Feedback from the EBF Workshop on ICH M10

Philip Timmerman – EBF

06 February 2024 – 15th JBF Meeting, Kyoto, Japan

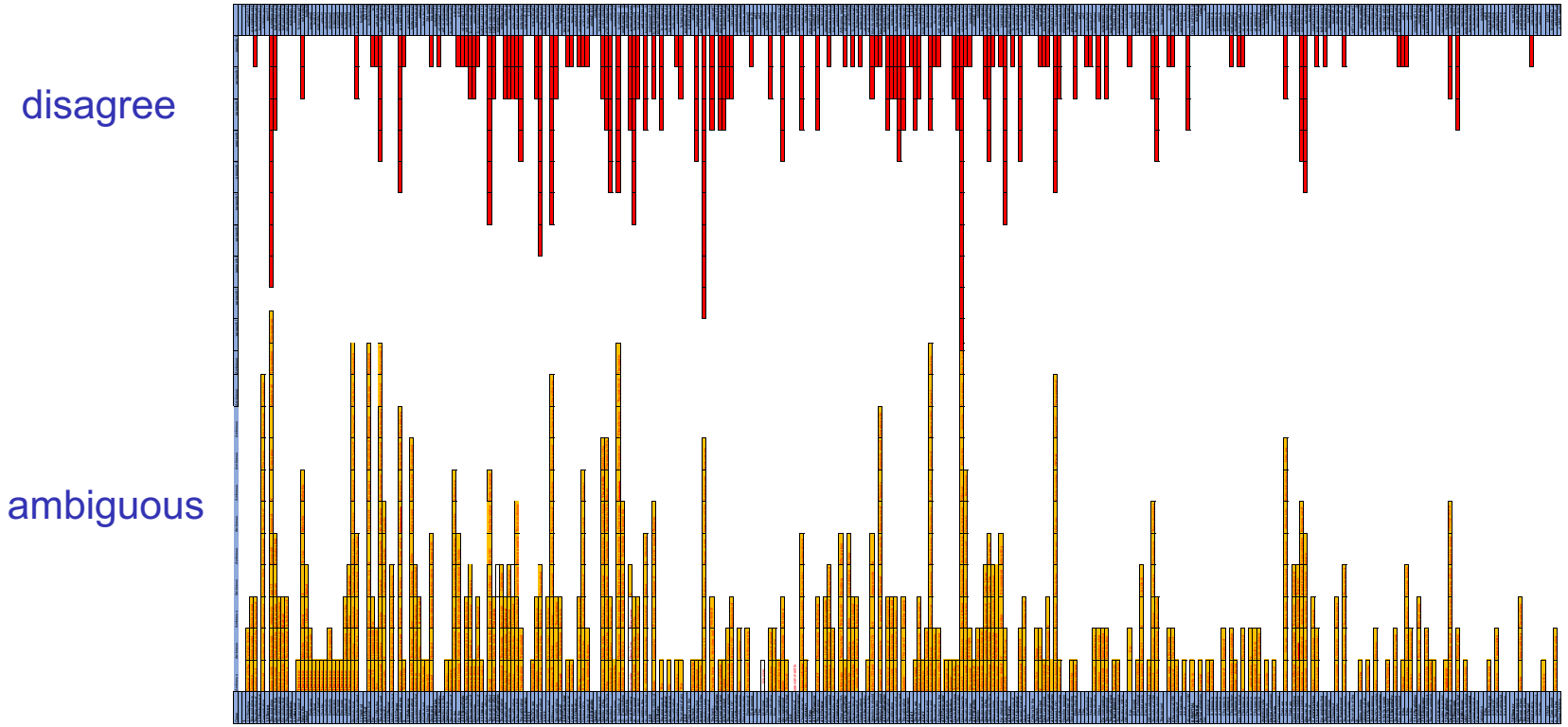
The road from 1 guidance to 1 guideline was paved with good intentions

- **Before 2009:** 1 guidance = FDA-2001
- **2009-2012**: EMA from draft to final, Anvisa on the horizon
- **2010** - Open letter from industry to regulators asking for harmonised (interpretation of) guidelines
- **2011** - @ OS, EBF suggesting regulators to connect and get ICH involved
- **2012 – 2016** – EBF working with industry partners (AAPS and JBF), investigating ICH involvement
  - **2015-2016** – working with EFPIA to put BMV on ICH radar
  - **2016** - EBF/AAPS/JBF Proposal submitted to EFPIA
- **2016** – MHLW submitting (leaner) proposal to ICH MC
- Off we went…

- **2009 – 2018**

Tsunami of regional guideline

ICH M10 Public Consultation – 2019 – EBF comments



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	Ambigous		
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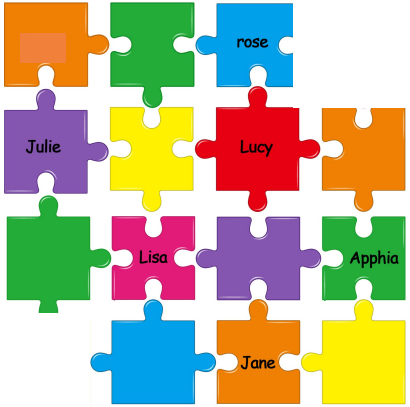
ICH M10 Final Guideline - 2022

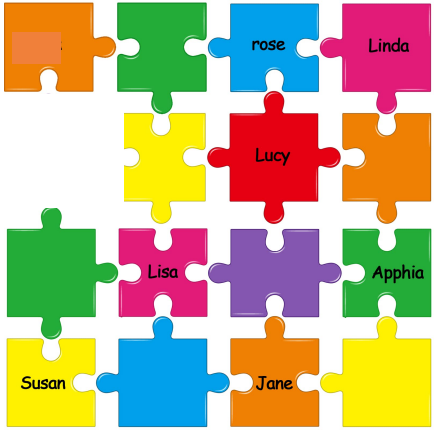
No or only partial uptake of industry comments to include science and experience-based refinements

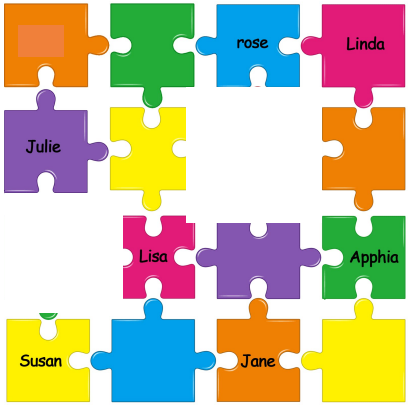
- 3Rs – incl. surrogate matrix
- FDC
- Documentation
- Scope
- Stability
- ISR
- Mdev
- Partial and cross validation
- GCP
- Specificity testing
- LTS Stability -80° LBA
- Decision base acceptance criteria
- Hybrid assays challenges
- And more…



