Submission of comments on 'Reflection paper on the qualification of non-mutagenic impurities'

Fields marked with * are mandatory.

* Name of organisation or individual

EFPIA

* Country of organisation or individual

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

Please click **here** to be redirected to the guideline text. The public consultation is launched on 30 January 2025 until 30 April 2025.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section.
If you need more rows to be added to the table, please contact dora.duarte@ema.europa.eu
Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 April 2025) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement

All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller.HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your

personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

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You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.
  - (●) Yes

- ○ No

Should you not want to give consent to publish, please send your objections to Datacontroller. HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

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1. General comments

	General comment
1	Major - There are multiple ICH guidelines (ICH Q3A, B, C, D, E and M7) which are implemented at different stages of development that ensure the diverse range of impurities in drug substances and products are controlled to levels that protect patient safety. The ICH Q3A/B impurity guidelines have been in operation for 30 years and provide details of the agreed frameworks for assessment and control of NMIs in drug substance and products respectively. It is recognized that the limited detail in specific sections of the ICH Q3A/B guidelines (as compared to other ICH impurity guidelines) has, in certain cases, led to a divergence of approaches regarding the NMI qualification that can require resolution on case-by-case basis with Health Authorities. As a consequence, industry sought harmonization on specific aspects of the NMI qualification process and outlined a series of proposals to augment the existing ICH Q3A/B NMI qualification frameworks [Slikkerveer (2024), Hasselgren (2024), Kenyon (2024), Lortie (2023) Mitra (2021), Graham (2021), Weidolf (2020), Harvey (2017)]. EFPIA sees the publication of the EMA draft reflection paper (DRP) as an opportunity for further discussion in this area and to provide greater clarity as to when ICH Q3A/B guidelines can be modified to better align with ICH Q9 risk management principles. EFPIA would appreciate further dialogue with EMA before the implementation of the proposed NMI framework. The NMI qualification process can be complex, requires interaction with multiple stakeholders including Quality and Safety, and as consequence it has the potential to have a significant impact on drug development and supply of established products to patients.
2	Major - The EMA DRP describes a wide range of alternative 3Rs orientated strategies, including in silico, in vitro and in vivo approaches for the qualification of new, or elevated levels, of NMIs identified in a drug substance or product after the conduct of pivotal in vivo toxicology studies. While EFPIA strongly supports 3Rs alternatives, greater clarity on EMAs proposed NMI qualification framework is required to ensure it is practicable and feasible given the diversity of scenarios encountered during pharmaceutical development. As written it is not clear if the intent of the EMA DRP is to (a) assert that the current ICH Q3A/B impurity qualification frameworks (and associated impurity identification and qualification thresholds) are insufficient, or (b) propose alternatives to improve the established processes for the assessment and control of NMIs in drug substance and products in certain circumstances (e.g., based on the level of concern described in the DRP). Although alternative approaches to NMI qualification are welcomed, it is EFPIA's opinion, that many the majority of the proposed in silico, in vitro and in vivo approaches outlined in the EMA DRP are not sufficiently developed or validated for the routine assessment of impurities of drug substance or drug products in the context of a regulatory setting at this time.

3	Major - For example, validated in silico computational toxicology (Q)SAR approaches for the identification of general (chronic) toxicity in major target organs and systems (e.g., liver, kidney, cardiovascular, gastrointestinal, central nervous and respiratory systems) are not currently available (aside from SAR approaches to identify general toxicophores). In our opinion, the only in silico computational toxicology approach that has the potential to be viable in the short term to augment the ICH Q3A/B aligned NMI qualification process is read across (RAX) assuming that it can be empirically derived based on consensus cheminformatics approaches. It would be beneficial to develop and publish examples detailing the current in silico RAX tools that are considered adequate to augment the existing ICH Q3A/B NMI qualification frameworks, as well as providing further guidance on when and where they could be applied. In addition, application of in silico approaches that categorise NMIs according to alternative safety-based threshold of toxicological concern (TTC) values (e.g., PQRI, Cramer, etc.) would result in a marked change to the existing impurity identification and associated qualification thresholds outlined in ICH Q3A/B guidelines. Application of these alternative TTC values are not considered to be practicable from an analytical or process chemistry perspective, nor warranted from a safety perspective (these limits have not been used for this purpose since ICH Q3A/B were implemented). In EFPIA's view, the application of ICH Q3A/B NMI identification and qualification thresholds (e.g. 1 mg/day), augmented with robust SAR approaches to discriminate unusually potent or toxic compounds, would be considered more appropriate than these alternative TTC values for the assessment and control of NMIs in drug substances and products

4	Major - Likewise, to EFPIAs knowledge validated in vitro NAMs for the identification of general (chronic) toxicity in major target organs and systems for use in regulatory decision making are not currently available (see New Approach Methodologies EU-IN Horizon Scanning Report February 2025 EMA/56850/2025). Clearly application of such NAMs could have a significant 3Rs impact in many areas of toxicology; the combination of in silico and in vitro technologies to inform on potential hazard and risk for NMIs could provide a valuable proof of concept for their introduction into toxicology testing cascades within R&D and remains a valuable topic for further discussion. Regarding in vivo NMI qualification in general toxicology studies, it is recognised that ICH Q3A/B guidelines provide different approaches (i.e., testing of new drug substance containing NMIs or the testing of isolated impurities if appropriate). The focus of the EMA DRP appears to be on the latter approach, which requires additional discussion given the likely 3Rs consequences (i.e., a single in vivo toxicology study in which multiple NMIs are qualified as compared to multiple in vivo toxicology studies in which single NMIs are qualified). Also, it has been proposed in the DRP to calculate a benchmark dose (BMD) from testing of NMIs, which requires sufficient statistical power, hence an adequate number of animals per group and an adequate number of dose groups. EFPIA therefore recommends further discussion about the in vivo study design proposal from Table 2 for the testing of neat NMIs (e.g., absence of a dose range finding study, the number of animals per group, addition of TK groups and the number of treatment groups) to determine if it (1) would be a sufficiently powered study for BMD modeling and (2) will achieve the 3Rs aims regarding NMI testing.
5	Major - In summary, in EFPIA's view the majority of the proposed alternative in silico, in vitro and in vivo approaches for the assessment of NMIs outlined in the EMA DRP and adherence to the alternative NMI acceptable limits cannot be implemented at this time. They are either not technically feasible / validated or they would create significant ambiguity given they are not aligned with ICH Q3A/B guidelines. Adoption of the principles outlined in the EMA DRP as written may delay the development and supply of new medicines and has the potential to significantly increase in vivo toxicology testing. As a consequence, further detailed consideration (e.g., an impact analysis) is required prior to implementation. In our opinion, implementation in its current form will likely result in (1) the default application of ICH Q3A/B principles or even more stringent requirements in the R&D phase (2) a significant unwarranted impact on CMC analytical and manufacturing activities (3) a divergence in NMI qualification expectations across regulatory agencies and a resulting increase in Health Authority interactions and (4) a negative 3Rs impact (additional ICH Q3A/B in vivo impurity qualification studies) none of which are considered to provide additional safety benefit to patients given the frameworks outlined in the current ICH Q3A/B guidelines.

