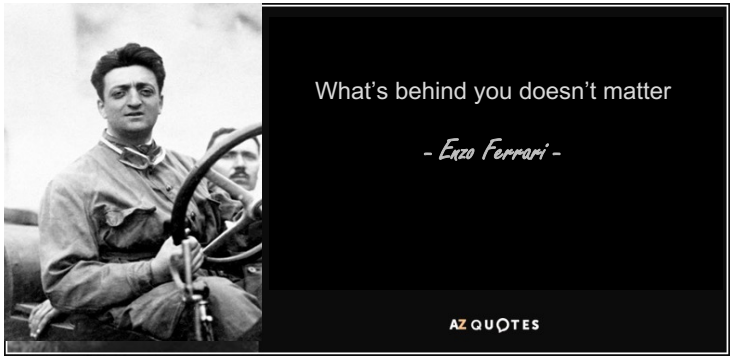
Workshop on ICH M10

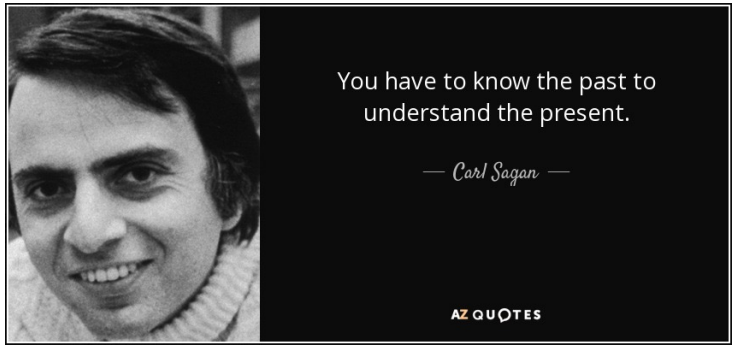
Introduction to the Workshop

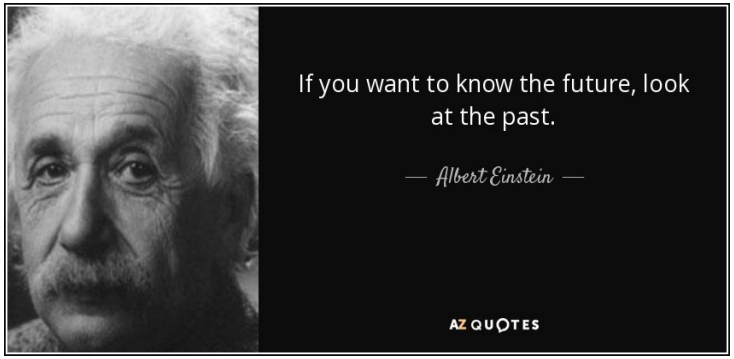
Philip Timmerman – EBF

14 November 2023 – Barcelona, Spain

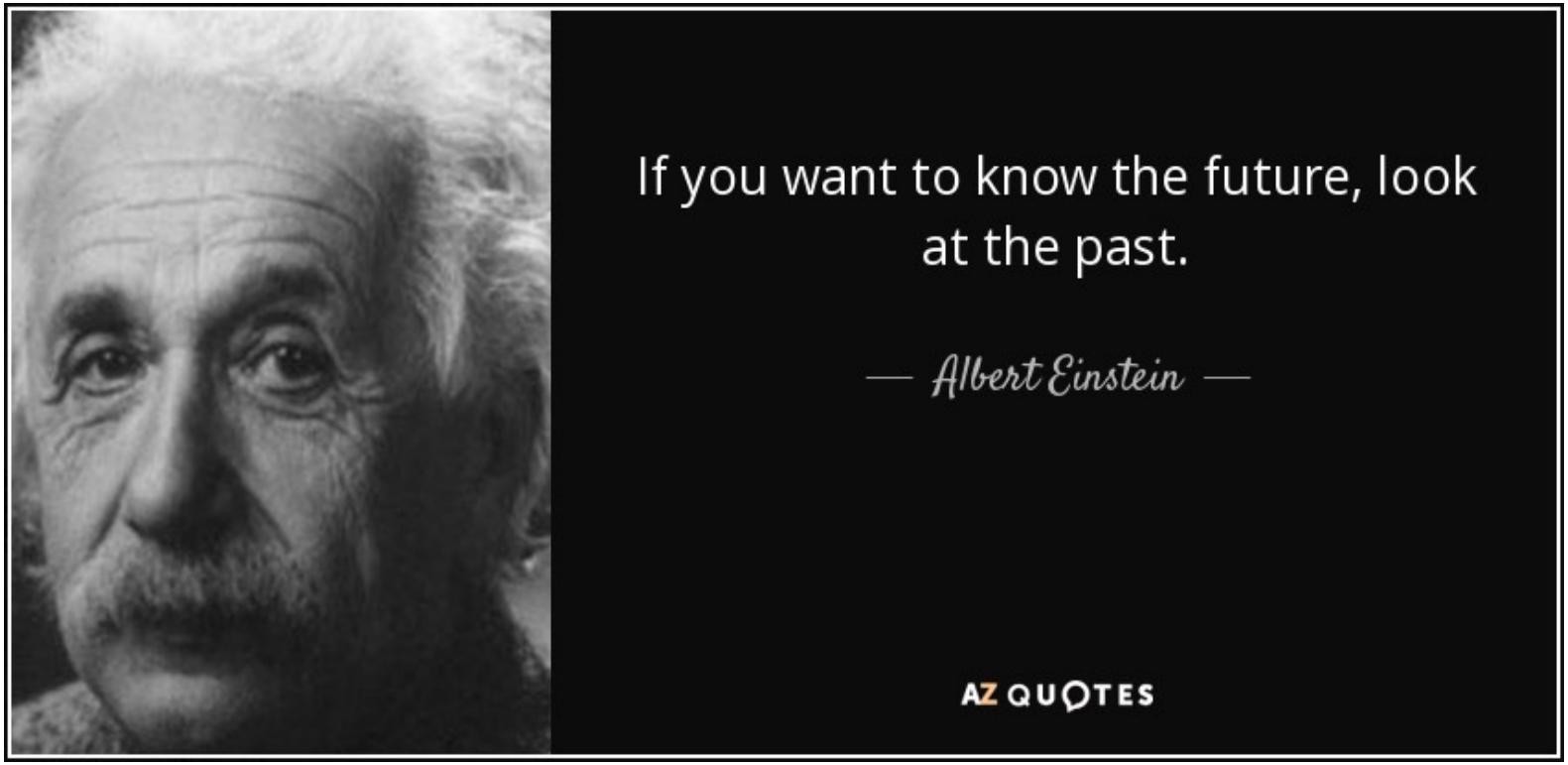
Before we start







Before we start



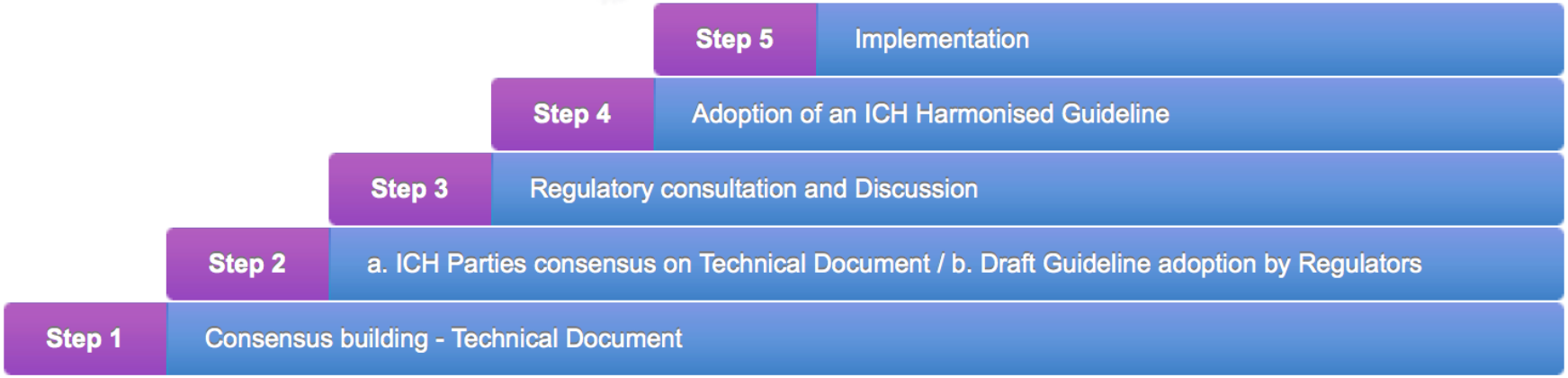
The road from 1 guidance to 1 guideline was paved with good intentions

- **2011** - @ EBF OS, asking regulators to connect and ICH getting involved - Which couldn't work as ICH requires more regions to have a guideline
- **2012** - Open letter from industry to regulators asking for harmonised (interpretation of) guidelines
- **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