HA 1

HA 2





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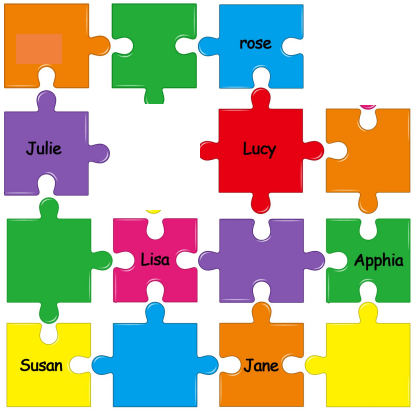
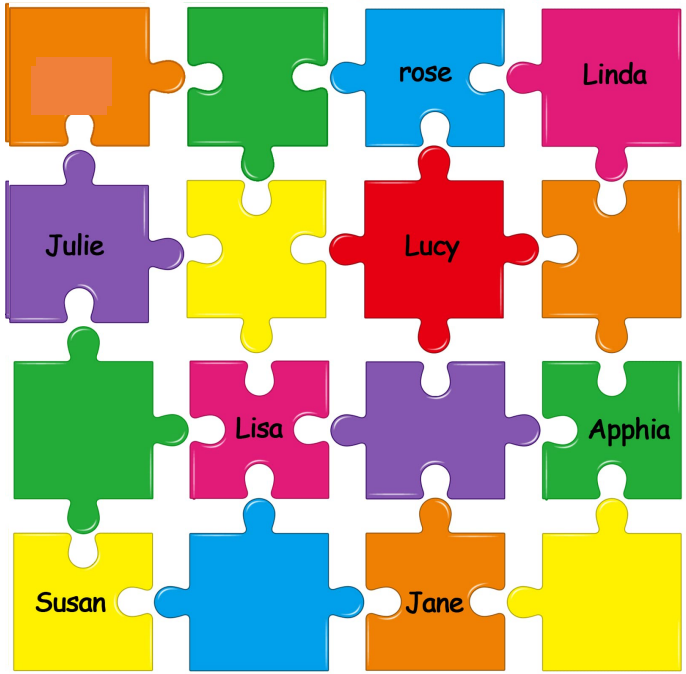
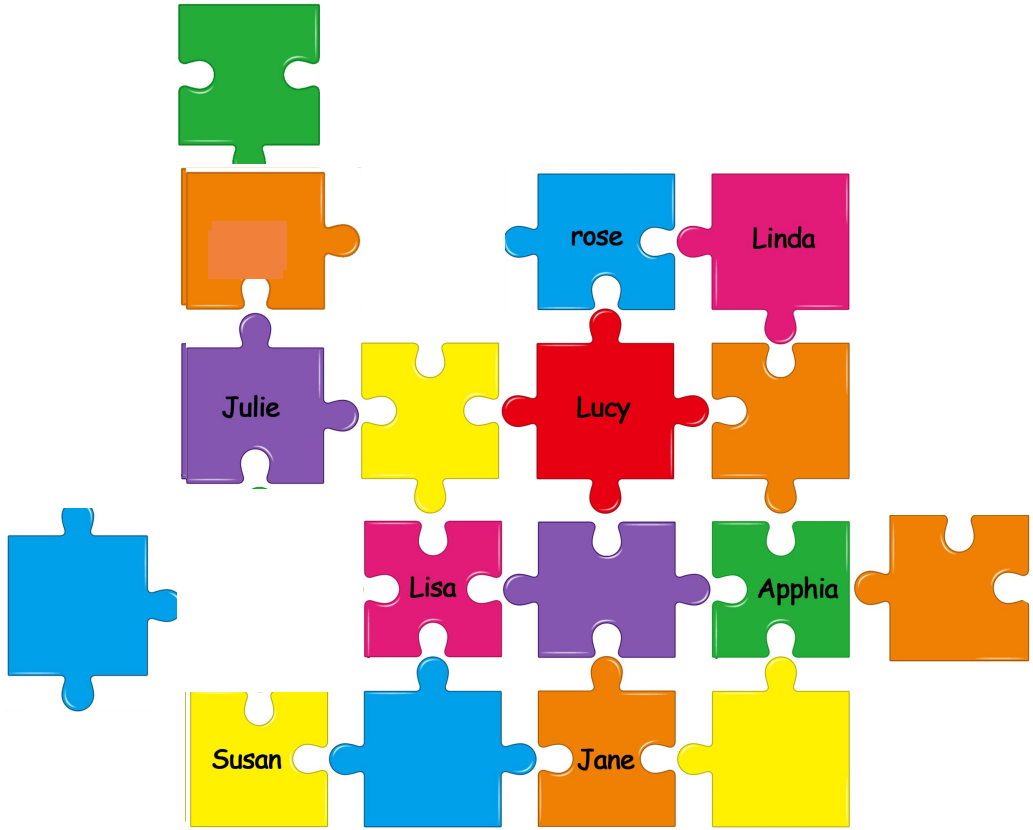


Note: names in the jigsaw puzzle pieces have no meaning



Harmonisation = sum of all?

Note: names in the jigsaw puzzle pieces have no meaning



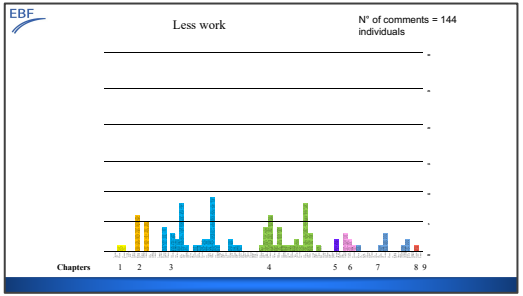
actually…Harmonisation = Sum of all adding or removing paragraphs considering public comments, and adding new requirements from regulators?

