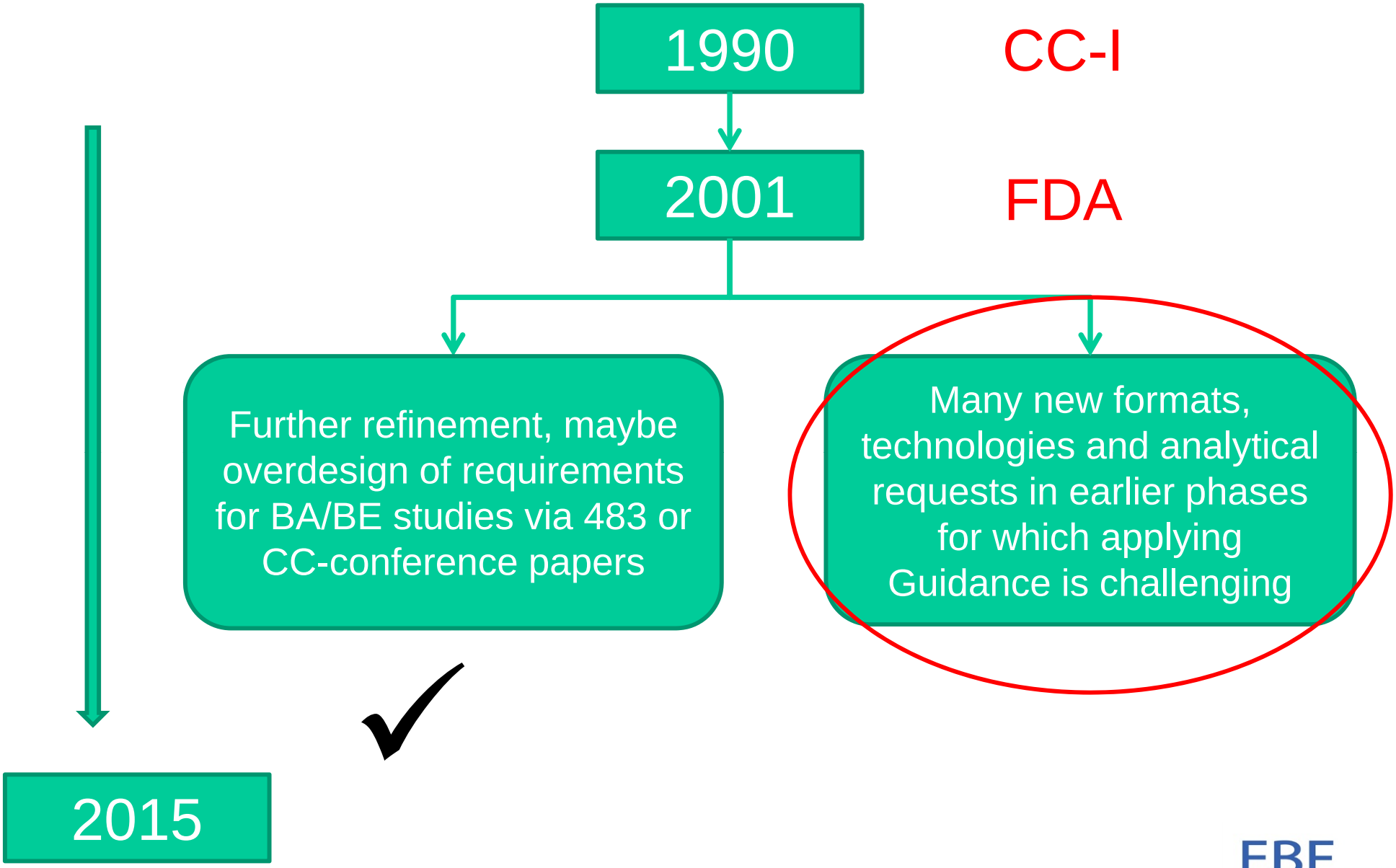
EBF Tiered approach final recommendation of Scientific Validation criteria