The ICH Process

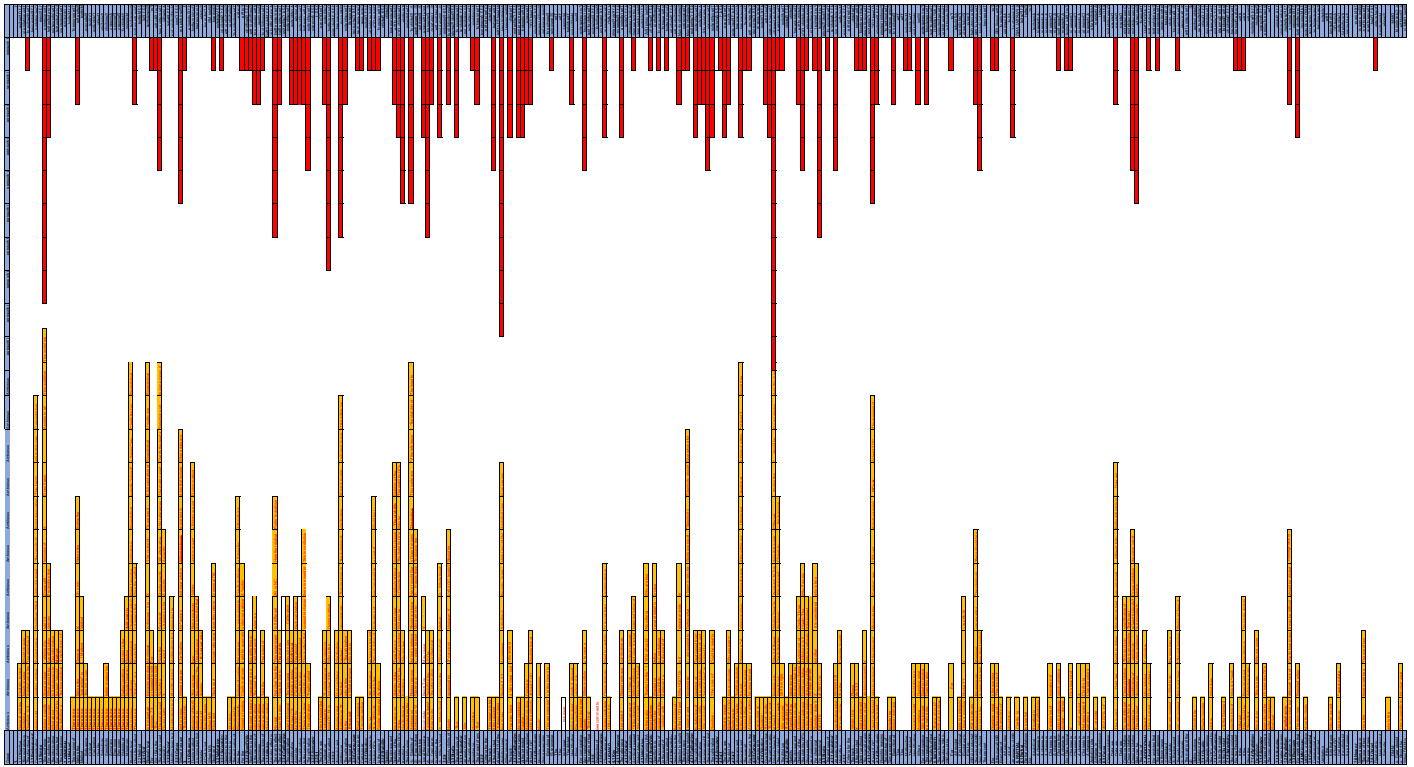


http://www.ich.org/products/process-of-harmonisation/formalproc.html

Public Consultation- 2019

disagree

ambiguous



	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

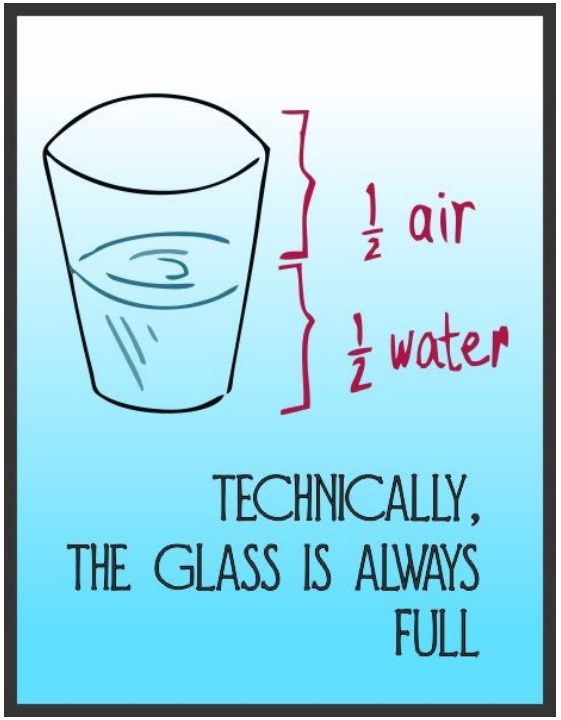
	Ambigous		
4.1.2 Critical Reagents	9		9
4.2 Validation	5		5
4.2.1 Specificity	12	2	14
4.2.2 Selectivity	14		14
4.2.3 Calibration Curve and Range	11	8	19
4.2.4 Accuracy and Precision		6	6
4.2.4.1 Preparation of Quality Control Samples	4	3	7
4.2.4.2 Evaluation of Accuracy and Precision	18	2	20
4.2.5 Carry-over	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