Note: names in the jigsaw puzzle pieces have no meaning

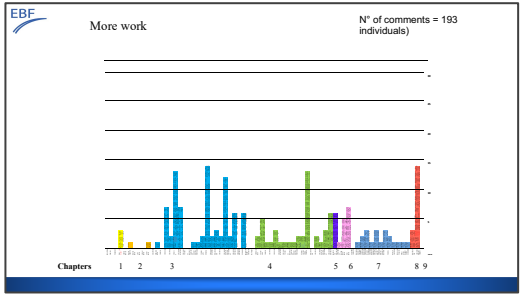
ICH M10 Final Guideline – 2022

EBF evaluation when released

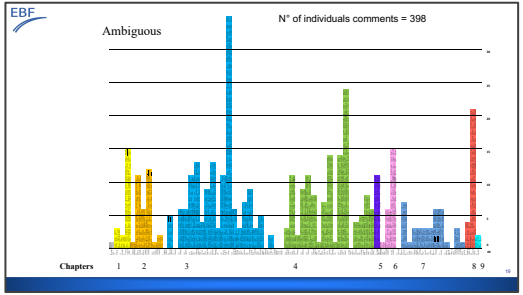
challenge



applause



ambiguous

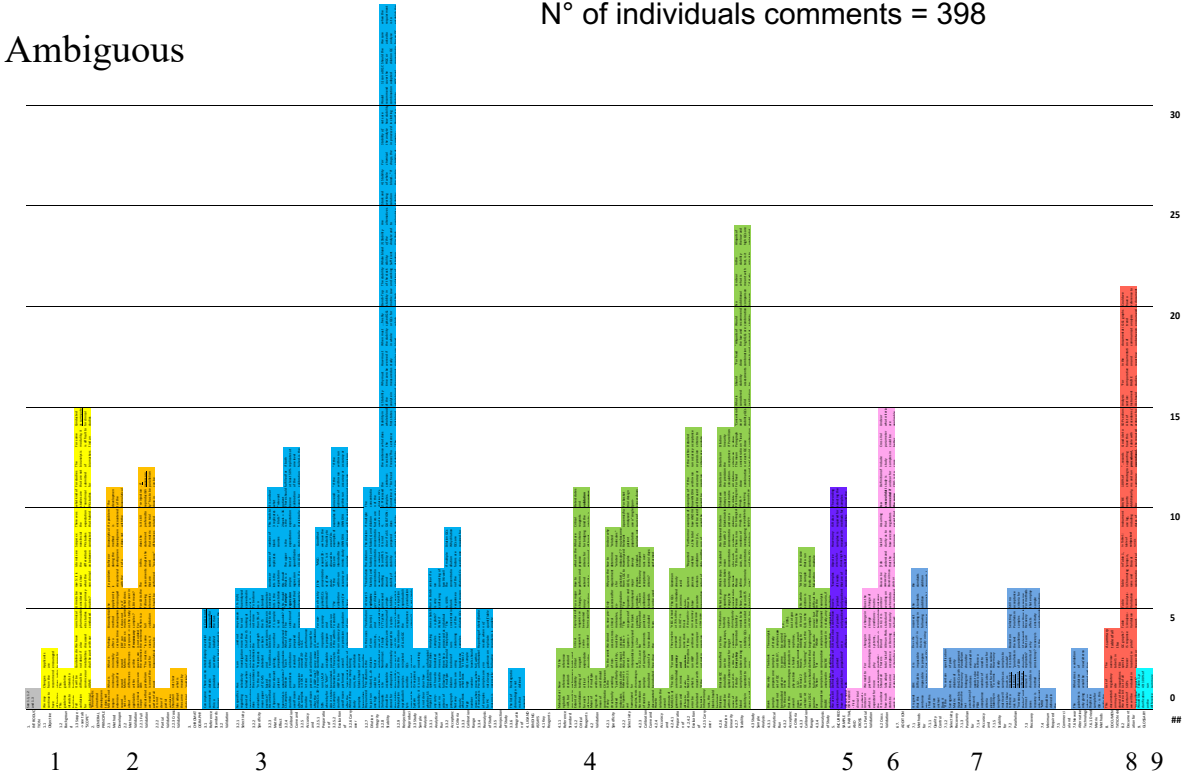


EBF

EBF

Ambiguous

N° of individuals comments = 398



March 2023 – EBF Strategy Meeting

During the ICH discussion

1. Differences in interpretations
2. Differences in implementations
3. Disappointment on valid/data driven comments given during public consultation being rejected
4. ICH M10 already at risk of becoming the next guideline with individual mis-, over-interpretation by industry, and differently applied by regulators

Action:

- Need to stay connected as industry in this first phase of implementation
- Need to stay connected with HA


EBF
One Year into ICH M10 - Keeping our Finger on the Pulse
EBF Workshop – 14 November 2023

Building the agenda – selection or themes

From a survey in the EBF Community,

- ca. 20 areas were identified as ‘at risk’ of creating confusion.

For each area, a mini-survey was issued to delegates and full EBF community

- From those responses (n=56 companies), we built the workshop

We shared the survey with the JBF. In addition, we received FB from the JBF WS on ICH M10 held in Yokohama (Oct 2023) and included this into our meeting

Intended outcome of the workshop

1. Hoping to answer most of industry questions (likely utopia)
2. **Provide recommendations** for our industry on areas of ambiguity
3. **Create awareness**
   - and **share our worries** where the industry already observes different interpretation by regulators and for which industry/regulators need to stay connected
   - and **provide FB to HA** on ambiguities and jointly resolve these.

NOT on the agenda

- **Areas of disagreement/disappointment from public consultation**
  - Areas where we believe the guideline requires either too much work, there is no scientific basis
  - Not having them at the workshop doesn't mean we now agree…we should we keep them on our radar (e.g. some ICH Guidelines do get revised..)
- **Chapter 7:**
  - Not the bulk of our work - Requires separate discussion
- **Chapter 8: documentation**
  - Significant increased workload - Requires separate discussion
- **Method development** (documentation)
- **ADA** and **Biomarkers -** Not in scope of ICH M10

ON the agenda

Round tables General Themes:

- Scope interpretation A - primary matrix definition
- Scope interpretation B - rare matrix vs. tissues
- Scope interpretation C - Defining pivotal studies
- Updating historical validations - when, how and why (not)?
- Is it allowed to re-analyse positive predose in BE study?
- Cross validation - working in the new paradigm

Round tables CHROM Themes:

- hybrid assays in ICH M10 - our day-to-day practice
- Whole blood stability
- Analytes and matrices: focus on urine
- Dilution QCs during assay validation & sample analysis
- Stock and working solutions stability
- Surrogate/rare/preclinical matrix for CHROM

Round tables LBA Themes:

- Dilutional Linearity & Parallelism
- Singlicate vs duplicate analysis
- Surrogate/rare/preclinical matrix for LBA
- Chrom. requirements infecting LBA, incl. tissues and blood stability
- Dilution QCs during sample analysis

Scope interpretation

Round tables General Themes:

- Scope interpretation A - primary matrix definition
- Scope interpretation B - rare matrix vs. tissues
- Scope interpretation C - Defining pivotal studies

Paragraphs we may have forgotten to read – 1/2

1.1. Objective

This guideline is intended to provide recommendations for the validation of bioanalytical methods for chemical and biological drug quantification and their application in the analysis of study samples. Adherence to the principles presented in this guideline will ensure the quality and consistency of the bioanalytical data in support of the development and market approval of both chemical and biological drugs.

The objective of the validation of a bioanalytical method is to demonstrate that it is suitable for its intended purpose. Changes from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided. Applicants are encouraged to consult the regulatory authority(ies) regarding significant changes in method validation approaches when an alternate approach is proposed or taken.

Paragraphs we may have forgotten to read – 2/2

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 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.

This guideline intends to facilitate development of drugs in accordance with the principles of 3Rs (Reduce, Refine, Replace) for animal studies, where valid.

Scope paragraph = well written…
but do we all read the same here?

1.3. Scope

This guideline describes the validation of bioanalytical methods and study sample analysis that are expected to support regulatory decisions. The guideline is applicable to the 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 toxicokinetic (TK) studies conducted according to the principles of GLP, nonclinical pharmacokinetic (PK) studies conducted as surrogates for clinical studies, and all phases of clinical trials, including comparative bioavailability/bioequivalence (BA/BE) studies, in regulatory submissions. Full method validation is expected for the primary matrix intended to support regulatory submissions. Additional matrices should be validated as necessary.

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.

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.

Out of scope….

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Creating continued ambiguity

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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. (other technologies…?)

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.

We all agree…
Out of scope: Biomarkers and Immunogenicity

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

Still…

- Where most of our industry understands that the ICH M10 guideline is not for biomarkers or immunogenicity, a significant group in our industry does use ICH M10 as reference for biomarkers.
- The EBF is a strong proponent to use the principles of Context of Use (CoU) for assays supporting both biomarkers as well as immunogenicity.

Scope interpretation by industry

- From the survey…..

Pre-workshop survey on scope interpretation

56 organisations provided FB

Up to 25 % of the responders are unclear on scope paragraph…

that's a lot for a guidance

Reading the detailed comments and responses from the survey…it's actually more than 25% being unclear

1. Primary matrix definition

Full method validation is expected for the primary matrix intended to support regulatory submissions. Additional matrices should be validated as necessary

Can we agree on '*primary*' vs. '*additional matrices*'

The recommendations for Primary matrix definition from the EBF workshop:

- Continue create awareness on how definition primary *vs.* secondary matrix.
- Consider using "additional matrix" instead of "secondary matrix"
- **If we cannot agree on defining primary *versus* additional matrix, the inherent risk is every matrix becomes in scope.**

2. Rare matrix vs. tissues –

Can we agree: *(1) unless exceptions, tissues are never 'primary matrix' are out of scope and (2) rare matrix are a subcategory*.

