Issues in Industry with Current Guidance

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on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

What should be the scope of the guideline and why.

including discussion on studies, development phases or analytes in/out of scope

The Altis Grand Hotel Lisbon,
Portugal September 24-26, 2017

Problem statement

Scope or area of expected adherence to Guideline/Guidance has broadened over the years resulting in increased cost no added value for the patient and Scientific and technological development is stifled

- Increasing areas where bioanalytical support is required
  - Earlier phases of development
  - Different matrices
  - Different analytes (metabolites, BM…)
- New technologies being applied in PK studies
- (Increased) attrition in drug development
- Increased outsourcing in earlier phases of development
  - No agreed scientific standard for bioanalytical methods except guidance/guideline

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ICH M10 Industry proposal to EFPIA

- Early 2016, AAPS/EBF/JBF issued a proposal for harmonization to EFPIA, to submit to ICH
- 3 areas of focus
  - Harmonization of regional Guidance/Guideline into one global guideline *
  - Remove areas of ambiguity of implementation (by industry) and interpretation (by industry and HA)
  - Definition of area of application (i.e. scope) of the guideline (and as such providing room for alternative approaches in areas out of scope)
- Proposal not submitted to ICH in view of similar proposal from MHLW (albeit with focus only on *)

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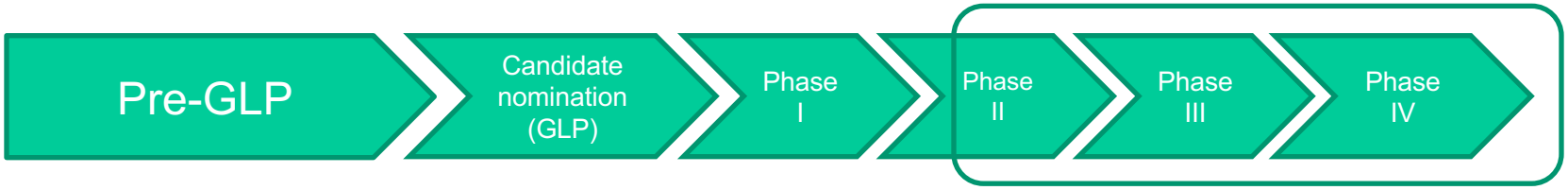
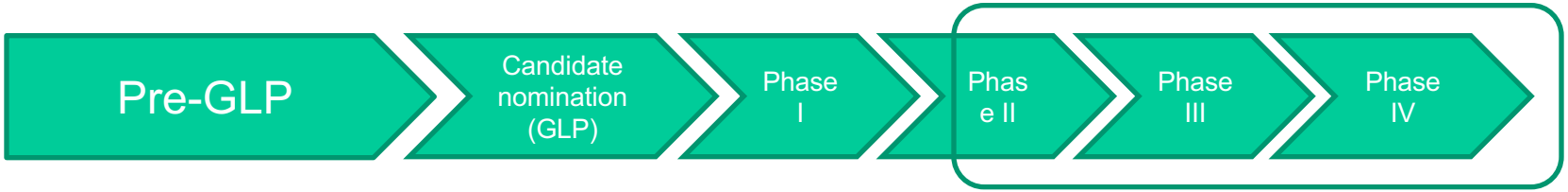
Scope of Guideline/Guidance: an historic perspective

1990: CC-I – scope of the scientific discussion



1990: workload in the bioanalytical lab

1990-2000: area of application of 1992 Shah-paper*



** Vinod P. Shah, Kamal K. Midha, Shrikant Dighe, Iain J. McGilveray, Jerome P. Skelly, et.al. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. Pharmaceutical Research 9(4), 588-592 (1992)*

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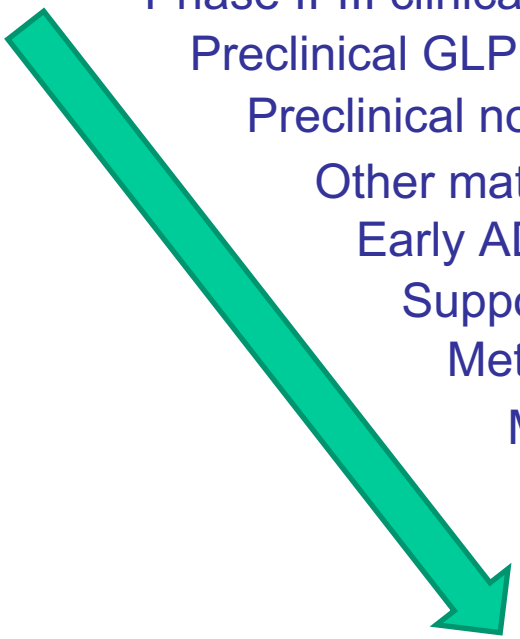
Workload: a changing landscape