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:

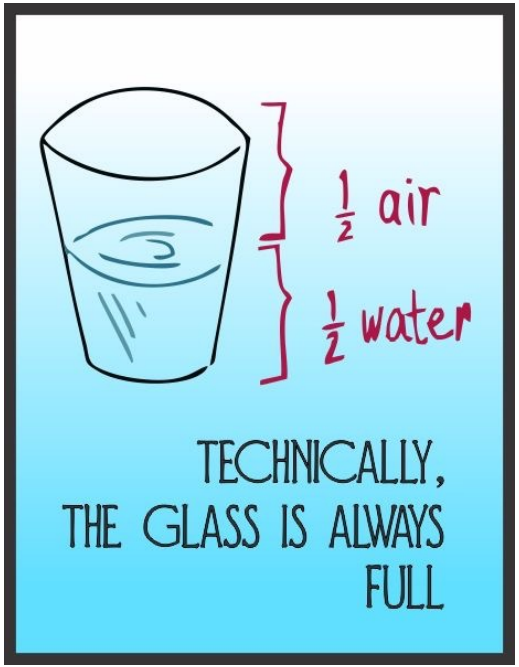
- The overall comment that the draft guideline is well written, which can only be improved for the final version;
- A separate section for LBA, removing the risk of 'chromatography creep', in other words, undue copying of requirements for chromatographic-specific assessments to LBA or cross-referencing 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.

In spite of the positive note…many of industries comments give during public consultation didn't condensate

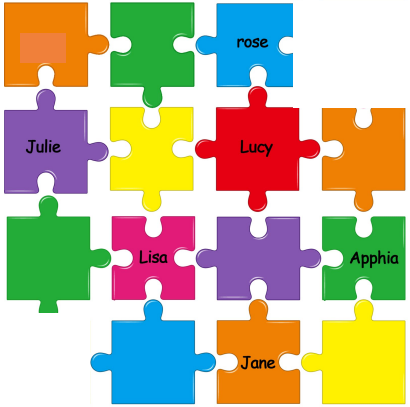


No or only partial uptake of industry comments to include science and experience based refinements