The recommendations for rare matrix definition from the EBF workshop:

- Interpretation of primary *vs.* additional matrix should, unless exceptions, by default lead to identifying tissues as an additional matrix
- **Understand CoU for data are generated. If the rare matrix or tissue is not a primary matrix ➔ apply appropriate fit-for-purpose validation considering the scientific requirements for the matrix and the data required.**
- The discussion on rare matrix *vs.* tissue should not be on "when to fully validate?", but on "where can we use a surrogate matrix?".
- The EBF plans to update publications on tissues and fit-for-purpose validations.

3. Defining Pivotal studies definition

‘Pivotal’ is only mentioned in the ISR section

From the comments, there are a variety of opinions on what is ‘pivotal’

The challenge: if we cannot identify ‘*expected to support regulatory decisions*’, or how broad can you interpret ‘*support*’, virtually all studies will become in scope

The recommendations for pivotal study definition from the EBF workshop:

- At the roundtable, there was an animated discussion on the word ‘pivotal’. Unless for final BA/BE studies, it is often unclear at the time of sample analysis to identify a pivotal study.
- An additional point of confusion is that “pivotal” for ISR may mean something different than “pivotal” for a development program, which may even be different from “pivotal’ for Health Authority evaluation at filing.
- **Providing more clarity on “pivotal" may need to be included in Q&A in the ICH M10 documentation**

General Themes related to chapter 2, 5 and 6

- **Updating Historical Validations - When, How and Why (not)?**
- Re-analyse positive predose in BE study
- **Cross Validation – Working in the New Paradigm**
- **Are Method Validations in Scope of GLP?**
- Biomarkers and Immunogenicity
- Incurred Sample Reanalysis (ISR)

Updating Historical Validations - When, How and Why (not)?

- The EBF recommends considering balancing resources going into (unnecessary) revalidations and come together as an industry to define best practices on when to revalidate and for which critical parameters.
- In most cases, methods validated towards current regulatory BMV Validation standards, will be adequate for the studies they have supported at that time.
- EMA is planning a guideline on *Implementation strategy of ICH Guideline M10 on bioanalytical method validation (EMA/449486/20233)*. The draft guideline offers a pragmatic stance – see next slide:

Updating Historical Validations – EMA draft guideline

1. If your development program started shortly before 21 January 2023, consider transitioning to ICH M10.
2. If your program is in Phase 3, ongoing studies may be completed without update, providing the methods were validated against the EMA Guideline on bioanalytical method validation from 2011.
3. If you have completed the clinical (and non-clinical) development before 21 January 2023 but are submitting your application after this date, there is no need to change or revalidate the bioanalytical methodology according to ICH M10.

EBF comment to EMA (on 22JAN2024):

- EMA position above is that dates for re-validation align with EMA BMV effective dates
- Those dates may differ when submitting in another region, where the regional guideline prior to ICH M10 have other effective dates. (i.e. 2014/2015 (MHLW) or 2018 (US-FDA)….
- Global alignment will be beneficial to prevent revalidation requirements from being a regional requirement for many years to come.

Re-analyse positive predose in BE study

The recommendation from the discussions at the workshop:

The analysis of positive pre-dose samples from bioequivalence studies should be cognizant of the following considerations:

- pre-dose samples are not part of pharmacokinetic (PK) evaluation and carry the risk of accidental unblinding.
- It was also mentioned that if re-analysis would be considered, only the positive pre-dose sample from the first period can be re analyzed.

Are Method Validations in Scope of GLP?

From the guideline

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.

EBF Recommendation: **Method Validations are not in scope of GLP**

- Scope of GLP = nonclinical safety studies. BMV≠ nonclinical safety studies
- https://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm

Incurred Sample Reanalysis (ISR)

- Industry continues to include ISR in more studies than called for by the guideline.
- In ISR paragraph, the word “pivotal” can be interpreted ambiguously. There may be more than one ‘pivotal first study in…’. It can therefore be valuable ask clarification from regulators or how the word pivotal should be read in the ISR chapter.
- EBF recommendation papers on ISR stays current*, ** → continue to stimulate industry to balance cost *vs.* added value of the (often-inflated) ISR investigations.
- Challenge was given on cost *vs.* value of the high number of samples required to be re-analyzed for ISR in large BA/BE studies.

** Timmerman P, Luedtke S, van Amsterdam P et al. Incurred sample reproducibility views and recommendations by European Bioanalytical Forum. Bioanalysis 1 (6), 1049 – 1056 (2009)*

*** Kall MA, Michi M, van der Strate B et al., Incurred sample reproducibility: 10 years of experiences: views and recommendations from the European Bioanalysis Forum, J. Bioanalysis Volume 10, Issue 21, November 2018, Pages 1723-1732*

Focus on Chromatography

Discussed at the workshop:

- **Fitting Hybrid Assays in ICH M10 – Day-to-Day Practice**
- **Whole Blood Stability**
- **Analytes and Matrices: Focus on Urine**
- Dilution QCs During Assay Validation & Sample Analysis
- Stock and Working Solutions Stability
- **Surrogate/Rare/Preclinical Matrix for Chromatography**
- Choosing the Right Regression Model for LC-MS assays
- Matrix Effect - Special Population, Hemolyzed and Lipemic
- **Metabolites**

Fitting Hybrid Assays in ICH M10 – Day-to-Day Practice

- The ICH M10 guideline does not specify hybrid assays(immuno-capture LC/MS assays).
- Continued discussion if hybrid assays should be considered LC-MS assays or LBA.
- The audience is undecided whether more clarity should be provided by ICH M10.
  - more clarity in the guideline would be appreciated to remove the fear of not meeting 'anticipated' regulatory expectations.
  - But… strict guidance and/or fixed criteria would hamper scientific freedom required given the complexity of many hybrid assays
- Additional discussions, including EBF recommendations *,**, in addition to the already published discussion and recommendation papers , were requested.

** Knutsson M, Schmidt R and Timmerman P, LC–MS/MS of large molecules in a regulated bioanalytical environment – which acceptance criteria to apply? Bioanalysis, 5(18), 2211– 2214 (2013).*

*** Barfield M, Blackburn M, Blattmann P et. al., Immunocapture LC–MS(/MS) assays for biotherapeutic and biomarker proteins: the European Bioanalysis Forum continuing discussions on scientific and regulatory challenges, Bioanalysis, Volume 15, Issue 9, May 2023, Pages 477-480*

Whole Blood Stability for chromatographic assays

- The industry is not fully aligned with what is being requested in ICH M10.
- More discussion is needed both the ‘how’ and the ‘when’.
- EBF recommendation paper from 2011 * is a good starting point for revisiting the scientific needs.
  - EBF may want to revise this recommendation in support of providing experimental clarity for blood stability testing in support of the ICH M10 guideline.