Philip Timmerman, on behalf of the EBF

8th EBF Open Symposium - 2015

The problem statement



Tiered approach – 1st appearance

Formally introduced in CC-III (2006) in relation to metabolites in early developmen

<<Characterization of UMMs should proceed using a flexible, " tiered " approach to bioanalytical methods validation. This tiered approach would allow metabolite screening studies to be performed in early drug development using bioanalytical methods with limited validation, with validation criteria increasing as a product moves into clinical trials. A tiered validation approach to metabolite determination would defer bioanalytical resource allocation to later in the drug development timeline when there is a greater likelihood of drug success. As a minimum, the specifics of this tiered validation process should be driven by scientifically appropriate criteria, established a priori >>

Workshop/Conference Report — Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays. CT Viswanathan et al., AAPS J. 2007 Mar; 9(1): E30–E42

Tiered approach – 1st appearance

- No clear definition or further context was given on waiver
- As a stand alone paragraph, it was not ‘ready for use’ as alternative approach, and hence not embraced
- Increased pressure of 483s/new Guidelines (EMA/Anvisa/…) took priority in BA community since 2010

So….Tiered approach?

Still…Early 2009

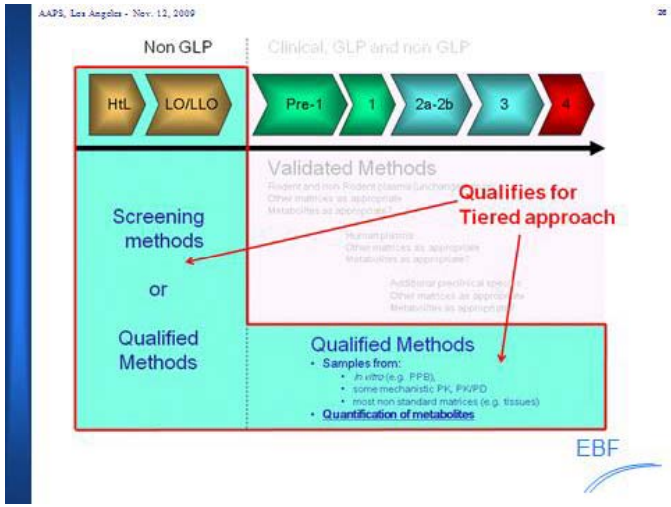
A Tiered Approach team was established in EBF

- Team members: Achim Freisleben (Merck), Ben Gordon (Servier), Morten Kall (Lundbeck), Philip Timmerman (JnJ), Richard Hucker (Pfizer), Sirpa Laakso (Orion)

- Survey on key elements of ‘qualified assays’ issued
  - EBF identified 3 tiers of quality: S-Q-V
  - 34 questions translating ‘*method validation criteria*’ into ‘*refined criteria for qualified assays*’
  - Plans to refine and publish in 2010

AAPS Annual Meeting 2009

- FB from EBF on their efforts to further develop the principles of tiered approach as guidance principle for many studies, with initial focus on MIST



- Presentation by Brian Booth on reflections to refine tiered approach into Low/Medium/High validations

But…

- Late 2009:
  - Discussions refocussed on ICH M3 (R2)
  - Team decided to publish on metabolite quantification first:
  - *Ref: Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum. Bioanalysis, July 2010, Vol. 2, No. 7, Pages 1185-1194*

- Mid 2010:
  - GBC formed
  - A2 tiered approach identified as team
  - EBF decided to postpone further publication plans and feed current results of EBF discussion into GBC

2009 - 2015, Overcoming the hurdles: building, brick by brick

Industry:

- Refinement of semantics of qualified/research/non-validated nomenclature into “scientific validation/regulatory validation” → *Ref. Tiered Approach revisited: introducing Stage-Appropriate or Assay-Appropriate Scientific Validation, Bioanalysis, Vol. 6, No. 5, Pages 599-604.*
- Frequently challenging the value of regulatory validation as checkbox for all studies.
- Identified areas where alternative approaches can be proposed
- Took a fresh look at how existing regulations should or should not impact day-to-day practice (GLP, ICH, GCP, CSV,..)