- 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…

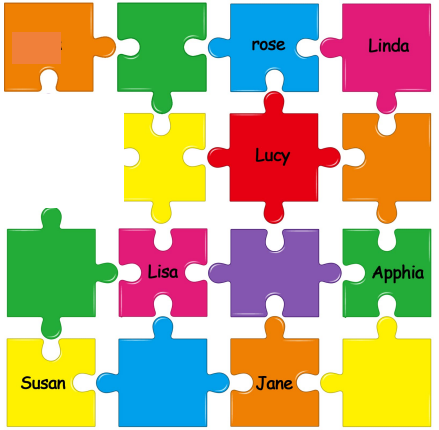


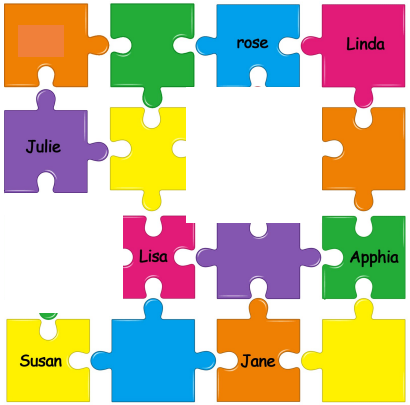
The end product ICH M10



HA 1

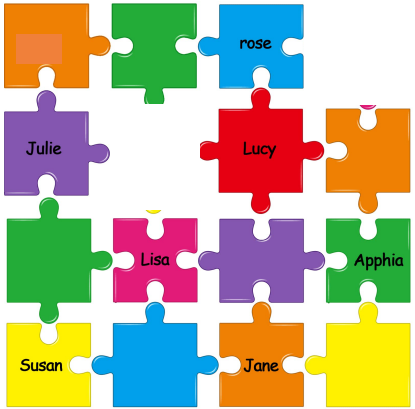
HA 2

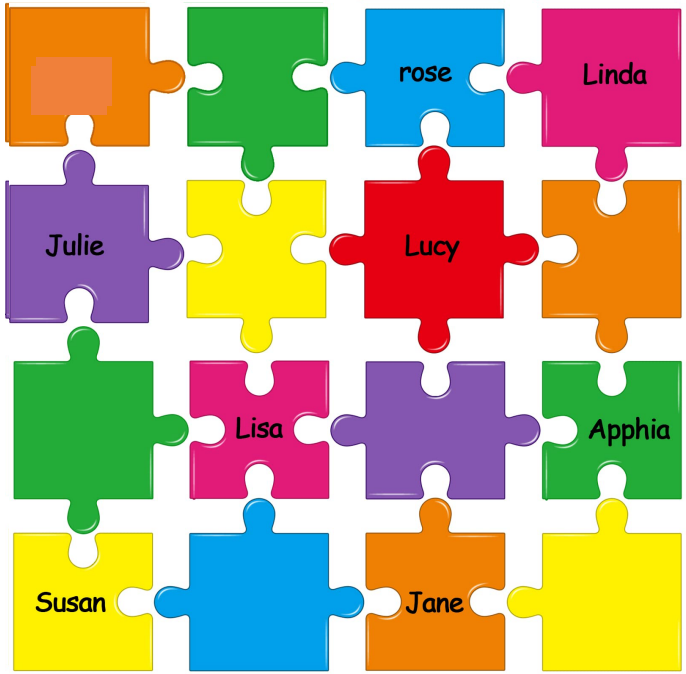




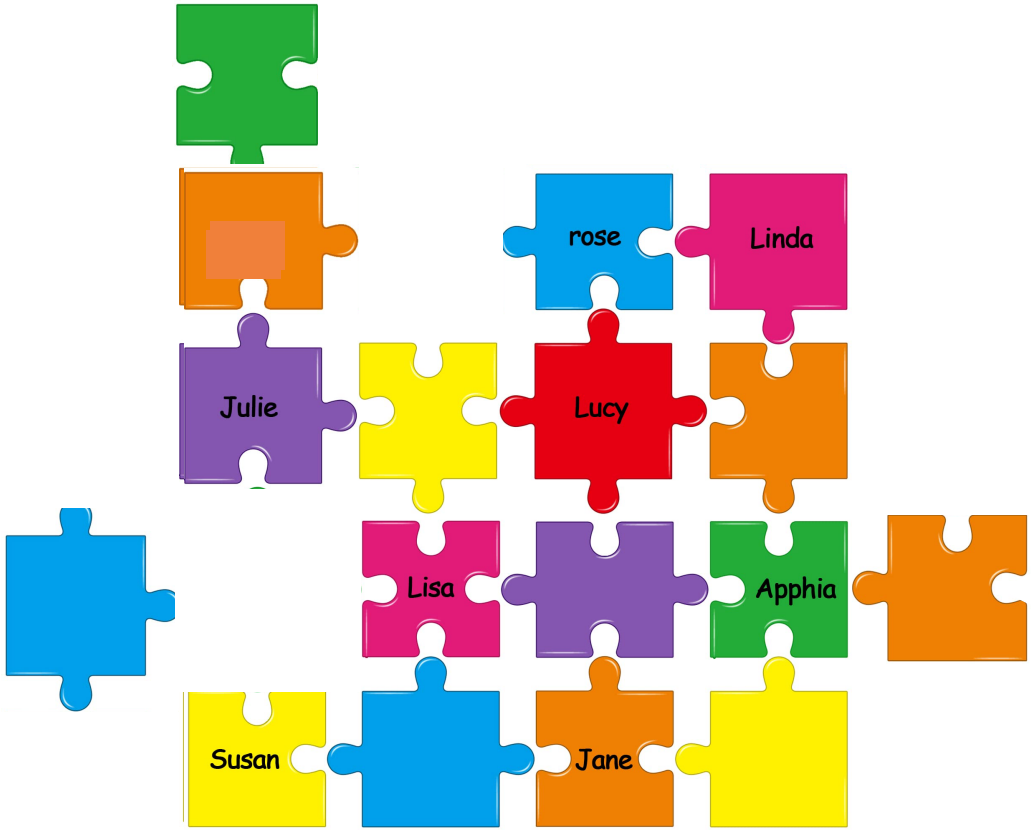
HA 3

HA 4



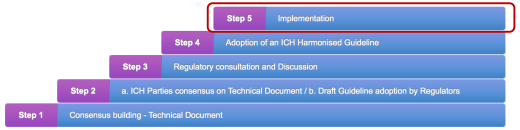


Harmonisation = sum of all?



Or…Harmonisation =
Sum of all plus or minus refinements based on public comments?

Are we there?



