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ICH M10 Bioanalytical Method Validation

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Contents

Foreword

The importance of good guidance

Measuring the concentrations of therapeutic products and their metabolites forms a critical component of the regulatory decisions made regarding the efficacy and safety of drug products. Reliable drug concentration data are crucial for the evaluation and interpretation of toxicokinetic and pharmacokinetic study data. Therefore, it is imperative that the bioanalytical methods used to generate these drug concentrations are appropriate and well characterized.

Different regulatory agencies have each issued their own bioanalytical method validation guidelines, but the aim of the ICH M10 guideline is to overcome the regional differences and provide a harmonized recommendation for the validation of both chromatographic and ligand-binding assays. The ICH M10 guideline describes the procedures and acceptance criteria for the assessment of the selectivity, specificity, calibration curve, limits of quantitation, accuracy, precision, dilution linearity, carry over and stability during method validation. Several options are given to overcome the analytical challenges during the validation of assays for analytes that also are endogenous compounds. In addition, the ICH M10 guideline specifies the criteria for calibration and quality control samples during bioanalysis, the execution of incurred sample reanalysis and the documentation requirements for validation and bioanalytical reports.

This eBook will review first impressions on the ICH M10 guidance as well as key feedback gathered during the public consultation period.

We hope you enjoy this eBook.

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Supplement

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Bioanalysis

European Bioanalysis Forum feedback on draft ICH M10 guideline on bioanalytical method validation during the Step 2b public consultation period

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Once released, the ICH M10 Guideline on bioanalytical method validation will become one of the most important milestones in the history of regulated bioanalysis, closing a chapter on intense discussions among the industry and health authorities started in Crystal City in 2001. In this manuscript, the European Bioanalysis Forum community reports back on their feedback on the ICH M10 draft guideline gathered during the public consultation period. The comments given are intended to contribute to a guideline that combines several decades of experience and current scientific vision. They should provide future generations of bioanalytical scientist a regulatory framework so their bioanalytical work can contribute to safe, effective and high-quality medicines, which can be developed and registered in the most resource-efficient manner.

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Harmonization of legislation or guidelines has been at the apex of discussions within regulated bioanalysis community for many years. With the ICH M10 guideline on bioanalytical method validation (BMV) on the horizon, there is the expectation that many of the current differences and/or ambiguities in regulatory expectations and/or interpretations of the guidelines can be harmonized or resolved and considering the ICH mission to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed and registered in the most resource-efficient manner.

This article provides feedback based on the comments from the European Bioanalysis Forum (EBF) community after the public consultation on the ICH M10 draft guideline, which was held in the spring/summer of 2019.

The comments reflect the consolidated opinion from all 66 EBF member companies (as of March 2019) and were submitted to the ICH [1] via the EMA [2] at the end of the public consultation period in August 2019.

The EBF comments are very similar to those provided by the European Federation of Pharmaceutical Industries and Associations (EFPIA) [3], considering that most of the EFPIA member companies are EBF members. The comments from both organizations were gathered in parallel and using identical surveys among the EBF and EFPIA members. As a community, EBF collaborated closely with the American Association of Pharmaceutical Scientists (AAPS) [4] and co-organized two workshops (referred to as 'sister meetings'), held in Barcelona (EBF, May 2019), [5] and Silver Spring (AAPS, June 2019), respectively. These meetings were organized as global events

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in collaboration with the China Bioanalysis Forum and Japan Bioanalysis Forum (JBF). The comments from the AAPS sister meeting were recently published in the *AAPS* journal [6].

The road to ICH M10

The road to ICH M10 has been a long one. In 2009, in an era where there was only one finalized guideline on regulated bioanalysis (i.e., the US FDA/CDER guidance on BMV May 2001), with the EMA having their regional guideline on BMV in draft, the industry expressed a desire for harmonization. In an open letter [7] to the EMA and the FDA, the industry expressed their concerns about two developments: differences in expectations or interpretation of the aforementioned FDA/ Center for Drug Evaluation and Research (CDER) guidance from individual auditors/inspectors or regional health authorities; inherent risk that new sets of bioanalytical method validation requirements or nuances to the FDA/CDER guidance would become effective when other regions would issue their regional guidelines on BMV.

The worries from the open letter have become today's reality and have stimulated many of the later discussions on the subject of harmonization.

Of course, having different interpretations of guideline requirements is not unique to regulators. Furthermore, everybody potentially has a different view on how to implement a regulatory requirement in the industry. In fact, harmonized interpretation by industry of regulatory requirements was one of the reasons why the EBF was formed in 2006 and is documented in its mission statement [8].

In an effort to connect more globally, the Global Bioanalysis Consortium (GBC) was formed in 2010. Intensive discussions in 20 GBC expert teams covering all areas of the BMV, led to 15 publications bringing an industry based state-of-the-art overview of regulated bioanalysis [9]. Nevertheless, recognizing GBC provided an industry-only perspective; the suggestion was made at the 2012 EBF Open Symposium to involve the ICH as the partner to achieve harmonization. This idea was echoed at the 5th Crystal City meeting in 2013. After 2012, no additional GBC activities were initiated.

From 2012 to 2015, several new legislation [10] and guidelines [11–14] became effective. In an effort to revive the harmonization discussions, representatives from the AAPS, JBF and EBF connected at the end of 2015 to prepare a formal request to the ICH to consider supporting 'harmonization of bioanalytical method validation guidelines' through the ICH. A draft concept paper was shared by the AAPS/EBF/JBF with EFPIA at the end of March 2016 for submission to ICH. Industry's requests highlighted two areas of focus:

- Added value of a harmonized global BMV guideline for industry. The AAPS/EBF/JBF proposal stated: "With drug development being global, a report from one bioanalysis study will be submitted to health authorities in numerous countries and thus, needs to comply with regulations in these different countries. While the small differences in the current bioanalytical guidelines/guidance are deemed irrelevant for the quality of the final concentration data, the industry is required to manage these differences through additional nonvalue-added and/or repetitive work. By issuing one harmonized ICH Guideline, the ICH partners can agree on removing procedural ambiguity and/or create single global standard platform for regulated bioanalysis." (sic).
- Ambiguity of studies in scope of a current BMV guideline. The AAPS/EBF/JBF proposal stated: "Providing clarity on what bioanalytical work conducted during drug development must be in compliance with all aspects of bioanalytical method validation guidance/guidelines. Harmonization in this regard will ensure that bioanalytical data of in-scope work is conducted in a manner that meets the expectations of regulators, while eliminating the need to conduct scientifically irrelevant work in support of studies deemed outside the scope of guidance/guidelines. In turn, scope harmonization/clarification permits bioanalytical scientists to implement validation activities for out of scope studies at an appropriate level of scientific rigor based on the intended use of the data." (sic).

Unbeknown to the AAPS/EBF/JBF team at that time was that there was a similar proposal from the Japanese Ministry of Health, Labour and Welfare (MHLW) being submitted for discussion at the June 2016 ICH management meeting. The MHLW proposal focused on the harmonization aspect, but did not specify the industry's second area of focus. The MHLW proposal was endorsed by the ICH Management Committee in October 2016 as a potential new multidisciplinary guideline referred to as M10 [15].

As per the ICH process, the endorsed draft concept paper from the MHLW was refined into a final concept paper. An expert working group with representation from industry and health authorities from ICH members was

assigned and the intensive discussions to draft a global guideline begun. In February 2019, the expert working group reached the stage where this draft guideline could be shared for public consultation (Step 2b) [16].

The road to consolidated EBF comments

With the draft guideline available for public consultation, actions were initiated within the EBF community (and of course within the global bioanalytical community at large) to provide comments.

To get opinions from their members, a detailed survey was issued in which all members could comment paragraph by paragraph (longer paragraphs were divided into sub-paragraphs), resulting in 340 (sub-)paragraphs for the body text (excluding the glossary, which could be commented on separately) and 60 (sub-)paragraphs for the documentation table. Three key questions were asked for each of the 400 (sub-)paragraphs:

- Do you agree with this (sub)-paragraph?
- Do you feel this (sub)-paragraph is ambiguous?
- Do you disagree with this (sub)-paragraph?

For the second and third questions, members could indicate the reason for their response and suggest rephrasing of the text.

The survey was issued early March 2019 and the responses were used as the basis of a 2-day face-to-face meeting with all EBF member companies during the annual EBF Strategy Meeting in Hasselt, Belgium (12–14 March 2019).

Some statistics

We received written responses from 46 out of 66 member companies.

For the first question, on average, our members agreed with 145 from the 400 (sub-)paragraphs (ranging from 107 to 323). Looking at the responses from another angle: per paragraph, on average, 56% disagreed with the proposed text for individual paragraphs, ranging from 17 to 95%. This indicates that for none of the (sub)-paragraphs, all agreed or disagreed unanimously. However, for some paragraphs, up to 95% of our members commented.

For the second and third questions, we received 1140 individual comments: 647 on ambiguities in the draft guideline (Question 2), 280 on areas of disagreements (Question 3) and 213 on the documentation table (sum of Questions 2 and 3).

