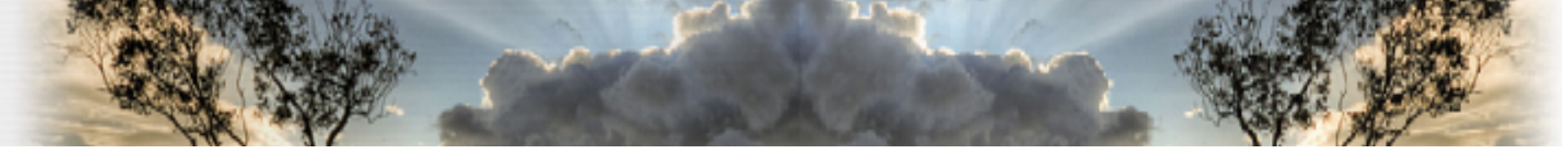

EBF Open Symposium

N° 13 From Cyberspace - Staying Connected

17-20 November 2020

ICH M10 Public Consultation - the Essence of our Comments

Steve White , Jean-Mark Gnoth, Michaela Golob and Tom Verhaeghe
on behalf of the EBF

Disclaimer

The FB on ICH M10 in this presentation was prepared on behalf of EBF, incorporating to the best of our ability the outcome of internal EBF discussions, - surveys, discussions from the EBF Barcelona Industry Focus Workshop (sister meeting) and from EFPIA discussions.

The opinions expressed in this presentation do not necessarily reflect the view of any individual expert, EBF or EFPIA member company nor that of the ICH M10 Expert Working Group (EWG).

Presentation flow

(0) Introduction
(1) acceptance criteria
(2) GCP,
(3) 3R
(4) 3R: a recent FotP surrogate matrix
(5) FDC Stability
(6) Mid QC considerations
(7) LT Stability LBA
(8) Selectivity/Specificity LBA
(9) Standards and key reagents
(10) Calibration range
(11) ISR
(12) Method development,
(13) Partial and Cross validation
(14) Documentation
(15) Scope

(0) Introduction

EBF FB → consolidated community opinions.

Input gathered from:

- Internal EBF surveys:
- comments on ICH M10 Guideline (March 2019) – 45 companies provided written FB, 65 companies participated in pre-FW discussions during an internal EBF face-to-face meeting
- Gauge for Agreement/ambiguity/disagreement with paragraphs
- Include legacy EBF recommendations on relevant BMV sections – publications available in Bioanalysis Journal

All meeting delegates were invited fill out a similar survey:

- We received written comments from 21 companies.
- All presenters were asked to integrate comments from delegates in their presentations.

> 1.100 individual comments

Why do we have so many industry comments on a “30-y old Guideline” ?

1. Some paragraphs in ICH M10 are new and are not part of any Guideline. As such, they have not been discussed in full
2. Most comments are not related to “harmonisation” per se, but to continued challenge from industry on regional guidelines
3. Fear that global guideline has a wider scope than any current regional guideline

Comments were provided to EFPIA on 26 August 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission of comments on ICH guideline M10 on bioanalytical method validation

(EMA/CHMP/ICH/172948/2019)

Comments from:

Name of organisation or individual
This document contains the consolidated comments from the European Bioanalysis Forum vzw (EBF vzw, non-profit). Following companies (Pharma R&D and CRO) are member of the EBF vzw

Full Details can be found on the EBF website: https://e-b-f.eu/publications/

Our feedback was published in Bioanalysis in May 2020

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

Philip Timmerman*[,1], Joanne Goodman[2], Michaela Golob[3], Tobias Haslberger[4], Magnus Knutsson[5], Robert Nelson[6], Tom Verhaeghe[7] & Steve White[8]

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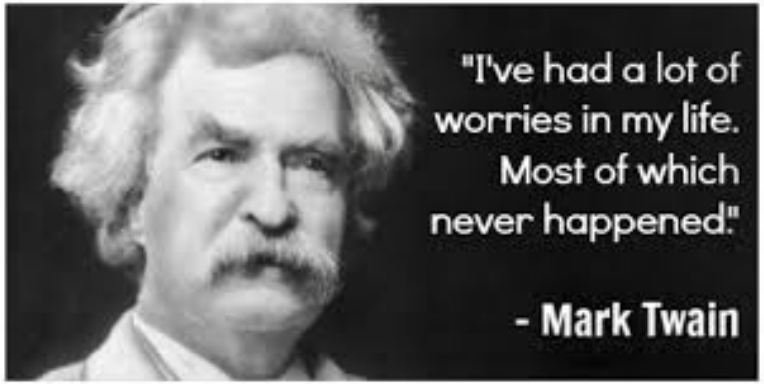
So….1140 Comments

Industry expressed a lot of worries, made suggestions to remove ambiguity, remove testing that has no added value or resource intensive (providing alternatives) or to consider 30y of experience and progress in science and technology.

We want to remind you of some of them in today's presentations



Unlike Mark Twain, we do see our worries already happening

Presenters, on behalf of the EBF

Steve White Mark Gnoth Michaela Golob Tom Verhaeghe

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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.

(1) Acceptance criteria

Why do we continue to rely on technology based criteria to support PK decisions? The data support similar safety or efficacy decisions…

EBF would like the industry and HA to consider an open and science based discussion on the added value of integrating harmonized decision-based acceptance criteria for PK bioanalytical assays

In this way, we create a transparent platform to facilitate the use of new technologies in the toolbox of the regulated bioanalytical scientist

White Paper

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Bioanalysis

Toward decision-based acceptance criteria for Bioanalytical Method Validation: a proposal for discussion from the European Bioanalysis Forum

Philip Timmerman*,[1], Michaela Golob[2], Joanne Goodman[3], Magnus Knutsson[4], Robert Nelson[5], Marianne Scheel Fjording[6] & Steve White[7]

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*Author for correspondence: Tel.: +32 479 91 01 32; chair@e-b-f.eu

* ***Bioanalysis*** *(2018), 10 (16), 1255-1259*

(2) GCP considerations

- Adherence to GCP remains controversial and ambiguous in BA labs
- Challenges within the bioanalytical lab to be resolved through continuous improvement and advancement of relevant GCP processes and trainings

EBF/EFPIA - recommendation to EMA/EWG

1.3 Scope - cntd
For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the bioanalysis of study samples should also conform to their requirements.

For studies that are subject to Good Laboratory Practice (GLP) the bioanalysis of study samples must also conform to its requirements. In accordance with Good Clinical Practice (GCP), the bioanalysis of clinical study samples must be conducted as described by the study protocol and within the limits of the informed consent agreed to by study participants.

- More info and concerns were expressed in our GCP workshop from Day 3

(3) 3Rs – what is it?

- The Three R's is a principle that the use of animals in research should be minimised as much as possible, without compromising the scientific integrity of the research.

- *Replacement*
  - Methods which avoid or replace the use of animals
- *Reduction*
  - Methods which minimise the number of animals used per experiment
- *Refinement*
  - Methods which minimise animal suffering and improve welfare

FB from EBF and delegates

same biological matrix, this will restrict those who choose to use human matrix for curves and non clinical QCs. 3Rs

4.2.6 Dilution Linearity and Hook Effect - should be allowed to use buffer for dilution instead of matrix if proven valid in order to save matrix (3R)

Including DilQC samples (not the actual diluted study samples). Agree that dilution should be validated, but this makes no scientific sense and is not ethical (3Rs)

3Rs, an alternative matrix could be used for dilutions if it is proven to be acceptable.

Matrix effect: 3R, in NC species less than 6 should be fine

4.2.6 Dilution Linearity and Hook Effect - This may not be feasible for rare matrices. We suggest adding text to allow for the use of surrogate matrices, consistent with the 3Rs.

Calibration matrix: 3R, alternative matrix (e.g. human) for animal species as long as it has been demonstrated that the use of alternative matrix does not affect precision and accuracy, selectivity etc.

M10 Guidance on use of matrix

- ICH M10 774-777

*"Dilution linearity should be demonstrated by generating a dilution QC… and diluting this sample … with **blank matrix** to a concentration within the calibration range."*

- ICH M10 705-6

*"Calibration standards should be prepared in the **same biological matrix** as the study samples"*

- ICH M10 790-792, 795-798

"The storage and analytical conditions applied to the stability tests, …should reflect those used for the study samples."