6	Major - EFPIA agrees with the intent of the EMA DRP, however its complexity and uniqueness merits further dialogue for industry to provide perspectives on the robustness and feasibility of the proposed framework. This would also allow for discussion of additional ICH Q3A/B aligned in silico computational toxicology and RAX approaches for the assessment of NMIs (that exceed the established ICH Q3A/B qualification thresholds) supporting the 3Rs aspirations outlined in the EMA DRP. EFPIA welcomes a long-term scientific collaboration with EMA to successfully develop and implement the intended vision of the DRP.
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2. Specific comments on text

2.1. Executive summary

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	41-46	Major - The executive summary states “ICH Q3A and Q3B guidelines provide a framework for qualifying Non-Mutagenic Impurities (NMI) in drug substances and products but offer limited guidance on new or elevated impurity levels.” The scope (as defined on lines 160-163) should be defined and added to the executive summary (i.e. new or elevated levels of impurities above ICH impurity qualification thresholds that are identified after non-clinical toxicology studies are complete)	“The ICH Q3A and Q3B guidelines provide a framework for qualifying Non-Mutagenic Impurities (NMI) in drug substances and products but offer limited guidance on new or elevated impurity levels above existing ICH Q3A or B impurity qualification thresholds that are identified after non-clinical toxicology studies are complete.”
2	43-46	Major - The executive summary refers to considerations related to impurities being metabolites and/or API-like but does include the central tenet of ICH Q3A/B i.e. that impurities are qualified when present in the drug substance or drug product batches used in non-clinical safety studies during development. Despite reference to it in the introduction (lines 84-86). This should be added to the executive summary.	“Impurities can also be qualified when present in the non-clinical repeated dose toxicity studies at level that does not impact the outcome of the toxicological assessment of API.”
3	44	The word “significant” is not required here given the alter discussion on metabolites	“Impurities may be qualified when these are also present as metabolites in animals or humans.”

4	49-50	The following statement appears to be out of place “The Threshold of Toxicological Concern (TTC) is an effective risk assessment tool for low-level exposures.” The practical application of the framework for the assessment and control of non-mutagenic impurities in DS and DP is currently unproven and as such it should be considered experimental approach and moved to lines 52-60	“The Threshold of Toxicological Concern (TTC) may be an effective risk assessment tool for low-level exposures.”
5	52-60	This section has no reference to the reporting, identification, and qualification threshold levels that are in place with existing ICH Q3A/B guidelines and could therefore be interpreted as a requirement to determine Acceptable Levels for all new or elevated impurity levels of non-mutagenic impurities - irrespective of the existing ICH Q3A/B thresholds.	See comment 1 for lines 41-46
6	56	The statement “It involves selecting a point of departure (PoD) from toxicological studies and applying assessment factors” infers that in vivo toxicology data on isolated impurities will be readily available. It is recognised within ICH Q3A/B that such data does not typically exist for impurities that are structurally related to the parent API (hence the concept of impurity qualification i.e. testing of drug substance containing impurities). This central tenet of ICH Q3A/B (referred to in the introduction and scope) should be reflected in the executive summary to avoid confusion.	See comment 2 for lines 43-46

7	66	Major - The scope of the reflection paper requires clarification and should be added to the executive summary. As written, it states “Impurities in investigational medicinal products should be evaluated according to ICH M3(R2)...” ICH M3 R2 refers to ICH Q3A & B (that are applicable for drug substance /product registration) and ICH M3 also states specific studies are not warranted before phase III (or in specific cases phase II). The reflection paper states the approaches are for new or elevated impurity levels identified after non-clinical toxicology studies are complete that implies they would be needed for registration activities or post marketing.	“When there is a need for additional safety data (i.e. to support registration activities or post marketing activities) the principles in this reflection paper can be applied.”
8	67	The statement “Impurities in investigational medicinal products should be evaluated according to ICH M3 (R2), with special attention to impurities of higher concern, as well as considering short-term treatment as a de-risking element.” would benefit from a definition of what constitutes “higher concern”. Is there a definition or are there examples that could be included (outside of those endpoints covered by ICH M7)	“Impurities in investigational medicinal products should be evaluated according to ICH M3(R2), with special attention to impurities of higher concern (e.g.XXXXX), as well as considering short-term treatment as a de-risking element.”
9	74	There may be a word missing from this statement “A weight-of-evidence (WoE) approach that includes an all aspects that determine the level of concern, could be sufficient to decide that the NMI can be considered safe at the specified level.”	To be defined
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2.2. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	83	Major - The statement “For NMI outside the scope of these guidelines little guidance is available on how these impurities should be qualified.” is not accurate – ICH Q3A/B do provide guidance, albeit anchored to qualification of impurities in in vivo general toxicology studies	“For NMI outside the scope of these guidelines little guidance is available on how these impurities should be qualified beyond the conduct of additional in vivo general toxicology studies”

2	90-97	Major - It is stated that the ICH Q3A/B approach to qualification has limitations because it only demonstrates the biological safety of a drug substance (DS) or drug product (DP) with a given impurity profile, rather than characterizing the safety of an impurity. It is not clear why it would be necessary to characterize the safety profile of a low-level non mutagenic impurity rather than assuring safety at a clinically relevant exposure given that they are generally specific to a given product or product formulation. Most DS and DP related NMIs addressed by ICH Q3A/B are unique and hence different from the other types of more commonly encountered impurities addressed in other ICH guidelines (e.g. ICH M7, ICH Q3C, ICH Q3D etc), in these cases it is useful to derive PDEs based on available data given common wide-spread use. It is recommended that consideration be given to the value of fully characterizing the safety profile of DS and DP related NMIs that will generally only be applicable to a given DS or DP formulation in comparison to the current approach where the impurity is evaluated in a manner more relevant to the exposure scenario (i.e., as an NMI in DS or DP).	The following ICH Q3A/B position should be recognised and included “Impurities can also be qualified when present in the non-clinical repeat dose toxicology studies at levels that do not impact the outcome of the toxicological assessment of API.”