In preparation for the face-to-face members meeting, after anonymization, all comments were shared with members in order to ensure that no premeeting bias was introduced for the discussions. All 66 member companies were present and contributed to the discussions in the meeting, which were organized in four sessions. For the general themes, the sessions were plenary. For chromatography or ligand-binding assays (LBA)-specific topics, the group was divided into breakout sessions ensuring focused discussion with the respective experts.

The four sessions were as follows:

- General themes – background and scope.
- General themes – full/partial validation, method development, incurred sample reanalysis (ISR), documentation, dried matrix methods, commercial and diagnostic kits, analytes that are also endogenous compounds.
- Breakout chromatographic assays.
    - Key validation parameters: selectivity, specificity, matrix effect, calibration curves, accuracy and precision, quality control samples, carryover, stability assessments, dilutions, reinjections.
    - Study sample analysis: run acceptance criteria, calibration range, reanalysis and reinjection of study samples, (re)integration of chromatograms.
- Breakout LBA.
    - Key validation parameters: selectivity, specificity, calibration curves, accuracy and precision, quality control samples, carryover, stability assessment, dilution linearity and Hook effect.
    - Study sample analysis: run acceptance criteria, calibration range, reanalysis of study samples,.
    - Reference Standard and critical reagents.
    - Parallelism and minimum required dilution.

Prior to the discussions, a small team preselected some paragraphs for deeper discussions. These were the paragraphs having received either the highest number of comments (nominal) or the most intense comments of disagreement or ambiguity. To make this selection, the team used the statistics from Questions 1 as well as the content/frequency of the comments from Questions 2 and 3. The selected paragraphs are underlined in the above list and are also discussed in more detail in the next paragraphs of this manuscript.

Details on the consolidated view on these and all other paragraphs can be found in the feedback document submitted by the EBF to ICH via the EMA [17].

The proceedings from the discussions from the meeting were the basis of all other EBF interactions with industry and regulators thereafter.

First and foremost, they are the backbone of the official comments provided by the EBF to the ICH. After considered additional input from meetings and interactions mentioned in continuation, these comments were refined and submitted for final review and approval to all EBF members, then subsequently submitted to the ICH (via the EMA) [17].

The additional discussions/interactions aimed to stimulating a harmonized approach for industry commenting on the draft guideline included:

- The aforementioned sister meetings [5,6].
- EFPIA interactions.
- A meeting organised by the Delaware Valley-Drug Metabolism Discussion Group [18] in Langhorne, PA, USA (July 2019).
- The annual China Bioanalysis Forum meeting in Suzhou, China (June 2019).
- The Reid Bioanalytical Forum in Cambridge, UK (September 2019).
- A National Medical Products Administration organized meeting in Beijing, China (September 2019).
- The 2019-Biobridges meeting in Prague, Czech Republic (September 2019) [19].

This way, the EBF contributed to a consolidated feedback process to ensure that the industry comments are representative of as many companies/experts as possible in a consolidated and structured manner.

More details on the EBF comments

On a positive note

Although 1140 comments were received suggesting otherwise, many comments and discussions recognized the positive changes in the draft guideline. Changes that will contribute to the removal of ambiguity or non-added value work. A few examples include:

- The overall comment that the draft guideline is well written, which can only be improved for the final version;
- A separate section for LBA, removing the risk of 'chromatography creep', in other words, undue copying of requirements for chromatographic-specific assessments to LBA or cross-referencing back to chromatography sections;
- Biomarkers and immunogenicity assays being out of scope;
- Removal of the matrix factor as a mandatory test;
- Refinement of blood stability evaluation to a scientifically more meaningful test;
- Possibility to include *in silico* data for selectivity testing in chromatographic assays;
- Acceptability to extrapolate the stability at one temperature (e.g., -20°C) to lower temperatures (e.g., -70°C) for chemical drugs;
- The use of singlicate versus duplicate wells for LBA methods;
- For critical reagents, the use of re-test dates rather than inflexible expiry dates;
- Parallelism to be assessed on a scientific basis rather than a routine parameter as per some regional guidelines;
- No need for detailed certificate of analysis (CoA) or evidence of purity for the internal standard (IS);
- No freshly prepared quality control sample (QCs) required for assessment of accuracy and precision;
- Monitor quality of critical reagents by performance of the actual bioanalytical assay;
- Refinement of ISR sample selection process;
- Refinement of the re-analysis process for bioavailability (BA)/bioequivalence (BE) studies.

Considering the world around us

At the mid-March EBF Strategy Meeting, we did not immediately dive into the details of the guideline text. Several comments did not relate to one specific paragraph per se and were more general in nature. Three strategic comments were prominent: a request was made to include a broader view on bioanalytical requirements for GCP, on the 3Rs [20] and to reconsider assays or study acceptance criteria in general.

Related to GCP, EBF feels more discussion with and training for the bioanalytical community on what 'compliance to GCP' means in a bioanalytical environment is needed. Today there is certainly ambiguity on this subject; laboratories are implementing their interpretation of what is required, which can lead to mis/overinterpretation. With only the Medicines and Healthcare products Regulatory Agency having an active GCP inspection program for UK-based bioanalytical labs, there is a risk that expectations from one region/country get copied into a global requirement without the necessary discussion. In the EU, repeated reference is made to the EMA reflection paper [21]. But in both cases, the industry is confused and at risk of mis- or overinterpreting.

Related to the 3Rs, the draft ICH M10 guideline copies requirements for frequency of testing and number of replicates required for many validation parameters from the existing guidelines. Progress in science and increased emphasis on animal welfare should be considered in a sustainable and science-based guideline for future generations. Hence, the EBF would like the ICH not to require unnecessary use of animals and to stimulate 3Rs recommendations where possible. Suggestions made include:

- Replace: allow surrogate matrix use when proven valid (e.g., sample dilutions and calibrators);
- Reduce: allow less replicates or fewer individual sources of matrix in validation experiments for preclinical assays;
- Refine: no additional hurdles for micro-sampling assays and promote noninvasive technologies.

One of our more strategic recommendations challenges the current practices for assay or study acceptance criteria. For decades, acceptance criteria have been technology based. This has divided our world to follow two sets of criteria: chromatography assay criteria and LBA criteria. Today, with new modalities and hybrid technologies becoming more routine, this difference is blurring, maybe even disappearing. The EBF is aware that the aim of the ICH M10 harmonization never intended to challenge the technology-based acceptance criteria and that there has not been enough discussion on a recent discussion paper published by the EBF in 2018 [22]. Nevertheless, we feel the time is right to consider harmonized decision-based acceptance criteria rather than technology-based criteria for the future. Additionally, this would prepare the guideline for new modalities and future technologies entering the regulatory BMV space.

Paragraphs from the guidance in the spotlight

In the next section, we focus on the paragraphs having received either the most comments (nominal) or the paragraphs with the most important area of either disagreement or ambiguity from the draft guidance. It is noteworthy that we are not discussing all comments we received, but summarize them to capture the strategic importance of the recommendations.

Furthermore, details can be found in the feedback document submitted by the EBF to ICH [17].

Scope & background

In total, we received 49 written comments on scope and background. The majority of those comments related to ambiguities in the text (36 comments). A major comment that consistently featured was that the scope was too broad. In addition, our members struggled with how to define 'pivotal', how to interpret 'support regulatory submissions' versus 'make regulatory decisions, or wrestled with what comprises a 'primary matrix/matrices' versus 'alternative matrices' and with the requirement to consider other ICH and regional regulatory documents to define the scope.

One of the key issues is that when developing a drug is that the bioanalytical laboratory may not know which studies will end up in a registration file. During the course of drug development, these studies may become pivotal or be used to make claims on safety and efficacy unbeknownst to the bioanalytical laboratory. As a consequence, the bioanalysts may not know which analytes and matrices or which methods require validation at the time the study is conducted. Regarding the use of 'other ICH and regional regulatory documents', only the ICH M3 (R2) guideline [23] stands out. To date, we could not identify other guidelines that would help defining which studies are in or out of scope for the ICH M10 guideline. An additional worry would be that opening up the ICH M10

scope definition to other regional guidelines, the final ICH M10 may not achieve its global status as it could be continuously influenced and/or re-interpreted based on regional guidelines definitions.

In addition to feedback stating the scope was too broad, we also received feedback from some members who felt the scope was clear. To understand this, we performed a second survey at the face-to-face meeting. In this second survey, we asked our members to indicate for ten different study types (representing all phases of drug R&D) if a certain study or analyte (dosed drug or metabolite[s]) or matrix (plasma/serum, urine, blood, tissues) were interpreted to be included as the intended scope of the draft guideline. The result of this socond survey was an eye opener and visualized the ambiguity, also for the members that originally saw no issue. Most of the members agreed that early discovery studies and final BA/BE studies were respectively out of scope and in scope of the guideline, but for all other studies (dose-range finding, early GLP, early clinical, mechanistic nonclinical studies, Phase II and Phase III [population] pharmacokinetics (PK) studies) there was no consensus on the analytes, matrices or even the study to be included as the intended scope of the draft guideline. All had their own opinion based on previous experience/inexperience with regulatory interaction, sponsor/vendor relations and/or individual different levels of risk averseness. As a consequence and if not further specified, we fear that the final scope of the guideline in daily practice may gravitate to 'all studies, all analytics and all matrices in all phases of development'.

