27 September 2019

Submission of comments on *Reflection paper on the qualification of non-genotoxic impurities* (EMA/CHMP/SWP/545588/2017)

Comments from:

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| EFPIA/IQ |

*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) |
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|  | EFPIA/IQ welcomes the opportunity to provide EMA with comments on the principles laid down in the 'Reflection paper on the qualification of non-genotoxic impurities' (EMA/CHMP/SWP/545588/2017)’ further referred to as Reflection paper. Given the conceptual nature of the Reflection Paper, only high-level comments are provided and in order to facilitate further discussion, EFPIA/IQ would welcome the opportunity to further discuss the concepts outlined in the Reflection Paper and any aspect of these comments. EFPIA/IQ believes that a workshop would be useful to clarify aspects of the reflection paper.  **The comments presented here reflect the joint considerations of EFPIA and IQ[[1]](#footnote-1).**  Companies welcome the initiative of EMA to initiate the discussion on the best way to reduce animal testing and improve methods for impurity testing. Companies have significant experience with the execution of in vivo qualification studies to qualify impurities in Clinical Trial Material (CTM) and the final drug product in support of MAA. Any initiative to reduce these in vivo qualification studies is considered valuable by EFPIA/IQ.  The statement in ICH Q3A and B that “qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified” remains fundamentally sound. The approaches applied to achieve this, perhaps have been constrained in the past by a lack of other approaches than by in-vivo impurity qualification studies. The initiative of the reflection paper to examine alternative approaches is therefore much appreciated.  However, companies think that major clarifications and scientific advances are needed for this Reflection paper to become the catalyst for the reduction in animal testing it is aiming to be. Industry is very willing to participate in this initiative to reduce the use of animals in this area of toxicology. |  |

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|  | For EFPIA and IQ companies the aim to reduce in vivo qualification studies has 5 major components:  A] Providing clarity on exceeding Q3A/B limits during early development.  B] Use of 1 mg as limit for all drug products under 2g under Q3A/B  C] Providing guidance on the acceptance of alternative methods to replace in vivo qualification studies when these are required.  D] Maximizing the results from in vivo studies used to show safety of the drug substance for qualifying impurities  E] Consideration of risk/benefit of the pharmaceutical for qualification of impurities. |  |
|  | **On A]** **Providing clarity on exceeding Q3A/B limits during early development.**  EFPIA/IQ companies were disappointed to see that the application of the Reflection paper was limited to Q3A/B and has been silent on qualification of impurities during drug development of a medicinal product. EFPIA/IQ appreciates the initiative on this topic together with EMA to work on defining pragmatic acceptable limits for impurities during (early) drug development (a F2F meeting is scheduled for October 9, 2019).  In industry’s view, the concept that most toxicities are dose and duration dependent provides an option that is ready to be applied to define non-genotoxic impurity (NGI) limits for the (early) development phase. This concept has been applied within the regulatory context before, e.g. in ICH M7 to derive less-than-lifetime limits for mutagenic impurities and in ICH Q3C and Q3D to allow for higher PDE limits for intermittent and short-term dosing.  However, the Reflection paper notes that the application of modified Haber’s rule to shorter treatment durations warrants further discussion: “*Whether the use of modified Haber’s rule for the extrapolation of safety of NGI from life-time to subchronic exposure durations is appropriate remains to be established. Therefore, the use of modified Haber’s rule for qualification of non-genotoxic impurities warrants further discussion*” (line 157-160).  The practice in pharmaceutical industry has a comprehensive suite of measures in place to ensure the safety of patients during clinical trials, and these cover all aspects of trial design including the test articles. Although it is appropriate to specifically call out potential mutagenic impurities (as these require control at low levels), general test article specifications are appropriately managed using existing measures for clinical trials and do not warrant any additional and specific measures over and above those already in place.  Most companies apply some sort of higher acceptance criteria than ICH Q3A/Q3B in well-controlled and short duration early phase clinical trials for identified impurities that present no particular hazard alerts; which practice generally finds acceptance by regulatory agencies. In addition, as synthetic chemistry is likely to be refined and changed over development, setting commercial specifications (i.e., ICH Q3A/Q3B limits) at such an early time-frame in development will result in more animal testing (on impurities that often may not be relevant to the final commercial process) to prevent exceeding ICH specifications. Notably, Q3A/Q3B limits are not a requirement for early phase investigational studies.  