*"Stability of the analyte in the studied matrix ... A minimum of three stability QCs should be **prepared** and analysed per concentration level/storage condition/timepoint."*

Changes to current (FDA, EMA, MHLW, China)

- **FDA 2018**
  - *When surrogate matrices are necessary, the sponsor should justify and validate the calibration curve*
- **EMA 2012**
  - *Although the use of extracted matrix (e.g. charcoal, immuno-affinity) or alternative matrix (e.g. protein buffers, dialysed serum) is not recommended, the use of such matrices may be necessary when there is no other strategy to quantify the analyte of interest. The calibration standard curve may be prepared in these surrogate matrices*
- Current guidance does not mandate use of matrix for sample dilutions

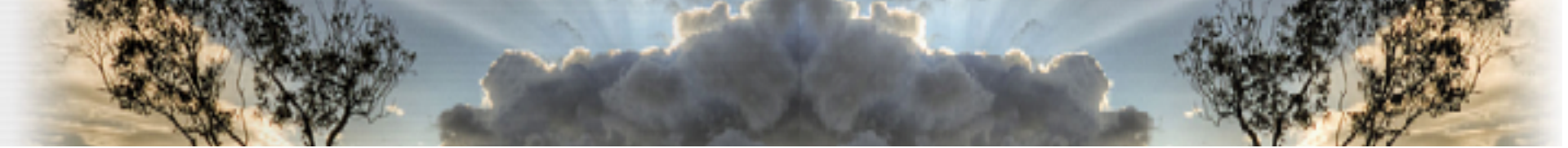
3Rs for ICH M0

The EBF community feels a modern, science based guideline should consider animal welfare and review unnecessary use of animals:

- Replace
  - Surrogate matrix used when valid. E.g. Sample dilutions, Calibrators
- Reduce
  - Using smaller volumes of sample or matrix. E.g. consider less replicates in preclinical assays, Reduce requirement for non-serial sampling or satellite groups
- Refine
  - Microsampling to reduce stress

(1,2,3) Acceptance criteria, GCP, 3R: Our fear

- In it's current wordings, the current draft guideline isn't prepared for new technologies rapidly moving into the reg. BA space, insufficiently considers the R3s and doesn't prepare us for practical GCP implementation for the BA lab
- We already see the impact in our day to day work for all 3 …



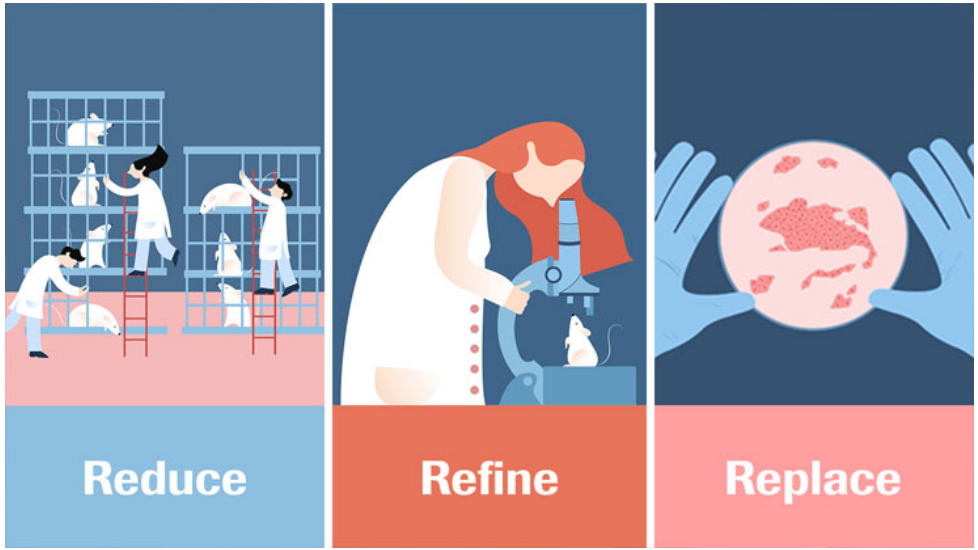
Finger-on-the-pulse (FotP)

Mixed matrix approach in pre-clinical safety studies

Compiled by Mark Gnoth

Bioanalysis Today

EFFICIENCY
Speed
Quality
Costs


Reduce
Refine
Replace

Some Statements from draft ICH M10

The matrix used for analytical method validation should be the same as the matrix of the study samples, including anticoagulants and additives. In some cases, it may be difficult to obtain an identical matrix to that of the study samples (e.g., rare matrices such as tissue, cerebrospinal fluid, bile). In such cases surrogate matrices may be acceptable for analytical method validation. The surrogate matrix should be selected and justified scientifically for use in the analytical method.

When MS detection is used, the use of the stable isotope-labelled analyte as the IS is recommended whenever possible.

Analytical runs containing samples that are diluted and reanalysed should include dilution QCs to verify the accuracy and precision of the dilution method during study sample analysis.

But…

- Although techniques and knowledge has increased we are asked to do more!
- Scientific evidence can be generated as part of method validation to optimise
  - Experience in early development/discovery is abundant
- 3R requirements are increasing and should stimulate us to change our process

Content of a FotP

In the scope of 3R but also from a cost perspective it might make sense to rethink the way we analyze samples from preclinical safety studies

Seven questions were submitted to investigate with main topics addressing:

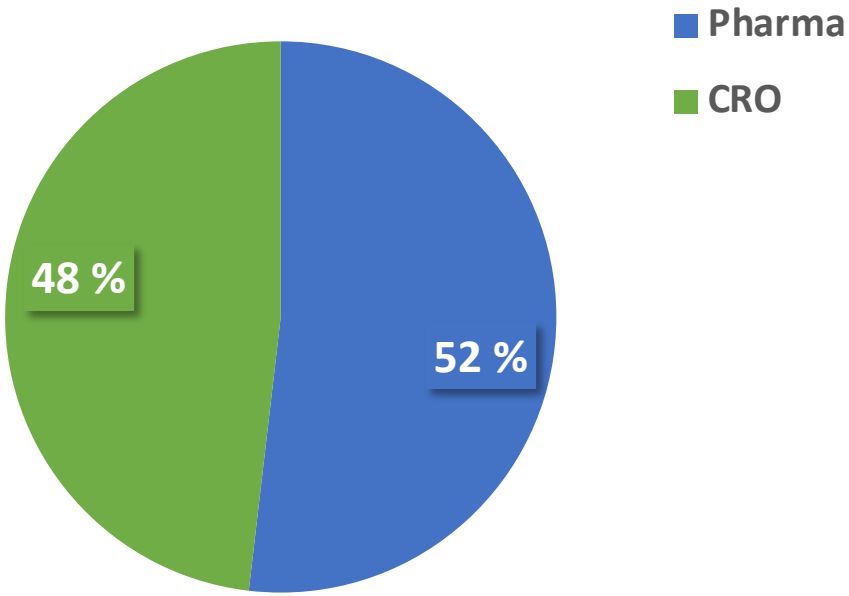
- how the EBF community thinks about a new approach in analyzing non-clinical safety studies
- who already uses this new approaches
- which risks are seen in not using the respective matrix of the unknown samples
- if it would be beneficial to publish data demonstrating the current experiences

➢ 27 responses were received

FotP Questions

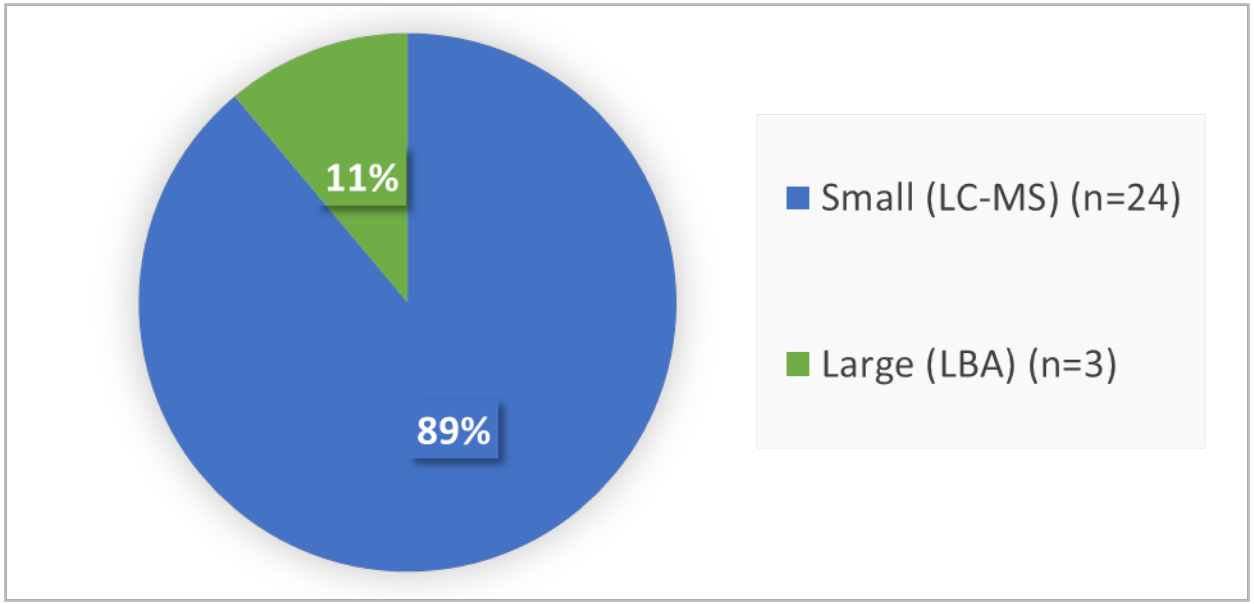
1. My organization is (Pharma/CRO)
2. Small or large molecules
3. Are you analyzing samples from preclinical rodent studies using the human LC-MS method after x-fold dilution with human plasma?
4. Do you use this strategy for non-clinical GLP safety studies?
5. From scientific point of view, do you see a value of using rodent plasma instead of human plasma for sample dilution?
6. Have you received any feedback from regulators regarding this strategy after submitting of data generated using this strategy?
7. Do you see a scientific value to publish data on this strategy to increase acceptance by regulators?

