note: this comment and proposed change concerns also Q&A 6.4 ("Ames mutagen", "Ames test") and Q&As 7.1 and 7.2 ("Ames positive impurity"). **Comment 2:** "*Addressing positive results in a clastogenicity assay is out of scope of ICH M7*". **Proposed change:** It would be useful to add a reference, which is considered relevant instead (e.g ICH Q3A/B or others).
Q 7.2	2	**Comments:** The response to question # 7.2 suggests that results from the *in vivo* gene mutation assay generated as per ICH M7 Note 3 cannot be used for setting compound-specific impurity limits since the endpoint is mutation and not carcinogenicity. However, it contradicts the statement "Results in the appropriate *in vivo* assay may support setting compound specific impurity limits" provided in section 6 Hazard Assessment Elements of the ICH M7 guideline, EMA/CHMP/ICH/83812/2013. **Proposed change:** More clarity should be provided in section 6 Hazard Assessment Elements in the ICH M7 guideline, EMA/CHMP/ICH/83812/2013 regarding the type of *in vivo* studies that can support compound specific limits for mutagenic impurities.
Q 7.2	5	**Comments:** It reads: *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.* **Proposed change:** Results from these tests could identify **a** mode of action and/or **a** direct further testing strategy to complement the available data for a weight of evidence approach.
Q 7.3	4	**"The LTL approach can be applied to compounds with exposure limits based on the TTC or a compound/class specific AI. However,**

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		this approach is not applicable to PDEs. Higher levels of exposure for short-term exposure (30 days or less) may be acceptable on a case by case basis" **Comments:** This point is critical in establishing values for short term products. Could this be expanded for more clarity. Is a Harber or modified Harber approach acceptable?
Q 7.4	1	**Comments:** In the list of bullet points, the second bullet makes reference to "new or increased acceptance criteria for existing impurities". There could be confusion about the scope that this statement applies to. **Proposed change:** "changes to the drug substance synthesis resulting in a new or increased acceptance criteria for existing impurities **in the drug substance**."
Q 8.1	3	**Comments:** When is it appropriate to use an Option 4 control strategy? What is considered as negligible (e.g. 1%TTC) for option 4?
Q 8.2	3	**Comments:** When predictive purge calculations are used for Option 4 control, what elements should be considered? **Proposed change:** Explain the expectation with regards to purge calculation
Q 8.5	3	**Comments:** Q&A8.5 is contradictory with ICH M7 Option 1 **Proposed change:** ***Please Clarify:*** The "no" implicates that batch control of <30% is not sufficient. However, For control option 1, the ICH M7(R1) guideline states that periodic verification testing is justified when it can show that levels of the mutagenic impurity in the drug substance are less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3 consecutive production scale batches. The no is contradictory. In addition, the Q&A says that option 1 should test either at release or upstream but ICH M7 is proposing periodic verification testing. This is contradictory too. The periodic testing approach when results are

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		consistently below 30% of the acceptance limit on a representative set of batches should be allowed as it is mentioned in the ICH M7 (R1)
Q 9.1	5	**Comments:** It reads: *As an example, in cases where there is reason to question the outcome of a negative prediction (e.g., an aromatic amine is present, but the model gave a negative prediction).* Has to prediction of the (Q)SAR outcome for aromatic amines changed since 2014? **Comments:** *It is recommended that the sponsor re-run (Q)SAR predictions prior to the initial marketing application to ensure predictions reflect the most current data available….. Reassessment may also be considered if the predictions made for the initial global marketing application did not use a recent version of the software.* Is the same point meant here, i.e. the most recent software version should be used for (initial) marketing application, than combine both sentences If subsequent application, e.g. for variations are meant than clarify please.
Q 9.2	3	**Comments:** For marketing applications, what content and Common Technical Document (CTD) placement recommendations could improve the clarity of an ICH M7 risk assessment and control strategy? **Proposed change:** Taking into account the chapter "Consideration on marketed products" of ICHM7 guidance, can it be clarified that these requirements of M2-M3 documentation apply only in the cases where ICHM7 is applicable for Marketed products as listed under this chapter?
Q 9.2	6	**Comments:** Q. 9.2 deals with content and placement recommendations for marketing applications. The response is appreciated. Likewise, content and placement recommendations for clinical trial applications would be helpful.