Data reviewed by Harvey et al. (2017)[[2]](#footnote-2) demonstrated the scientific principles underpinning of acceptance criteria used by companies in early development. It should be noted that Haber’s rule was modified to be more conservative over the 6-months duration. With c3 x t = k, this results in a 30-fold lower value of 5 mg/day versus straight linear extrapolation c x t = k. This “modified” Haber’s rule was reviewed by Gaylor (2000)[[3]](#footnote-3) and determined to be an appropriate and **conservative** approach for short dosing periods.  The practice of accepting higher levels of impurities in clinical trial material for early phase clinical trials is critical to chemical development of a molecule. Harmonization and transparency about this practice will reduce the need to test animals in order to raise levels above ICH Q3A/Q3B.  Most importantly, EFPIA/IQ companies are of the opinion that it is not wise to reject mathematical approaches to adjust limits to less than life span dosing, since such dismissal effectively discounts the currently most effective way of reducing unnecessary animal testing. Further dialogue with stakeholders would be welcomed on the use and utility of mathematical approaches such as modified Haber’s rule for application to less than life time exposure. By way of similarity, the use of mathematical approaches is well accepted for managing risk associated with mutagenic impurities over varying periods of exposure, and the principles are essentially similar for general organic impurities. |  |
|  | **B] Use of 1 mg lower limit for all drug products under 2g under Q3A/A3B**  Review of the IMI eTOX database containing 204 pharmaceuticals in development has shown that 95% of compounds have a NOEL >0.3 mg/kg/day and 99.5% of compounds have a No Effect Level (NOEL) of >0.02 mg/kg/day (Harvey et al, 2017). For a 50 kg human, this translates to doses of 15 and 1 mg/day, respectively, which will stay below the No Effect Level and can therefore be considered safe.  Industry is therefore of the opinion that a limit of 1 mg per day as mentioned in the ICH Q3A, can be considered as generally safe for lifelong treatment and that this makes the 0.15% restriction, as defined in ICH Q3A unnecessary. Regretfully this option has not been taken into consideration for instance as an alternative for the Cramer classification that has been discussed in the NGI Reflection paper. |  |
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|  | **C]** **Providing guidance on the acceptance of alternative methods to replace in vivo qualification studies when these are indicated.**  Companies would encourage the drafting of a flow schedule(s) and/or decision tree(s), such as illustrating the relationships with existing guidance and visualizing a step-wise approach to evaluating in silico and in vitro data with regard to impurity levels. Such schedules might provide a helpful catalyst for global scientific and regulatory discussion.  Industry has indicated that they do not understand the need for the proposals in the Reflection paper, especially where these result in stricter qualification levels, since the Reflection paper also recognizes “*that impurities generally are present in the API at low levels and that there is no concern at the anticipated low exposure levels (line 128-133)”.*  The comments can be grouped into   1. Lack of alignment process accepted by regulatory agencies for the qualification of impurities      1. Lack of validated and directly applicable methodology. EFPIA/IQ companies have indicated that they see no possibility to apply the principles of the Reflection paper in the short-term future. 2. Need to clarify the acceptance of current practice of in vivo qualification studies. EFPIA/IQ companies see a clear need to be able to continue the current practice under Q3A/Q3B until new methodologies have been validated and gained broad global acceptance. 3. Testing for pharmacology |  |
|  | **C.1 Alignment with other EMA and ICH guidances**  The Reflection paper is dramatically different from the processes accepted by regulatory agencies for the qualification of impurities. Currently read-across, in silico, and in vitro methodology are not accepted by regulatory agencies for the qualification of impurities, despite the fact that ICH Q3A/B already encompasses alternative approaches. To secure the intended reduction in in vivo testing, it is important that the alternative approaches can be accepted on a global basis.  The Reflection paper makes recommendations that are not consistent with current ICH guidelines and could greatly affect impurity qualification. Companies have indicated that better description of the place where the new Reflection paper would fit into the current practice of risk assessment of impurities would be very helpful.  Before attempting to implement these recommendations, it is critical that discussion and agreement occur at a global level to ensure a harmonized approach. Progressing such alternatives within one region only will not be sufficient to achieve the desired outcome of reduction of in vivo qualification studies.  