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4 Reflection paper on the qualification of non-genotoxic 5 impurities

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Reflection paper on the qualification of non-genotoxic impurities

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1. Introduction

The core ICH quality guidelines addressing qualification of NGI are ICH Q3A and Q3B. These guidelines state 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. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations. For DNA reactive (mutagenic) impurities, elemental impurities and residual solvents specific guidance is provided (ICH M7, Q3D and Q3C, respectively). However, for non-genotoxic impurities (NGI) little guidance is available on how these impurities should be qualified.

The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. This is the situation for most impurities that have been present in the drug substance batches throughout development. The problem with this approach is that qualification is *establishing biological safety* of a drug substance or drug product with a given impurity profile, which is not the same as characterising the safety profile of an impurity. Obviously, when toxicity is observed, it is usually not possible to discriminate between toxicity attributable to the active pharmaceutical ingredient (API) and toxicity attributable to the impurities present in the drug substance batch. The safety testing only establishes that a drug substance batch with a certain impurity profile has a specific safety profile. This limits the possibilities of extrapolating the safety of a drug substance or product with a given impurity profile to a drug substance or product with the same API but with an increased level of an impurity, when no impurity-specific data are available. Also when new impurities arise due to manufacturing changes or novel degradants are discovered at a later stage of development, and these impurities cannot be controlled at a level below the qualification threshold, a lack of impurity-specific safety data complicates the qualification process.

According to the ICH Q3A/B guidelines, additional safety testing should be considered in such cases. These guidelines do not explain in detail how NGI should be qualified or which criteria should be applied. The guidelines state that factors such as patient population, daily dose, and route and duration of drug administration may be considered in deciding which studies can be regarded as appropriate. The guidelines also state that safety assessment studies to qualify an impurity should compare the new drug substance/drug product containing a representative amount of the new impurity with previously qualified material. Furthermore, the guidelines express that studies using isolated impurities may sometimes be appropriate. Finally, the ICH Q3A/B guidelines describe in a note that if general toxicity studies are desirable, study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies may be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

Although this guidance seems straightforward, concerns have been expressed from a scientific and 3R's perspective. When using a study design comparing qualified and non-qualified material, impurities exceeding the qualification threshold in drug substances/products may in fact be dosed in these animal studies at such low levels, that it is unlikely that a safety signal would be detected in such studies. Especially when the API dose is low. Furthermore, the background toxicity of the API itself may mask any new toxicity caused by the impurity. In those cases, the scientific rationale for the design of the qualification study is compromised, and from a 3R's perspective no animal studies should be performed if these studies are unlikely to provide relevant information.

In the literature, novel non-animal strategies to evaluate the toxicity of compounds have been described (e.g. Berggren et al. 2017; Blaauboer et al. 2016). A recent overview of these developments in the EU has been provided by Zuang et al. (2017). In this reflection paper, there is a discussion on

how a more impurity-specific evaluation could be followed making use of these novel approaches. Such an approach may provide more useful information than the generic approach of testing a batch with the specified level of impurity in a short/medium term toxicology study in animals.

The current document does not contain explicit guidance on which non-clinical approaches are most suitable. Rather it tries to establish a framework to facilitate future discussions among stakeholders. The thresholds above which qualification is required are defined in the ICH Q3A/B guidelines. It is recommended to consider the approaches discussed in this reflection paper when qualification is required and data from the regular (non-)clinical development with the API batches is not considered sufficient. Also when the level of an impurity is below the qualification threshold defined in ICH Q3A/B guidelines, but a toxicological concern may still exist, the approaches discussed in this reflection paper may be considered. This could be the case when high dose pharmaceuticals are concerned, or when a concern exists that the impurity involved is unusually potent, producing toxic or pharmacological effects at a level equal to or below that of the identification threshold.

2. Scope

This reflection paper considers the safety evaluation of NGI in chemically synthesised pharmaceuticals.