3	107-116	Major - It is recommended that this section be revised to align with the existing ICH Q3A/B guidelines - It is reasonable to assume that the NOAEL in in vivo impurity qualification studies are related to the parent drug, however there is no clear explanation in the text as to why this would compromise the scientific rationale for such a study with respect to the assessment of the biological safety of an individual impurity. As written, the section implies that demonstration of impurity related toxicity is a prerequisite for an ICH Q3A/B aligned in vivo impurity qualification study to be considered valid. This is not aligned with ICH Q3A/B and seems to contradict the subsequent position that impurities that have been qualified in nonclinical toxicology studies are out of scope of the alternative approaches outlined in the reflection paper.	The following ICH Q3A/B position should be recognised and included “Impurities can also be qualified when present in the non-clinical repeated dose toxicity studies at level that does not impact the outcome of the toxicological assessment of API.”
4	110-119	Major - It is stated that qualification studies performed with NMIs in an active pharmaceutical ingredient (API) do not provide useful information and are therefore in violation of Directive 2010/63/EU. It is recognised that many in vivo qualification toxicology studies with parent API containing NMIs have not demonstrated clear examples of NMI related toxicities (see reviews on lines 112 &119) however, this in itself does not compromise the robustness of these studies (see comment on lines 107-116). As outlined in the ICH Q3A /B framework the studies demonstrate that the DS or DP containing the NMI at a clinically relevant level has been adequately qualified (since one is able to define a NOAEL in the study it can be considered applicable to the dose of the NMI or the API).	Propose deleting statement "This compromises the scientific rationale for the design of the qualification study and is in violation of Directive 2010/63/EU on the protection of animals used for scientific purposes, as from a 3Rs perspective, no animal studies should be performed if these studies are unlikely to provide relevant information. "

5	110-119	Consideration of the recent analyses supporting NMI qualification thresholds in relation to exposure duration (e.g. 1 mg/day lifetime exposure or 5 mg/day threshold for <10 years exposure) could be included as part of the 3Rs considerations within the DRP. As would consideration of the framework for the identification of potentially potent classes of compounds for the identification of NMIs that might require control below the defined ICH Q3A/B limits.	Provide references to Slikkerveer (2024), Hasselgren (2024), Kenyon (2024), Graham (2021), Harvey (2017)
6	124-126	Running qualification studies with “neat” impurity is not considered to be aligned with the 3Rs principles and not relevant to the levels that the sponsor is seeking to “qualify” in the DS/DP. This statement also contradicts lines 163-165 and 180-181 in the refection paper (that are consistent with ICHQ3A/B) i.e. “the level of any impurity present in a new drug substance or drug product that has been adequately tested in safety and /or clinical studies is considered qualified” and “Impurities that are also metabolites in animals and/or humans may be qualified based on studies conducted with the API in relevant species”.	As outlined in previous comments the text should be revised to acknowledge that numerous impurity qualifications studies are conducted using “spiked” impurities within the API at levels representative of final DS/DP specifications that have been adequately assessed for safety asper ICH Q3A/B i.e. “Impurities can also be qualified when present in the non-clinical repeated dose toxicity studies at level that does not impact the outcome of the toxicological assessment of API.”
7	136-138	Major - The EMA DRP should recognise that the assessment and control of NMIs involves both safety and quality considerations. Several of the proposed approaches could not be practically implemented from a quality perspective (for example see proposals for parenteral drug products on lines 370 -405). Although quality perspectives are not within in scope of the DRP they need to be considered concurrently with safety perspectives and not as a separate discussion.	No proposed text - Consideration of established ICH Q3A & B reporting, identification and qualification thresholds need to be added to the reflection paper; worked examples should be provided
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2.3 Scope

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	160-165	Major - The scope of the DRP is not clearly defined due to the use of the word “primarily” in line 160 “The principles and methods discussed in this reflection paper should primarily…”	“The principles and methods discussed in this reflection paper should primarily be considered for the qualification of novel impurities arising from changed manufacturing processes, discovered after safety studies have been concluded, or when higher levels need to be qualified and existing data from safety studies are not sufficient for qualification.”
2	160-165	The scope of the DRP is not clear due to the use of the term “novel impurities” on line 161 “The principles and methods discussed in this reflection paper should primarily be considered for the qualification of novel impurities…”	“The principles and methods discussed in this reflection paper should be considered for the qualification of new or elevated impurity levels (above existing ICH Q3A or B impurity qualification thresholds) that are identified after non-clinical toxicology studies are complete.”
3	167-171	Major - This section indicates that the approaches in the DRP should be considered during clinical development, which is not aligned with ICH Q3A/B or broadens the scope and potential impact (as discussed in the general comments) of the proposals considerably “Impurities present in products in clinical development are not in scope of ICH Q3A/B. See however, section 4.8. 4.8. In clinical trial approval procedures, the qualification of impurities has been a matter of debate and in lieu of specific guidance, this reflection paper will discuss how the principles and methods described can be of help when considering the potential increased risk for clinical trial participants due to the presence of (novel) impurities.”	The sentence should be revised to provide clarity on the scope. e.g. “ICH M3 (R2) provides guidance about when ICH Q3A/B NMI qualification approaches may be necessary during clinical development”
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2.4.1 General outline for risk assessment of NMIs

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	204-207	Given the complexity of the proposed alternative approaches (as detailed in Figure 2) a definition of what would be an acceptable or unacceptable risk is required	“If the potential risk is considered acceptable (i.e. XXXX), no further data may be necessary. If the level of concern points to a potentially unacceptable risk (i. e., XXX) at the maximum daily exposure, the impurity level should be lowered, or further toxicological data should be acquired.”
2	208	Major - A definition of “exceptional circumstances” should be provided given the uncertainties associated with the predictivity of available in vitro methods for the assessment of organ level toxicities (see later comments on NAMS (section 4.5)	“Only in exceptional circumstances (i.e. XXXXX) when acquisition of relevant data is only possible in in vivo studies, should conduct of in vivo studies be considered (see section 4.7. In vivo qualification studies).”
3	211	Major - Figure 1 should include reference to the ICH Q3A/B qualification paradigm that is referenced in lines 121-123 “In case impurities have not already been qualified in previous safety studies (i.e. novel impurities) or when higher levels of impurities need to be qualified (that were previously qualified at a lower level), it is recommended to use alternative methodologies.” to clarify the scope of the guidance	The first diamond in the schematic should include “ICH Q3A/B/C/D and M7 applicable”
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2.4.2 Metabolites

