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.

First draft submitted: 4 March 2020; Accepted for publication: 14 March 2020; Published online: 23 April 2020

Keywords: [comments](#) • [EBF](#) • [harmonization](#) • [ICH M10](#) • [public consultation](#)

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

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 second 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 citations 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.

Acknowledgments

The authors wish to acknowledge the EBF member companies (August 2019) having contributed to the comments submitted to the EMA. From March 2019 to August 2019, some of the EBF member companies merged resulting in 64 companies finally contributing to the submitted to EMA: A&M Labor, Abbott Healthcare Products, AbbVie, ABL (Ardena Bioanalytical Laboratories), ABS, Accelera, Alderley Analytical, Almirall S.A., Amgen, Aptuit (an Evotec Company), ARCinova, ArgenX, Ascendis Pharma, AstraZeneca, AZ Biopharma, Atlanbio-Citoxlab, Bayer Pharma AG, Bioagilytix, Boehringer-Ingelheim, Celerion, Charles River, Comac Medical, Concept Life Sciences, Covance, Dynakin, Eurofins, F Hoffmann-La Roche, Ferring Pharmaceuticals, GlaxoSmithKline, Genmab, Grünenthal, Intertek Pharmaceutical Services Manchester, Idorsia Pharmaceuticals Ltd, Janssen R&D/Biologics, Kymos, Leo Pharma a/s, LGC, Lundbeck a/s, Merck Serono, MSD, Novartis, Novimmune (currently Sobi), NovoNordisk, Nuvisan GmbH, Orion Corporation Orion Pharma, Orphazyme, pharm-analyt Labor GmbH, Pharmaron-UK, Pierre Fabre, PRA Health Sciences, PSIOXUS, QPS Netherlands, Recipharm, Sanofi, Servier, SGS, Swiss BioQuant, Symphogen, SYNLAB Analytics & Services Switzerland AG, Synthon, Syrinx Bioanalytics, UCB Biopharma, Unilabs, Svar Life sciences.

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Financial & competing interests disclosure

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

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