This reflection paper will not address the qualification of solvents and elemental impurities since specific guidance is provided in ICH Q3C and ICH Q3D, respectively.

This reflection paper does not consider the qualification of impurities in biological medicines, oligonucleotides and synthetic peptides. However, in some instances the use of the principles discussed in this reflection paper could be considered to the appropriate extent.

3. Key considerations

Integrated risk assessment

To assess whether a NGI has acceptable safety at the proposed specified level a case-by-case approach should be used. The integrated risk assessment (IRA) may encompass several or all of the approaches discussed in more detail in the subsequent sections, but may also be limited to a single or only few steps. In this reflection paper no specific recommendations are made which *in silico* tools or *in vitro* methods to use. However, regulatory acceptance of any tool or assay should be supported with data showing the method is suitable for its intended purpose, as explained in following sections.

A reasonable first step could be to assess whether the exposure to the NGI would remain below a threshold of toxicological concern (TTC). When this is the case and it can also be corroborated that no relevant pharmacological activity would occur, the evaluation could end.

When a risk cannot be excluded on the basis of negligible exposure, further information may be retrieved from toxicological databases, (Quantitative) Structure Activity Relationship ((Q)SAR) approaches and read-across (RAX) approaches. When sufficient relevant information is available on comparable structures indicating low risk, the evaluation could be concluded.

It could also be possible that insufficient information is available or that specific concerns are identified. In that case, risk-driven choices for appropriate *in vitro* testing should be made to fill data gaps and inform on potential risks and safe exposure levels. The interpretation of in vitro data would depend on comparison with data obtained for structurally similar compounds or compounds having a similar activity profile *in vitro*. The ability to link the data would to a large extent depend on the granularity of the databases and knowledge on the predictivity of the data.

Further integration of *in vitro* and *in silico* data could indicate a potential impact of the NGI on specific adverse outcome pathways (AOPs). AOPs are currently in development and once sufficient data are available it may be possible to assess a compound based on a signature of data obtained *in vitro*.

Additional analyses could encompass quantitative *in vitro-in vivo* extrapolation (QIVIVE) and PBPK modelling in order to extrapolate the data obtained in vitro to the human situation.

Dose considerations

Daily exposure levels

In the ICH Q3C and Q3D guidelines, acceptance of a specified level of an impurity is regulated by setting a compound specific health based level defined as a permitted daily exposure (PDE) associated with an acceptable risk level. The older ICH Q3A and Q3B guidelines still regulate acceptability on a concentration based approach resulting in a variable patient exposure to impurities depending on the dose of the API. As is the case for elemental impurities and residual solvents, any conclusion on the safety of a NGI at a specified level can only be based on a safety evaluation considering the daily intake of the impurity. For this the maximal daily dose of the medicinal product should be taken into account to calculate the daily intake of the NGI.

To comply with pharmaceutical quality, specified levels for impurities will be low, usually close to or below 1%. Consequently, exposure to these impurities will be low. Therefore, the focus of a safety evaluation of any new impurity or impurity with an increased specified level would be to identify impurities with toxic properties, even at these low levels of exposures. Ultimately, the goal is to determine whether the NGI can be considered safe at the specified level. Many NGI will have a low or moderate toxicity, which would not be of concern at the anticipated low exposure levels.

Application of TTC values

A well-known principle is the TTC. Making use of TTC values would provide a sound basis to conclude on the absence of risk for those NGI for which it has been calculated that the daily intake is below the appropriate TTC. Oral TTC values have been delineated for NGI based on Cramer-classification (Munro et al. 1996; Tluczkiewicz et al. 2011). For pharmaceuticals administered through different routes, different TTC values may be appropriate. When products administered by inhalation are concerned, local toxicity effects may be of greater concern than systemic effects and lower levels may apply (Schüürmann et al. 2016). On the other hand, dermally applied pharmaceuticals may have a low systemic exposure and it may be feasible to refine oral derived TTC values to adjust for this lower exposure scenario (Williams et al. 2016). In the case of parenterally used pharmaceuticals, oral bioavailability data could be used to transform oral to parenteral TTC values, but if no bioavailability data are known, a standard conversion factor of ten could be used.