Health Authorities

- Seem to be supporting the evolution

From pie in the sky into practice - 1

Until 2014, discussion was mainly focussed in EU and in BA community only → Action

- Actively engage other regions
  - US/NA @ Joint DV-DMDG meeting – Jan 2015
  - Japan @ Discussion at JBF – March 2015
  - China @ CPSA China – April 2015
  - Initiated contact with ICH – Q1/2 2015
- Reach out to other stakeholders
  - Get perspective from QA, ClinPK, Toxicology (@ CPSA US, 2015)
  - Seek FB from regulators (@ EBF-2014 (David Jones, MHRA), @ AAPS Open Forum 2015 → FB Faye, next presentation)

From pie in the sky into practice - 2

- Identify what is still missing for the BA community
  - Manage fear
  - Show successes
  - Provide better tools to share the added value and the details of TA (*in the mean time re-worded into Scientific validation*) with stakeholders
    - Clear criteria → 2015 EBF Recommendation → next pages
    - Define areas of application (…..as a way to define areas on non-application) → 5 proposed areas
      - Tissue
      - Urine
      - Metabolites
      - Early *non pivotal* GLP
      - Early *non pivotal* Clinical

A value proposition

Can Industry / HA agree on an alternative approach for validation of assays in support of non-pivotal studies in early development.

At all times concentration data generated should be in scientific compliance with key bioanalytical quality criteria:

- documented evidence of accuracy, precision, selectivity, sensitivity, stability and reproducibility of the bioanalytical method to make the right decision in a study/project
- no cutting corners
- Allow scientific freedom to answer the questions asked
- Facilitates retrospective review of data quality to support other decisions if so required later in development