The EBF suggested a more detailed scope definition which provides more clarity but would also foster the scientific freedom in earlier phases of drug development being a valid approach when transparently documented. Our comments are aligned with, but adds some more refinement to, the scope definition given by the AAPS at the sister meetings in Barcelona [5] and Silver Springs [6]. An additional confounding factor may be that this guideline could become legislation in some regions, removing any scientific interpretation.

At the same time, we realize it will be impossible to write a scope definition which is 100% clear for all. Therefore, it is even more important to continue intense communication and provide training for industry, regulatory reviewers and inspectors from the moment the guideline is released to continuously calibrate the scope expectations and prevent undue scope creep by all stakeholders involved.

Method development documentation

In total, we received 49 comments on the method development paragraph. Again, the majority of those comments related to ambiguities in the text (45 comments). The feedback was very consistent: the paragraph on method development and the associated documentation, albeit a valuable reference to what method development could encompass, may become over-interpreted by industry and/or become an expectation for regulators. If not interpreted flexibly, method development will become a tick box, and will increase resource requirements for industry, whilst stifling the scientific freedom required in the method development arena. The EBF suggests to leave method development as a 'scientific responsibility' for industry and to limit the scope of method development documentation to changes that are made in later stages of drug development, to already validated methods. This would also align with the original intent as discussed at the Crystal City V meeting in 2013 [24], where the focus was on ensuring transparent documentation of changes to the method for BA/BE studies in Phase III/IV as part of filings.

Matrix effects

Although only ten comments were received on matrix effects, during the face-to-face meeting, our members were happy to see 'matrix factor' being removed. Nevertheless, the paragraph can still be significantly enhanced by including 3R considerations on replicates to be tested.

Stability assessments for chromatographic assays

Numerous concerns were shared on the requirements for stability testing for chromatographic assays. In total we received 81 written comments, 29 being disagreements.

Highest on the list were the challenges to the requirement to perform stability testing for co-administered drugs. The studies in scope are interpreted to significantly differ compared to the initial requirement which involved studies with a fixed dose combination (FDC) regimen. However, the EBF community has challenged and continues to challenge the scientific rationale of this requirement in the absence of data showing analyte stability issues in biological matrices with FDC or co-administered studies. In the absence of a scientific rationale or data showing the issue, the consolidated recommendation of the EBF community was, and remains, to remove this requirement. Being aware our proposal is likely not acceptable, we alternatively recommend to limit this requirement in comparison with current guidelines rather than suggesting it could extend to all studies with co-administration regimens such

as drug–drug interaction studies (DDI). This would include the possibility of referring to the known chemistry and stabilities of the individually dosed drugs, or Chemistry, Manufacturing & Control data for co-formulated drugs as a basis for determining whether additional stability studies are needed.

One other area of concern in the stability assessments for chromatographic assays relate to 'single versus triplicate aliquots for long term stability testing'. This requirement, which came into the picture after a Clarifax from Health Canada in 2016 [25], has generated numerous concerns and additional work in industry because many companies had to re-do the long term stability testing as per Clarifax requested process. Unpublished industry data from a significant number of projects and a recent publication from the FDA [26] have shown there is no scientific merit for this requirement but leads to more work and more matrices being used. Considering a modern science-based and data-driven guideline stimulating smart use of resources, the EBF recommends the removal of this requirement. Additional comments and concerns on stability assessments for chromatographic assays can be found in the full version of the EBF comment [17].

Selectivity/specificity in LBA

A large number of concerns were shared by the LBA community relating to selectivity and specificity requirements:

- Requirement to investigate selectivity as well as specificity at a high QC level. Scientifically there is no need to test selectivity/specificity at high QC or even at the ULOQ as all issues that may occur for these validation parameters impact the LLOQ level. Selectivity/specificity at higher concentrations has little to no impact.
- Requirement to evaluate selectivity in lipemic samples and hemolyzed samples only if considered relevant for this indication.

Both requirements are scientifically questioned, but need large volumes of individual matrices, which is in contrast with the concept of saving matrix (3R for animal matrix) and the mission of ICH harmonization.

Stability assessments for LBA

Comments and concerns were also received on the stability requirements, where the EBF suggests it is also acceptable for biologics to extrapolate the stability at one temperature (e.g., -20°C) to lower temperatures (e.g., -70°C). There is no available data to show that biological drugs that are stable at -20°C are unstable at lower temperatures. Therefore, if freezing to -20°C is considered acceptable, there is no reason to investigate lower temperatures.

The stability chapter of the ICH M10 raised another concern related to the fact that an ultra-high stability QC should be tested because study of high dilutions are frequently necessary. This requirement is not considered relevant due to the fact that stability with high concentration samples are not an issue.

In addition, the 'Single versus triplicate aliquots for long term stability testing' issue discussed for chromatographic assays holds true for LBA as well, supporting the recommendation to remove this requirement.

Study sample analysis

Regarding the calibration range, the draft ICH M10 guideline recommends that sample analysis should be stopped if an unanticipated clustering of samples at one or the other end of the calibration curve occurs and that the calibration range including QC levels should be revised. The EBF community feels that the costs and consequences to put this requirement into reality, which is at least a partial validation and a delay in delivering clinical sample analysis results, are much higher than the actual benefit. The assay range has been fully validated during the validation phase, demonstrating robust, precise and accurate analyte quantification. In addition, dilution linearity experiments carried out during validation prove reliable titration of samples into the assay range. Taken this together, the EBF community suggests removing this paragraph.

The EBF received many comments in asking for detailed clarification on the reanalysis of study samples. An overarching theme was to consider clarifying that reanalysis is related to samples that produced valid results (i.e., concentration in range vs >ULOQ or <LLOQ).

Reanalysis of samples from failed or rejected runs that did not produce acceptable results should not be viewed as 'reanalysis' in the context of this paragraph. Hence, we suggest to clearly separate the examples to reflect both cases:

- Reanalysis of a sample that did not give a reportable concentration, is not reanalysis per se as it generates a first reportable result.

- Reanalysis of a sample for which the first reportable result is 'unexpected' (e.g., positive placebo, unexpected PK [excluding BA/BE]), is reanalysis. It should be performed in replicate and compared with the original result with the aim to confirm or disprove this original result.

In addition, samples of a rejected run are not considered valid and should not be listed in a reanalysis table.

ISR

In total, we received 37 comments on ISR, focusing on three concerns: the number of studies in which ISR is expected to be performed; the number of samples required for ISR; and the timing of ISR experiments.

With respect to the number of studies in which ISR is required, the industry may be barking up the wrong tree when challenging any guideline. In fact, for a long time, most laboratories have been performing ISR in virtually every study, even when it is not required by any guideline. The recent 2018 FDA Guideline [27] has widened the expectation to include more studies in scope for ISR, but the ICH M10 guideline re-aligns with previous expectation from FDA [28] and current guidelines from EMA [29] and MHLW [12,13].

The upside of this acronymic 'Industry Self-Inflicted Regulatory creep' to perform ISR across more studies than required has resulted in a huge database on ISR results showing the frequency and types of studies where ISR failure occurred [30]. These data could be used to refine the ISR requirements for the ICH M10 guideline, not only for which studies, but after data mining, likely also for the number of samples required. From this and supported by many other papers providing scientific evidence that reanalysis of large sets of samples does not add scientific value [31–33], we commented to consider a cap, that is, a maximum sample number to be analyzed as part of ISR: reanalyze 10% of the study samples, with a minimum of 20 and a maximum of 100 samples.

Cross validation

From almost all comments given, it appeared that our members did not fully understand the new philosophy with respect to the proposal regarding the cross-validation approaches in the draft guideline. Most comments related to asking for pass/fail criteria, whereas the proposed requirements for cross validation focused on understanding a potential bias between two validated methods. Hence, we suggest to add some explanation of this philosophy in the guideline to indicate that cross validation is conducted to evaluate the bias between methods (or laboratories) such that the results from studies using them can be appropriately interpreted and that cross validation allows the comparison of two methods (laboratories) and informs us how they are related.

In view of this changed requirement of what a cross validation aims at, the EBF strongly recommends intensive training and a consideration on defining the responsibilities related to "how to define 'a disproportionate bias?"' and on who owns the decision and is responsible for downstream actions of "the impact on the clinical data interpretation should be assessed."

Documentation

We received 213 comments on the documentation table, reflecting the major concern that industry has with this section. In essence, we understand and have no issue with the documentation requirements if restricted to final BA/BE studies at filing. In fact, our members are already complying with most of the suggested requirements. However, we strongly feel that the documentation requirements for other studies should be simplified and allow retention at the analytical site rather than requiring unmanageable levels of documentation in bioanalytical reports. The EBF therefore suggests to limit the scope of Table 1 in the ICH M10 draft Guideline to BA/BE studies.