Where sufficient data are available, category-specific TTC values may have been derived and can be used (Kroes et al. 2004).

Duration of exposure

Another consideration related to dose is the duration of exposure. It has been argued that modified Haber's rule could be used to justify that exposures for a short duration could be higher than for life-long exposure. Haber's rule is appropriate for extrapolation to different durations of exposure for conditions where the dose rate is not the determining factor and only total dose dictates the biological effect. (Gaylor, 2000). Where the dose rate does matter, modified Haber's rule has been proposed to justify that exposures for a short duration could be higher than for life-long exposure (ten Berge et al 1986; Gaylor, 2000; Harvey et al., 2017). However, the dose rate-time relationship in modified Haber's rule is based on data from ten Berge and co-workers (ten Berge et al, 1986) who studied

noxious gasses and exposure durations of less than 2 hours. 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.

Structure activity relationships

When a risk cannot be excluded on the basis of its anticipated daily exposure and a TTC approach, (Q)SAR approaches may be used to evaluate both the pharmacological and toxicological properties of the NGI. To successfully apply (Q)SAR, the tools used should be shown to be suitable for their intended purpose. This means that it should be clear which defined endpoint is predicted; the algorithm used should be unambiguous; the domain of applicability should be defined; appropriate measures of goodness-of–fit, robustness and predictivity should be provided; and - if possible, consideration should be given to a mechanistic interpretation of the model used. These are the principles reflected in the OECD Principles for the validation, for regulatory purposes, of (quantitative) structure-activity relationship models (OECD 2004). Detailed guidance on how to apply (Q)SAR has been published by ECHA for the implementation of REACH (ECHA 2008). No such detailed guidance exists for ~~the~~ pharmaceuticals. However, when required, the ECHA guidance may be consulted. Currently, no established procedures exist for investigating the toxicity of compounds with *in silico* methods. Which endpoints to investigate and which specific method to use may vary and efforts are being made to develop more standardised protocols (e.g. Myatt et al 2018). The endpoints to be considered in *in silico* approaches for the qualification of NGI can be affected by several factors, such as intended use and route of administration of the pharmaceutical and existing knowledge on comparable compounds. Usually endpoints will be limited to those associated with organ-specific toxicity. For products administered topically or by inhalation, sensitising potential should be considered.

NGI may either have a structure that is related to the API, only having deviating substructures, or have a structure not resembling the API. For NGI only having a deviating substructure, the goal would not be to predict the similarity in toxicity profile with the API. To the extent that the profile would be similar, the NGI, being present at such low levels, would not contribute significantly to the overall safety profile of the drug substance. Instead it would be relevant to look at the differences and determine whether any substructures that have not been identified in the API alert for specific types of toxicity.

For NGI bearing a structure not related to the API, RAX approaches may provide relevant safety information when sufficient compounds with similar structure as the NGI exist for which toxicological data are available.

From a pharmacological perspective it may be considered that closely related impurities may have enough similarities to the API to show activity at the same primary target. Provided that the pharmacological action at this target is similar, this would not be of concern, since the relative contribution of the NGI to the total pharmacological activity would be negligible. However, pharmacological activity could be a concern when for example an agonist becomes less efficacious in the presence of an antagonistic impurity.[1] To evaluate these possibilities medicinal chemistry expertise may be required.

[1] This could be a theoretical concern only. Examples for this situation are searched for. Depending on the outcome it will be decided whether this paragraph will be maintained.