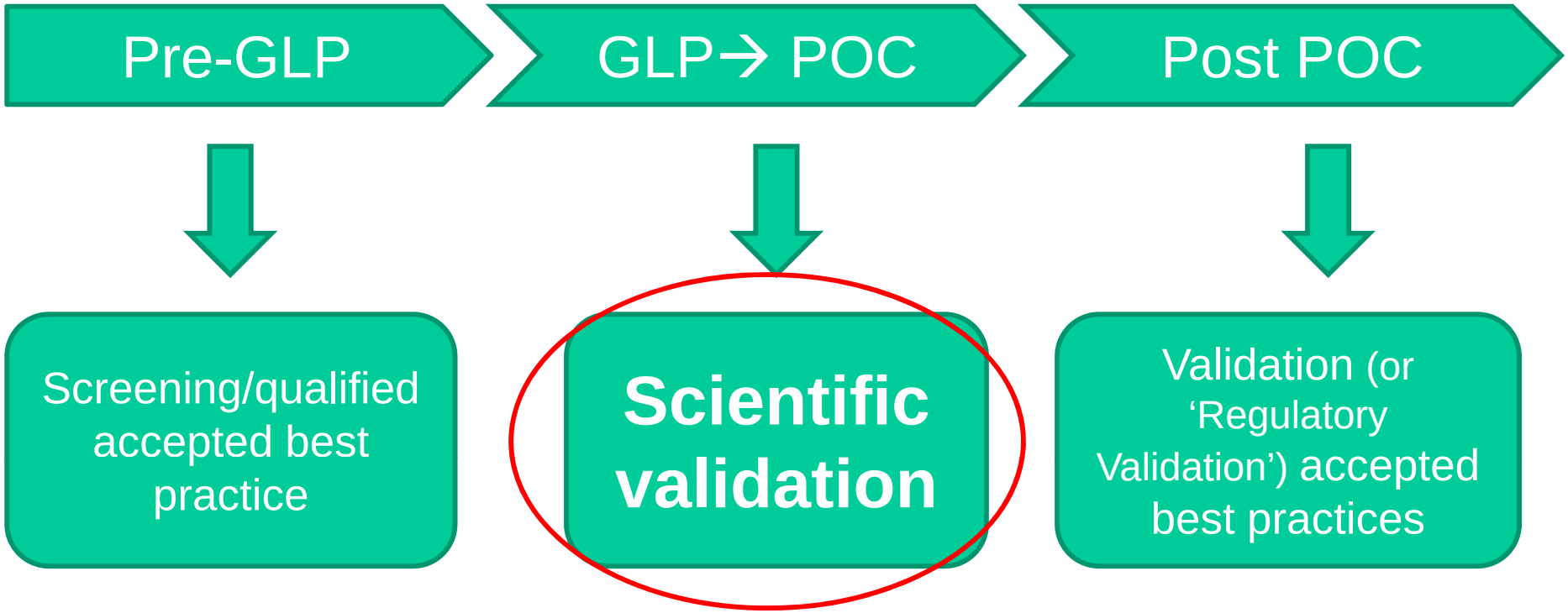
EBF recommendation

Reference:

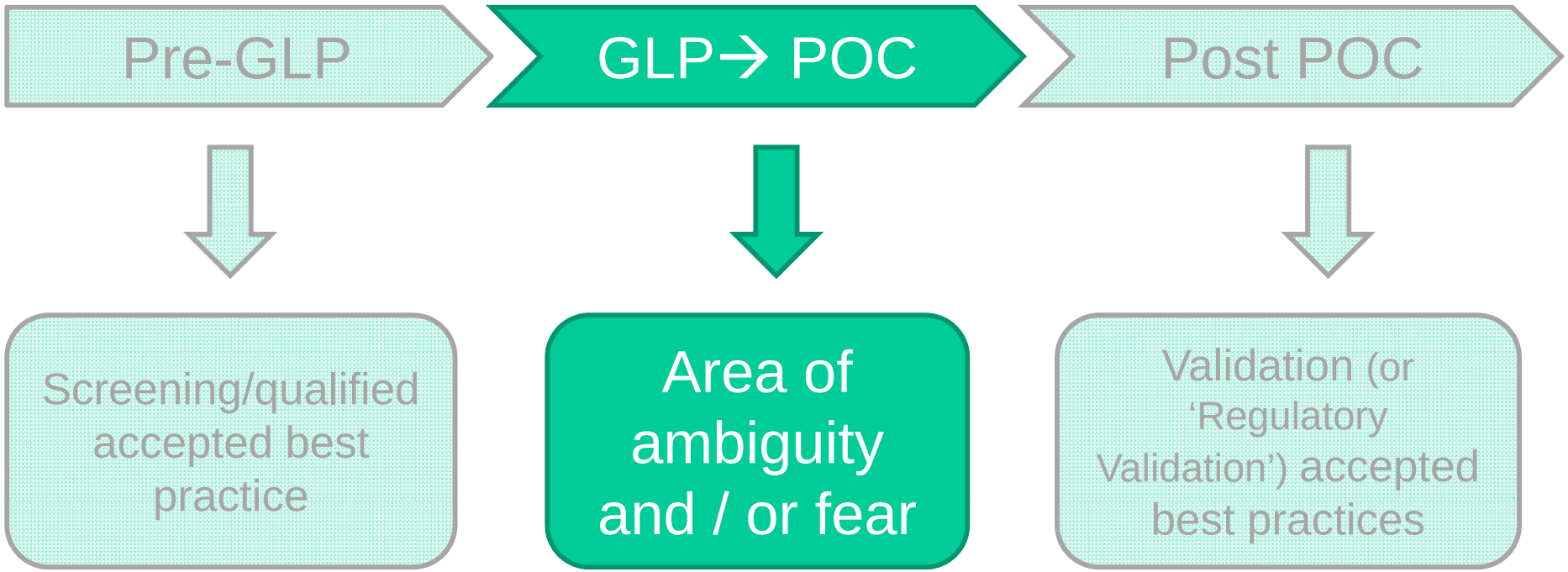
Tiered approach into practice - scientific validation for chromatography-based assays in early development: a recommendation from the European Bioanalysis Forum.