** Freisleben A, Brudny-Klöppel M, Mulder H et al. Blood stability testing: European Bioanalysis Forum view on current challenges for regulated bioanalysis, Bioanalysis Volume 3, Issue 12, June 2011, Pages 1333-1336*

Analytes and Matrices: Focus on Urine

- It remains unclear if urine is a primary matrix or should be categorized as an additional matrix. Even if urine is considered additional matrix, many include urine in scope for full validation.
- The outcome of the discussions provided clarity that urine is rarely a primary matrix.
  - Consequently, the EBF recommends that when validating urine, copying the procedures for full validation may not be covering all the scientific requirements.
  - EBF feels it is important the community embraces the specific scientific challenges for urine samples
- An earlier EBF recommendation paper on additional scientific considerations for scientific validation applied to urine samples.

Timmerman P, White S, McDougall S et al. Tiered approach into practice: scientific validation for chromatography-based assays in early development – a recommendation from the European Bioanalysis Forum. *Bioanalysis* 2015: 7(18), 2387-2398

Dilution QCs During Assay Validation & Sample Analysis

- The majority of the workshop delegates include dilution QCs at each applied dilution factor with the purpose of process control.
- From the workshop, it was recommended to review the scientific requirement of additional validation experiments during sample analysis for lower dilution factors when the higher dilution factor was already fully validated.
  - Because these validation experiments are currently required according to ICH M10 the audience agreed to optimize the dilution scheme during validation and to apply a limited number of dilution factors during sample analysis.

Stock and Working Solutions Stability

- All participants demonstrate stability of the analyte in solution to cover the duration of use of the solution. However, for working solutions many do not assess stability when immediately used upon preparation and the remainder discarded.
- Since no acceptance criteria are mentioned in the guidance, criteria differ from 5 to 10% or even 15% in case of large molecules analyzed by LC-MS. The Q&A section of the guideline mentions that two stock solutions can be used interchangeably provided their content is within 5%. Therefore, many use the same criterion for demonstrating solution stability.
- Solution stability for stable isotope labelled internal standards (IS).
  - These materials are expensive and scarce.
  - Since all include a zero sample in every analytical run to verify the absence of unlabeled analyte and the same amount is added to every sample within a run and the IS is not used for absolute quantification, the general sentiment is that demonstrating solution stability is for stable isotope labelled IS of no added scientific value.

Surrogate/Rare/Preclinical Matrix for Chromatography

- At the workshop, all delegates supported the request from the EBF to maximize the principles of the ‘3Rs’ in our industry.
- The EBF is currently generating experimental data as a scientific stepstone for reducing the use of preclinical matrices wherever possible.
- The EBF invites other organizations to join a data-driven discussion with the health authorities on maximizing the principles of the 3Rs.

Choosing the Right Regression Model for LC-MS assays

- Survey data: A linear model with $1/x^2$ weighting is utilized as the standard
- We recommended that a linear model with $1/x^2$ weighting can be utilized as the default for LC-MS assays. (with appropriate documentation of policy in e.g. SOP)
  - If the validation data meets the predefined acceptance criteria using this default approach, no further action would be required.
  - If the validation data fails the predefined acceptance criteria using this default approach, it is recommended that the reason for selecting an alternative model and/or weighting is documented.

Matrix Effect - Special Population, Hemolyzed and Lipemic

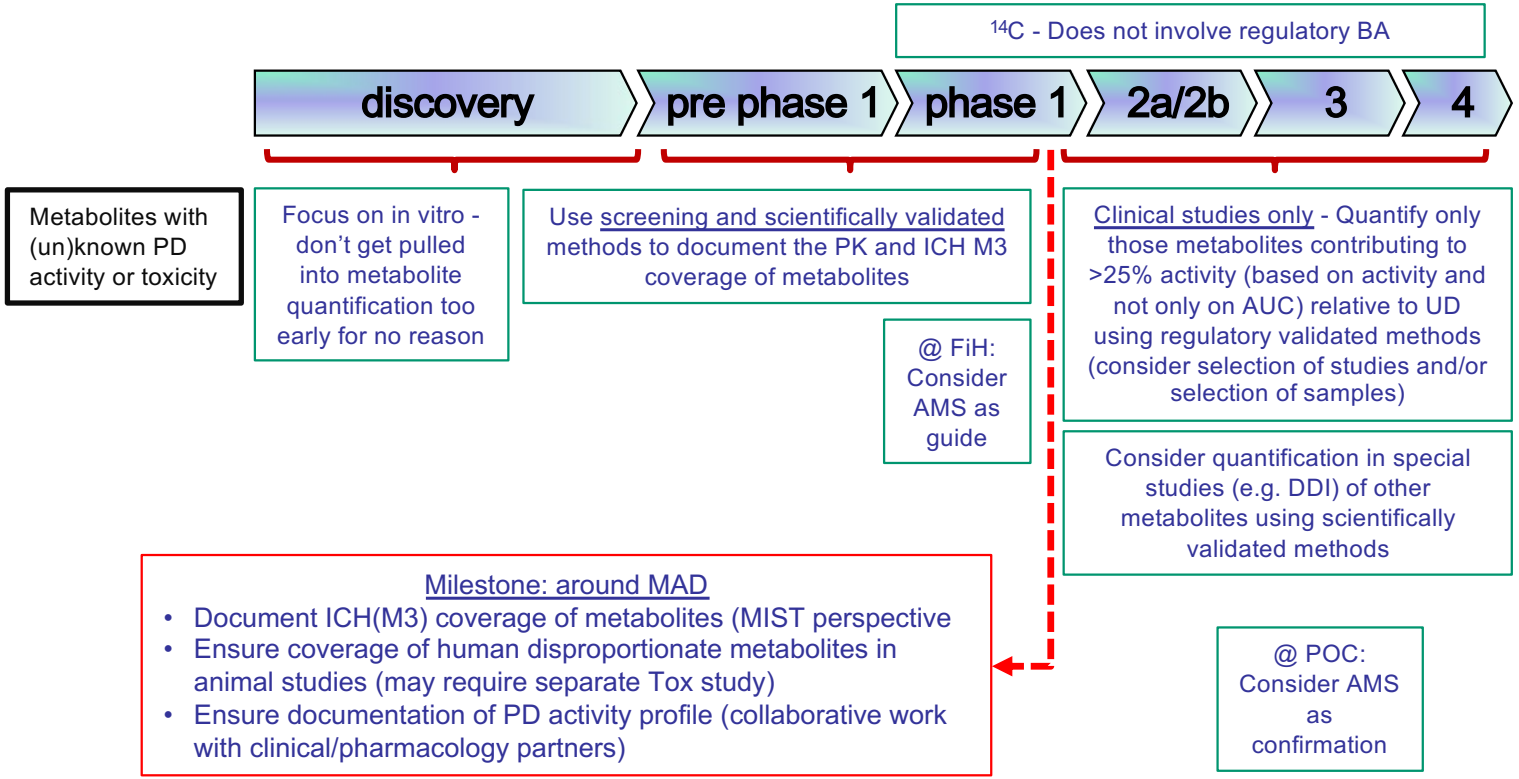
- Hepatic or renally impaired patients, are recognized as special populations. The classification of other groups such as different age or ethnic groups or those in heathy versus diseased states, remain unclear. Further discussions, revolving around “concept of use” are proposed.
- It was agreed that matrix effects should be validated in hemolyzed and lipemic matrices to support clinical studies.
- Ideally, the matrices used should be naturally occurring and representative of the samples.