Use of pharmacological and toxicological databases

Historical toxicological and pharmacological data are increasingly being collected in proprietary and public databases, including both *in vivo* and *in vitro* data. Making use of these data will permit the derivation of more specific TTC values. Also such databases are the starting point for the application of (Q)SAR and RAX approaches. When using data from these databases it should be considered what the applicability domain of the database is to qualify the use of the database for the safety evaluation of NGI. An example of a database containing information of pharmaceuticals is the IMI eTox database. Other databases may also be useful, provided that the applicability domain fits with the structure of the impurity for which a safety evaluation is being performed.

In vitro approaches

When (Q)SAR predictions raise concerns, further qualification data may be needed. Targeted use of *in vitro* methodologies (2D and 3D cell systems and microphysiological systems) with careful selection of endpoints may be considered. No single assay would provide a definitive answer to the question whether an impurity can be considered safe at the specified level. Scientific efforts are ongoing to develop batteries and strategies using *in vitro* approaches. When applying an *in vitro* approach to evaluate the safety of a NGI, assays should be carefully selected based on concerns identified from SAR or RAX analyses and their applicability justified. Targeted *in vitro* models might not be validated/qualified for their use for regulatory purposes. This should not prevent the use of non-standard *in vitro* methods. To facilitate an assessment of the quality of data produced and their potential utility in regulatory applications, supportive information should be provided, showing that the method is suitable for its intended purpose. Useful guidance to this end can be found in the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) and the OECD Guidance document for describing non-guideline in vitro test methods (OECD 2014).

It is expected that more valuable information would be obtained from assays in which the purified NGI is tested. Adding spiked samples of the API to test systems would complicate the interpretation of the read-outs, as the API itself may also have an effect in the model employed.

Qualification of the NGI at the specified level

For NGI qualification there is no strict-requirement to determine a NOAEL for the NGI in order to draw a conclusion on the safety of the NGI at the specified level. The only requirement is to determine that at the specified level no adverse effects are expected. This alleviates the need to extend the safety evaluation to a very detailed level in many cases.

To reach a conclusion a weight-of-evidence (WoE) approach may be applied. This approach should describe both the evidence pointing to a risk and the evidence showing the absence of risk. In addition the uncertainty of the evidence should be made clear. Lastly, the balance between potential risk and absence of risk should be discussed, before a conclusion is drawn.

Reduction of animal use

Following the 3R strategies described in this reflection paper will in many cases obviate the requirement to perform a dedicated animal study. In fact, by generating impurity-specific safety data and integrating this with existent knowledge, it is likely that these approaches will provide a better understanding of the safety of the NGI than by following the conventional approach of testing an active substance batch containing the NGI in an animal study.

4. Conclusion

When impurity-specific safety information is required, alternative strategies to gather this information may be followed, including the use of TTC, (Q)SAR, RAX and *in vitro* approaches. This information can be used in an integrated risk assessment. A WoE approach including an assessment of the level of uncertainty may be used to decide whether the NGI can be considered safe at the specified level.