1. My organization is?



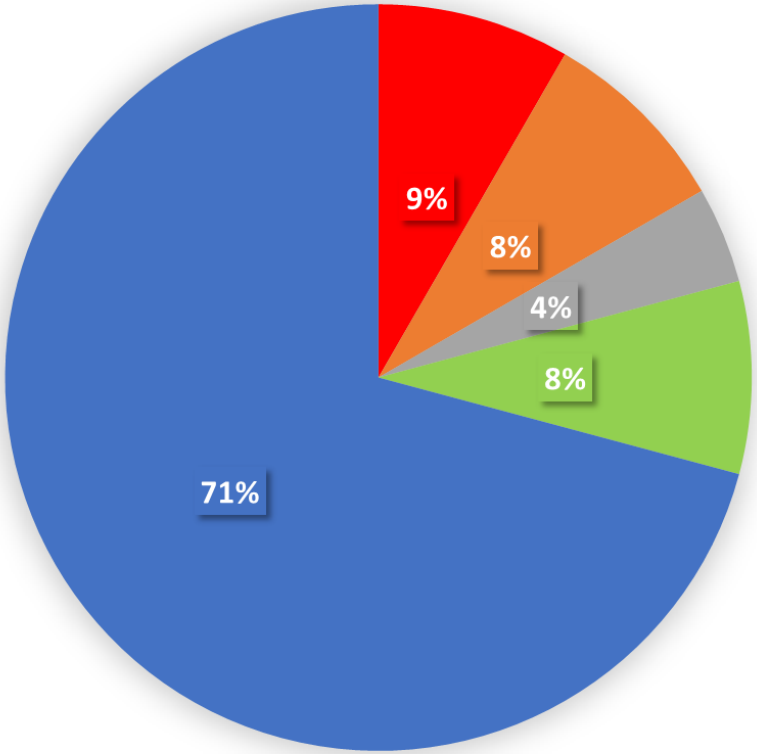
Pharma	14
CRO	13

2. Small or Large Molecule?



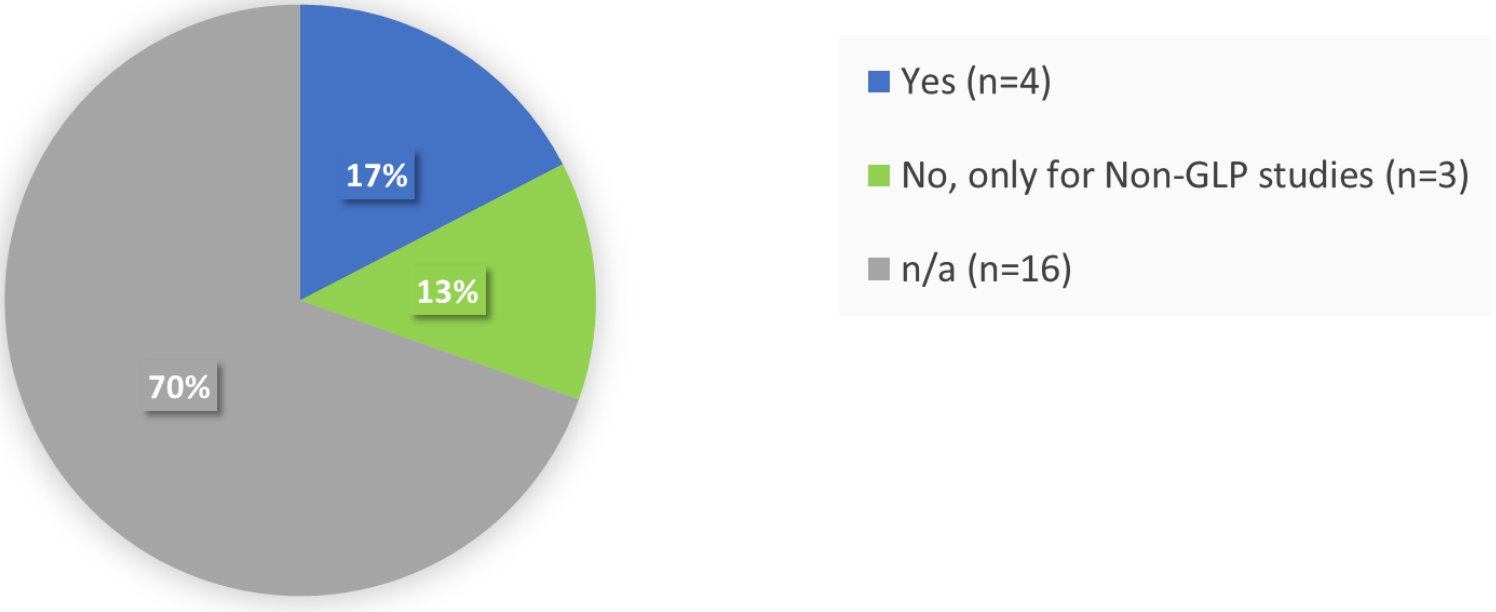
No double counting with regard to modalities, focus on small

3. Are you analyzing samples from preclinical rodent studies using the human LC-MS method after x-fold dilution with human plasma?

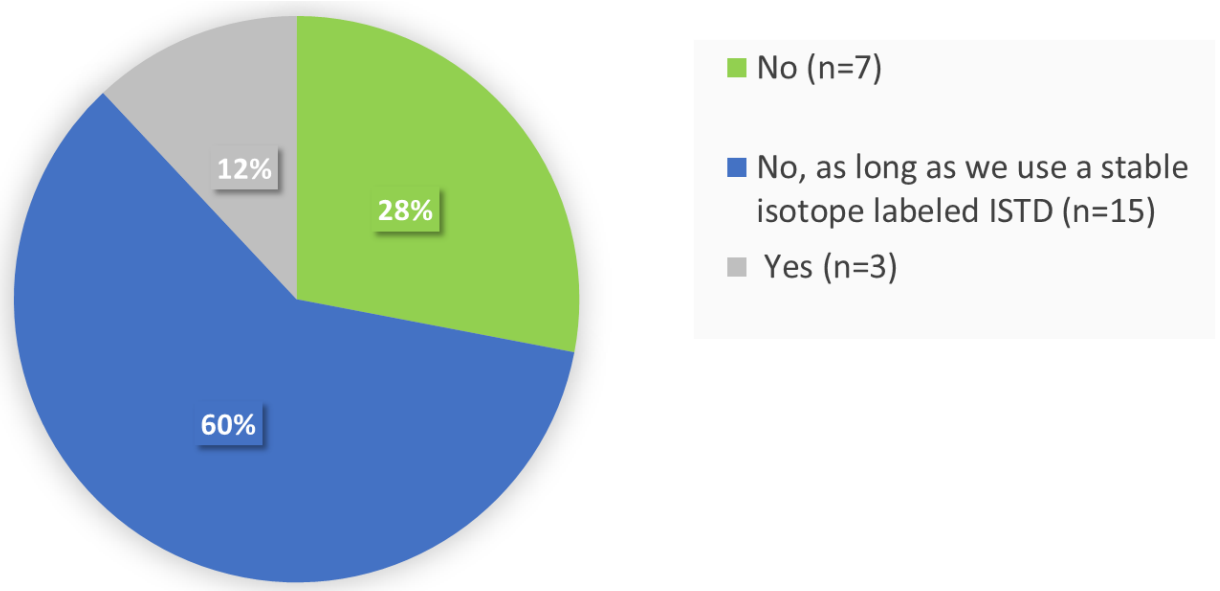


- Yes, we use Cals and QC prepared in rodent plasma and dilute them to the same extend as the unknowns with human plasma (n=1)
- Yes, as a) but we but we prepare Cals in human plasma instead of Cals prepared in rodent plasma (n=2)
- We don't dilute rodent samples only but include an extra set of QCs prepared in rodent plasma diluted with human plasma (n=2)
- Alternative strategy to safe rodent plasma (n=2)
- No, we don't follow this strategy (n=17)