There is a concern in industry that the Reflection paper will become a set of additional requirements to be met in the EU and as such become another requirement on top of the existing ICH and local guidances. This would forfeit the aim of the Reflection paper, and constrain industry in ways, which were not envisaged at the time that ICH Q3A/B were developed. It is recommended that the authors of the Reflection paper strongly emphasize that suggestions and examples in the Reflection paper are an invitation to replace animal studies, but should not be interpreted as creating new requirements that should be enforced by regulatory agencies.  It is noted that ICH Q3A/B already provides the flexibility to adopt such non-animal approaches where appropriate (e.g. “Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale”). Additionally, Q3A/B is not specific, it only states that “qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified”. It is convention and common application of these guidelines that has resulted in industry and regulators thinking that this requirement must met by testing or examining the level of impurity in a drug by nonclinical and/or clinical studies. But this is actually a self-imposed constraint; ICH Q3A/B is much more open in approaches to deliver product safety to patients. |  |
|  | If the industry understands correctly, the refection paper advocates for any NGI that is not qualified under Q3A/B, to check if the levels are below “the TTC”. However, the Reflection paper leaves room for interpretation on which TTC to apply. Mention is made of the Cramer classification and category specific TTC as defined by Kroese et al. (2004). Most impurities associated with pharmaceutical compounds will fall into Class 3, because of differences between their chemical space and that of the Cramer classification, with a limit of 90 µg/day.  In an example for a drug substance of 750 mg, this TTC approach would result in a limit that is 11 times lower than the level of 1 mg under Q3A. Phrased in another way: any Cramer Class 3 impurity in a drug substance with a daily oral dose of >60 mg will then have an impurity limit of less than the ICH Q3A of 0.15%. As visible by these two examples, industry does not understand why the safety limit for an impurity that is not qualified under Q3A/B will have to be LOWER than the safety limit for an impurity which is qualified. Companies have expressed great difficulty understanding the logic of this proposal.  Use of a TTC is not supported by recent analysis of toxicology databases demonstrating that very few chemicals exhibit any toxicity at doses of 1 mg or less in humans (Harvey et al, 2017). It is emphasized that application of Q3A/B has not given rise to human safety risks since ICH defined these guidelines. Therefore, industry thinks that the Cramer classification TTC’s need to be considered with caution and consideration, and cannot be applied as a general principle.    If the ICH Q3A/Q3B limits get dramatically lowered to TTC-based levels, it will not be economically feasible to control impurities as it will likely result in impurity limits well below what is currently being detected. This will result in more animal testing in order to raise impurity levels to more feasible limits. In order to reduce impurities further purification is required. This has significant implications both in terms of cost and environmental impact, i.e. increase in waste. Furthermore, such purification is dependent on a number of factors relating to the physicochemical properties of the desired product and associated impurities and thus is not a simple case of recrystallize and it will be purified. |  |
|  | **C.2** **Lack of well-established tools**  The Reflection paper proposes non-animal strategies to qualify non-genotoxic impurities, in particular focussing on the TTC, QSAR, read-across (RAX) and in vitro approaches. Although these methodologies are interesting from an academic point of view, it is premature to expect that these can already be used reliably in the context of the regulatory toxicology testing and the qualification of NGI in chemically synthesized pharmaceuticals. EFPIA/IQ companies have indicated that they see no possibility to apply the principles of the Reflection paper in the short-term future. This industry assessment is based on individual companies’ experience with using non-animal approaches to qualify impurities during development, at MAA and during variations. Additionally, very few specific in silico and in vitro approaches are at level of maturity where they could be applied for impurity qualification.    While in silico and in vitro approaches may provide insights to *hazard identification*, the extrapolation of the hazard into the translatable in vivo data and ultimately into human *risk*, however, will require additional information, such as on exposure considerations (see Berggren et al. 2017), the adaptability of biology and/or translatability of predicted animal observations to humans.  