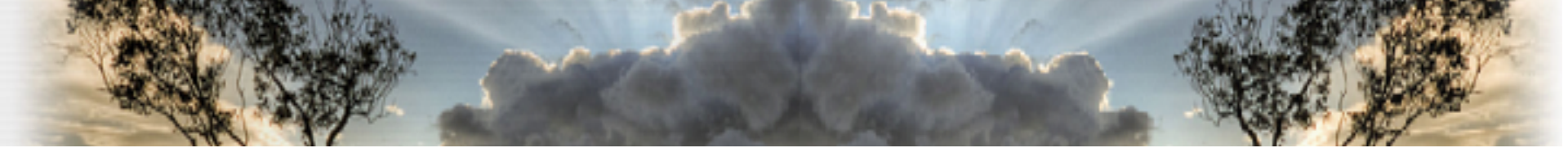


ICH M10
Other Areas of Biggest Impact

Steve White, on behalf of the EBF

12th EBF Open Symposium
Imagine! A new bioanalytical Earthrise

http://www.e-b-f..eu

Disclaimer

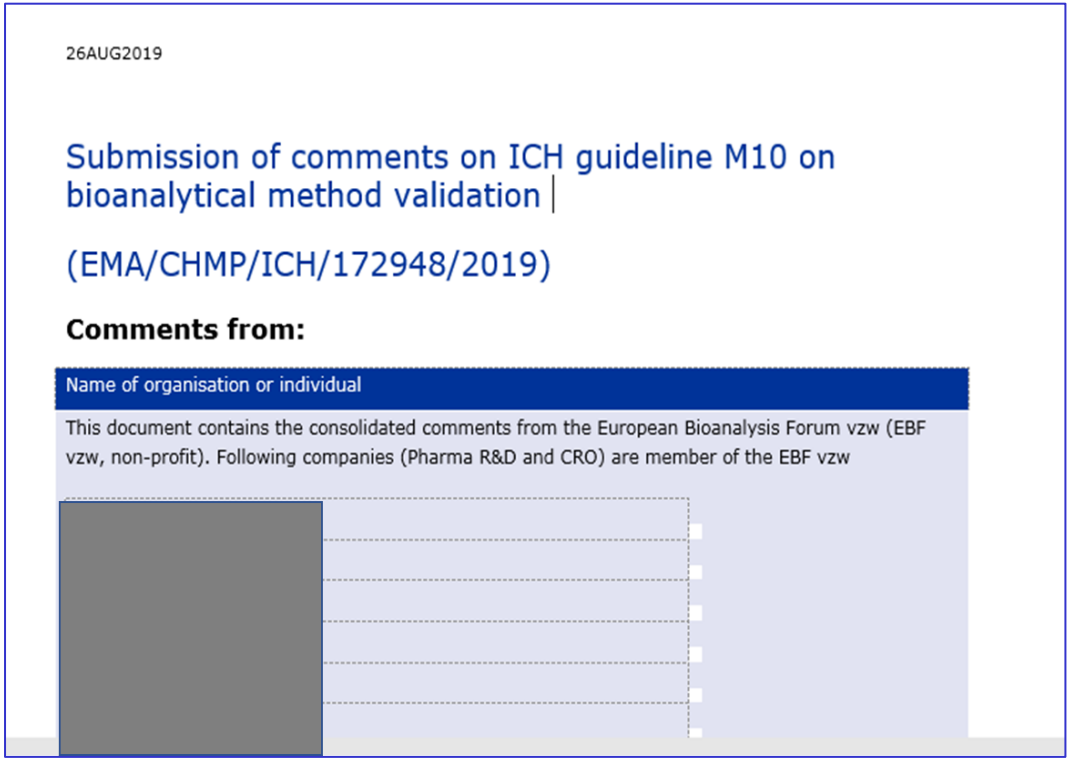
This presentation was prepared on behalf of EBF, incorporating to the best of our ability the outcome of internal EBF discussions, - surveys, discussions from the EBF Barcelona Industry Focus Workshop (sister meeting) and from EFPIA discussions.

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).