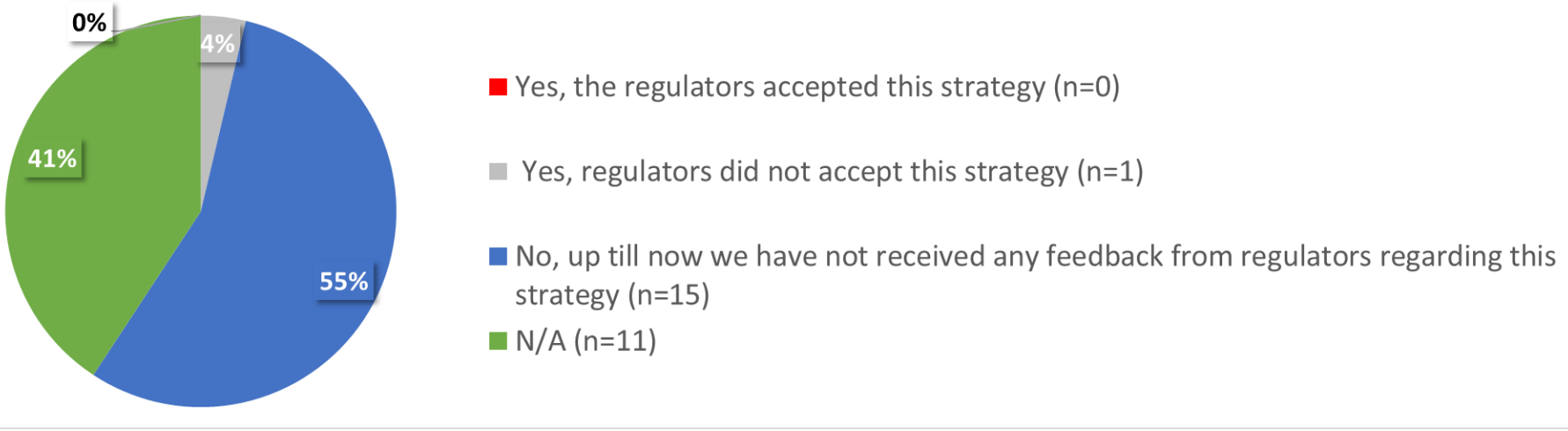
4. Do you use this strategy for non-clinical GLP safety studies?



5. From scientific point of view, do you see a value of using rodent plasma instead of human plasma for sample dilution

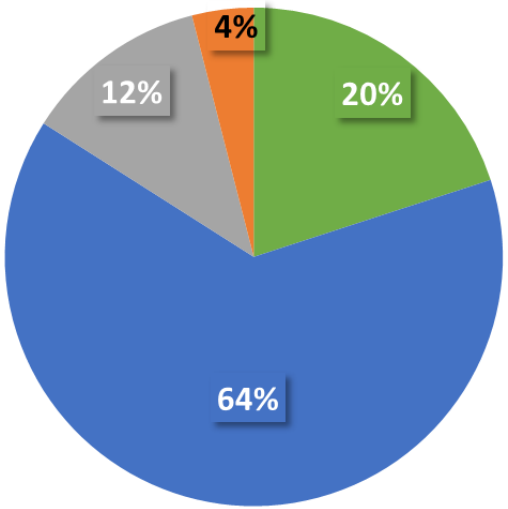


6. Have you received any feedback from regulators regarding this strategy after submitting of data generated using this strategy?



- **None of the companies that uses this approach has so far received push back from regulators**

7. Do you see a scientific value to publish data on this strategy to increase acceptance by regulators?



- Yes, I would be willing to provide blinded data (n=5)
- Yes, but I don't want to participate actively (meaning we do not have data to share as we have not been using this approach) (n=16)
- No (n=3)
- Not sure – we do not have data to show 1:1 comparison; data of successful validations is not very attractive to publish (n=1)

Summary and conclusions

- There is a value to use non-rodent or human plasma to dilute plasma from mice and rats to save animals and money
- Currently about 30% of the companies dilute their rodent samples using human plasma or alternative strategies
- Half of the companies that follow this approach only apply this for non-GLP samples
- About 90% of the participants of the FotP see no risk in using this alternative approach
- Only very limited experience available regarding feedback from regulators
- There is interest seen to follow up on this topic

Use one method for all species and adjust the plasma if WR allows

Before we dive into FDC stability

We had a lot of comments related to the stability testing requirements (3.2.8)

Comments on Stability

a picture tells and contains a 1000 words..

3.2.8 Stability	
Stability of the analyte in the studied matrix is evaluated using low and high concentration stability QCs. Aliquots of the low and high stability QCs are analysed at time zero and after the applied storage conditions that are to be evaluated. A minimum of three stability QCs should be prepared and analysed per concentration level/storage condition/timepoint.	Stability of the analyte in the studied matrix is evaluated using low and high concentration stability QCs. Aliquots of the low and high stability QCs are analysed ~~at time zero and~~ after the applied storage conditions that are to be evaluated. A minimum of three aliquots of each of the stability QCs should be stored and analysed per concentration level/storage condition/timepoint. Analysis of the stability QCs prior to storage (e.g. at t=0) may be informative with respect to confirming that they have been correctly prepared, but is not required. (this proposal is in alignment with Health Canada expectations. Not clear if EFPIA wants to push back)
The stability QCs are analysed against a calibration curve, obtained from freshly spiked calibration standards in a run with its corresponding freshly prepared QCs or QCs for which stability has been proven. The mean concentration at each QC level should be within ±15% of the nominal concentration. If the concentrations of the study samples are consistently higher than the ULOQ of the calibration range, the concentration of the high stability QC should be adjusted to reflect these higher concentrations. It is recognised that this may not be possible in nonclinical studies due to solubility limitations.	The stability QCs are analysed against a calibration curve, obtained from freshly spiked calibration standards in a run with its corresponding freshly prepared QCs or QCs for which stability has been proven. The mean concentration at each QC level should be within ±15% of the nominal concentration. ~~If the concentrations of the study samples are consistently higher than the ULOQ of the calibration range,~~ Stability should be demonstrated at a concentration within 25% of the maximum observed in study samples. Hence, additional stability assessment is necessary in the event that study sample concentrations greater than 125% of that of the high stability QC are measured in study samples, unless it is recognised and documented that this is not ~~may not be~~ possible ~~in nonclinical studies~~ due to solubility limitations. (25% specification based on the fact that High QC is approximately within 25% of the ULOQ of the standard curve)
If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.	If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix containing all dosed compounds should be considered. In the case of a fixed combination stability information of the combination dosage form may be considered. *(would delette this sentence as it is scientifically not relevant and in many cases difficult to obtain)* In the case of a drug regimen, the known chemistry and stabilities of the individually dosed drugs should be used as a basis for determining whether additional stability studies are needed. DDI studies are not is scope of this requirement
The following stability tests should be evaluated:	
1) Stability of stock and working solutions The stability of the stock and working solutions of the analyte and IS should be determined under the storage conditions used during the analysis of study samples by using the lowest and the highest concentrations of these solutions. They are assessed using the response of the detector. Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector. If the stability varies with concentration, then the stability of all concentrations of the stock and working solutions needs to be assessed. If no isotopic exchange occurs for the stable isotope-labelled IS under the same storage conditions as the analyte for which the stability is demonstrated, then no additional stability determinations for the IS are necessary. If the reference standard expires, or it is past the retest date, the stability of the stock solutions made previously with this lot of reference standard are defined by the expiration or retest date established for the stock solution. The routine practice of making stock and working solutions from reference standards solely for extending the expiry date for the use of the reference standard is not acceptable.	1) Stability of stock and working solutions The stability of the stock and working solutions of the analyte and IS should be determined under the storage conditions used during the analysis of study samples by using the lowest and the highest concentrations of these solutions. ~~They are assessed using the response of the detector. Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector.~~ If the stability varies with concentration, then the stability of all concentrations of the stock and working solutions needs to be assessed. If no isotopic exchange occurs for the stable isotope-labelled IS under the same storage conditions as the analyte for which the stability is demonstrated, then no additional stability determinations for the IS are necessary. If the reference standard expires, or it is past the retest date, the stability of the stock solutions made previously with this lot of reference standard are defined by the expiration or retest date established for the stock solution. ~~The routine practice of making stock and working solutions from reference standards solely for extending the expiry date for the use of the reference standard is not acceptable.~~ (reference to methodology removed to provide flexibility)
2) Freeze-thaw matrix stability: To assess the impact of repeatedly removing samples from frozen storage, the stability of the analyte should be assessed after multiple cycles of freezing and thawing. Low and high stability QCs should be thawed and analysed according to the same procedures as the study samples. Stability QCs should be kept frozen for at least 12 hours between the thawing cycles. Stability QCs for freeze-thaw stability should be assessed using freshly prepared calibration standards and QCs or QCs for which stability has been proven. The number of freeze-thaw cycles validated should equal or exceed that of the freeze-thaw cycles undergone by the study samples, but a minimum of three cycles should be conducted.	2) Freeze-thaw matrix stability: To assess the impact of repeatedly removing samples from frozen storage, the stability of the analyte should be assessed after multiple cycles of freezing and thawing. Low and high stability QCs should be thawed and analysed according to the same procedures as the study samples. Stability QCs should be kept frozen for at least 12 hours between the thawing cycles. Stability QCs for freeze-thaw stability should be assessed using freshly prepared calibration standards and QCs or QCs for which stability has been proven. The number of freeze-thaw cycles validated should equal or exceed that of the freeze-thaw cycles undergone by the study samples, ~~but a minimum of three cycles should be conducted.~~
3) Bench top (short-term) matrix stability: Bench top matrix stability experiments should be designed and conducted to cover the laboratory handling conditions for the study samples.	
Low and high stability QCs should be thawed in the same manner as the study samples and kept on the bench top at the same temperature and for at least the same duration as the study samples. The total time on the bench top should be concurrent; it is not acceptable to use additive exposure to bench top conditions (i.e., adding up time from each freeze-thaw evaluation is not acceptable). Low and high stability QCs should be thawed in the same manner as the study samples and kept on the bench	Low and high stability QCs should be thawed in the same manner as the study samples and kept on the bench top at the same temperature and for at least the same duration as the study samples. The total time on the bench top should be concurrent; it is not acceptable to use additive exposure to bench top conditions (i.e., adding up time from each freeze-thaw evaluation is not acceptable). ~~Low and high stability QCs should be thawed in the same manner as the study samples and kept on the bench~~
4) Processed sample stability: The stability of processed samples, including the time until completion of analysis (in the autosampler/instrument), should be determined. For example (i) Stability of the processed sample at the storage conditions to be used during the analysis of study samples (dry extract or in the injection phase) (ii) On-instrument/ autosampler stability of the processed sample at injector or autosampler temperature.	4) Processed sample stability: The stability of processed samples, including the time until completion of analysis (in the autosampler/instrument), should be determined if quality control samples are not processed contemporaneously with study samples. The assessment is conducted by analyzing aged extracts of quality control samples against freshly prepared calibrators. Data generated during assay validation should support the longest period that is anticipated to elapse between sample extraction and analysis. ~~For example (i) Stability of the processed sample at the storage conditions to be used during the analysis of study samples (dry extract or in the injection phase) (ii) On-instrument/ autosampler stability of the processed sample at injector or autosampler temperature.~~
5) Long-term matrix stability: The long-term stability of the analyte in matrix stored in the freezer should be established. Low and high stability QCs should be stored in the freezer under the same storage conditions and at least for the same duration as the study samples. For chemical drugs, it is considered acceptable to extrapolate the stability at one temperature (e.g., -20°C) to lower temperatures (e.g., -70°C). For biological drugs, it is acceptable to apply a bracketing approach, e.g., in the case that the stability has been demonstrated at -70°C and at -20°C, then it is not necessary to investigate the stability at temperatures in between those two points at which study samples will be stored.	5) Long-term matrix stability: The long-term stability of the analyte in matrix stored in the freezer should be established. Low and high stability QCs should be stored in the freezer under the same storage conditions and at least for the same duration as the study samples. ~~For chemical drugs,~~ It is considered acceptable to extrapolate the stability at one temperature (e.g., -20°C) to lower temperatures (e.g., -70°C). ~~For biological drugs, it is acceptable to apply a bracketing approach, e.g., in the case that the stability has been demonstrated at -70°C and at -20°C, then it is not necessary to investigate the stability at temperatures in between those two points at which study samples will be stored.~~
In addition, the following test should be performed if applicable:	~~In addition, the following test should be performed if applicable:~~
1) Whole blood stability: Sufficient attention should be paid to the stability of the analyte in the sampled matrix (blood) directly after collection from subjects and prior to preparation for storage to ensure that the concentrations obtained by the analytical method reflect the concentrations of the analyte in the subject's blood at the time of sample collection. If the matrix used is plasma or serum, the stability of the analyte in blood should be evaluated during method development (e.g., using an exploratory method in blood) or during method validation. The results should be provided in the Validation Report.	~~1) Whole blood stability:~~ Sample collection integrity: Sufficient attention should be paid to the ~~stability~~ integrity of the analyte in the sampled matrix ~~(blood)~~ directly after collection from subjects and prior to preparation for storage to ensure that the concentrations obtained by the analytical method reflect the concentrations of the analyte in the subject's ~~blood~~ sample at the time of ~~sample~~ collection. Conditions for sample collection should be identified during method development or validation. If the matrix used is plasma ~~or serum,~~ the stability of the analyte in blood should be ~~evaluated~~ considered during method development ~~(e.g., using an exploratory method in blood),~~ and, in the case of molecules that are, based on their structure, potentially unstable, assessed during method validation. The results of such assessments or, in the event they are not conducted, rationale for their absence, should be provided in the Validation Report.