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	236	The Cmax is the peak concentration (not the average) the text needs clarification “The average plasma concentration Cmax in the relevant dose group of animals or patients/volunteers would be considered to represent the MOC.”	“The average plasma concentration in the relevant dose group of animals or patients/volunteers would be considered to represent the MOC.” Or “The Cmax plasma concentration in the relevant dose group of animals or patients/volunteers would be considered to represent the MOC.”
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2.4.3 API-like vs. non-API-like impurities

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	251- 283	Major - An assessment of the structural similarity of an NMI to parent API is considered to be of value in establishing the biological safety of unqualified impurity that exceeds the ICH Q3A/B qualification limits. However, the subjectivity associated with the definition of structural similarity can make the implementation of the approach challenging (e.g. Thresholds for Tanimoto coefficient, significant variations in physical chemical & pharmacokinetics parameters etc) hence further details should be added to the guidance (including case studies for different modalities) as outlined in the comments on sections 4.5.1 and 4.5.2.	See comments on sections 4.5.1 and 4.5.2.
2	251- 283	Major - The concept of differentiating between API-like and non-API-like impurities is an important one. This concept, if accepted by global regulatory agencies, will certainly decrease the number of qualification studies needed, increasing the speed at which new pharmaceuticals can reach the market and decreasing development costs. However, the definition of API-like is far from well-defined. We would ask that EMA be an active participant in collaboration with other global regulatory agencies and pharma consortia to better define this concept. This would include defining relevant toxicophores, structural similarity, and physicochemical similarity	See comments on sections 4.5.1 and 4.5.2. It is recommended that available tools and process be recommended for determining structural similarity to API. It would be helpful for EMA/Industry to collaborate on the evaluation of tools and a framework for the implementation of this approach.

3	251	How does on define functional groups - do the EMA mean pharmacological functional groups? The majority of specified NMIs are high-molecular weight impurities with high similarity to the API. Would all these NMIs not be considered API-like?	See comments on sections 4.5.1 and 4.5.2.
4	252	“[…] e.g. clobetasol propionate, clobetason-17-propionate and betamethasone.” The three examples appear very specific. It is unclear what value they add. A more general framework would be of greater value.	Recommend removing this sentence
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2.4.4 Level of concern considerations

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	284-297	Major - The reflection paper proposes a risk-based approach to assessing whether an impurity at a given exposure level presents a concern that may require follow-up. Considerations of clinical context of use, including duration of exposure, in a risk assessment is valuable. It is noted that the risk assessment for determining level of control must consider each of the risk factors in the context of all other aspects. However, there is lack of guidance on how these assessments would actually be made with all risk factors integrated. Given that there is subjectivity involved in these analyses, without a clear framework, it is likely that there will be different opinions on concern level, which could lead to a conservative approach of assuming that all impurities need further assessment to avoid regulatory disagreement or an increase in scientific advice meetings to ensure regulatory alignment. This could result in an unintended consequence a negative 3Rs impact (i.e. commissioning of additional ICH Q3A/B in vivo impurity qualification studies)	No proposed text - Additional guidance should be provided regarding the proposed framework for performing the risk assessment as well as examples demonstrating how to consider each risk factor in the context of the other risk factors

2	306	Major - According to Figure 2, a clinical safety margin of 10x might be considered acceptable (depending on integration with other factors), while a margin of 100x is considered lower concern; however, later in the DRP, there is discussion of needing at least a 500x margin (lines 733-734). Margins of 10x are typically considered reasonable for most toxicities that are not severe, depending on the dose response curve. Further clarification is required regarding acceptable safety margins in the proposed NMI qualification framework in EMA DRP.	No proposed text - Additional guidance should be provided regarding the proposed framework for performing the risk assessment as well as examples demonstrating how to consider each risk factor in the context of the other risk factors
3	Line 316-319	Major - Recognition that the ICH Q3A impurity qualification limit of 1 mg/day could be used as part of a WOE to establish the biological safety of an unqualified NMI could have a significant impact from a 3R's perspective. Consideration of the use of this 1 mg /day value (examined by Kenyon 2024 and Slikkerveer 2024 etc regarding NMI assessment in clinical development) alongside an appropriate SAR assessment to ensure an impurity was not unusually toxic (e.g. as outlined by Hasselgren et al., (2024) Regul. Toxicol. Pharmacol. 150:105645) would enable the adoption of this approach that would be aligned with the ICH Q3A/B guidance.	"For most chemicals of low concern, exposure levels below 1 mg/day are considered to be safe provided that an assessment of their structure provides assurance that they do not belong to a chemical class known to be associated with toxicities at lower exposure levels (Hasselgren et al., 2024)."

4	319-321	Kenyon et al. (2024) did not just evaluate compounds with a NOAEL of 0.02 mg/kg/day. Kenyon et al. calculated the 5th percentile NO(A)EL from a diverse set of compounds (tested over different durations) and considered allometric scaling to adjust for species differences to evaluate the robustness of the ICH Q3A 1 mg/day qualification limit (i.e. 5th percentile NOA(E)L = 0.1 mg/kg/day x 50 kg human/5 allometric scaling = 1 mg). This approach is similar to the approach taken to define the Threshold of Toxicological Concern used in ICH M7. The Kenyon et al., publication supports the ICH Q3A aligned 1 mg/day limit for an NMI.	“In addition, it also needs to be considered that inter- and intraspecies differences in sensitivity may occur. In addition, animal toxicity shorter duration, whereas administration to patients can be long-term. Although many of these factors were considered by Kenyon et al., (2024) at this point the ICH Q3A 1 mg/day exposure level is not considered by EMA to be a definitive cut-off value”
5	322, 339, 390, 419	Please consider a table to better describe the different scenarios	