EBF Comments on ICH M10 submitted to EMA

- > 1100 individual comments received from initial survey

- Consolidated comments from 64 companies were submitted to EMA
- General remarks = 5
- Specific comments on text = 164



26AUG2019

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

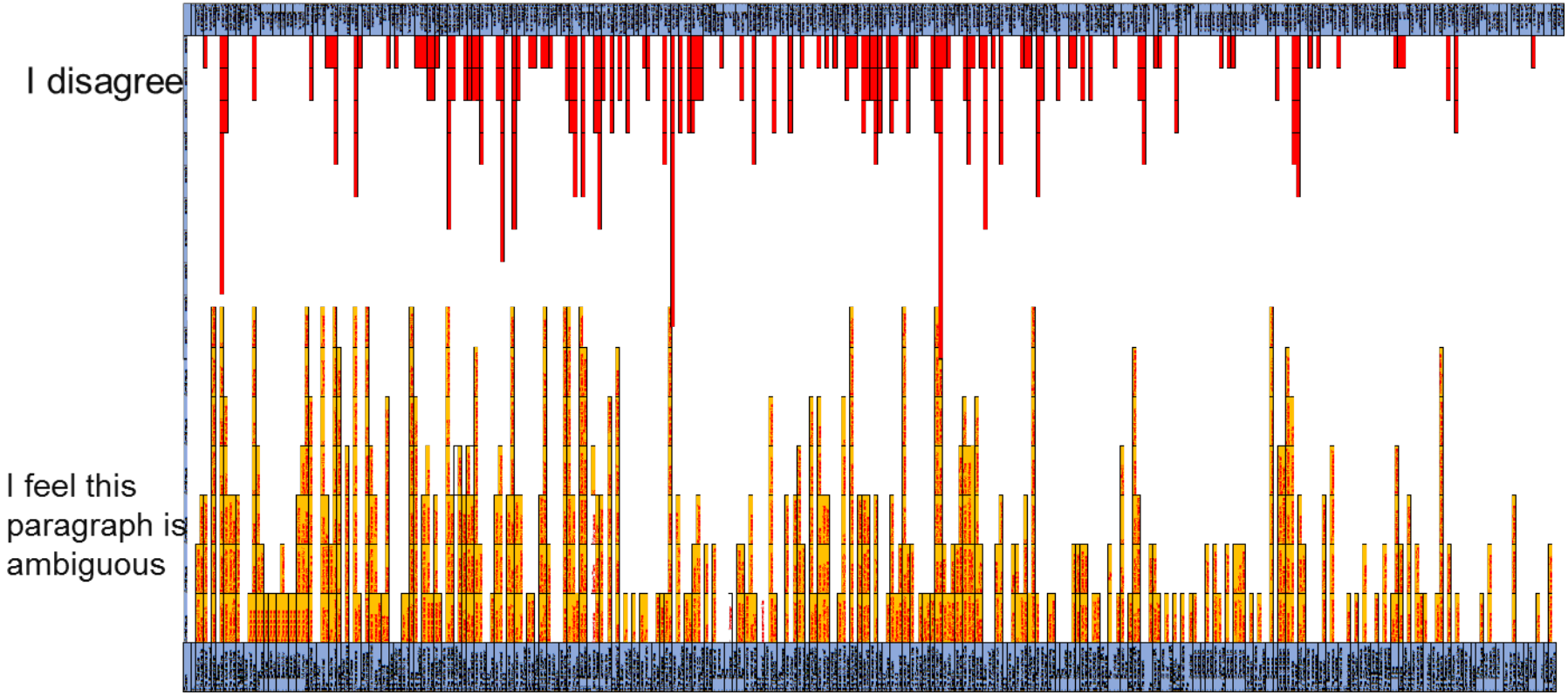
Boiling it all down…

Boiling it all down…

I feel this paragraph is ambiguous

Green	Ambiguous	Ambiguous	Ambiguous	Ambiguous	Ambiguous	Ambiguous	Ambiguous
1							
1.1 Objective	General: will the	Certain topics					
This guideline is	Guideline	Needs greater	Would change				
The objective of	Question: Is it	A statement in the	The objective of				
1.2 Background							
Concentration	please add	wording unclear	Suggest some	Questions: What	while statement	*The results of*	Exact descriptio
1.3 Scope							
This guideline	please specify	Scope unclear	*obtained in*	see 1.2	Scope still	Inclusion of	X
For studies that	propose scope	What about fit for	Are all studies	primary	For studies that		
The information	What about	Is it necessary to	The information				
For studies that	What about fit for	the term 'should'	**Method**				
The bioanalysis	By definition, a	The bioanalytical	A definition of				
2 GENERAL							
2.1 Method							
The purpose of	**There is no**						
Before the	**There is no**	Before the	General	X	In vivo	Before the	Before the
Method	**There is no**	"extracting" is	[...] Method	Method			
· Reference	**There is no**	This list is very					
· Critical	**There is no**						
· Calibration	**There is no**						