We could highlight many, and you can find all our comments on our webpage, but let's focus on 1 which illustrates a general desire:

Stimulate "Science driving Regulations".

(5) FDC

If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.

(5) FDC

To date, industry has no scientific data to support a claim that one drug has an impact on the stability of another drug in a biological matrix. Actually, we have the opposite: there is no impact.

And the experiment was performed hundreds of times…

If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.	Comment: rephrase Proposed change (if any): If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix containing all dosed compounds should be considered. In the case of a fixed combination stability information of the combination dosage form may be considered. In the case of a drug regimen, the known chemistry and stabilities of the individually dosed drugs should be used as a basis for determining whether additional stability studies are needed. DDI studies are not is scope of this requirement.

(5) FBC: Our fear

- In it's current wordings, industry will interpret the ICHM10 Guideline to request experiments which 30+ y of experience have documented they are not relevant or too extensive (e.g. concentration levels to be documented, number of repeats, irrelevant for certain matrices, patient/subject/species populations)
- We already see this trend happening
- We doubt there is a need and an added value considering there are valid and more cost effective scientific alternatives

(6) Mid-QC

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-m10-bioanalytical-method-validation-step-2b_en.pdf

Chapter 3: During method validation the QCs should be prepared at a minimum of 4 concentration levels within the calibration curve range: the LLOQ, within three times of the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC) and at least 75% of the ULOQ (high QC).

Chapter 4: The analyte should be spiked at the LLOQ, within three times of the LLOQ (low QC), around the geometric mean of the calibration curve range (medium QC), and at least at 75% of the ULOQ (high QC) and at the ULOQ.

The study samples, QCs and calibration standards should be processed in accordance with the validated analytical method.

The problem we have,

Current (ANVISA, FDA, EMA, MHLW, CFDA)

Guideline	Text
EMA	within three times the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC)
FDA	low (L: defined as three times the LLOQ), mid (M: defined as mid-range), and high (H: defined as high-range)
ANVISA	amostra de controle de qualidade de média concentração (amostra de CQM): amostra de matriz adicionada do analito em concentração próxima à média entre os limites inferior e superior de quantificação *(Medium-concentration quality control sample (QCM sample): Matrix sample of the analyte in a concentration close to the mean between the lower and upper quantification)*
MHLW	The low-level should be within 3 times the LLOQ, the mid-level is around the midpoint on the calibration curve, and the high-level should be at least 75% of the upper limit of the calibration curve
NMPA	the LLOQ, within three times the LLOQ (low QC), near midrange of the standard curve (medium QC), and at about 75% of the upper standard curve range (high QC).

CAL	1 (LLOQ	2		5	10	20	50	100	200		500 (ULOQ)
QC		QC_LO				QC_ME?	⟷		QC_ME?	QC_HI	

Feedback from EBF & Delegates - Chromatography

I disagree. Geometric mean MQC for geometric standard curve

geometric mean would make more sense

During method validation the QCs should be prepared at a minimum of 4 concentration levels within the calibration curve range: the LLOQ, within three times of the LLOQ (low QC), around **the geometric mean** of the calibration curve range (medium QC) and at least 75% of the ULOQ (high QC). Otherwise a large part of the calibration line is not covered by QCs and will trigger issues since study samples should be covered by at least 2 QCs"

Disagree with medium QC is defined as arithmetic mean (30-50%)

Why is the medium QC not the geometric mean.

Was never sure of the rational or logic of why we stopped validating assay at ULOQ. Technically, assay is not proven to be valid between HQC and ULOQ (25% of range), where the study drug concentration have potentially the greatest influence on PK. The focus is strangely on LLOQ, where even quite large changes on terminal concentrations have very little influence on AUC

LBA recognizes that the medium QC should be a geomean concentration, but this is different here. I would suggest that the geomean concentration is equally important here, due to often wider assay ranges in chromatographic analyses

not clear if the medium QC conc. should be based on arithmetic or geometric mean

Why not QC mid at the geometrical mean as in LBA. Should be striving for consistency between the two techniques.

level QC-M is according to EMA (not FDA).