Putting the magnitude of comments into context

One overall comment from the EBF community was that the document is well written. Nevertheless and also to our surprise, we received 1140 comments, some of them very detailed and even challenging established requirements. Where lies the contradiction? In trying to understand the background of the industry's worries commenting so strongly on a guideline that captures the requirements of current regional guidelines in use for a few decades already, we identified three potential areas:

- Most comments are not related to 'harmonization' per se, but to continued challenges from industry on requirements in the individual regional guidelines. Many see this as a last opportunity to challenge areas where there has been disagreement for a long time and have been receiving citings by reviewers: ISR in practice, stability

assessments for fixed dose combinations, placement of the mid-QC or number of replicates for long-term stability assessment are just a few examples.

- Some of the paragraphs in the ICH M10 are new and are not part of any current guideline. As such, they have not been discussed in a way the industry is used to, for example, the Crystal City workshop discussion being our reference point. Method development, cross validation, some paragraphs in '7. Additional Consideration' in are good examples.

3. There is a real fear that the global guideline will have a significantly wider scope than any of the current regional guidelines, leading to additional work in areas where it has previously not been required (or necessary) and failing to meet the mission statement of development of safe, effective and high-quality medicines in the most resource-efficient manner.

Conclusion & future perspective

The bulk of this manuscript inevitably discusses concerns that the EBF has on the draft ICH M10 guideline. We wish to repeat the comment that the draft guideline is well written and provides solutions for several existing issues.

When in place, this guideline will be the reference point for generations of bioanalytical scientists to come. Therefore, it is important for all parties involved that we get this right. Hence, the focus of our comments is on what is not yet achieved, even if it will be difficult to do so.

We realize that it is impossible to remove all disagreements, disappointments and ambiguities from the final ICH M10 guideline. Hence, this final guideline should be a solid basis for good science and good documentation but allow for open discussions (preferably a priori) between health authorities and applicants on areas of ambiguity. A cautionary note for future discussions; many new modalities are entering the drug-discovery pipelines as well as new technologies (or repurposed technologies). So, is the current draft guideline really ready for this development? If not, what is required to ensure a global perspective on these questions?

Finally, effective implementation of the guideline can only be achieved by continued training and open discussions on any potential interpretation differences. Therefore, an ICH training program is essential for successful implementation of the guideline. Building this training should involve both industry and regulators. The EBF is committed to give all support to any training initiative as felt appropriate.

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ICH M10 impressions: 60 seconds with Monique Putman

Monique Putman joined QPS Netherlands in 2002 and is currently Director of Translational Medicine. In this position, Monique serves as manager of three teams for the development and validation of ligand-binding assays, cell-based assays, activity assays and FACS assays to support the development of biological drugs.

Prior to joining QPS, Monique held a position of Staff Scientist and Biological Safety Officer at the Hercules European Research Center (Barneveld, The Netherlands). Monique studied Food Technology at The Wageningen University (The Netherlands) and received her PhD in the Molecular Microbiology Group of the Groningen Biomolecular Sciences and Biotechnology Institute (GBB) of The University of Groningen (The Netherlands).

1 What was your first impression of the ICH M10 guideline?

Overall, I feel that the draft ICH M10 guideline is well written. Most items can be recognized from the current FDA and EMA guidelines, that are the guidelines in use at our CRO. In contrast to the FDA guideline, the ICH M10 guideline presents the validation of chromatographic assays and ligand-binding assay separately, making the differences in requirements more clear. The guideline is applicable to the methods used for pivotal nonclinical studies and all clinical trials in regulatory submission. Unfortunately, for a CRO it is often not clear whether a study will end up in a registration file. Consequently, more methods may be validated to this extend than necessary.

2 Will the ICH affect the QPS validation approach?

As QPS is a global CRO, the SOPs on method validation cover both the requirements of the current FDA and EMA guidelines. When looking at the requirements for ligand-binding assays, I noticed changes to the intra-run precision and accuracy and the dilution linearity. Currently, the intra-run precision and accuracy is assessed with 5 aliquots at each level in 1 run. According to the draft ICH M10 guideline, it should be addressed with 3 aliquots at each level in at least 6 runs. Similarly, for the dilution linearity we will need to change from the assessment of 5 replicates per dilution factor in 1 run to an assessment in at least 3 runs.

ICH M10 impressions: 60 seconds with Monique Putman

3 What was unexpected in the draft ICH M10 guideline?

Over the past years, there has been a large interest from the industry for a fit-for-purpose approach in an attempt to limit unnecessary use of resources and materials. In that respect, I was expecting a more clear definition of the type of studies that are in or out of scope of the ICH M10 guideline.

Further, I did not expect a section on method development. Clearly, before the start of the validation of an assay all indicated parameters are typically checked. However, I am concerned that including this section in the guideline will increase the documentation on method development, in order to demonstrate that all items have been included in the method development prior to the validation.

4 What would you like to see changed?

In the current version of the ICH M10 guideline there is no distinction between the validation for nonclinical and clinical assays. Due to the number of validation runs and the number of replicates required for the validation parameters, and the fact that the calibration standard should be prepared in matrix, the volume of nonclinical matrix used for validation is considerable. I would welcome the option to use surrogate matrix and/or reduction of the required number of replicates in validation experiments for nonclinical assays to reduce the use of animals.

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Bioanalysis

The effectiveness of quality control samples in pharmaceutical bioanalysis

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The use of quality control (QC) samples in bioanalysis is well established and consistent with regulatory guidance. However, a systematic evaluation of whether QC samples serve the intended purpose of improving data quality has not been undertaken. The Translational and ADME Sciences Leadership Group (TALG) of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) conducted an evaluation to assess whether closer agreement is observed when comparing pharmacokinetic data from two passed runs, than when comparing data from failed and passed (retest) runs. Analysis of data collected across organizations, molecular types and analytical platforms, revealed that bioanalytical methods are very reproducible; and that QC samples improve the overall quality of pharmacokinetic concentration data and justifies their continued use.

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Keywords: bioanalysis • bioanalytical data quality • failed runs • QC failure • QCs • quality controls • repeat runs • sample retesting

Quality control (QC) procedures are commonly applied to a variety of processes and products across industries including healthcare, manufacturing, environmental health and safety, and many others. Although the procedures and specific approaches to QC vary according to the industry and the nature of the application, the overarching goal is the same: to ensure that a product or procedure meets specific predefined acceptance criteria designed to ensure quality, integrity and reliability. The pharmaceutical industry utilizes QC processes extensively across the various functions necessary to discover, develop and manufacture drugs to treat human diseases and conditions. One such application is the mandated use of QC samples during pharmacokinetic (PK) and biomarker bioanalysis to ensure that the validated method, and the analytical run in question, is within acceptable accuracy and precision limits and that the data acquired are trustworthy. The longstanding approach of assessing the validity of an analytical

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run based on the performance of the calibration standards and QC samples is well defined by regulatory agencies globally, in Guidance Documents and in Pharmaceutical White Papers [1–6]. Underlying this common practice is an implicit assumption that acceptable accuracy and precision of QC sample measurements serves as a robust reflection of the reliability of the test sample data and can be used as gating criteria for data acceptance. In other words, pharmaceutical scientists infer that the measurement of QC samples of known concentration predicts the accuracy of measurements made on test study samples of unknown concentration during bioanalysis runs. Although this assumption has a logically sound basis, to the authors' knowledge there has been no systematic evaluation of whether QC samples actually serve this intended function and protect bioanalysis laboratories from reporting inaccurate and misleading data.

Including QC samples in drug development bioanalysis comes at a cost. Doing so reduces the number of study samples that can be accommodated in each assay run, and when runs fail due to unacceptable QC accuracy, retesting samples adds to the overall expense of study conduct. Further add to this the effort to prepare, test and store QC samples; and then expand these expenses to include immunogenicity and biomarker bioanalysis, and it becomes apparent that the costs associated with QC sample use are significant. Additionally, the matrix required to prepare QC samples should be considered in the context of the pharmaceutical industry's commitment to reduce animal usage (3 Rs) [7,8]. Given the effort and expense, International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) initiated the current study to evaluate the value added by QC samples with respect to data quality and our ability to accurately establish PK and biomarker associated properties of drugs (and ultimately patient safety and efficacy). Such questions are particularly important in contemporary society as pharmaceutical companies strive to reduce the costs to bring novel products to market, improve patient access and relieve financial pressure on struggling healthcare systems.

Reanalysis of samples for drug concentration is performed only under very specific, predefined and well-established circumstances [1,2]. For example, the concentration values of all samples from a run that failed to meet prespecified run acceptance criteria, the 4-6-15/20 rule; where 4 of 6 QC samples must fall within 15% of their nominal concentration for chromatographic assays/small molecules or 20% of their nominal concentration for ligand binding assay (LBA)/large molecules – are disqualified, and the samples must be retested. In cases where individual test sample concentration values fall above the validated quantitative range of the assay, those samples would be diluted, retested and the concentration values accepted only if they fell within the quantitative range of the method (with the final reported value multiplied by appropriate dilution factors). For mass spectrometry bioanalysis, samples may be retested due to interfering peaks/poor chromatography, unacceptable internal standard response, injection malfunction, carryover, etc. Again, it is important to note that this is an acceptable practice only when prestudy criteria are established for these parameters [1,2]. In the above cases, sample concentration data from failed runs is captured but not reported. Upon acceptable retesting, new concentration values are derived and reported. One could safely assume that concentration values from failed and retested (passed) runs would be different. In fact, even concentration values from two passed runs would be expected to differ to some degree, given the inherent imprecision of any analytical method.