Current methodologies have been developed to raise “alerts”; it is completely unknown how data from these novel approaches would be used to support quantitative risk assessment (i.e., setting an impurity specification). Therefore, further discussions are needed on selection of appropriate in silico or in vitro approaches and validation of the selected approaches in the chemical space of impurities in pharmaceutical products.  Additionally best practices on the number of model systems and the type of model systems to be used would have to be developed similar to the prediction of mutagenicity for ICH M7.  Industry is concerned that confirmation of the absence of the identified hazards will be required in the future, essentially necessitating the execution of in vivo animal studies. Given the high level of false positives outcomes in “in silico” prediction systems, which have been developed with sensitivity in mind, this potentially may increase the number of in vivo studies. Also, it is uncertain if the absence of such alerts would mean eliminating the need for in vivo data.  Industry understands the potential in the application of new technologies, but is critical on the extent to which these can already be applied. Comments provided on technologies and practical aspects are summarized below:   * The currently existing systems have not been validated for pharmaceutical type molecules (RAX, QSAR, in vitro) * The currently available systems focus on the prediction of one type of toxicity/endpoint (e.g. mutagenicity; hepatotoxicity), but lack the ability to screen for a large set of endpoints as is possible in classical toxicity studies. Only very few of these in silico and in vitro approaches are at level of maturity where they could be industrialised for regulatory use for impurity qualification (as per ICH M7). * Explicitly, organ-specific toxicities are mentioned as desirable to assess for in the Reflection paper. Despite there being QSAR models and structural alerts developed for organ toxicities in the public domain, these systems have been built typically on small test sets and have a very limited applicability domain. In the case of QSAR models, the structural alerts are often generic in nature. In addition, these have not been extensively validated on well-defined test sets, it is not clear what sensitivity, and specificity can be expected. * For in vitro systems, the Reflection paper suggests that these can be used to test the purified NGI when QSAR predictions raise concerns. The envisaged process is unclear e.g. with respect to cut-off points when a hazard would need to be followed up with testing. In addition, in vitro systems have rarely been validated for predicted values for risk assessment. At the same time the Reflection paper indicates that established test batteries and strategies are not available yet (line 210-211) and acknowledges that targeted in vitro models might not be validated/qualified for their use in regulatory purposes (line 213-214). Unfortunately, there is no outline of a plan how to come to the point that these systems can be applied. * Industry thinks it would be useful to have more clarity on the expectations of model usage, both with respect to endpoints and what is expected in determining the validity of a prediction * The authors indicate that read-across approaches may provide relevant safety information when sufficient compounds with similar structure as the NGI exist, for which toxicological data are available (line 187-189). Industry is particularly critical on the possibilities to apply read across. Industry experience is so far that the data of “related compounds” are not available. Moreover where attempts have been made to apply read across, the result has been rejected by regulatory authorities. * Industry considers the proposal to use weight of evidence approaches appropriate and fit for purpose. It makes sense to integrate all types of data available (literature, QSAR, RAX, in vitro, etc.) in order to decide whether the NGI can be considered safe at the specified level, once these data can be generated reliably. * However, it is realized that any integrated assessment will be open to challenge. Providing examples of what an acceptable integrated assessment looks like to qualify an impurity would be very helpful.   EFPIA/IQ companies are of the opinion that the alternative methodologies should be clearly demonstrated to be robust enough before they are applied to the qualification of NGI, to avoid raising unnecessary concern, creating more work and increasing the use of resources in the production of medications. Notwithstanding, industry understands and strongly supports the wish to reduce the use of animals in the qualification of NGI and is willing to support initiatives which contribute to this aim. |  |