Impact on our industry – value for industry

Aspect	Geometrically medium QC	Arithmetically medium QC
Consistency within the guideline	Yes please, prevents mistakes and builds consistency in SOPs etc. Reduces chances of rejected filings.	
Costs	Chance of detecting a not optimal calibration model => optimize assay	Somewhat less change of batch rejection. Drug development process will be a (tiny) little bit faster and cheaper
Scientific: Analytical	Of course !	Not really
Scientific: PK	Marginal, if at all	
Ease of implementation	Piece of cake (if consistent)	
Value for the Patient	Marginal, if at all	

GEOmean or ARITHmean doesn't make much difference in execution and impact for the BioA lab. But it is utterly illogical to use 30-50% of ULOQ for the mean QC while everything else in bioanalysis and PK analysis is based upon the logarithmic (geometric) distribution of concentrations and derived data

Suggested comment to EMA/EWG

Current text in draft M10	Suggested changes
Line 419-421, Paragraph 3.2.5.1 During method validation the QCs should be prepared at a minimum of 4 concentration levels within the calibration curve range: the LLOQ, within three times of the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC) and at least 75% of the ULOQ (high QC).	Action to be taken: Correct text During method validation the QCs should be prepared at a minimum of 4 concentration levels within the calibration curve range: the LLOQ, within three times of the LLOQ (low QC), around geometric mean of the calibration curve range (medium QC) and at least 75% of the ULOQ (high QC).
Line 816-819, Paragraph 4.2.4.1 The QCs should be prepared at a minimum of 5 concentration levels within the calibration curve range: The analyte should be spiked at the LLOQ, within three times of the LLOQ (low QC), around the geometric mean of the calibration curve range (medium QC), and at least at 75% of the ULOQ (high QC) and at the ULOQ.	Action to be taken: NONE *Post public comment note: One can even doubt the value of the discussion around the placement of the mid-QC given the irrelevant scientific value of one versus the other*

(6) Mid-QC placement: Our fear

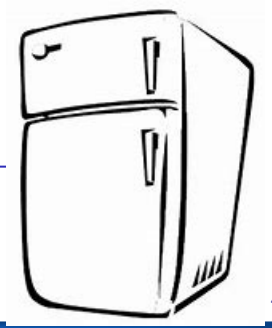
- For CHROM assays, the Mid-QC discussion seems scientific irrelevant. Our fear relates to HA no accepting Mid-QC placement based on no scientific impact or relevance at all.
- We already see this trend happening…

(7-1) LBA - Stability at one storage temperature

Paragraph from ICH M10

…For **chemical drugs**, it is considered acceptable to extrapolate the stability at one temperature (e.g., −20ºC) to lower temperatures (e.g., −70ºC).

For **biological drugs**, it is acceptable to apply a bracketing approach, e.g., in the case that the stability has been demonstrated at −70ºC and at −20ºC, then it is not necessary to investigate the stability at temperatures in between those two points at which study samples will be stored...



EBF discussion & perspective

- Demonstration of frozen storage stability at one temperature and time −20ºC validates the use of lower temperatures for storage for the same period of time.
  Scientifically this is applicable for both chemicals as well as biologics – variable values seen might not be a real storage issue but assay variation
- Any evidence that extrapolation is not applicable for biological drugs?
  - All data collected by EBF members support extrapolation of the stability at one temperature (e.g., -20ºC) to lower temperatures (e.g., -70°C).
  - Apparently regulators have seen cases where stability is different at lower temperatures. Is this just assay variability? Is this the exception? ICHM10 should not focus on the exception rather than norm.

EBF perspective:
There is no available data to show that biological drugs that are stable at −20ºC are unstable at lower temperatures.
Stick to the FDA recommendation: "determination of stability at −20ºC would cover stability at colder temperatures".

(7-2) LBA - High concentrated stability QCs

Paragraph from ICH M10

…Since sample dilution may be required for many LBA assays due to a narrow calibration range, the concentrations of the study samples may be consistently higher than the ULOQ of the calibration curve. If this is the case, **the concentration of the stability QCs should be adjusted, considering the applied sample dilution, to represent the actual sample concentration range**…

EBF discussion & perspective

- In case of pivotal tox study support the highest sample volume is often not known at the time of validation: Could this only apply to BA/BE studies?
- Is this than adding an additional upper high QC mimicking the actual sample concentration of the study samples in addition to the low and high stability QC?
- Normally low concentrations are stability indicating. It is very unlikely for a high concentrated sample failing stability if low concentration sample is stable
- High concentration sample testing is are already included in dilution linearity and Hook effect assessment
  - Blank matrix sample spiked at or above anticipated Cmax or at highest feasible concentration
  - At least one spike >ULOQ (for hook) and 3-5 dilutions within assay range

EBF perspective:
This requirement is not considered relevant due to the fact that stability with high concentration samples are not an issue.

(7-3) LBA - Multiple stability QC preparations

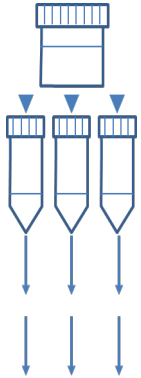
Paragraph from ICH M10

Stability of the analyte in the studied matrix is evaluated using low and high concentration stability QCs. Aliquots of the low and high stability QCs are analysed at time zero and after the applied storage conditions that are to be evaluated. **A minimum of three stability QCs should be prepared and analysed per concentration level/storage condition/timepoint.**

Changes to current (EMA, MHLW, FDA)

Tube numbers in QC preparation of stability testing:

ICHM10



Blank matrix + analyte

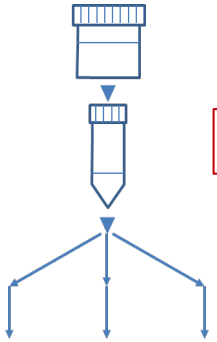
3 aliquots

Storage

Analysis

3 measured values

EMA, MHLW and FDA as well as industry proposal for ICHM10 in 2016



Blank matrix + analyte

1 aliquot

Storage

Analysis

3 measured values

EBF discussion & perspective

- Definition on what is requested in practice by "…three stability QCs are prepared…"
- Independent preparations of stability QCs per concentration level/storage condition/timepoint will require
  - more matrix, is this ethical (3R!)
  - more preparation time and storage space

Multiple QC preparations in stability tests will increase validation effort, but will not increase data quality.

EBF perspective:

This requirement should be removed, QC preparation should be performed with one aliquot for storage, analysed 3 times.

(8) LBA - Selectivity/specificity

Paragraph from ICH M10

Selectivity is the ability of the method to detect and differentiate the analyte of interest in the presence of other "unrelated compounds" (non-specific interference) in the sample matrix.

- …Therefore, selectivity is evaluated using blank samples obtained from at least 10 individual sources and by spiking the individual blank matrices at the LLOQ **and at the high QC level**. …
- Selectivity should be **evaluated in lipemic samples and hemolysed samples** (Refer to Section 3.2.1). …

Specificity is evaluated by spiking blank matrix samples with related molecules at the maximal concentration(s) of the structurally related molecule anticipated in study samples. …

- The accuracy of the target analyte at the LLOQ **and at the ULOQ** should be investigated in the presence of related molecules at the maximal concentration(s) anticipated in study samples….

EBF discussion & perspective

- 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.

EBF perspective:

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.

(9) LBA - Standards and key reagents

Paragraph from ICH M10

- The Reference standard should be well characterized and documented. It is recommended that, **whenever possible**, the batch of drug substance used to support bioanalysis is **derived** from the same batch that is used for dosing

- Critical reagents should be identified and defined in the assay method. Reliable procurement should be considered early in method development. Changes may need additional validation experiments

(9) LBA - Standards and key reagents

Paragraph from ICH M10

- It is recommended that the manufacturing batch of the **reference standard** used for the preparation of calibration standards and QCs is derived from the same batch of drug substance as that used for dosing in the nonclinical and clinical studies **whenever possible**. If the reference standard batch used for bioanalysis is changed, bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are within the acceptance criteria.
- **Critical reagents** should be identified and defined in the assay method. Reliable procurement should be considered early in method development. **Changes may need additional validation experiments**.

EBF discussion & perspective

- **Reference standard**
  - If proper comparison of different batch done in GMP environment there should not be a requirement to use same batch of Ref Std for Cal & QC preparation as the dosing batch

- **Critical reagents**
  - Identify the critical reagent and clearly document
  - Identify the noncritical reagents and monitor during routine sample analysis
  - Ideally, ensure enough material is available to support an entire study and/or drug development program
  - Use GBC definitions to evaluate what constitutes a minor or major change
  - Where one single lot cannot be sourced for the entire period of use, retain enough material of the old lot for head-to-head comparison with new lots

(10-1) LBA - Calibration range/ Validation

Paragraph from ICH M10

The calibration curve demonstrates the relationship between the nominal analyte concentration and the response of the analytical platform to the analyte.

Calibration standards, prepared by spiking matrix with a known quantity of analyte, span the calibration range and comprise the calibration curve.

Calibration standards should be prepared in the same biological matrix as the study samples.

The calibration range is defined by the LLOQ, which is the lowest calibration standard, and the ULOQ, which is the highest calibration standard.

There should be one calibration curve for each analyte studied during method validation and for each analytical run.

EBF discussion & perspective

“Calibration standard should be prepared in same biological matrix as the study samples”

- Creates issues for target capture assays/matrix with target, suggest text to be open for using a surrogate matrix with a proper rational/justification

- Suggest copying text from section on kits/endogenous compounds, as appropriate wording is already present here. Alternatively use text from the FDA or EMA guidelines to allow for surrogate matrices.

EBF perspective:
Calibration standards prepared in a matrix different from the study samples should be justified and appropriate experiments should be performed.