In order to demonstrate bioanalytical method reproducibility using actual study samples, the practice of incurred sample reanalysis (commonly referred to as ISR) was introduced following the Crystal City III conference [9,10]. ISR has been formally adopted by the EMA and US FDA and published in bioanalytical method validation guidance documents [1,2]. In an ISR experiment, a subset of incurred samples that have already been tested in runs that passed acceptance criteria, is retested. Retest runs must pass the same run acceptance criteria as the original run.

The objective of the current study carried out by IQ member companies, is to assess the utility of QC samples by comparing study sample drug concentration data from bioanalytical runs in which QCs passed, to corresponding ISR retesting data (i.e., two passed runs); and then conduct a second comparison of concentration data from failed runs (due to failing QCs) with corresponding retest data (i.e., one passed and one failed run). If QC samples effectively reflect overall run quality and protect bioanalytical labs from reporting inaccurate data, one would expect closer agreement between concentration values from two passed runs, than between concentration values from a failed and passed run.

This manuscript was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

Materials & methods

Data eligibility rules

All IQ member companies were invited to contribute blinded PK data from their respective studies to this project through the data sharing procedure established within the consortium. To establish an optimized, robust dataset of drug concentration values from passed and failed runs, rules were established to minimize data selection bias and maximize data diversity across companies and bioanalytical platforms. For each company contributing data, eligibility was restricted to the first 1, 2 or 3 large molecule toxicokinetic (TK)/PK bioanalysis projects; and/or the first 1, 2 or 3 small molecule TK/PK bioanalysis projects, completed in 2015 (regardless of start date), that included at least one run failure due only to unacceptable QC accuracy (i.e., runs must have met all other acceptance criteria such as calibrator accuracy). Not more than 3 large molecule and 3 small molecule datasets were permitted from any single company. Furthermore, only bioanalytical datasets where ISR was performed and passed acceptance criteria were permitted. To best compare test and retest data from accepted runs (i.e., the original bioanbalytical run and the ISR run), all ISR data for a dataset (i.e., a study) were included in the analyses, not just ISR data from samples that were also included in failed and retested run comparisons.

Both nonclinical and clinical study data were eligible for inclusion, and any bioanalytical platform (LC–MS, meso scale discovery [MSD], ELISA, etc.) was considered acceptable. For consistency of data interpretation, only datasets where the 4-6-15/20 run acceptance criteria were applied, were eligible. For the purpose of this study, a 'dataset' was defined to include: all data from all bioanalysis batches/runs from within a study that failed due only to unacceptable QC recovery; all data from the retest batches/runs, and; all the corresponding ISR data for the dataset. Important to note, the current project excluded studies that did not include ISR, or where ISR failed to meet acceptance criteria.

Along with PK/TK data from study samples, QC data from the corresponding runs were also collected as part of this project. If accuracy of QC samples truly reflects run performance more generally, one would expect that the magnitude of QC deviation from nominal concentrations to be reflected in the degree of discordance upon retesting. In other words, if QC accuracy results were significantly outside acceptable ranges in a particular run, the study sample concentration data on that run should deviate more significantly when compared with study sample data from test and retest runs where QC accuracy results were only slightly outside the acceptable range on the first run. However, the ability to make such comparisons in this project proved impractical as there were an insufficient number of runs in which QC accuracy deviated to an extreme extent (data not shown).

Database construction

Individual company datasets were collected in a templated worksheet created in Excel 2016. The data-entry cells in the template utilized several techniques such as conditional formatting and text-based fields with controlled vocabularies accessible via pull-down menus to help minimize data entry errors and guide the user during the data entry process. Using a web-interface, the data in the completed templates were uploaded and stored in a custom-built, flat database hosted by a database framework established by IQ. During the upload process, the Excel worksheet was subjected to a QC check by the database software to ensure that only the controlled vocabulary was used as inputs where applicable and that all mandatory fields were completed. Each upload would generate a log file which in the case of a failed upload attempt would contain information related which cells caused the failure along with the reason. Upon a successful quality check, the data were inserted into the database with a re-assignment of the original 'Molecular ID' identifier provided in the template to a unique, random identifier as a final blinding step. Upon conclusion of the data collection process, users of the database were able to view the full, consolidated dataset comprising data contributions from all participating IQ members. This dataset was then made available for download as a comma-separated values formatted file for offline analysis.

Statistics & data visualization

In this section, we describe the strategy used for comparing agreement between original (passed or failed) and retested (passed for ISR or retested due to failure) PK concentration data that were collected in the database. All statistical analyses were conducted in R [11]. For these purposes, a scatterplot of original run concentration values versus retested run values for each study sample was generated to visualize the overall reproducibility of bioanalytical methods across all platforms. Additional platform-specific scatterplots were created to compare data from passed bioanalytical runs and corresponding ISR data (labeled 'ISR'), and data from failed bioanalytical runs and retested values (labeled quality control failure [QCF] for QC failure). All scatterplots included a 45-degree identity line to

represent an idealized state where values for original and retested runs are equal. Graphs were generated in original and logarithmic scales. Because a similar pattern of scatter around the line of identity was observed across assay platforms, representative graphs are provided.

An inspection of the scatterplots in original scale indicated that the differences between original and retested runs increased with nominal concentration. This suggested that degrees of agreement between bioanalytical runs should be quantified using a measure of relative difference that considers magnitude of the concentration. In this investigation, the relative percent difference was used to quantify degrees of agreement between bioanalytical runs. The relative percentage difference (RPD) is defined as:

$$RPD = \frac{C_R - C_O}{\left(\frac{C_R + C_O}{2}\right)}$$

where C_O and C_R correspond to the original and retested bioanalytical runs, respectively, and $(C_R + C_O)/2$ is the average of the two bioanalytical runs. Traditionally, the RPD is expressed as percentage by multiplying by 100. For convenience, this indicator is expressed as a decimal value. Note that the conclusions are not affected by using decimal values instead of percentages.

The use of RPD to quantify agreement has several advantages. RPD is the same index used by regulatory agencies for assessing agreement between results in the context of ISR criteria (meaning that 2/3 of cross-validation samples fall within ±20% of the mean of the original and retested assay values (±30% for LBA) [1,2]. Because it considers the magnitude of the concentration, RPD is perfectly suited to quantify agreement in this study where comparison of degrees of agreement across a wide range of concentration values is required.

To quantify differences in the degrees of agreement between sample concentration data (ISR vs QCF), we investigated the probability distribution of RPD values. Histograms of RPD values indicate that the distribution of RPD values exhibits a pronounced sharp peak around the central value and heavy tails. Thus, the histogram suggests that, in general, a normal distribution does not provide effective description of the distribution of RPD (data not shown). The Laplace distribution is an alternative distribution that captures most of the main features of the distribution of RPD values [12,13]. The Laplace and normal distributions were superimposed on the histograms of RPD values for ISR and QCF samples for each assay platform. The graphs indicate that the Laplace distribution provides an adequate representation of the distribution of RPD, whereas in most cases the normal distribution does not provide an effective description. This was also consistent with other graphical assessment of the distribution such as Q-Q plots, P-P plots and the cumulative distribution function of observed data.

The Laplace distribution, like the normal distribution, has a location parameter (at the center) and a scale parameter to describe spread or variability, which are estimated by the sample median and the mean absolute deviation from median. The mean absolute deviation from median (MnAD) is defined by:

$$MnAD = \frac{\sum_{i=1}^{N} |RPD_i - Med\,(RPD)\,|}{N}$$

where *RPD* represents the relative percent difference from ith pair, and N is the total number of pairs, and Med (RPD) is the median of the N observed RPD values. The location parameter (median) of the Laplace distribution describes bias in agreement between bioanalytical runs and the scale parameter (MnAD) describes the level of agreement between bioanalytical runs. Summaries of bias (location) and spread are provided for the different QC samples, assay platforms and sample types, along with tolerance intervals based on Laplace distribution with two-third and 95% coverage probability with 95% confidence. The tolerance intervals describe the range within which an expected percentage of future degrees of agreement (RPD) is expected to fall based on the current sample with a given level of confidence.

Results

The final database for this investigation included 32 datasets collected across 12 companies, enabling thousands of comparisons from passed, failed and retested samples across platforms and molecule types as shown in Table 1.

At the highest level, the reproducibility of bioanalytical PK methods across platforms – whether comparing two passed runs or a failed run and passed run – is noteworthy as shown in the scatterplot below (Figure 1), where original run values and retest values cluster mostly around the 45° line of identity. However, as the figure also shows,

Table 1. Summary of data collected.