6	323-405	Major - It is stated that when exposure levels of impurities are above TTC and below 1 mg/day the level of concern needs to be evaluated; however, considering that the scope of the reflection paper is for new impurities identified after safety studies have been conducted or higher levels of impurities included in prior safety studies, it is difficult to understand how the use of the proposed TTCs would be helpful. Considering the ID thresholds in ICH Q3A/B, except for low dose drugs, new impurities would all be above the strictest Cramer classifications (75 mcg/day or 5 mcg /day parenteral). For example, an impurity qualification threshold of 75 mcg/day (TTC value for Cramer class 3 compounds) would be lower than the ICH Q3A impurity qualification threshold of 0.15% for drugs where the maximum daily dose is > 50 mg. Similarly, an impurity qualification threshold of 5 mcg/day (PQRI limit for extractables and leachables) would be lower than the ICH Q3A impurity qualification threshold of 0.15% for drugs where the maximum daily dose is > 3.3 mg. Further explanation of the compatibility of this proposed framework with the safety and quality thresholds in ICH Q3A/B should be provided (see comment on line 136-138). It is unclear how the TTC would practically be applied.	No proposed text - Consideration of established ICH Q3A & B reporting, identification and qualification thresholds need to be added to the reflection paper; worked examples should be provided

7	419	Major - As noted in Hasselgren et al (2024), in an analysis of non-mutagenic compounds with animal toxicity data, although a high percentage of more potent compounds were predicted as Cramer Class 3 (75 ug/day), there was also a high false positive rate with positive predictivity of only 4%. Additionally, most drug-related impurities will likely fall outside the applicability domain of the tool used to assign the Cramer classification, which would result in default of Cramer class 3. Together, this would likely result in a large number of compounds being unnecessarily assessed. As noted in Hasselgren et al, only 2.4% of the >2000 non-mutagenic compounds in the analysis have a NOAEL <0.2 mg/kg/day (equating to 10 mg /day, or 2 mg/day if a factor of 5 (rat) for allometric scaling is included). And structural motifs potentially associated with more potent toxicity have been identified. If the TTC approach is to be maintained, further explanation of the compatibility of this proposed framework with the safety and quality thresholds in ICH Q3A/B should be provided. It is recommended that the current ICH Q3A/B thresholds be maintained with the addition of a review of compounds to identify those that may require additional considerations based on these potent structural motifs.	No proposed text - The use of the Cramer classification system in the proposed framework should be reconsidered

8	329-405	Many of these thresholds are being considered for leachables and/or extractables in DS/DP, that are likely to chemically distinct from NMI (that are typically related to parent API). These thresholds are also commensurate with the levels of leachables that are seen from container systems used in drug product manufacturing (as opposed to API-related impurities that are typically seen at ICH Q3A/B limits). Further consideration of the domain of applicability and the practicality of applying these thresholds for NMI API-related impurities should be given.	No proposed text - The use of the TTC frameworks in the proposed framework should be reconsidered
9	399-405	It is recommended that reference to ICHQ3E regarding TTC based limits should not be included until the ICH Q3E guidance is near final. Please consider removing this sentence from the DRP.	Delete sentence
10	421-423	Additional text could be provided regarding parenterally administered DPs, such as those delivered directly into the systemic circulation via intravenous injection that ensure 100% bioavailability. For other parenteral routes, such as subcutaneous and intramuscular injections, most drugs show between 60 and 100% bioavailability due to little or no metabolism in the skin or muscle References: Stielow et al., 2023 Molecules 28(24):8038. doi: 10.3390/molecules28248038	The text could be revised as follows “By definition, compounds administered via intravenous injection have 100% bioavailability. Due to little or no metabolism in the skin or muscle, most drugs show between 60 and 100% bioavailability after subcutaneous and intramuscular injections (Stielow et al., 2023). Consequently, parenteral routes pose the highest concern, as opposed to compounds administered via routes where limited absorption may reduce the systemic exposure.”

11	424	Local toxicity is mentioned multiple times in the DRP (lines 416,417,424 and 1034). Each of these is only a passing mention and none of these provide guidance regarding local tolerance testing. The topic could be discussed in more detail, or (preferably) be removed from the scope.	No proposed text
12	426-427	Additional clarification around physical and chemical properties of molecules and the in silico tools that can be used to estimate bioavailability should be given (e. g. via addition of references)	No proposed text – addition of references
13	436-441	Major - The reflection paper identifies three sensitive populations when establishing level of concern for NMI. If sensitive populations are to be maintained as a “level of concern” factor, the DRP would benefit from additional references or guidelines to support the establishment of limits for these sensitive populations.	No proposed text – but additional guidance is required

14	442-451	Major - The DRP suggests flexibility for NMI qualification exists based on duration of treatment, however no guidance is provided. Application of higher qualification thresholds for short-term exposure is consistent with allowances made in other ICH impurity-related guidelines. For example, ICH Q3C(R9) and ICH Q3D indicate that it may be acceptable to exceed recommended limits for residual solvents and elemental impurities, respectively, to support short-term dosing (i.e., ≤ 30 days). ICH M7 (R1) explicitly references Haber's Law in recommending higher mutagenic impurity limits for less-than-lifetime exposures It is noteworthy that, per ICH M7(R1), the default limit for 6 months exposure to a mutagenic impurity is > 10-fold higher than the lifetime limit (i.e., 20 µg/day for 6 months vs. 1.5 µg/day for lifetime exposure). In comparison, the proposed short-term qualification threshold for non-mutagenic impurities described by Harvey et al. (2017) and Kenyon (2024) is more conservative as it limits exposure to only 5-fold over the ICH qualification threshold for lifetime exposure (i.e., 5 mg/day for 6 months vs. 1 mg/day for lifetime exposure). Further guidance should be provided.	No proposed text – but discussion of durational adjustments proposed elsewhere should be add to the section
15	474-486	The reflection paper identifies three sensitive populations when establishing level of concern for NMI. Additional guidance is needed on how to adjust NMI limits for these populations if it is to be maintained in the guidance.	No proposed text – additional discussion on considerations for sensitive populations is required
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2.4.5 New approach methodologies

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	488-633	Major - The EMA NMI DRP provides a significant opportunity to present a framework for the implementation of New Approach Methodologies (NAMs) into the regulatory toxicology setting. However, as written the DRP calls for use of nearly every NAM approach without clear supporting evidence that they would be appropriate to assess the potential toxicity of an NMI. In EFPIA's opinion the only currently viable or acceptable NAM approach to achieve this is read across (RAX) primarily due to its practicality and precedented use in other areas (e.g. chemical safety). As noted in the EMA New Approach Methodologies EU-IN Horizon Scanning Report (EMA/56850/2025), currently EMA has not qualified any NAMs for regulatory use in new medicine development. As written the disproportionate focus on NAMs within the DRP (without adequate clarity of their applicability) serves as a distraction to the broader implications of NMI qualification framework that could have a detrimental impact with regards to the 3Rs.	No proposed text – the section needs revising with a focus on the NAM approaches that could be viable alternatives to the established ICH Q3A/B qualification paradigms (e.g. RAX)