(10-2) LBA - Calibration range/ Sample analysis

Paragraph from ICH M10

At least 2 QC sample levels should fall within the range of concentrations measured in study samples.

At the intended therapeutic dose(s), if an unanticipated clustering of study samples at one end of the calibration curve is encountered after the start of sample analysis, the analysis should be stopped and either the standard calibration range narrowed (i.e., partial validation), existing QC concentrations revised, or QCs at additional concentrations added to the original curve within the observed range before continuing with study sample analysis.

It is not necessary to reanalyse samples analysed before optimising the calibration curve range or QC concentrations.

EBF discussion & perspective

- Text seem to have been copied from chromatography section
- For chromatography methods no change of method is needed when adjusting calibration range, however, for LBA it would mean a new method needs to be established (e.g. titration of reagents, change of reagents,…).
- Section is not clear since dilutional linearity during method validation will show that samples can be diluted into the calibrator range, and parallelism tests will give support for dilution of study samples.
- The questions is also why 2 dilutional QCs is included? Why is dilutional QCs needed if dilutional linearity and parallelism shows that the sample results are acceptable?

EBF perspective:

Please delete - Paragraph not applicable for LBA

(7, 8, 9, 10) Our fear

- In it's current wordings, the draft ICH M10 Guideline insufficiently considers experience from industry to optimise resources (*(7) and (8)*) or did not use the opportunity to fully clarify existing ambiguities (*(9) – 10)*)

(11) ISR

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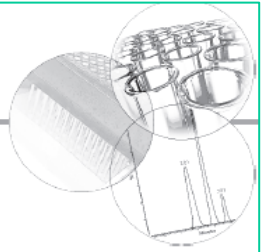

Incurred sample reproducibility: views and recommendations by the European Bioanalysis Forum

White Paper

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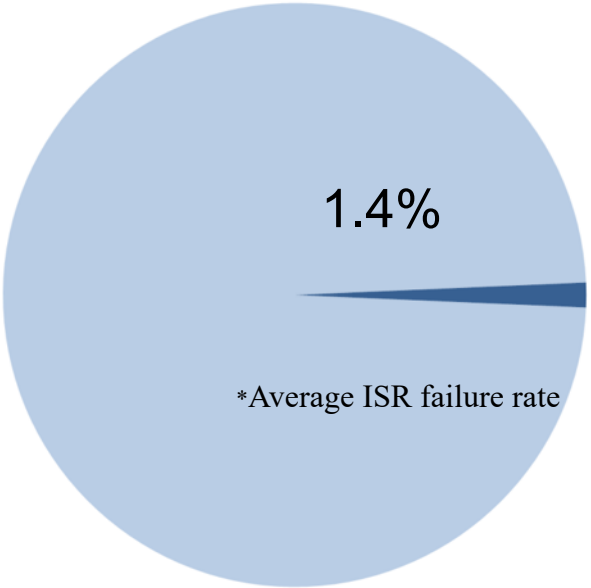
Bioanalysis

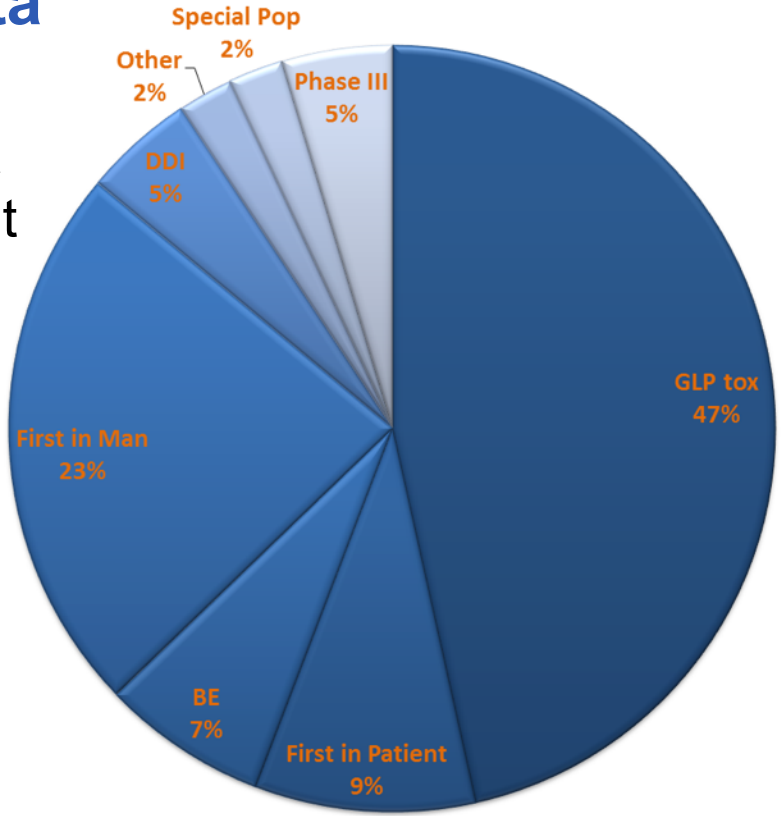
Incurred sample reproducibility: 10 years of experiences: views and recommendations from the European Bioanalysis Forum

66

Industry position based on data



1.4% = about 80 studies out of 5500



*n > 5500 studies

Let the data speak

- ISR failure rate was, in a survey with more that 5500 studies including regulated Bioanalysis and ISR, low (app. 1.5%) and failures were mostly in earlier development studies.
  - Did we ever consider if Failed ISR has a real impact on patient safety?
- Based on current experiences (1.5% ISR failure rate), causes and impact of failed ISR, the 10 + 5 % repeats is a high number not adding value.
- The number of ISR should be aligned with number of spiked QC's in a run (5% - in alignment with AAPS)*
- Consider Fixed number approach as an alternative to Fixed ratio?

EBF comment to ICH on ISR

Haven’t we done enough to refine our process?

Please consider to provide a cap, i.e. a maximum for sample number to be analyzed as part of ISR. There are strong scientific data suggesting that reanalyses of large portions of samples do not added scientific value. Literature suggests that 30 samples should be sufficient power in any study size. A consensus proposal could be: For ISR, reanalyse 10% of the study of samples, with a minimum of 20 and a maximum of 100 samples.

(11) ISR: Our fear

- In it's current wordings, the draft ICH M10 Guideline insufficiently considers experience from industry to optimise resources
- With ISR being a significant resource intensive, will inevitably lead to inefficient use of resources
- Good to repeat: also industry continuous to overinterpret the guidelines and performs ISR in many studies not called for in any guideline.
  - If done 'because scientists feels the need' → OK
  - If done 'because scientists (are lead to) believe(s) it is required → Not OK

(12) Method development requirements

- The risk of current method development requirements:
  - Loss of scientific freedom
  - Industry take documentation to a level which is unmanageable
  - HA start expecting

- The proposal
  - For "Method Development," we suggest to limit to scope to changes to already validated methods in later stages of development (e.g. changes of methods during the analsyis if BE-study samples).
  - Current practices on documenting other Method Development and changes to methods (e.g. validation reports, 2.6.4/2.7.1) should not be duplicated and should be sufficient.

(12) Method development requirements: Our fear

- Paragraph 2.1: Method Development" carries the risk of becoming overinterpreted and are increasing the resource requirements for industry, whilst stifling scientific freedom required in the method development arena (and not aligned with the mission of ICH).
- We already see this happening in industry, with labs producing “Method development reports”
  - If done ‘because scientists feels the need’ → OK
  - If done ’because scientists (are lead to) believe(s) it is required → Not OK

Changes to current (FDA, EMA, MHLW, NMPA)

Some things are new:

- 100% of chromatograms BA/BE studies (and corresponding validation report)
- IS plots
- Run summary sheet (containing oa. analyte and IS responses, retention times)
- List of regulatory site inspections including dates and outcomes (in CTD?)
- Some requests are limited to BA/BE studies

- “Table 1: Documentation" seem very focussed on BA/BE studies, where they make sense (with the exception of a few requirements which are new and insufficient discussed with industry – as per previous slide)
- We suggest to limit the requirements in table 1 to BA/BE-studies, and allow reporting of other studies to be less detailed (i.e. less in reports but allow documentation to be available at the analytical site)

(13) Partial & Cross validation

(13-1) Partial Validation

- Except for a few minor worries, industry has no real comments on partial validation

- Training may be needed to emphasise that Partial validation is only to document changes to an already fully validated method. After 30y, industry still is confused on this simple principle
- One Concern: Risk of transferring **stability data** between CRO/Pharms (what happens if the stability data is deficient, who gets the regulatory citing?). A company/CRO may consider stability data owned by another company as not shareable

Cross validation however...

6.2 Cross Validation

Cross validation is required to compare data under the following situations:

- Data are obtained from different fully validated methods within a study
- Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.
- Data are obtained within a study from different laboratories with the same bioanalytical method.

Cross validation is not generally required to compare data obtained across studies from different laboratories using the same validated method at each site.