Boiling it all down…



Boiling it all down…

	Ambigous		
1. INTRODUCTION			
1.1 Objective	6		6
1.2 Background	9		
1.3 Scope	21	8	38
2. GENERAL PRINCIPLES			
2.1 Method Development	26	3	29
2.2 Method Validation		1	1
2.2.1 Full Validation	21	4	25
2.2.2 Partial Validation	4		4
2.2.3 Cross Validation	8	4	12
3. CHROMATOGRAPHY		1	1
3.1 Reference Standards	18	1	19
3.2 Validation			0
3.2.1 Selectivity	14	2	16
3.2.2 Specificity	12	6	18
3.2.3 Matrix Effect	9	3	12
3.2.4 Calibration Curve and Range	18	9	27
3.2.5 Accuracy and Precision			
3.2.5.1 Preparation of Quality Control Samples	7	8	15
3.2.5.2 Evaluation of Accuracy and Precision	18	5	23
3.2.6 Carry-over	2	1	3
3.2.7 Dilution Integrity	12	4	16
3.2.8 Stability	42	22	64
3.2.9 Reinjection Reproducibility	6	2	8
3.3 Study Sample Analysis	1	3	4
3.3.1 Analytical Run	3	3	6
3.3.2 Acceptance Criteria for an Analytical Run	13	13	26
3.3.3 Calibration Range	7	6	13
3.3.4 Reanalysis of Study Samples	13	5	18
3.3.5 Reinjection of Study Samples	1	2	3
3.3.6 Integration of Chromatograms	5	2	7
4. LIGAND BINDING ASSAYS	1		1
4.1 Key Reagents			0
4.1.1 Reference Standard	3	3	6

	Ambigous		
4.1.2 Critical Reagents	9		9
4.2 Validation	5		5
4.2.1 Specificity	12	2	14
4.2.2 Selectivity	14		14
4.2.3 Calibration Curve and Range	11	8	19
4.2.4 Accuracy and Precision		6	6
4.2.4.1 Preparation of Quality Control Samples	4	3	7
4.2.4.2 Evaluation of Accuracy and Precision	18	2	20
4.2.5 Carry-over	1	2	3
4.2.6 Dilution Linearity and Hook Effect	23	13	36
4.2.7 Stability	26	12	38
4.3 Study Sample Analysis		1	1
4.3.1 Analytical Run	5	3	8
4.3.2 Acceptance Criteria for an Analytical Run	7	2	9
4.3.3 Calibration Range	9	4	13
4.3.4 Reanalysis of Study Samples	11	10	21
5. INCURRED SAMPLE REANALYSIS (ISR)	24	10	34
6. PARTIAL AND CROSS VALIDATION	1	0	1
6.1 Partial Validation	17	2	23
6.2 Cross Validation	26	10	48
7. ADDITIONAL CONSIDERATIONS	3		3
7.1 Analytes that are also Endogenous Compounds	10	3	13
7.1.1 Quality Control Samples	3	1	4
7.1.2 Calibration Standards			0
7.1.3 Selectivity, Recovery and Matrix Effects	9	3	12
7.1.4 Parallelism	3		3
7.1.5 Accuracy and Precision	4		4
7.1.6 Stability			0
7.2 Parallelism	5		5
7.3 Recovery	2	2	4
7.4 Minimum Required Dilution	1		1
7.5 Commercial and Diagnostic Kits	3		3
7.6 New or Alternative Technologies	3		3
7.6.1 Dried Matrix Methods	3		3

Hot Topics

Consider the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Cross validation

Documentation

Hot Topics

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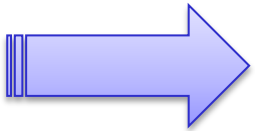
Documentation



Covered previously by Tom

Topics for Discussion

Consider the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Consider the world around us: 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 HAs 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

* *Toward decision-based acceptance criteria for Bioanalytical Method Validation: a proposal for discussion from the European Bioanalysis Forum* ***Bioanalysis*** *(2018), 10 (16), 1255-1259*

Consider the world around us: GCP considerations

- Adherence to GCP remains 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.