Bioanalysis, Vol. 7, No. 18, Pages 2387-2398

The focus of the recommendation



Being aware…..



Not all in industry are convinced of added value of scientific validation. Some are convinced but not supported by their environment. Their main concerns:

- fear for 483, more FB in AAPS/EBF/JBF survey
- Are we really saving resources? → see teaser

EBF recommendation - areas

Five areas where applying scientific validation can be or has proven to be a valid alternative for regulatory validation.

1. All **Urine** analysis – clinical/preclinical
2. All **tissue** homogenate analysis
3. All **metabolites** analysis prior to decision which metabolites require continued quantification using regulatory validation based on ICH(M3) and EMA-DDI:
4. A **selection of non-pivotal ED clinical studies:** focus on phase 0 and First into Man
5. All **(Non pivotal) Early GLP studies**: principles of scientific validation are compatible with GLP regulations

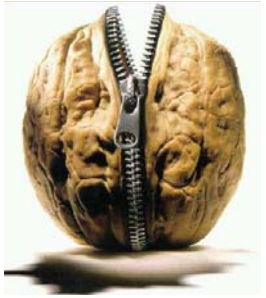
Recommended approach

- Not built on loose sand:
  - Builds on 25 y of experience with Guideline criteria
  - Refines them to the right balance of **scientific requirements**, **scientific freedom** and **resource requirements**

Recommended approach

- Tries to integrate discussions from many in industry
- Proposes clear, recognizable and refined criteria based on key elements of bioanalytical quality for harmonized day-to-day application.
- Focuses on the scientific challenge of study.
- Allows better use of resources, both in the execution and reporting
- Can withstand scientific scrutiny and regulatory review if needed
- Facilitates retrospective review of data quality to support other decisions than intended if so required later in development

In a Nut Shell



Scientific Validation

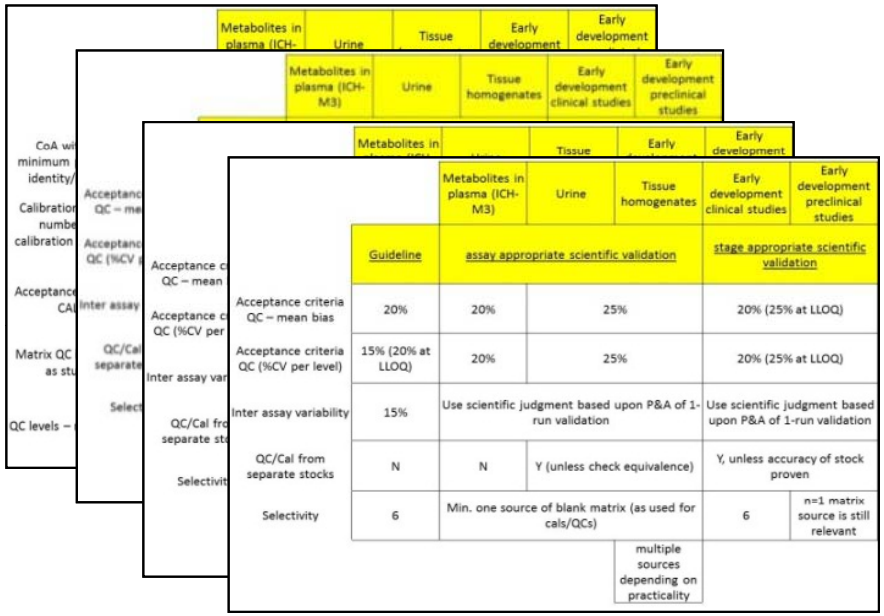
- Single run pre-study validation when it makes sense to do so
- Consider in-study validation for certain elements (e.g. stability, dilution integrity)
- Combine stability experiments to simplify
- Wider P&A criteria may be appropriate for the end point decision (e.g. 20%/25%)
- Increased focus on in-study study performance

Exclude experiments that make no scientific sense (based on industry experience...)