Description	Number
Companies contributing data	12
Small molecule LC–MS data sets	21
Large molecule ELISA data sets	4
Large molecule MSD data sets	7
Passed/passed (ISR) pair comparisons	2279
Failed/passed (QCF) pair comparisons	2445

ISR: Incurred sample reanalysis; QCF: Quality control failure; MSD: Meso scale discovery.

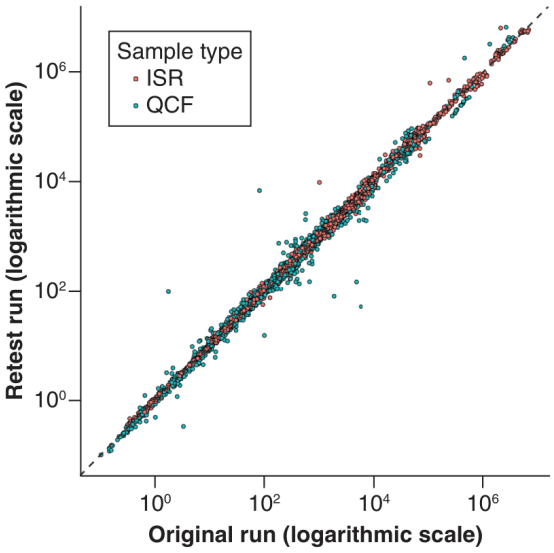

Figure 1. Scatterplots (logarithmic scale) of original runs and retested runs for study samples. The ISR and QCF samples are superimposed for comparability purposes. The graph shows a similar pattern of spread around the line of identify for ISR and quality control samples.
ISR: Incurred sample reanalysis; QCF: Quality control failure.

a pattern emerges even in this high-level visual representation of the data, with more variability apparent around the 45° line in the QCF comparison group (failed/passed runs) than in the ISR group (passed/passed runs).

As the data are examined by assay platform type and further visualized with method-specific scatterplots and histograms, the overall pattern remains the same (Figures 2, 3 & 4). More variability (lower agreement) is observed in the QCF data comparisons than in the ISR comparisons. Interestingly, representation of the data in scatterplots reveal that the degree of discordance increases with the magnitude of the concentration. The histograms, and the Laplace distributions, generally demonstrate a wider distribution of RSD in the QCF datasets compared with ISR. This is especially evident for ELISA and LC–MS datasets (but also true for MSD) and may reflect the fact that higher concentration samples are more likely to include additional dilution steps compared with samples at lower concentrations, potentially resulting in additional variation.

To quantify the patterns seen in the QCF and ISR data comparisons, the Median RPD and MnAD were calculated (Table 2). The former was used to assess whether any significant high/low bias was observed upon sample retesting; and the latter was employed to quantitatively describe the degree of agreement between original and retest results across the two comparisons. Unsurprisingly, retesting study samples did not result in any pharmacokinetically meaningful bias in concentration values (i.e., a meaningful difference of median RPD from zero), whether the original result was generated in a run that passed or failed and was consistently observed across all platforms. The MnAD calculations confirmed what was visualized in scatterplots and histograms, namely that for each platform and across the entire study, the magnitude of the deviation from the median (discordance of original and retest values) was significantly higher in the QCF comparisons than in the ISR comparisons. Simply put, there is less agreement when comparing original and retested concentration values from failed and passed runs, than when comparing values from two passed runs.

Finally, when tolerance intervals are created based on Laplace distribution to describe the range within which an expected percentage of future degrees of agreement (RPD) is expected to fall based on the outcome of these analyses, the ranges are significantly wider for the QCF group than the ISR group (Table 3). Again, supporting the conclusion that there is more variability present when comparing data from failed runs with passed runs.

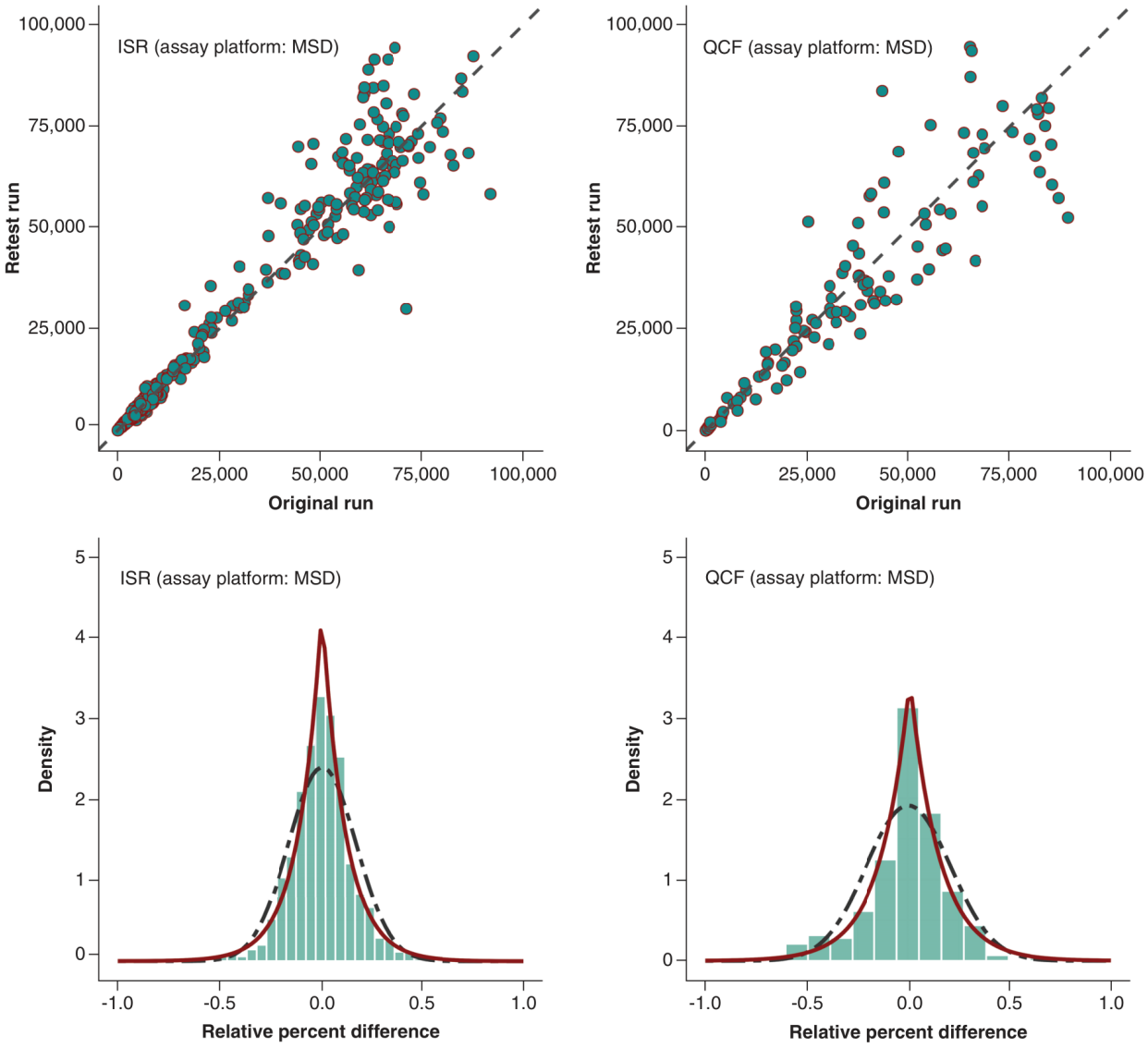

Figure 2. The upper panels show scatterplots (original scale) of original run and retested run for meso scale discovery assay data. The dashed gray lines represent the identity lines. The scatterplots indicate that the differences between original runs and retested runs increase with the magnitude of the concentration. The lower panels show histograms of observed relative percentage difference values for ISR and QCF samples for MSD. The red lines represent the Laplace distribution and the gray dashed lines the normal distribution. The Laplace distribution captures the main features of the distribution of relative percentage difference. The normal curve is included for reference purposes. ISR: Incurred sample reanalysis; MSD: Meso scale discovery; QCF: Quality control failure.

Table 2. Quantitative representation of relative percentage difference by assay platform: parameter estimates of Laplace distributions.

Assay platform	QC sample	Median	MnAD	n of pairs
ELISA	ISR	-0.028	0.104	133
	QCF	-0.025	0.183	152
LC–MS	ISR	-0.002	0.071	1425
	QCF	-0.020	0.134	1774
MSD	ISR	0.007	0.115	721
	QCF	0.011	0.145	519
All platforms	ISR	0.000	0.087	2279
	QCF	-0.014	0.140	2445

ISR: Incurred sample reanalysis; MnAD: Mean absolute deviation from median; MSD: Meso scale discovery; QC: Quality control; QCF: QC failure.