2	488-633	A focus on the most viable NAM approaches (e.g. RAX) for NMI qualification would accelerate their development and implementation in the regulatory setting. To establish RAX approaches in this area, EFPIA would recommend development of cheminformatic approaches to (1) ensure RAX were empirically derived and (2) address potential challenges related to applicability domains. . Additional clarity on the implementation of RAX, (Q)SAR, and other cheminformatic approaches is required.	No proposed text – the section requires further details and references to proposed frameworks and examples
3	508-516; 526-541	Major - As per the previous comment the use of RAX could have a significant impact regarding the qualification of NMI's. For instance, an NMI closely related to the API based on most established RAX guidance would enable the API to be the RAX substrate for the NMI, however, this framework would require development and implementation There needs to be a clear framework RAX in the DRP. This section needs to provide additional guidance for appropriate tools to utilize for the various aspects of the similarity comparison as well as provide some examples of an acceptable RAX demonstrating level of detail expected in the analysis. Finally, provide guidance on documentation that should be submitted (e.g. are full (Q)SAR reports from the software required or just a summary of output).	No proposed text – the section requires further details and references to proposed frameworks and examples
4	553-554	This this section is not clear. What are the AI/ML approaches that are considered to be of practical use for NMI qualification.	No proposed text – the section requires further clarification and references supporting the proposed framework

5	521-523; 533-534; 543-551; 581-584	Major - EFPIA are aware that some validated SAR models exist for the prediction of organ toxicities, however their performance (sensitivity, specificity etc) are not well defined. EFPIA are not aware of (Q)SAR models for the organ toxicities defined in the DRP. The use of in silico SAR or (Q)SAR tools to assess the NMIs could conceivably be useful for assessing safety of a given impurity. However, given lack of validated methods and the complex justification required and described in lines 558-574, utility of this approach at this time is uncertain. Additional guidance on tools that can be utilized and considerations for interpretation of results is necessary to practically implement use of in silico tools in the assessment of impurities. Please provide references for acceptable (Q)SAR models that could be utilized for toxicophore identification that fulfil the validation criteria outlined in the reflection paper (see lines 567-574).	No proposed text – the section requires references supporting the proposed framework

6	554-557	Major - This section is not clear. Is the intent to restrict the use of NAMS to those toxicological pathways defined by the established adverse outcome pathways (e.g. in silico and in vitro systems as a means to derive NOAEL or BMDL values based on targets as described in Brennan, 2024) Please provide a reference for the AOP framework for organising data at the chemical and biological level (e.g. targets listed in Bowes, 2012, Lynch, 2017, Brennan 2024; ECHA guidance Read-Across Assessment Framework (RAAF), 2017). We also recommend providing an example (Appendix), which evaluates and compiles multiple methods/in silico tools as described Brennan (2024) 10.1038/s41573-024-00942-3 Bowes (2012) 10.1038/nrd3845 Lynch (2017) 10.1016/j.vascn.2017.02.020	No proposed text – the section requires references supporting the proposed framework
7	559	Additional details regarding expectations for Expert Review are necessary. For example, see 10.1016/j.yrtph.2018.04.014, 10.1016/j.yrtph.2019.104403, 10.1016/j.comtox.2021.100187, 10.1016/j.comtox.2021.100188, 10.1016/j.comtox.2021.100191	No proposed text – the section requires references supporting the proposed framework

8	595-598	The statement mentions that multiple predictive tools (commercial or free) are available for assessing, e.g., general toxicity endpoints or skin sensitization potential. However, the predictive tools described in the references were limited in terms of the number of endpoints they cover, specifically bacterial mutagenicity, skin sensitization, and respiratory endpoints. As noted in previous comments (lines 521-523; 533-534; 543-551; 581-584), please provide additional references covering predictive tools for a broader range of endpoints.	No proposed text – the section requires references supporting the proposed framework
9	602-623	In EFPIA's opinion, as validated in vitro models (or at least agreed upon approaches to assessing specific toxicities in vitro) are very limited, it will be difficult to consistently demonstrate NMI safety using this approach. Lack of clear guidance at this time is likely to result in the conduct of in vivo NMI qualification studies by default to reduce regulatory uncertainty or increased requests for scientific advice meetings to obtain regulatory alignment. EFPIA would recommend further dialogue on the implementation of these approaches (e. g. what in vitro NAMs are being considered and how would NMIs be assessed relative to parent API). If there are available in vitro NAMs validated for identifying organ level toxicities that the EMA considers appropriate for use for NMI qualification, please provide supporting references.	No proposed text – the section requires further clarification and references supporting the proposed framework
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2.4.6 Acceptable Level calculation

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	645-688	Major - The scope of Acceptable Level section and its application is not clear. It is assumed it relates to non-API like impurities that have been tested in isolation in vivo general toxicology studies and/or surrogate compounds that have been tested in isolation in in vivo general toxicology studies that are being used for RAX purposes? AL use may be considered more appropriate in these cases.	"For non-API like impurities that have been tested in isolation in in vivo general toxicology studies and/or surrogate compounds that have been tested in isolation in in vivo general toxicology studies that are being used for RAX purposes here we propose…"
2	638-688	As the scope is unclear in EFPIA's opinion the proposed approach is not consistent with current practice, and it could result in extremely low, conservative and unattainable limits for NMIs in DS /DP. Importantly, DRP does not provide any evidence that this is necessary (i.e. driven by experience). As the goal of NMI qualification is to understand the safety of an impurity at a clinically relevant level, it is unclear why calculation of an AL is necessary in order to support an NMI specification. This approach could be useful when existing toxicological data on a specific NMI is available. However, it should be noted that application of up to 7 adjustment factors could result in an AL of questionable validity. Additionally, selection of the appropriate safety factor is subjective in many cases (e.g., severity, LOAEL, RAX) and often debated. It is noted that a case-by-case approach would be taken (lines 686) that indicates additional guidance will be required regarding the implementation of this approach (in particular with the new RAX safety factor).	Unless the scope is clarified it is recommended that this be considered as a possible way to demonstrate that a proposed specification is protective of patient safety based on existing data. However, it would be more helpful to consider defining an adequate margin of exposure over human dose. "Here we propose the Acceptable Level (AL) method, by which similar toxicological principles are used (e.g. as described in ICH Q3C and ICH Q3D) as a possible way to determine a basis of safety for an impurity specification".