Metabolites

- Which metabolites to include in MVAL continues to be an area of discussion.
- ICH M10 is not clear on which metabolites to include when for full validation.
- Although from a technical perspective it is relatively easy to include metabolites in validations, the additional workload and costs should be considered and balanced against the added value for the project and the decisions made.
  - Alternative approaches should be considered, in collaboration with DMPK
- The industry is trending towards including metabolites relatively early in drug development, even as early as the first GLP studies, at the time when it is not clear what would be the added value for systematic quantification of metabolites.
- The EBF recommendation paper* on when and how to include metabolites in method validation also considers guidelines specific to MIST, DDI and/or how metabolites contribution to activity – flowchart on next slide.

** Timmerman P, Blech S, White S, et al., Best practices for metabolite quantification in drug development: updated recommendation from the European Bioanalysis Forum, J. Bioanalysis Volume 8, Issue 12, June 2016, Pages 1297-1305*

From the EBF Recommendation Metabolite quantification



LBA Themes

Discussed at the workshop:

- **Dilutional Linearity & Parallelism**
- **Singlicate *vs.* Duplicate Analysis**
- Surrogate/Rare/Preclinical Matrix for LBA
- Chromatography Requirements Copied into LBA Requirements, Including Tissues/Blood Stability
- Dilution QCs During Sample Analysis

Dilutional Linearity & Parallelism

Dilutional Linearity

- Industry practice: prepare a single ultra-high sample at or above the expected Cmax and evaluate in a single run with independent dilution series. The results are used to define the minimum and maximum dilutions in samples analysis.
- The scientific value of the dilutional linearity assessment was questioned by several delegates, as they did not see how dilution of a high concentration sample across the calibration range differed to the calibration curve itself.
- For preclinical assays, most delegates prepare samples by first performing the minimum required dilution (MRD), followed by further sample dilutions in assay buffer containing matrix driven by a desire to support 3Rs.
- For clinical assay there is a greater mix of those who perform dilutions in the same manner and those who dilute in 100% matrix prior to MRD.

Dilutional Linearity & Parallelism

Parallelism

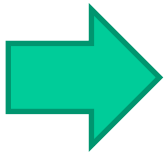
- Industry practice: parallelism is assessed on a case-by-case basis during sample analysis the first time that an assay was used in a new matrix.
- This is a similar approach to the (intended) application of ISR, and concerns were raised that this might slide down a similar slope to ISR and be over-applied in areas it was not merited.
- It was discussed that only Cmax samples may miss parallelism issues, as dilutions to bring the sample into range may dilute out interferences.
- There were very few cases of non-parallelism, reinforcing the ICH M10 statement that ‘lack of parallelism is a rare occurrence for bioanalytical methods for PK evaluation’.

Singlicate *vs.* Duplicate Analysis

- The EBF promoted the singlicate/duplicate discussion for more than a decade, resulting in a data driven recommendation paper* advocating the adoption a new mindset and embrace singlicate analysis for LBA assays in the regulated environment.
- **ICH M10 supports singlicate analysis of PK/TK samples**
- The majority in industry hesitates to apply singlicate analysis, for various reasons.
- **Singlicate analysis should not be limited to TK/PK assays**. Although immunogenicity assays are not in scope for ICH M10, it may be good to extend the singlicate/duplicate analysis for those assays too.

** Barfield M, Goodman J, John Hood J and Timmerman P, European Bioanalysis Forum recommendation on singlicate analysis for ligand binding assays: time for a new mindset. J. Bioanalysis, Volume 12, Issue 5, March 2020, Pages 273-284*

Surrogate/Rare/Preclinical Matrix for LBA



Surrogate/Rare/Preclinical Matrix for Chromatography

- At the workshop, all delegates supported a recommendation from the EBF to maximize the principles of the '3Rs' in our industry.
- The EBF is generating experimental data as a scientific stepstone for reducing the use of preclinical matrices wherever possible. Our community remains uncertain on its regulatory acceptance.
- The EBF invites other organizations to join a data-driven discussion with the health authorities on maximizing the principles of the 3Rs.

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Chromatography Requirements Copied into LBA Requirements, Including Tissues/Blood Stability

- Overall, chapter 4 is well written with only minimal occurrences of chromatography requirements coming into scope for LBA where industry questions the value.
- However, care should be taken that over time some requirements which are not specifically mentioned in chapter 4 do not spill over from chapter 3 to chapter 4, e.g.
  - extending the calibration range, selectivity and stability.
  - hemolyzed and lipemic samples (are they part of the ten required samples or are considered as additional samples), whole blood stability, fixed dose stability requirements, tissues

Dilution QCs During Sample Analysis

- The pre-meeting survey and the roundtable discussions assessed the interpretation of the guideline around the inclusion/exclusion of dilution QCs within sample analysis. Although not directly related to the question of the survey, the large majority workshop participants responded the guidance is quite clear in this regard, and they do perform dilution QCs analysis *only* during stability investigation. However, a minority of the responders (about 20%) are routinely using dilution QCs as process controls during sample analysis. When dilution QCs are used within sample analysis, half of the responders include the dilution factors which were already including in the dilution linearity assessment performed using the method validation. The majority of responders do not reject the complete run in cases where the dilution QC fails, but only reject the samples with additional dilutions.
- In conclusion, there is a good agreement among the community regarding not using dilution QCs during sample analysis as the dilution linearity was already demonstrated during validation.

Additional Considerations and conclusions – 1/2

Industry welcomed the harmonised guideline and is eager to implement is

But, ….

- The EBF workshop showcased harmonised interpretation is not achieved yet
- Industry stays concerned on comments public consultation not being considered in ICH M10 (cfr. slide 6)
- 3Rs is a specific concern
- Scope over-interpretation is a risk of increasing cost and lose scientific focus