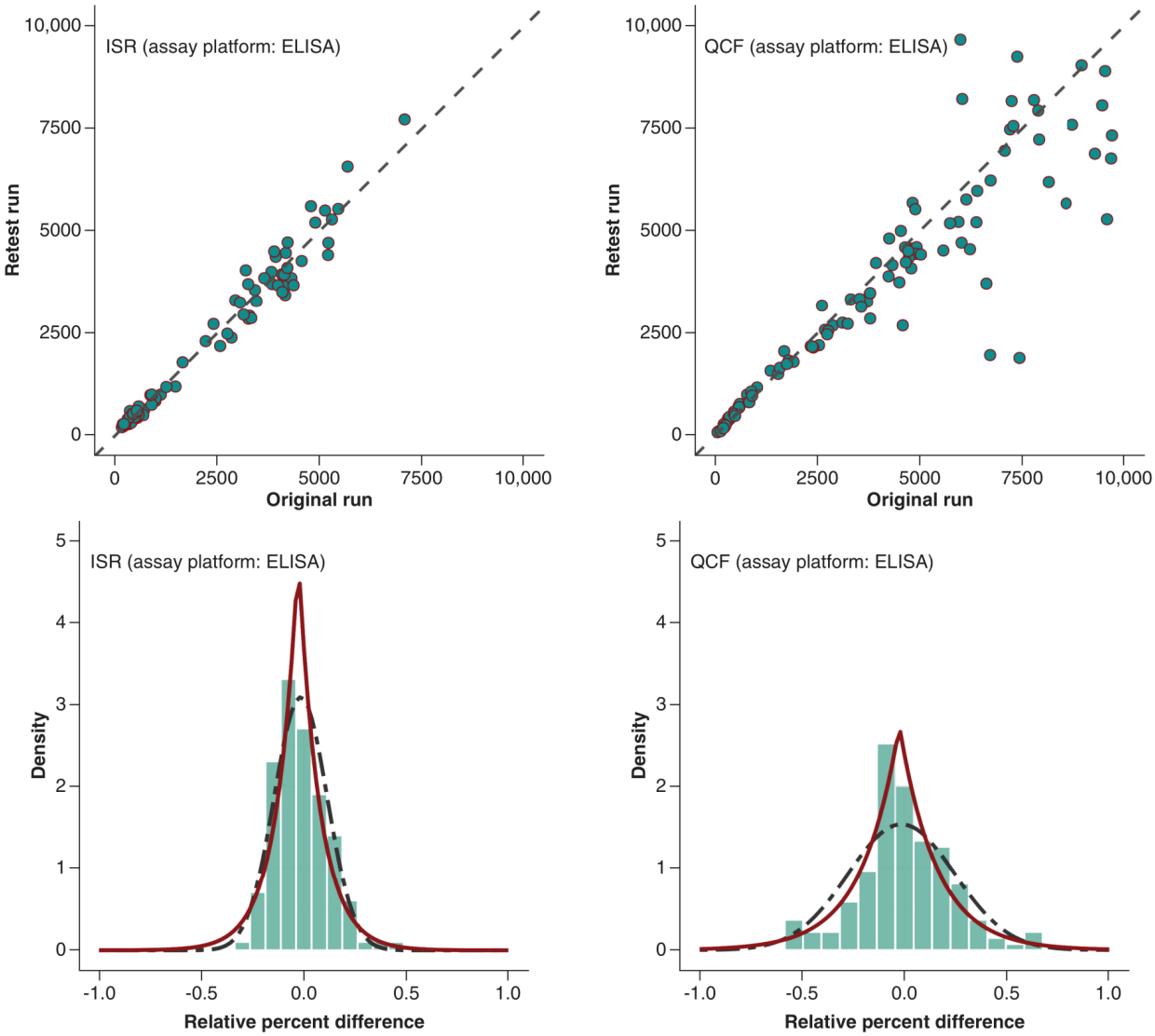

Figure 3. The upper panels show scatterplots (original scale) of original run and retested run for ELISA assay data. The dashed gray lines represent the identity lines. The scatterplots indicate that the differences between original runs and retested runs increase with the magnitude of the concentration. The lower panels show histograms of observed relative percentage difference values for ISR and QCF samples for ELISA. The red lines represent the Laplace distribution and the gray dashed lines the normal distribution. The Laplace distribution captures the main features of the distribution of relative percentage difference. The normal curve is included for reference purposes.
ISR: Incurred sample reanalysis; QCF: Quality control failure.

Table 3. Tolerance intervals of relative percentage difference values by assay platform and comparison type.

Assay platform	Comparison	66.7% coverage probability		95% coverage probability	
		Lower bound	Upper bound	Lower bound	Upper bound
ELISA	ISR	-0.172	0.117	-0.406	0.351
	QCF	-0.275	0.225	-0.681	0.631
LC–MS	ISR	-0.086	0.081	-0.227	0.222
	QCF	-0.178	0.137	-0.444	0.403
MSD	ISR	-0.133	0.147	-0.367	0.381
	QCF	-0.168	0.189	-0.465	0.486
All platforms	ISR	-0.101	0.101	-0.272	0.272
	QCF	-0.177	0.149	-0.452	0.424

All tolerance intervals have 95% confidence.
ISR: Incurred sample reanalysis; MSD: Meso scale discovery; QCF: Quality control failure.

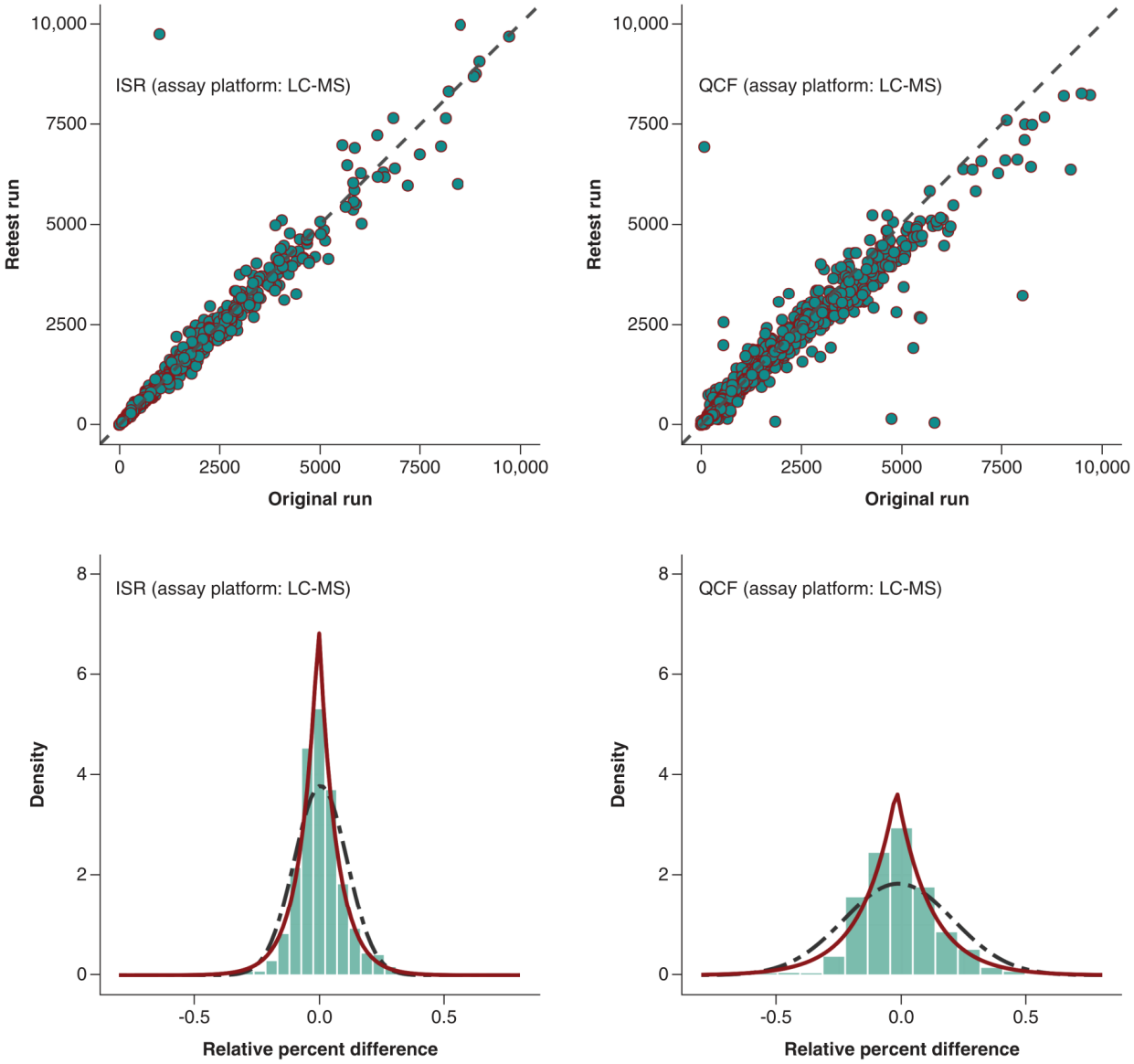

Figure 4. The upper panels show scatterplots (original scale) of original run and retested run for LC–MS assay data. The dashed gray lines represent the identity lines. The scatterplots indicate that the differences between original runs and retested runs increase with the magnitude of the concentration. The lower panels show histograms of observed relative percentage difference values for ISR and QCF samples for LC–MS. The red lines represent the Laplace distribution and the gray dashed lines the normal distribution. The Laplace distribution captures the main features of the distribution of relative percentage difference. The normal curve is included for reference purposes.
ISR: Incurred sample reanalysis; QCF: Quality control failure.