3	644	Use of BMD modelling should provide a more accurate measure of the POD than the default use of the NOAEL. Use of the BMDL, as opposed to the BMD itself, adds an additional level of conservatism regarding the determination of the POD. Use of the BMDL with the exact same composite adjustment factors that would be used if a NOAEL was used as the POD would add an additional unwarranted level of conservatism to the derivation of an acceptable level of an NMI. Use of a more precise method to define a POD should require less composite uncertainty - the number of assessment factors when using BMD modelling should therefore be reconsidered.	Proposed text “when using BMD modelling to determine the POD which would be more accurate than use of the NOAEL) the number of assessment factors could be adjusted accordingly”
4	677-679; 729-731	Major - No information is given on the relevant BMR to be used depending on the toxicity to be assessed. further discussion would be required to seek consensus on the definition of a critical effect size for organ level toxicity endpoints (i.e. modelling BMDR for continuous, dichotomous or ordered categorical variables would be required) for this approach to be adopted. A discussion on appropriate guidance is required (e.g. EPA Benchmark Dose Technical Guidance (EPA/100/R-12/001 from June 2012) or in the WHO EHC 240: Principles for Risk Assessment of Chemicals in Food; Chapter 5 Dose-response assessment and derivation of health-based guidance values (second edition, 2020) before the framework could be adopted.	No proposed text – the section requires further clarification and references supporting the proposed framework
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2.4.7 In vivo qualification studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	692-708	Major - EFPIA disagree and consider that NMI qualification studies (as per ICH Q3A/B principles) using spiked NMIs do provide confidence that at the tested level in the presence of API, the impurities do not impact the toxicity profile of the API and therefore are not a safety concern for the patient. This section of the DRP contradicts other statements (e.g. lines 163-165; 180-181; 302-05) that are aligned with ICH Q3A/B framework for NMI qualification. We recommend aligning with other statements in the DRP where it is stated that NMIs present in safety or clinical studies at lower levels (not neat) are adequately qualified	We recommend removing line on 692 “Furthermore, in vivo studies…” and replacing it with the following “Impurities can also be qualified when present in the non-clinical repeated dose toxicity studies at level that does not impact the outcome of the toxicological assessment of API.”

2	709-711	The framework regarding the testing of an isolated or “neat” NMI in in vivo general toxicology studies represents some significant challenges. From a practical perspective, late stage changes in chemistry manufacturing and control process often results in the need for qualification of more than one NMI and therefore under the proposed framework more in vivo toxicology studies would be required, which could have a detrimental impact on the 3Rs. From a technical perspective it should also be noted that there are various examples where synthesis of “neat” impurity is not feasible and instead have relied of “stressing” the DS/DP to get the impurity at higher levels in order to be tested within the DS/DP. From a scientific perspective the spiking of NMIs provides a more realistic amount of the impurity in the DS/DP and considers the potential interaction - potential ADMET interactions between the NMI in question and the pharmacologically active API (i. e. mixture effects). In contrast testing of an isolated NMI at maximum tolerated doses in repeat dose toxicology studies will result in a high likelihood in toxicological effects that are not relevant at the human exposures to the NMI via DS/DP. Testing of commonly used organic compounds in various drug synthesis may be of value (and should be published if possible to support 3Rs principles) however, extensive in vivo testing of unique-drug related NMIs to derive a POD for AL determination should be reconsidered from a 3Rs perspective.	We recommend that the reflection paper be updated to recommend that, if necessary after application of concepts in previous sections of the paper, an in vivo impurity qualification study could be conducted that is consistent with current practice “As per ICH Q3A/B such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate” for DS/DP-related impurities. Add Section 4.7.1.1: In vivo study design when testing drug substance containing impurities Detail preferred design. Section 4.7.1.2 In vivo study design when testing isolated impurities Details of proposed design from the DRP

3	714	The DRP refers to the industry proposal to limit impurity qualification studies to a duration of 28 days in most instances. However, in EFPIAs understanding this has not been accepted globally where some agencies still request 90-day studies for chronic use drugs.	No proposed text - It is recommended that the section also refers to ICH Q3A/B regarding study duration
4	726-729; 740	Major - Without additional clarification or references it is not clear whether the new approach is aligned with the 3R principles as compared to current recommendations for ICH Q3A/B NMI qualification. For example, the proposed study design including 4 treated groups in addition to vehicle control with 3 animals/sex/group will require more animals for each impurity than are recommended in spiking studies that may include multiple impurities (Mitra 2021). Additionally, it is unclear if 3 rats/sex/group is sufficient to provide statistically meaningful data for BMD analysis especially if there is unanticipated loss of animals during a study (e.g. due to the proposal to not conduct a dose range finding study). On this basis consideration of current ICH Q3A/B aligned in vivo NMI qualification practices for DS/DP related NMI should be added to the section. The proposed approach might be more appropriate for NMIs that are commonly used organic compounds; however, it is recommended that there is discussion in the reflection paper on the whether 3 animals/sex/group provides sufficient power and why, with consideration given to possible animal loss during a study.	“In light of this, and for designing in vivo studies using neat impurity to qualify common organic impurities, it is recommended to include at least four treated dose groups (besides a vehicle group) as well as 3 rats/sex /group to ensure sufficient study power for modelling the dose-response data from the experimental animal studies. 3 rats/sex/group will provide sufficient statistical power for BMD analysis based on XXX”