Industry working together and with regulators towards harmonised interpretation and implementation

A first readout in 2022

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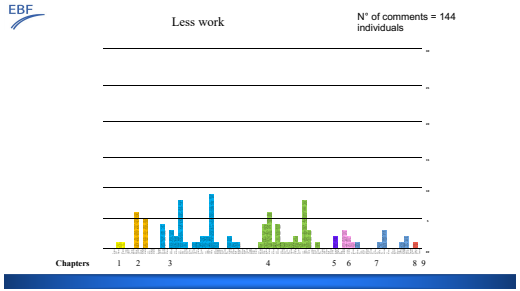

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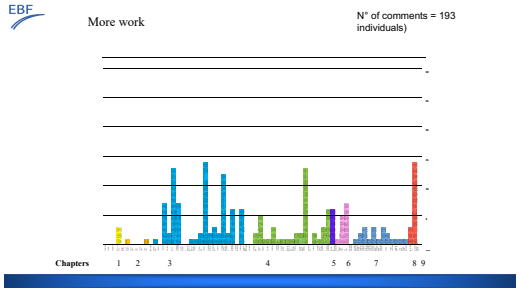

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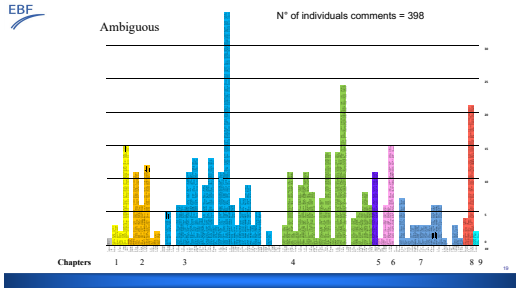

March 2023 – EBF Strategy Meeting

During ICH Sessions

1. Different interpretations
2. Different implementations
3. Disbelieve on some public consultation comments rejected
4. ICH M10 already at risk of becoming the next guideline with individual mis-, over-interpretation by industry, and differently applied by regulators

Decision:

- Need to stay connected as industry in this first phase of implementation to prevent bullet 1, 2 and 4
- Need to stay connected with HA to prevent above bullet 4 and communicate on bullet 3 for our future generations

Area of focus – why did we select these?

From a survey in the EBF Community,

- ca. 20 areas were identified as ‘at risk’ of creating confusion.
- For each, a mini-survey was issued to delegates and full EBF community
- From those responses, we decided on ‘round table’ and ‘plenary’

For round table

Round tables General Themes:

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

Logistic break – move to Chrom or LBA tables/rooms

Round tables CHROM Themes:

- hybrid assays in ICH M10 - our day-to-day practice
- Whole blood stability
- Analytes and matrices: focus on urine and metabolites
- 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

For plenary discussion

- Tissues
- Choosing the right regression model
- Matrix effect - special population, haemolysed and lipemic
- Carry over assessment during samples analysis (.....)
- Metabolites
- ISR

Continued at 16th OS

- 3R – surrogate matrix
- Xval
- Tissues
- GCP

Intended outcome

1. Hoping to answer most of your questions (likely utopia)
2. **Provide recommendations** for our industry on areas of ambiguity identified today
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 for today

- **The areas of disagreement**
  - Areas where we believe the guideline requires either too much work, there is no scientific basis, i.e. items not accepted from public consultation
  - Should we keep them on our radar (e.g. some ICH Guideline get revised..)? Or live with it and stop whining
- **Chapter 7:**
  - Not the bulk of our work - Requires separate discussion

Not for today

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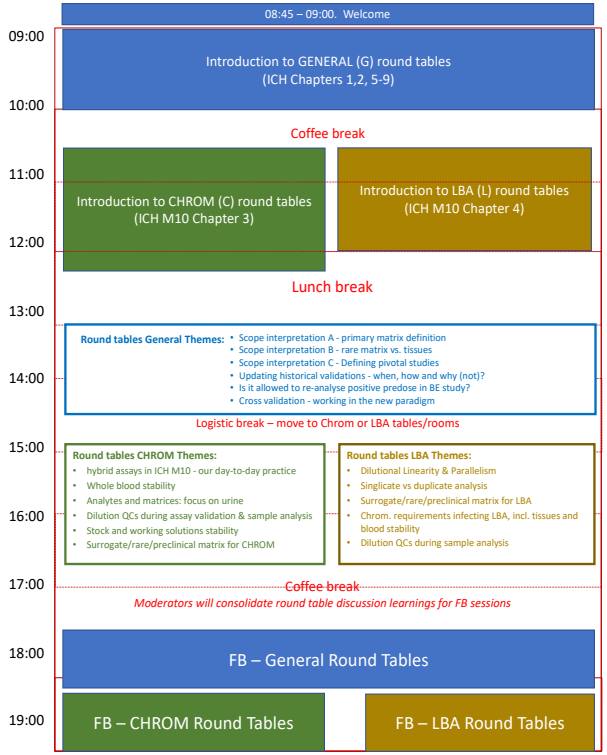
  - Areas where we believe the guideline requires either too much work, there is no scientific basis, i.e. items not accepted from public consultation
  - Should we keep them on our radar (e.g. some ICH Guideline get revised..)? Or live with it and stop whining
- **Chapter 7:**
  - Not the bulk of our work - Requires separate discussion
- **Chapter 8: documentation**
  - Significant increased workload - Requires separate discussion
- **Method development** (documentation) and
- **ADA** and **Biomarkers**
  - Not in scope