Discussion

Bioanalytical scientists follow various health authority guidelines, recommendations from White Papers, conference proceedings, common industry practices and respective company specific SOPs to ensure the quality of bioanalytical data. Methods are validated to ensure suitability for intended use prior to testing samples and run acceptance criteria are applied to safeguard the validity of the bioanalytical data. The goal of such measures is, of course, to most accurately characterize the PK and pharmacodynamic properties of pharmaceutical products, thus minimizing risk and maximizing benefit to patients. During PK sample analysis, run acceptance is based on the performance of both calibration standards and QC samples. Run acceptance based on calibration standards follows an approach where a predefined number of standards must fall within prespecified ranges based on their nominal concentrations. The details of run acceptance will depend on the method platform (e.g., LC–MS vs LBA), calibration standard concentrations relative to limits of quantitation, number of replicates, etc., but the general approach is well-described and commonly practiced.

Bioanalytical QC samples are prepared by spiking drug into the appropriate matrix at concentrations representing the quantitative range of the method (typically at low, mid and high concentrations relative to the range). When study samples require predilution prior to analysis, a dilution QC is typically added to the set of QCs to be tested in those runs. In each assay run, 2 QC samples at each concentration are included among the study samples tested and run acceptance is based on QC sample results follows the well-established 4-6-15/20 convention. Furthermore, the total number of QC samples in a run/batch must be at least 5% of the total number of samples (at least 6 on each 96-well plate).

Since both calibration standards and QCs are made from the same or matched (a.k.a. verified) stock solutions, and especially if they are prepared/processed at the same time, one can question the purpose of the QC samples within a run/batch – since any trends/inaccuracies would also be reflected in the calibration standards. If this is the case, failure of QC samples to meet acceptance criteria would most likely represent random error rather than systematic problems with a given run, and sample concentrations from passing and failing runs would not differ significantly. On the other hand, if accuracy of QC samples reflects general run performance, one would expect sample concentration data from failed runs to be significantly different than subsequent data from passed runs. This project was designed to evaluate these two possibilities and address the question of whether QC samples serve their intended purpose.

The majority of dataset comparisons performed in this study revealed PK concentration data from original runs being very similar to retested values, even when the original run failed. This was true for ELISA, MSD and LC–MS methods and implies that bioanalytical methods are generally very reproducible, perhaps not surprising given the extent of development and validation work invested in such methods. Based on this high-level observation, one might question the value of QC samples in pharmaceutical bioanalysis. However, on closer examination, the data also reveal a consistent pattern across platforms and companies – PK data from samples tested in two passed runs is closer in agreement overall than data from failed and passed runs. This pattern was consistent across all analytical platforms included in this study, despite the differences in QC acceptance criteria. In fact, the general pattern of close agreement between failed and passed run study data, combined with the observation of better agreement between two passed runs, suggests that the true utility of QC samples for run acceptance purposes comes in safeguarding against the occasional run where a systematic problem did occur during sample testing, and sample values were significantly inaccurate. For this reason alone, our evaluation conclusively demonstrates that the inclusion of QC samples adds value to pharmaceutical bioanalysis. It was not possible given the design of this study and the nature of the data collected (e.g., no PK timepoints), to fairly assess the impact of that contribution in characterizing the PK properties of drugs, but the value is clearly apparent. It should be acknowledged that one limitation in the analyses performed was that only ISR data from studies that passed ISR criteria (meaning that 2/3 of retested samples fell within ±20% of the mean of the original and retested values (±30% for LBA) were included. This could introduce a bias toward tighter agreement between original and retest values than would have been seen if the database included data from methods that failed ISR (QCs passed run acceptance, but agreement of original/retest data failed the rule above). However, given the relative infrequency of failed ISR studies [14], the authors believe any such bias would be insignificant.

There are also additional uses for QC data that need to be considered. For example, QCs add significant value to each analytical batch in circumstances where bulk QCs are prepared, and aliquots are frozen alongside study samples for use during sample analysis along with calibration standards that were also prepared separately in bulk and frozen. This approach seems to be the standard practice across most bioanalytical labs, especially when supporting large multi-year clinical studies. In such a situation, the QCs are extremely valuable in understanding potential data bias in study sample concentrations revealed when bulk prepared, frozen QC samples are tested and concentrations interpolated from a standard curve created from freshly (or separately) prepared calibrators. The analyses conducted in this report were not designed to assess such biases, no attempt was made to capture when and how QCs and calibrators were prepared and stored.

Another use for QC data comes from in-study method validation. Tabulating QC recoveries at the end of a study from every analytical run allows one to better estimate the 'true' analytical performance of a method, originally estimated with prestudy method validation data from a limited number of assays runs. Collecting QC data from dozens (or hundreds) of runs over many months (or years), enables refinement of accuracy, precision and total error estimates for bioanalytical methods. When combined with ISR, such in-study validation data provide bioanalytical scientists, pharmacologists and regulatory agencies, additional confidence in the bioanalytical data and the resulting PK assessments.

Conclusion

Overall, the data collected in the current study indicate that bioanalytical methods for TK/PK assessment are demonstrated to be very reproducible. Most importantly given the goals of this project, the overall tighter agreement of TK/PK study sample data between 2 passed runs than between a failed and passed run, affirms the utility of QC samples for run acceptance purposes. While there may be room for further exploration of the significance of differences seen in this study (e.g., the impact to calculated TK/PK parameters), and of alternative approaches to run acceptance, the topline outcome combined with the additional value of QC data collected for other purposes during study support, clearly justifies the continued investment in QC sample use in pharmaceutical bioanalysis.

Future perspective

The current study demonstrates that the overall reproducibility of bioanalytical methods is quite impressive, even when comparing bioanalytical data from failed runs and subsequent retested values. However, the degree of agreement between those values was not as close as when comparing data from two passed runs. Thus, the overall conclusion from this study supports the continued use of QC samples in pharmaceutical bioanalysis to maintain data accuracy. It must be noted that no attempt was made to compare calculated PK parameters from data attained in failed runs and passed runs to assess the magnitude of this benefit. Sample timepoints were not included in the database and there were legitimate concerns associated with recalculating PK parameters expressed by companies contributing data. Thus, there is room for further exploration to better describe the implications of such differences; and to potentially identify alternative, more efficient and improved approaches to pharmaceutical bioanalytical run acceptance.

Executive summary

- Quality control (QC) samples are commonly used for run acceptance in pharmaceutical bioanalysis, though their utility in controlling the reporting of inaccurate concentration data have not been definitively demonstrated.
- The current study uses paired comparisons of pharmacokinetic concentration data to test the hypothesis that agreement will be tighter between concentration values from two passed runs (one being incurred sample reanalysis), than between values from failed runs and subsequent (passed) reanalysis runs.
- Statistical analyses of data contributed by 12 pharmaceutical companies, across multiple platforms, confirms that the use of QC samples for run acceptance, protects bioanalytical labs from reporting inaccurate data from an occasional run in which a systematic problem occurred.
- Based on these observations, we propose that QC samples should continue to be included in pharmaceutical bioanalysis.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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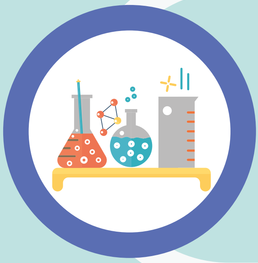
An Overview of ICH M10 Bioanalytical Method Validation Guideline

What is ICH M10?

The aim of the **ICH M10 guideline** is to overcome the regional differences in bioanalytical method validation guidelines and provide a harmonized recommendation for the validation of both chromatographic and ligand binding assays.

Why is this important?

Reliable drug concentration data are crucial for the evaluation and interpretation of toxicokinetic and pharmacokinetic study data.



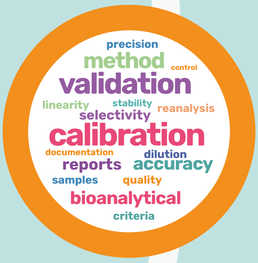
How does ICH M10 help?

These guidelines ensure that the bioanalytical methods used to generate these drug concentrations are appropriate.

What are the components of ICH M10?

The ICH M10 guideline describes the procedures and acceptance criteria for the assessment of:

- The selectivity, specificity, calibration curve, limits of quantitation, accuracy, precision, dilution linearity, carry over and stability during method validation
- Criteria for calibration and quality control samples during bioanalysis
- The execution of incurred sample reanalysis
- The documentation requirements for validation and bioanalytical reports



How are the new guidelines different?

In contrast to the FDA guideline, the ICH M10 guideline presents the validation of chromatographic assays and ligand binding assays separately, making the differences in requirements clearer.

How could it be even better?

Distinction between the validation for nonclinical and clinical assays would be helpful. Also, the option to use surrogate matrix and/or reduction of the required number of replicates in validation experiments for nonclinical assays - to reduce the use of animals.

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