5	733-734	See line 306 - This proposal does not appear to be aligned with ICH Q3A/B (i.e. 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) and requires further explanation. It is assumed that this relates to studies on NMI tested in isolation and that the proposal would always result would require a 10-fold margin over a BMDL established in the 1-month rat study proposed in the DRP (e.g. given a 500 mg/day DS with an impurity present at 2%, equating to a 0.2 mg/kg/day impurity dose in a 50 kg human. The BMDL would need to be 500-fold higher than 0.2 mg/kg/day (100 mg/kg/day))	Proposed text – “As per ICH Q3A/B such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate” for DS/DP-related impurities. When considering in vivo studies using neat impurity to qualify common organic impurities the usual assessment factors for deriving an AL, the BMDL used as PoD should be at least 500-fold higher than the anticipated AL using the clinical route of administration” No proposed text regarding a further explanation for the 500 value however details should be provided.
6	740	TK analysis - It is not clear why evidence of exposure is required since NMI qualification is based on comparative dose in non-clinical species as compared to humans. In current spiked NMI qualification studies, TK is typically only included for the API to understand any possible toxicity differences compared to prior studies of API that may be due to exposure differences from study to study (Mitra 2021). While Table 2 recommends that TK be assessed in main study animals, this may not be feasible (given it can interfere with clinical chemistry assessments) that would likely necessitate additional groups in the proposed study design and have a detrimental impact from a 3Rs perspective.	Title: “Preferred design of in vivo studies for qualification of neat impurities” Delete TK analysis from table 1

7	743-746	Please expand to address ICH S9 indications, not just cytotoxic oncology products. Align with ICH S9 and Q&A, particularly Q4.1.4	Add: “Given the compressed development timelines for oncology products, drug substance manufacturing processes may not be fully mature at the time of making the marketing application. Therefore, if new impurities are observed above ICH Q3A/B qualification thresholds after the completion of registration toxicology studies, qualification studies may not be necessary in all cases when an impurity is found above / is specified above the ICH Q3A/B qualification threshold when the product is being developed under ICH S9 (See ICH S9 Q&A, Q4.14 for details on assessing risk).”
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2.4.8 Products under clinical development

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	66; 754-765	Major - The scope of the reflection paper requires clarification and should be added to the executive summary and the section 4.8. As written, it states "Impurities in investigational medicinal products should be evaluated according to ICH M3(R2)..." ICH M3 R2 refers to ICH Q3A & B (that are applicable for drug substance/product registration) and ICH M3 also states specific studies are not warranted before phase III (or in specific cases phase II). The DRP states the approaches are for new or elevated impurity levels identified after non-clinical toxicology studies are complete (lines 160-163) that implies they would be needed for registration activities or post marketing.	"When there is a need for additional safety data (i.e. to support registration activities or post marketing activities) the principles in this reflection paper can be applied."
2	754-765	If this alternative framework is intended to be recommended for products in clinical development further discussions regarding its implementation is required	No proposed text
3	754	ICH M3 (R2) refers to ICH Q3A/B and notes that qualification is generally not warranted before phase III or for significant new impurity profile to support phase II or later. (see comment on lines 167-171)	"ICH M3 (R2) provides guidance about when impurity qualification may be necessary during clinical development and recommends ICH Q3A/B qualification approaches."

4	762-763	If this alternative framework is intended to be recommended for products in clinical development, further guidance is required regarding this statement “This evaluation also includes considerations of short-term treatment as a de-risking element, which can be a relevant aspect in the clinical trial setting.” and should be connected to figure 2	“This evaluation also includes considerations of short-term treatment as a de-risking element (e.g. via XXXXXX) which can be a relevant aspect in the clinical trial setting.”
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2.5 Conclusion

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	766-771	Major - EFPIA agrees with the intent of the EMA DRP; however, given its complexity and uniqueness we would welcome further dialogue to provide industry perspectives on the robustness and feasibility of the proposed framework. It would also allow the discussion of additional ICH Q3A/B aligned in silico computational toxicology and RAX approaches for the assessment of NMIs (that exceed the established ICH Q3A/B qualification thresholds) that would support the 3Rs aspirations outlined in the EMA DRP. EFPIA would welcome a long-term scientific collaboration with EMA in order to successfully develop and implement the intended vision of the DRP.	No proposed text
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2.6 References

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	541	Please include reference from Hasselgren (2024).	Hasselgren, C., Kenyon, M., Anger, L.T., Cornwell, P., Watt, E., Bercu, J. (2024) Analysis of non-mutagenic substances in the context of drug impurity assessment – few are potent toxicants. Regul. Toxicol. Pharmacol. 150:105645. https://doi.org/10.1016/j.yrtph.2024.105645
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2.7 Appendix

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	913 -1047	Our understanding is that discussion of adjustment factors has been part of the ICH Q3E - please consider alignment with the outcomes of the ICH QE EWG	
2	1025	The proposed default oral bioavailability of 1% is considered to be conservative for typical organic impurities “Where appropriate bioavailability data were not available, and in lieu of NAM-derived estimates of bioavailability, a default modifying factor of 100 is suggested for AF6. “. A justification for use of 1% as default should be included into the text.	“Where appropriate bioavailability data were not available, and in lieu of NAM-derived estimates of bioavailability, a default modifying factor of 100 is suggested for AF6 (add justification XXXXX)”
3	1045-1046	As written this sentence is currently ambiguous. “When RAX strategy is utilised, a factor of up to 5 could be used depending on the level of (dis)similarity.” A rationale should be added for the AF of 5 for RAX depending on the level (dis)similarity. Additionally, more guidance on appropriate factors from 1-5 based on (dis)similarity would be helpful; case examples demonstrating use of different factors could be helpful.	When RAX strategy is utilised, a factor of up to 5 (based on XXXX) could be used depending on the level of (dis)similarity.
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Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	37	Change “ADME: adsorption, distribution, metabolism and excretion"	“ADME: absorption, distribution, metabolism and excretion
2	37	Change DNA: Desoxyribonucleic acid”	DNA: Deoxyribonucleic acid”
3	71; 217; 267-268; 483; 693; 759; 767	We recommend removing the word “required” as ICHQ3/B do not use the word “required.” We recommend aligning language in reflection paper with complimentary guideline language.	Line 71: “In summary, when impurity-specific safety information for NMI is recommended, …” Line 217: “defines the threshold of 10% for when additional safety data on a metabolite is recommended.” Line 267-268: “Consequently, no further investigations are recommended, …” Line 483: “should consider specific evaluations…” Line 693: ” qualification of new impurities as recommended by ICH Q3A …” Line 759: “could lead to a request for lower batch levels or inclusion of more data to qualify the impurity” Line 767: “When impurity-specific safety information for NMI may be necessary, …”
4	404-405	Cite Table 1 and add section # for clarity	“The TTC and DST values that can be used for NMI are summarised in section 4.4.1.3 (Route of administration), Table 1.” Or “The TTC and DST values that can be used for NMI are summarised in Table 1.”
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Thank you for your contribution.

Contact

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