5. References

- Berggren, E., White, A., Ouedraogo, G., Paini, A., Richarz, A.-N., Bois, F. Y., Exner, T., Leite, S., Grunsven, L. A. van, Worth, A., & Mahony, C. (2017). Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods. Computational Toxicology, 4, 31-44.
- Blaauboer BJ, Boobis AR, Bradford B, Cockburn A, Constable A, Daneshian M, Edwards G, Garthoff JA, Jeffery B, Krul C, Schuermans J. Considering new methodologies in strategies for safety assessment of foods and food ingredients. Food Chem Toxicol. 2016 May;91:19-35.
- ECHA 2008. ECHA Guidance on information requirements and chemical safety assessment chapter R.6 QSARs and grouping of chemicals.
- EMA 2016. Guideline on the principles of regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012).
- Gaylor D.W. The use of Haber's Law in standard setting and risk assessment. Toxicology 149, 2000, pp. 17-19.
- Harvey J, Fleetwood A, Ogilvie R, Teasdale A, Wilcox P, Spanhaak S. Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development. Regul Toxicol Pharmacol. 2017 Mar;84:116-123.
- ICH M7 (R1) Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
- ICH Q3A(R2) Impurities in New Drug Substances
- ICH Q3B(R2) Impurities in New Drug Products
- ICH Q3C(R5) Impurities: Guideline for Residual Solvents
- ICH Q3D Guideline for Elemental Impurities
- Kroes, R., Renwick, A., Cheesman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Wurtzen, G., 2004. Structured-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42, 65–83.
- Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of toxicological concern. Food Chem. Toxicol. 34, 829–867.
- Myatt GJ, Ahlberg E, Akahori Y, Allen D, Amberg A, Anger LT, Aptula A, Auerbach S, Beilke L, Bellion P, Benigni R, Bercu J, Booth ED, Bower D, Brigo A, Burden N, Cammerer Z, Cronin MTD, Cross KP, Custer L, Dettwiler M, Dobo K, Ford KA, Fortin MC, Gad-McDonald SE, Gellatly N, Gervais V, Glover KP, Glowienke S, Van Gompel J, Gutsell S, Hardy B, Harvey JS, Hillegass J, Honma M, Hsieh JH, Hsu CW, Hughes K, Johnson C, Jolly R, Jones D, Kemper R, Kenyon MO, Kim MT, Kruhlak

NL, Kulkarni SA, Kümmerer K, Leavitt P, Majer B, Masten S, Miller S, Moser J, Mumtaz M, Muster W, Neilson L, Oprea TI, Patlewicz G, Paulino A, Lo Piparo E, Powley M, Quigley DP, Reddy MV, Richarz AN, Ruiz P, Schilter B, Serafimova R, Simpson W, Stavitskaya L, Stidl R, Suarez-Rodriguez D, Szabo DT, Teasdale A, Trejo-Martin A, Valentin JP, Vuorinen A, Wall BA, Watts P, White AT, Wichard J, Witt KL, Woolley A, Woolley D, Zwickl C, Hasselgren C.. In silico toxicology protocols. Regul. Toxicol. Pharmacol. 2018 Jul;96:1-17

- OECD 2004. OECD principles for the validation, for regulatory purposes, of (quantitative) structure-activity relationship models. http://www.oecd.org/chemicalsafety/risk-assessment/37849783.pdf.
- OECD 2014. Guidance document for describing non-guideline in vitro test methods. http://www.oecd.org/publications/guidance-document-for-describing-non-guideline-in-vitro-test-methods-9789264274730-en.htm
- Schüürmann G., Ebert R.-U., Tluczkiewicz I., Escher S.E., Kühne R. Inhalation threshold of toxicological concern (TTC) — Structural alerts discriminate high from low repeated-dose inhalation toxicity. Environment International 88 (2016) 123–132.
- ten Berge W.F., A. Zwart, L.M. Appelman. Concentration—time mortality response relationship of irritant and systemically acting vapours and gases. Journal of Hazardous Materials, Volume 13, Issue 3, 1986, pp. 301-309.
- Tluczkiewicz, I., Buist, H.E., Martin, M.T., Mangelsdorf, I., Escher, S.E., 2011. Improvement of the Cramer classification for oral exposure using the database TTC Repdose — a strategy description. Regul. Toxicol. Pharmacol. 61, 340–350.
- Williams F.M., H. Rothe, G. Barrett, A. Chiodini, J. Whyte, M.T.D. Cronin, N.A. Monteiro-Riviere, J. Plautz, C. Roper, J. Westerhout, Ch. Yang, R. Guy, Assessing the safety of cosmetic chemicals: consideration of a flux decision tree to predict dermally delivered systemic dose for comparison with oral TTC (Threshold of Toxicological Concern), Reg. Toxicol. Pharmacol. 76 (2016) 174–186.
- Zuang V., Viegas Barroso J.F., Belz S., Berggren E., Bernasconi C., et al. EURL ECVAM status report on the development, validation and regulatory acceptance of alternative methods and approaches (2017). Publications Office of the European Union