- extensive selectivity (incl. haemolysed/lipemic)
- co-meds, OTCs, FDC testing
- Recovery
- Replicates of pre-study
- matrix, LLOQ, ULOQ testing

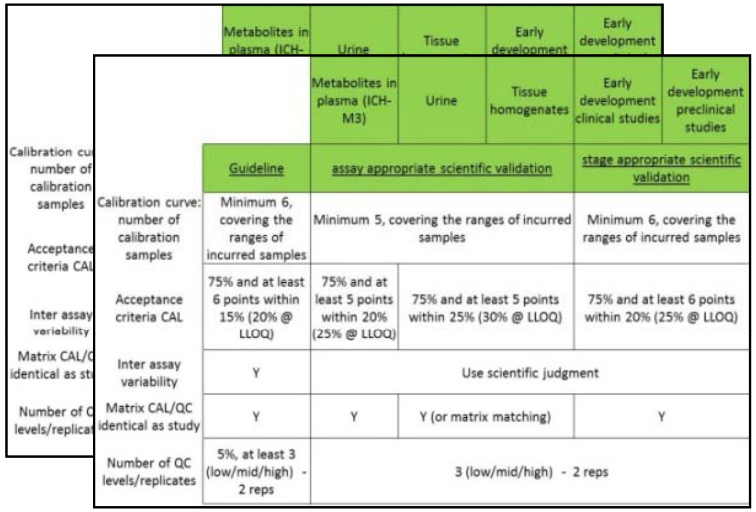
How does it work

Pre-study acceptance criteria



	Guideline	assay appropriate scientific validation		stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Acceptance criteria QC – mean bias	20%	20%	25%		20% (25% at LLOQ)	
Acceptance criteria QC (%CV per level)	15% (20% at LLOQ)	20%	25%		20% (25% at LLOQ)	
Inter assay variability	15%	Use scientific judgment based upon P&A of 1-run validation			Use scientific judgment based upon P&A of 1-run validation	
QC/Cal from separate stocks	N	N	Y (unless check equivalence)		Y, unless accuracy of stock proven	
Selectivity	6	Min. one source of blank matrix (as used for cals/QCs)			6	n=1 matrix source is still relevant
				multiple sources depending on practicality		

In-study acceptance criteria



	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Calibration curve: number of calibration samples	Minimum 6, covering the ranges of incurred samples	Minimum 5, covering the ranges of incurred samples			Minimum 6, covering the ranges of incurred samples	
Acceptance criteria CAL	75% and at least 6 points within 15% (20% @ LLOQ)	75% and at least 5 points within 20% (25% @ LLOQ)	75% and at least 5 points within 25% (30% @ LLOQ)		75% and at least 6 points within 20% (25% @ LLOQ)	
Inter assay variability	Y	Use scientific judgment				
Matrix CAL/QC identical as study	Y	Y	Y (or matrix matching)		Y	
Number of QC levels/replicates	5%, at least 3 (low/mid/high) - 2 reps	3 (low/mid/high) - 2 reps				

In detail: pre-study validation

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
CoA with at minimum proof of identity/purity	y	N	Y or use dosed batch			
Calibration curve: number of calibration samples	Minimum 6, covering range incurred samples	Minimum 5, covering range incurred samples			Minimum 6, covering range incurred samples	
Acceptance criteria CAL	75% and at least 5 points within 15% (20% @ LLOQ)	75% and at least 5 points within 20% (25% @ LLOQ)	75% and at least 5 points within 25% (30% @ LLOQ		75% and at least 6 points within 20% (25% @ LLOQ)	
Matrix QC identical as study	y	Y	Y (or matrix matching)		Y	
QC levels – replicates	4 (LLOQ/low/mid/high) – min. 5 reps	3 (low/mid/high) – min 3 reps			4 (LLOQ/low/mid/high) – min. 5 reps	