|  | **C 3.** **Need to clarify the acceptance of current practice of in vivo qualification studies.**  EFPIA/IQ companies are of the opinion that it is not wise to disregard the current practice of in vivo testing and see a clear need to be able to continue the current practice under Q3A/Q3B until new methodologies have been validated and globally accepted.  The quality of and the predictive value to humans has been proven with the standard approach of impurity qualification by testing spiked or non-spiked API batches in vivo. In case, the use of in vivo qualification studies is no longer acceptable, issues with medication supply can be anticipated.  Companies have indicated that they would also benefit from more clarity on acceptable designs for in vivo qualification studies. Current practices vary significantly between companies, with many studies/ study designs being overly large. In the view of EFPIA/IQ companies, in vivo qualification studies can best be performed using API batches at the NOAEL or NOEL for the API, spiked, as necessary, with adequate levels of the impurity/(ies) which needs to be qualified. Under such conditions, interference with API toxicity can be avoided.  Companies have indicated confusion about understanding to which impurities the Reflection paper applies. Such confusion can be avoided by stating clearly that the approaches suggested in the Reflection paper are intended only for impurities that are not yet qualified by Q3A/Q3B or one of the specific impurity guidelines: M7, Q3C, Q3D. |  |
|  | C 4: testing for pharmacology  EFPIA/IQ companies do not consider it necessary to evaluate pharmacological activity of impurities (lines 100-102). During research and development, API structure and activity are optimized to generate the intended pharmacological activity. Theoretically and practically, API derived products (impurities) are very unlikely to have a stronger pharmacological effect on the intended target and these are likely to be present at much lower quantities. For non-target related effects it is equally unlikely that a more than 100 times more potent effect would be found (based on the assumption that there is 1% impurities [line 129]), which would not be detected in a toxicity assessment.  This is the foundation of the practical observations over many decades that, with the exception of genotoxicity, a limit of 1 mg per day limit as mentioned in the ICH Q3A can be considered as generally safe for lifelong treatment, and higher limits are generally acceptable for less than lifetime exposure. It is essential, in the development of any new guidance, that this foundation is always kept in mind, so as to avoid over-emphasis or over-concern on the validation of substances which have been proven safe and acceptable over decades of pharmaceutical production and patient exposure.  Given that the number of pharmacological targets is considerably higher than the number of toxicology targets, companies consider this suggestion not needed and not executable. |  |
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|  | **D. Maximizing the results from the in vivo studies used to show safety of the drug substance for qualifying impurities**  Industry feels the best way to immediately limit animal testing for impurities is by maximizing the studies already done to understand the safety of the drug substance. These studies already contain a certain level of impurities and can be applied to demonstrate qualification. Suggesting that testing the API masks the toxicity of impurity will eliminate using normal development studies and result in more animal testing to qualify each individual impurity in isolation. In reality, the calculation of the qualified level of impurity is typically at the NOAEL, so it is unlikely the toxicity will be “masked”.  The drug substance toxicity studies can be maximized for qualifying impurities by clarifying the calculation for qualification of impurities. In ICH Q3A it states that the level of impurity can be qualified by determining “the actual amount of impurity” and making sure exposure to that impurity does not exceed this amount. However, this has been interpreted differently and various additional safety factors or conservative assumptions have been added to the calculation. This can lead to additional impurity qualification studies as the toxicity study used to develop the drug substance is no longer sufficient to qualify the impurity. |  |
|  | **E]** **Consideration of risk/benefit of the pharmaceutical for qualification of** **impurities.**  EFPIA/IQ companies are disappointed that the Reflection paper did not include consideration for clinical benefit of the therapeutic (e.g., those for advanced cancer or other life-saving indications such as antimicrobials). The concept of benefit versus risk is important for impurity qualification and should be incorporated in the paper. It is a missed opportunity to rectify the apparent confusion that exists around impurity qualification levels for the above indications. Companies have indicated that they encounter regular requests to qualify impurities to standard levels for API’s that are severely toxic, i.e. cytotoxics. |  |

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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Please add more rows if needed.

1. International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community. [↑](#footnote-ref-1)
2. Harvey J, Fleetwood A, Ogilvie R, Teasdale A, Wilcox P, Spanhaak S. 2017. Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development. Regul Toxicol Pharmacol. 84:116-123. [↑](#footnote-ref-2)
3. Gaylor DW. 2000. The use of Haber's law in standard setting and risk assessment. Toxicology. 149(1):17-9. [↑](#footnote-ref-3)