Additional Considerations and conclusions

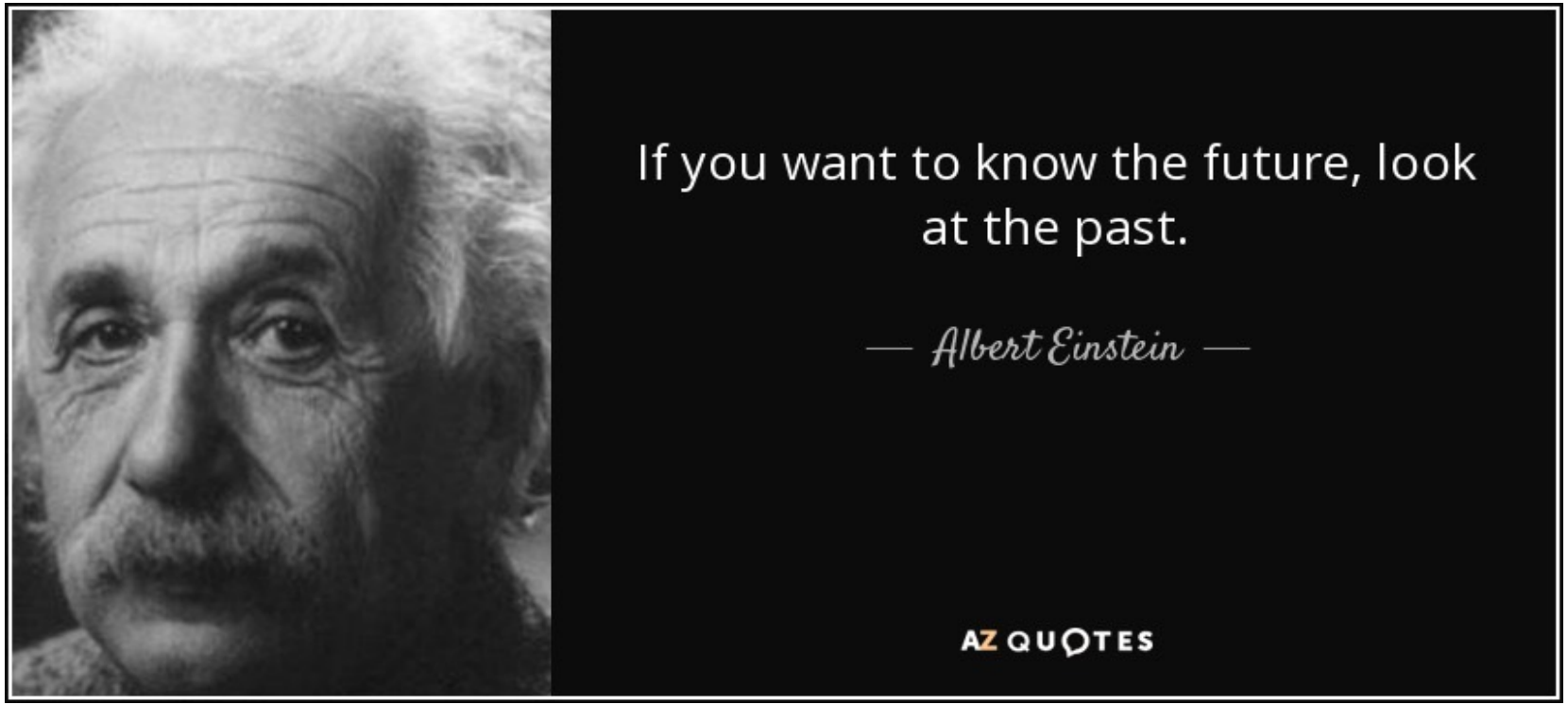
ICH M10 has raised the bar

Industry's fear leading to over-interpretation of ICH M10 is raising the bar

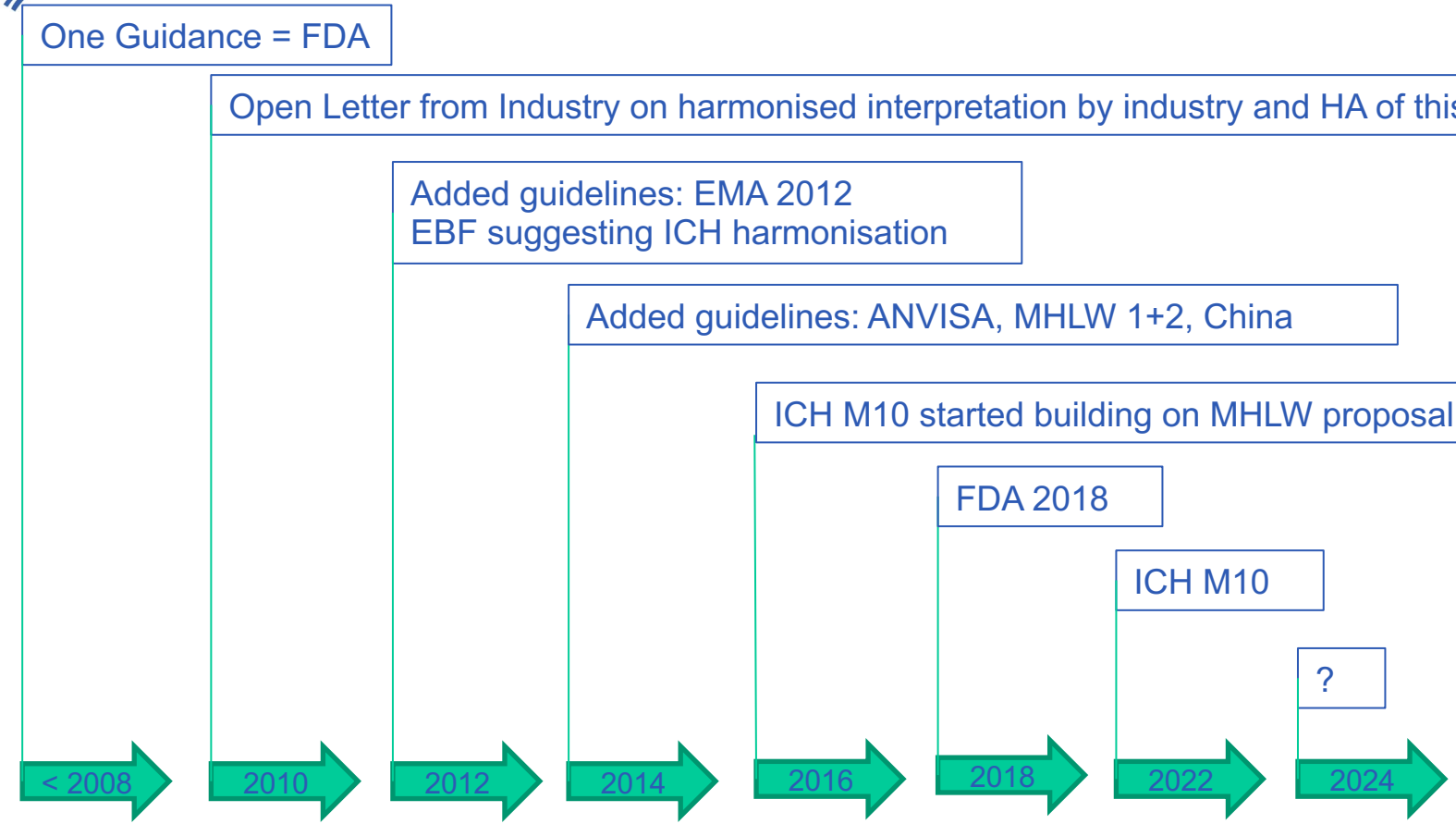
ICH M10 has also increased cost of BMV/Sample analysis

The industry and HA should (continue to) come together regularly and prevent undue overinterpretation of the requirements. Not achieving this, we are not living up to the mission of the ICH: i.e., *achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner*. .