Our plans for today…a logistic nightmare



→ All together

→ Split in 2 – **C**HROM and **L**BA – ‘split ratio’ will decide on location for C and L breakouts

→ Split in 6 – **pre-assigned** – in Jupiter and mezzanine breakout space 1 to 6

→ Split in 5 (L) + 6 (C) – **free** – in Mezzanine and auditorium breakout space 1 to 5 (L) and 1 to 5 (C)

→ All together

→ Split in 2 – **C**HROM and **L**BA

Lunch break

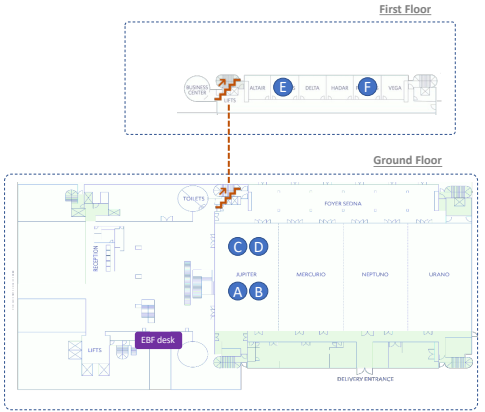
13:00

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

14:00

Logistic break – move to Chrom or LBA tables/rooms



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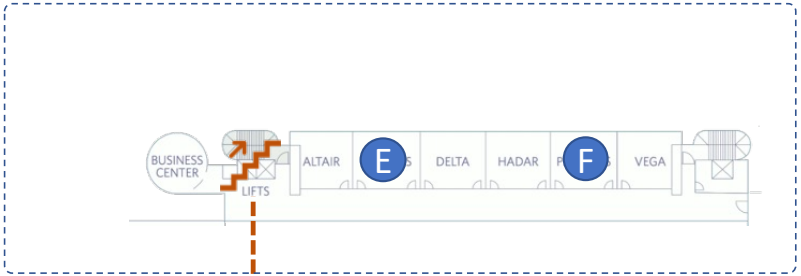
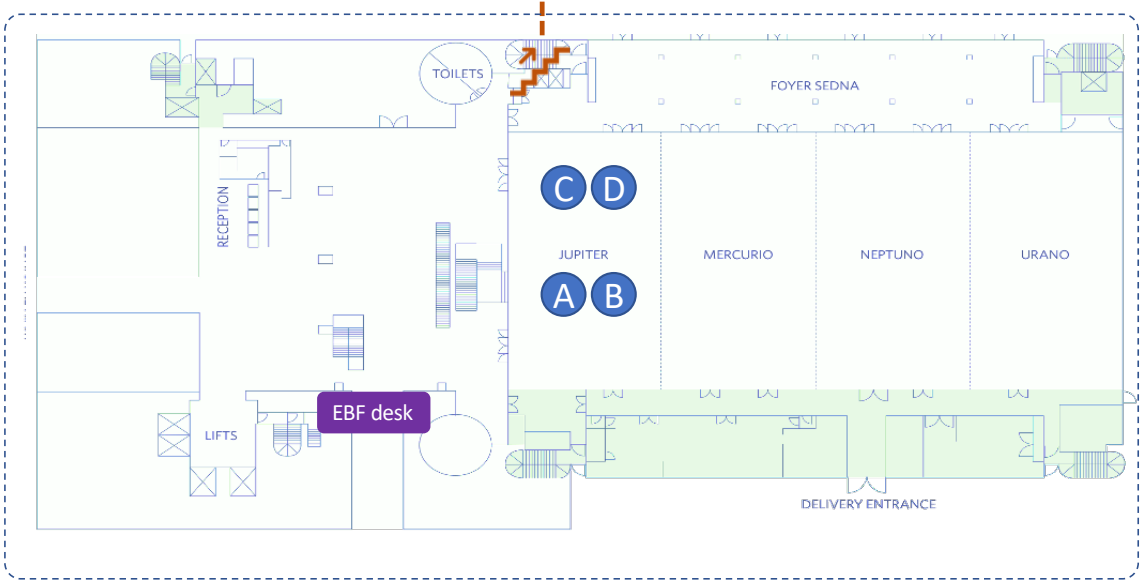
First Floor



Ground Floor



G Round tables - moderating order

1. Scope interpretation - primary matrix definition - (M: Enric Bertran/Delphine)
2. Scope interpretation - rare matrix vs. tissues - (M: Steve White/Salvatore)
3. Scope interpretation - Defining Pivotal studies definition - (M: Katja Zeiser/Michaela)
4. Updating historical validations - when, how and why (not)? - (M: Lee Goodwin/Robert)
5. Is it allowed to re-analyse positive predose in BE study? - (M: Tom Verhaeghe/Gwenda)
6. Cross validation - working in the new paradigm - (M: Tsvetelina Ivanova/Matthew Barfield)