Consider the world around us: 3Rs

The EU based BA community feels that a modern and science based guideline should consider animal welfare and not require 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

Topics for Discussion

Considering the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Method Development

- The risk:
  - Loss of scientific freedom
  - Industry takes documentation to a level which is unmanageable
  - HA expectations

- The proposal
  - Paragraph 2.1: Method Development carries the risk of becoming overinterpreted and increasing the resource requirements for industry, whilst stifling scientific freedom required in the method development arena **(and not aligned with the mission of ICH)**.
  - For "Method Development," we suggest to limit the scope to changes to already validated methods in later stages of development.

Topics for Discussion

Considering the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Stability: Fixed Dose Combinations

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

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

Stability: LTS at -20/-70 °C

To date, there is no data to support a claim that a protein is instable in an LTS experiment @ -70° when it was stable @ -20°. And the experiment was performed hundreds of times… 1F/T may impact

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.~~

Topics for Discussion

Considering the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Incurred Sample Reanalysis: “Pre-ICH” EBF position

- ISR failure rate was, in a survey with more that 5500 studies, low (approx. 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 which is not adding value.
- The number of ISR should be aligned with number of spiked QC’s in a run (5% => in alignment with AAPS recommendation)
- Consider a fixed number approach as an alternative to a fixed ratio?

ISR: In summary…EBF/EFPIA Position

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.

Topics for Discussion

Considering the world around us:

- Acceptance Criteria
- GCP considerations
- 3Rs

Method Development

Stability

Incurred Sample Reanalysis (ISR)

Background & Scope

Background & Scope

Background & Scope: The Regulator's perspective

When reviewing a file, it can be assumed that 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

Scope paragraph of M10 will likely do the job

Background & Scope: 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

is it really the intention to bring

all analytes in **all** matrices

from **all** studies into scope?

Where do we struggle?

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.

- ‘pivotal’
- ‘support regulatory submissions’ *vs.* ‘make regulatory decisions’
- ‘primary matrix(ces)’ vs. ‘alternative matrices’
- ‘described in other ICH and regional regulatory documents’

Summing Up…
EBF General Remarks on ICH M10

1. “Scope” is generally perceived as too broad and ambiguous. If unchanged, all studies, all matrices and all analytes are at risk of becoming in scope.

2. Some parts of stability assessment are perceived as too broad. Example given is co-med stability assessment.

3. Consider harmonised decision-based acceptance criteria rather than technology-based ones (LCMS vs LBA). (*Ref: Bioanalysis (2018) 10(16), 1255–1259*). Also, this would prepare the Guideline for future technologies entering the regulatory BMV space.

Summing Up…
EBF General Remarks on ICH M10 (Cont'd)

4. "Table 1: Documentation" and "Paragraph 2.1: Method Development" carry 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).

   - For "Documentation" 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)

   - For "Method Development," we suggest to limit to scope to changes to already validated methods in later stages of development.

Summing Up…
EBF General Remarks on ICH M10 (Cont'd)

5. 3Rs: EBF feels that a sustainable and science based guideline should consider animal welfare and not require unnecessary use of animals. (*Ref: https://www.nc3rs.org.uk/the-3rs*)

   - Replace = allow surrogate matrix used when proven valid (e.g. sample dilutions, calibrators,..)
   - Reduce = using smaller volumes/less replicates of sample or matrix in preclinical assays
   - Refine = facilitate micro-sampling assays

- All details from the discussion from Barcelona can be found on the EBF website:
- All slides: http://www.e-b-f.eu/fw201905-slides/
- Conclusion slides: http://www.e-b-f.eu/wp-content/uploads/2019/06/FW201905-061.-Recommendations-from-the-EBF-Spring-FW-2019.pdf
- This were the basis of the comments that were submitted to the EWG via EMA (both from EBF and EFPIA)

Acknowledgements

- EBF community
- Delegates to EBF/AAPS/JBF/CBF sister meeting (Barcelona, May, 2019)
- All of you


THANK
YOU

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