Cross validation should be performed in advance of study samples being analysed, if possible.

Cross validation should be assessed by measuring the same set of QCs (low, medium and high) in triplicate and study samples that span the study sample concentration range (if available n≥30) with both assays or in both laboratories.

Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two assays (e.g., concordance correlation coefficient) may be used too. Alternatively, the concentration vs. time curves for incurred samples could be plotted for samples analysed by each method to assess bias. If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed.

The use of multiple bioanalytical methods in the conduct of one comparative BA/BE study is strongly discouraged.

(13-2) Cross validation

- Many comments were given asking for “criteria”
- It looks like industry missed the new philosophy of the draft guideline?

> *Bias can be assessed by Bland-Altman plots or Deming regression. ……If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed.*

- Does this mean that, if the run passes, a cross validation cannot fail?
- Is the intention to investigate and documents a potential bias across studies?

If so, we are entering in new territory, at least for BA… (next slide)?

Cross validation

Questions that arise include:

- What is "*a disproportionate bias*? And who owns "*the impact on the clinical data interpretation should be assessed*" ?
- Who will decide on actions to be taken?
  - Will the BA scientist provide a new set of corrected concentrations?
  - Is it the PK scientist? The regulators?
  - And when, why , how….
- Are we experienced to apply this new requirement?
  - **More context will be required** → industry didn't recognise the expectation
  - **Intensive training will be required** to manage correct use (incl. documentation and responsibilities)

(13-2) Partial & Cross Validation: Our fear

- This is new
- Intensive training will be required, involving all stakeholders, to understand the hurdles, expectations and limitations of the new requirements
- The current lack of industry experience needs to be recognised

(14) Documentation requirements

Feedback from EBF

Results from reinjected runs does not make sense. Usually a run is reinjected if chromatography was poor or another analytical problem occurred. The data set of the first run is meaningless.

"list of regulatory site inspections including dates and outcomes for each analytical site if available. Suggesting to specify time frame (e.g., during the study conduct or 3 years frame?) for the regulatory inspections documents; which regulatory health authorities considered? Members of ICH (e.g. China NMPA, Japan PMDA, etc…)"

Please remove or provide justification of why it is important to include subject Ids for each and every shipment into the BA report. Deviations will be reported and all subject Ids are stored electronically anyway, just not in the report itself.

Bioanalytical Report: "For other studies, randomly selected chromatograms from 5% of the studies" ? typo? 5% of subjects?

Table 1, the column "validation report" contains requirements for BA/BE studies. Confusing because BA/BE study is not a validation.

Documentation at Site: Reason for missing samples is often not known to the analytical lab - they just did not show up

List of SOPs should not be documented in the BA-Report, too complicated

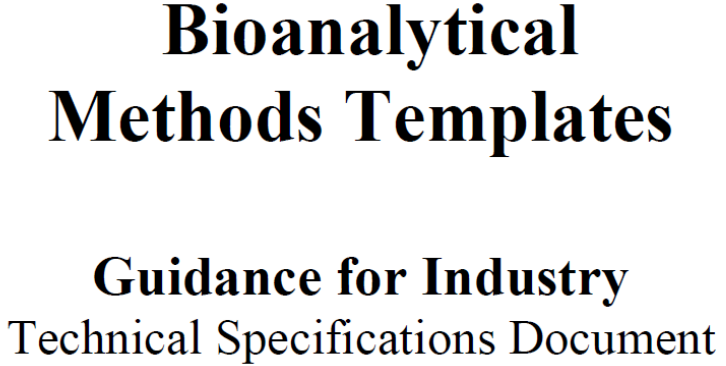
Blank matrix (receipt date) should not be documented in the validation or BA-Report// Storage conditions of QCs and CSs should not be documented in the BA-Report.

Clarify what are run summary sheets and expected content

(14) Documentation requirements: Our fear

- In it's current wordings, the chapter carries the risk of becoming overinterpreted and will be significantly increasing the resource requirements for industry
- We see Documentation requirements as per ICH M10, considering the uncertainty of studies in scope, as one of the bigger hurdles
- We already see this happening…

(14) Documentation requirements; one more thing: new FDA guidance



- Specifies in much detail how pre-study and in-study validation data should be provided in CTD 2.7.1
- Risk of each RA asking something different (e.g. Health Canada CS-BE)
- This should also be discussed as part of ICHM10

(15) Background and scope

1.2 Background

- Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials, including comparative bioavailability/ bioequivalence (BA/BE) studies, are used to make regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

1.3 Scope

This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in pivotal nonclinical TK/PK studies that are used to make regulatory decisions and all phases of clinical trials in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

For studies that are not submitted for regulatory approval or not considered for regulatory decisions regarding safety, efficacy or labelling (e.g., exploratory investigations), applicants may decide on the level of qualification that supports their own internal decision making.

The information in this guideline applies to the quantitative analysis by ligand binding assays (LBAs) and chromatographic methods such as liquid chromatography (LC) or gas chromatography (GC), which are typically used in combination with mass spectrometry (MS) detection and occasionally with other detectors.

For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the bioanalysis of study samples should also conform to their requirements.

The bioanalysis of biomarkers and bioanalytical methods used for the assessment of immunogenicity are not within the scope of this guideline.

The Regulator's perspective

When reviewing a file, it can be assumed it's clear which studies in the file are pivotal / used to make claims on safety and efficacy

- …and in extension, which analytes, matrices were analysed and which methods were used

Paragraph on Scope in ICH M10 will likely do the job

The Industry's perspective

Our surveys confirms that, when developing a drug, we may not know which studies will end up in the file to become pivotal / used to make certain claims on safety and efficacy…and in extension, which analytes, matrices were analysed and which methods require validation

Survey comments on “Scope”:

a few representative ones from the > 50 we received

Scope unclear, and why does ICH refer to regional documents that it is supposed to replace?

Exact description required which assays are meant. This guideline does e.g. not cover special requirements for free drug assays.

Scope could be better define. At the moment everything appears to be in scope.

Concerned that tissues are in same class a plasma with regard to level of validation

The scope of the guideline seems too broad.

Scope is too wide now that it includes nonclinical studies. Definition of pivotal is crucial. How do you know what pre-clinical studies are pivotal, especially PK? Why are all clinical studies included?

I would exclude early clinical studies (escalation/expansion phase) to be analyzed with fully validated method (mainly applicable for LBA): indeed, with new biologic formats, often MABEL approach is used meaning very low doses for starting. The range of quantitation is therefore not known and fixed. At this stage, a fit for purpose method validation seems more appropriate.

Suggested changes to Background and Scope - 1

1.2 Background
Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials, including comparative bioavailability/ bioequivalence (BA/BE) studies, are used to make regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. *The results of studies employing such methods contribute to regulatory decisions regarding the safety and efficacy of drug products.* It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions. (proposal deconvolutes background from scope)

Suggested changes to Background and Scope - 2

1.3 Scope	
This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in pivotal nonclinical TK/PK studies that are used to make regulatory decisions and all phases of clinical trials in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.	This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids ~~or tissues~~) obtained in nonclinical TK studies falling under the scope of the GLPs that are used to make regulatory decisions, nonclinical PK studies that are conducted as surrogates for clinical studies, and all phases of clinical trials in regulatory submissions for which a primary objective of the study is to assess, compare or characterize drug exposure. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Primary matrix(ces) are identified based on the objective(s) of individual studies and these *should be indicated in the study protocol or sample analysis plan. For non-primary analytes/matrices validation should be performed in line with the anticipated use of the data, using the appropriate/applicable principles (i.e. partial validation or alternative approaches).* The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ~~ICH and regional~~ regulatory documents. *(propose to delete the last sentence as other regulatory documents hardly describe this)*

Suggested changes to Background and Scope - 3

1.3 Scope - cntd	
For studies that are not submitted for regulatory approval or not considered for regulatory decisions regarding safety, efficacy or labelling (e.g., exploratory investigations), applicants may decide on the level of qualification that supports their own internal decision making.	For studies that are not submitted for regulatory approval ~~or not considered for regulatory decisions regarding safety, efficacy or labelling (e.g., exploratory investigations)~~, applicants may decide on the level of qualification that supports their own internal decision making. *(one does not know a priori if a study will be considered for regulatory decisions, thus in practice, only limiting to studies not included in submissions is possible)*

(15) Scope: Our fear

- In it's current wordings, industry will interpret the ICHM10 Guideline to bring **all** studies **all** matrices and **all** analytes in scope, starting from preclinical development onwards
- We already see this trend happening…
- We continue to be convinced there is a future need and added value to consider more cost effective scientific alternatives

Overall conclusions

- Covid-19 clearly has an impact on the timing of the ICH M10 progress
- We fear our industry comments, which already date from 2018/2019, may get diluted or lost in time
- It is good to remind ourselves and the EWG on the comments we made during public consultation
- We should be careful not to consider a draft Guideline to be the real thing. In doing so, we raise the bar.

Acknowledgement

- The EBF community
- Delegates at the several EBF Meetings discussing ICH M10

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