In Jupiter
In Mezzanine

A	F	E	D	C	B
B	A	F	E	D	C
C	B	A	F	E	D
D	C	B	A	F	E
E	D	C	B	A	F
F	E	D	C	B	A

C Round tables - moderating order

1. Fitting hybrid assays in ICH M10 - day-to-day practice - (M: Luca Ferrari/Kamil Sklodowski)
2. Whole blood stability - (M: Jörg Faber/Enric Bertran)
3. Analytes and matrices: focus on urine - (M: Delphine Maux/Steve White)
4. Dilution QCs during assay validation & sample analysis - (M: Petra Struwe/Rob Wheller)
5. Stock and working solutions stability - (M: Tom Verhaeghe/Rebecca Sleigh)
6. Surrogate/rare/preclinical matrix for CHROM - (M: Stuart McDougall/Lee Goodwin)

@ Mezzanine

C1	C6	C5	C4	C3	C2
C2	C1	C6	C5	C4	C3
C3	C2	C1	C6	C5	C4
C4	C3	C2	C1	C6	C5
C5	C4	C3	C2	C1	C6
C6	C5	C4	C3	C2	C1

L Round tables - moderating order

1. Dilutional Linearity & Parallelism - (M: Robert Nelson/Katja Zeiser)
2. Singlicate vs duplicate analysis - (M: Richard Hughes/Gwenda Pynaert)
3. Surrogate/rare/preclinical matrix for LBA - (M: Gregor Jordan/Michaela Golob)
4. Chrom. infecting LBA, incl. tissues/blood stability - (M: Jo Goodman/Kyra Cowan)
5. Dilution QCs during sample analysis - (M: Salvatore Calogero/Anna Laurén)

@ Auditorium

L1	L5	L4	L3	L2
L2	L1	L5	L4	L3
L3	L2	L1	L5	L4
L4	L3	L2	L1	L5
L5	L4	L3	L2	L1

Logistic break – move to Chrom or LBA tables/rooms

15:00

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

16:00

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

17:00 Coffee break

C Round tables - moderating order

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@ Mezzanine

C1	C6	C5	C4	C3	C2
C2	C1	C6	C5	C4	C3
C3	C2	C1	C6	C5	C4
C4	C3	C2	C1	C6	C5
C5	C4	C3	C2	C1	C6
C6	C5	C4	C3	C2	C1

L Round tables - moderating order

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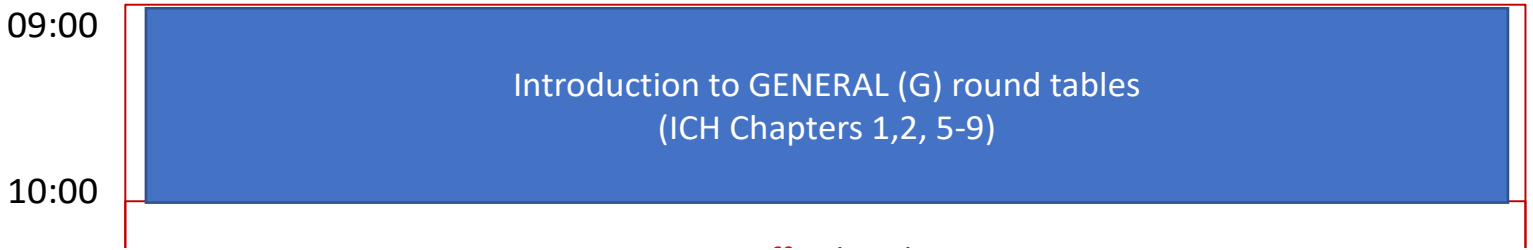
@ Auditorium

L1	L5	L4	L3	L2
L2	L1	L5	L4	L3
L3	L2	L1	L5	L4
L4	L3	L2	L1	L5
L5	L4	L3	L2	L1



Session 1: Setting the Scene - General items (Plenary)

Feedback from pre-meeting surveys on ICH M10 themes/chapters identified by the EBF and meeting delegates either as introduction to the afternoon GENERAL round tables or limited to session 1

09:00 - 09:15: Scope interpretation - matrix definition - pivotal studies (Philip Timmerman)
09:15 - 09:25: updating historical validations (Lee Goodwin)
09:25 - 09:35: Cross validation - working in the new paradigm (Tsvetelina Ivanova)
09:35 - 09:40: Is it allowed to re-analyse positive predose in BE study? (Tom Verhaeghe)
09:40 - 09:50: ISR, incl. case study rom regulatory Feedback (Stuart McDougall)
09:50 - 10:00: Feedback on General items from a recent JBF meeting on ICH M10