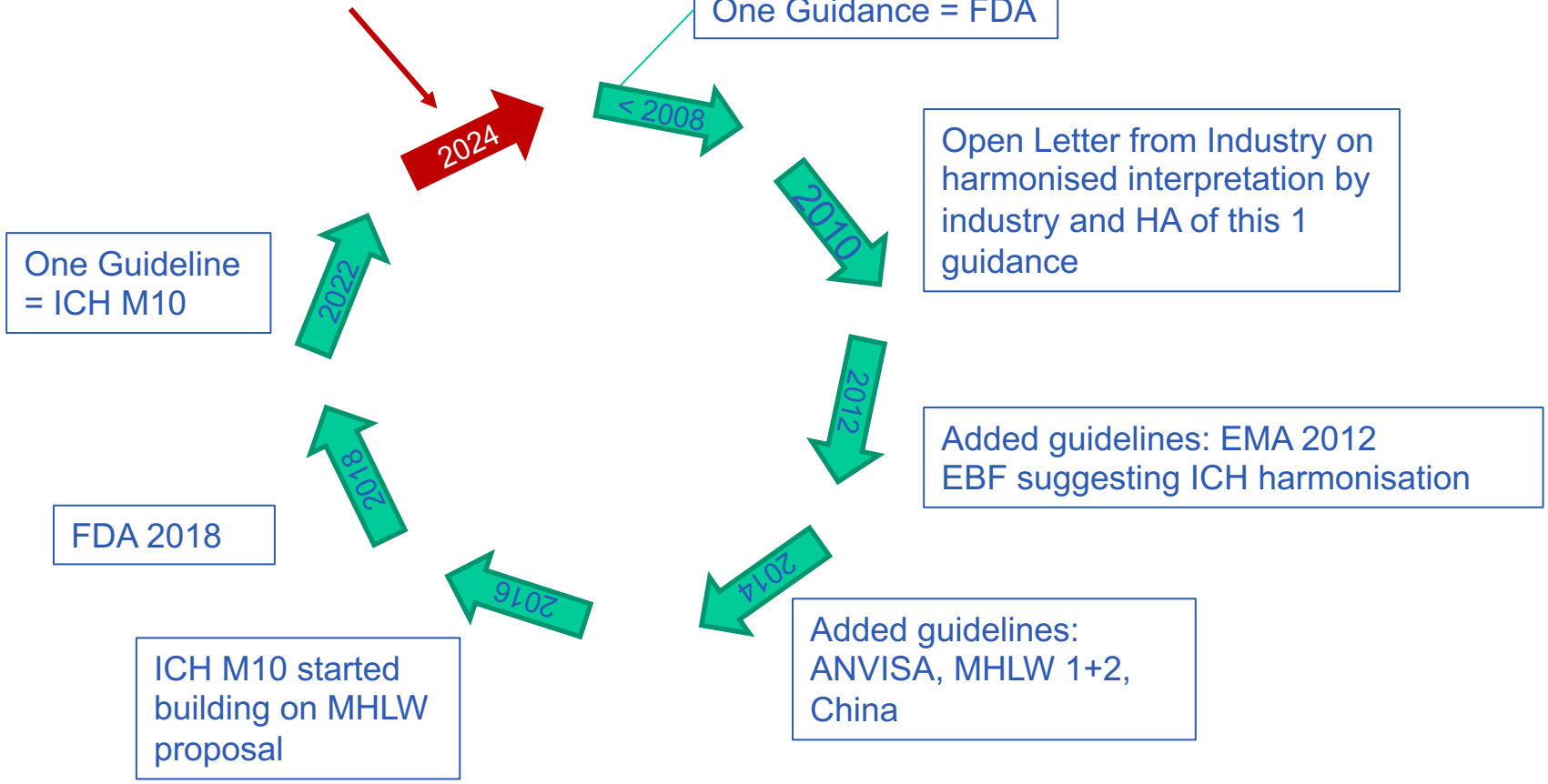
A final teaser



EBF


One Guidance = FDA
Open Letter from Industry on harmonised interpretation by industry and HA of this 1 guidance
Added guidelines: EMA 2012
EBF suggesting ICH harmonisation
Added guidelines: ANVISA, MHLW 1+2, China
ICH M10 started building on MHLW proposal
FDA 2018
ICH M10
?
< 2008
2010
2012
2014
2016
2018
2022
2024

And now?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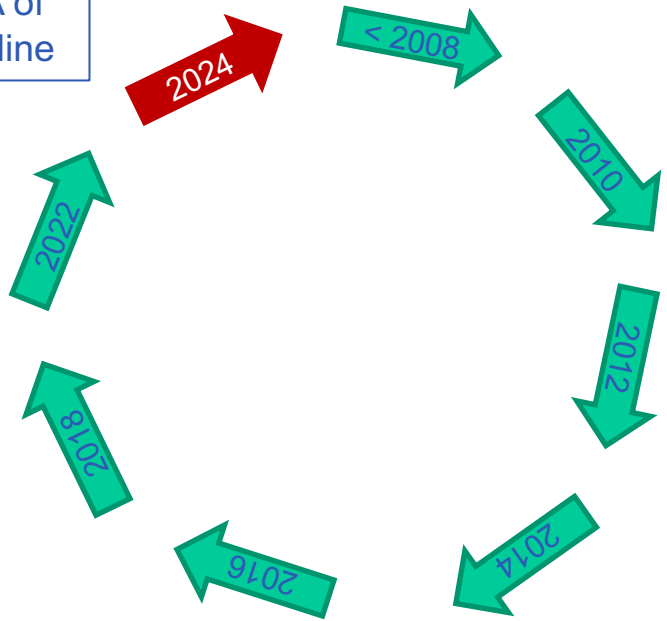
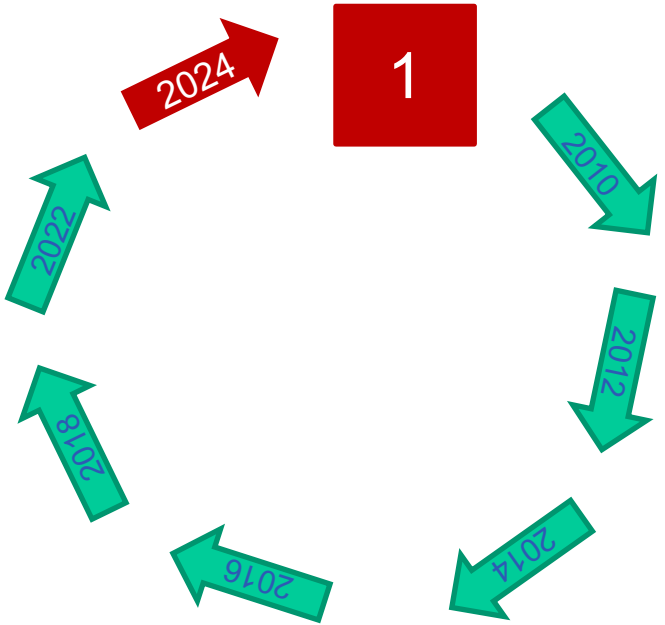
One Guideline
= ICH M10

Let's work together to prevent multiple interpretations by industry and HA of this single guideline



OR…we are back to square 1: one guideline which everybody reads differently



Acknowledgements

All EBF members, JBF and workshop delegates

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More details

1. European Bioanalysis Forum feedback on draft ICH M10 guideline on bioanalytical method validation during the Step 2b public consultation period. Bioanalysis, 2020 Mar;12(6s):1-11
2. All slides from the 2019 EBF Workshop: https://e-b-f.eu/fw201905-slides/
3. Public comments by the EBF: https://e-b-f.eu/wp-content/uploads/2020/03/EBF-comments-on-ICH-M10-during-public-consultation-as-submitted-to-EMA.pdf
4. Conference Report from the European Bioanalysis Forum Workshop: toward harmonized implementation of the ICH M10 guideline, Published Online:27 Jan 2023 https://doi.org/10.4155/bio-2022-0229
5. All slides from the 2022 EBF Workshop: https://e-b-f.eu/os-ws-2022-slides/
6. Recommendations and feedback from the European Bioanalysis Forum Workshop: One year into ICH M10 - Keeping our finger on the pulse. (*in press*)
7. All slides from the 2023 EBF Workshop: https://e-b-f.eu/ich-m10-workshop-2023-slides

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