In detail: pre-study validation

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QC/Cal from separate stocks	N	N	Y (unless check equivalence)		Y, unless accuracy of stock proven	
Selectivity	6	Min. one source of blank matrix (as used for cals/QCs)			6	n=1 matrix source is still relevant
				multiple sources depending on practicality		

In detail: pre-study validation

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Extraction recovery	N	N				
Carryover	Y	In study				
Matrix effect	Y	N, assess within study runs via IS response				
Dilution integrity	Y	In study				
LLOQ	As defined by acceptable LLOQ CAL standard	As defined by acceptable LLOQ CAL standard				
Comed selectivity (in support of DDI studies)	Y	N				
Over the Counter (OTC) stability	N	N				
Fixed Dose Combination stability	anticipated	N				

In detail: pre-study validation

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Processed sample stability/reproducibility	Y	N			scientific judgment	
Stock solution stability	Y	20% - minimal assessment	If available previously		Y, unless prepared the same day.	
Bench top stability	Y	N			Consider combined stability experiment to cover unknown samples	
Sample stability for duration of storage	Y	Y (20%)	N			
F/T stability	Y (3 cycles)	N, consider ISS	Y (1 cycle)			
Sampling conditions	Y	N	Y, consider including container and adsorption	Y, Specify conditions, consider EBF paper		

In detail: pre-study validation

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Whole blood stability	N	N, unless for known problem scaffolds	n/a		N, unless for known problem scaffolds [22]	
Hemolytic	N (Y, EMA)	N	n/a		N	
Hyperlipidemic	N (Y, EMA)	N	n/a		N	
Validation plan/protocol	Y (SOP or protocol)	at minimum SOP or short protocol summarizing scientific parameters to be tested				
Validation report	Y (Extensive)	At minimum a document summarizing scientific parameters tested				
Misc.		Consider longer run time instead of specificity experiment	# = during meth dev. Non Specific Binding / sampling conditions & aliquoting	Calibration matrix may be a surrogate		

In detail: in-study acceptance criteria

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
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Inter assay variability	Y	Use scientific judgment				
Matrix CAL/QC identical as study	Y	Y	Y (or matrix matching)		Y	
Number of QC levels/replicates	5%, at least 3 (low/mid/high) - 2 reps	3 (low/mid/high) - 2 reps				

In detail: in-study acceptance criteria

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
QC run acceptance (bias)	4-6-15, ½ of QC samples per level	4-6-20, ½ of QC samples per level	4-6-25, ½ of QC samples per level		4-6-20, ½ of QC samples per level	
Acceptance criteria QC – mean bias (for n>1 batch study sizes)	15%	20%	25%		20%	
ISR	EMA paper	N			Y, once	Y, once per species
Carry over	Y	Y, Assess impact				
Dilution integrity (may be QC)	Y	If required				
IS variability with criteria	Y	Scientific judgment			Refer to EBF paper	
Hemolytic	N (Y, EMA)	N	n/a		N, is part of IS tracking,– interrogate anomalous results	
					observation recorded by clinical Unit	

In detail: in-study acceptance criteria

	Guideline	assay appropriate scientific validation			stage appropriate scientific validation	
		Metabolites in plasma (ICH-M3)	Urine	Tissue homogenates	Early development clinical studies	Early development preclinical studies
Hyperlipidemic	N (Y, EMA)	N	n/a		N, is part of IS tracking	n/a
Anomalous result repeats	Y	N			Yes, as requested in duplicate	
Extrapolation beyond curve	N	scientifically based extrapolation justified				
Misc.			Selectivity by dilution of incurred samples	Protocol & report QA'd if claiming GLP		
Repeat if drug in placebo/control	Y				Yes in duplicate	

In-study validation as part of study sample analysis: if only in-study validation is performed (no pre-validation), include (with predefine acceptance criteria) those relevant missing parameters from scientific validation above mentioned (e.g. relevant stability)

Documentation/reporting

Keep it brief and relevant

- Include reference to Study Number, Protocol or SOP
  - signed by sponsor ???
- Template scope of scientific validation to frame the context
  - maybe with reference to EBF recommendation paper or other?
- Body:
  - (reference to) assay description
  - short summary table providing evidence of assay performance, range and stability
  - More detail in appendix as required or as per company desire (e.g. sponsor-vendor relationship)
- No need to include chromatograms
- No GLP claim on validation
- Signature of study responsible person

Finally…..“4-6-20” vs. “4-6-15”

Is the anxiety around more liberal acceptance criteria a valid worry or are we over-reacting?

- For SMOL BA current practice = 4-6-15, but most studies come in @ better acc&prec.
- In practice, also with more liberal criteria, most studies will be coming in at better acc&prec, than 4-6-20, and likely even 4-6-15.
- Having more pre-agreed liberal acceptance criteria, will prevent undue repeat for those studies which fall outside (too) stringent criteria for the purpose of the study

A teaser


Why all this effort for my study? Once my compound progresses, I need to redo the validation. So, I am doubling my workload

Let's make the math…for what's is worth

Using the attrition rate reported by the Tufts CSDD 2014 model, refined to match BA-attrition:

- preGLP → 250 compounds
- GLP → 25 compounds
- FIM → 12 compounds
- > MIST → 5 compounds
- POC → 2 compounds
- > POC → 1 compound

Current approach:

To get 1 compound to the market we need 3720 validation days*

- 319 regulatory validations

Alternative approach

To get 1 compound to the market we need 1393 validation days*

- 29 regulatory validations
- 209 scientific validations

** assumptions: 12/5 days for RV/SV, 1 metabolite/project from GLP onwards*

				Active					Metabolite					Urine					Tissue				
	Cpds	# RV	#SV	R	D	M	Ra	H	R	D	M	Ra	H	R	D	M	Ra	H	R	D	M	Ra	H
preGLP	250																						
GLP	25	250		1	1	1			1	1	1	1							3				
FIM	12	36						1					1					1					
> MIST	5	20					1	1					1					1					
POC	2	2						1															
> POC	1	2				1		1															
		310	0																				
		3720																					

				Active					Metabolite					Urine					Tissue				
	Cpds	# RV	#SV	R	D	M	Ra	H	R	D	M	Ra	H	R	D	M	Ra	H	R	D	M	Ra	H
preGLP	250																						
GLP	25		125	1	1														3				
FIM	12		84					1	1	1	1	1	1					1					
> MIST	5	25		1	1		1	1					1										
POC	2	2						1															
> POC	1	2				1		1															
		29	209																				
		348	1045																				
		1393																					

assumption

attrition rate cfr. Tufts model CSDD 2014 model

1 Regulatory full validation = 12 days

1 scientific validation = 5 days for plasma/urine/tissue/metabolites

Next steps

Recommendation

- can serve as a toolbox for the bioanalyst
- It is not intended as an endpoint of the discussion.
  - E.g. the CC-I, II, III,…. were no endpoints either.
  - As science progresses and experience builds, proposals can be a step stone for future refinements
- Continued need for intensified global discussion and feedback from the regulatory agencies:
  - A cross-regional team (EBF, AAPS/IQ, JBF) is being formed to take the discussion further
  - consideration an EBF/AAPS/JBF organized ‘CC-VII’ type meeting
  - Further discussions on how to approach ICH

Panel discussion

Questions to focus on:

1. What is needed to further implement scientific validation in the areas proposed?
2. Are there other areas where the principles of tiered approach add value?

Rome wasn’t built in a day, but they built it.

after John Heywood

Acknowledgements

Many friends and colleagues in industry, with special thanks to

- AAPS BFG
- DV-DMDG
- CPSA
- EBF
- GBC
- JBF

Publications

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