<1990

Phase I clinical study support of dosed drug



Phase II-III clinical study support of dosed drug

Preclinical GLP

Preclinical nonGLP

Other matrices – preclinical/clinical

Early ADME in vivo PK

Support of in vitro assays

Metabolites in late development

Metabolites in early development

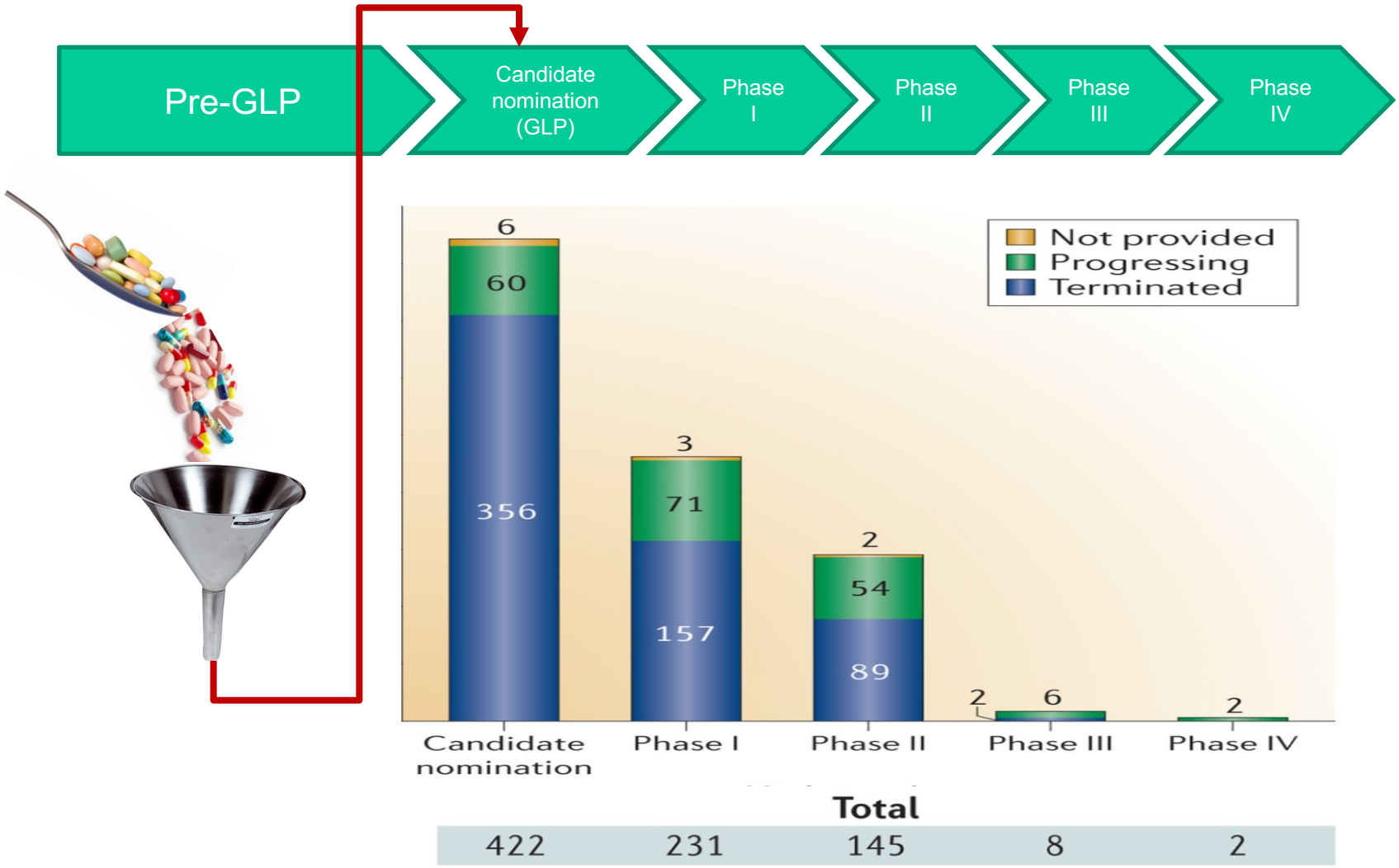
Biomarkers

Bedside monitoring

New technologies

today

Attrition



From: An analysis of the attrition of drug candidates from four major pharmaceutical companies
www.nature.com/reviews/drugdisc, JULY 2015 | VOLUME 14

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Industry is asking for an alternative standard in non-pivotal studies

- Not a new discussion
  - CC-III → Focussed on analysis of metabolites (Tiered Approach)
  - AAPS-2009 → Broadened the discussion into studies and matrices earlier phases of development, other matrices
  - Principles confirmed by regulators at other occasions across the globe
- Slow uptake by industry
  - No common standard
    - Common practice in internal Pharma labs
    - Difficult to implement in CRO environment

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So the theme of today is not new

But the challenge is rapidly increasing:

- Increased focus on regulations
- Increased risk averseness of our industry
- Increased outsourcing, fear of 483

➔ Industry tends to over-validate, even in absence of any 483 on the studies in scope of tiered approach

An additional risk that regulators, looking into industry, get the idea that all this rigor is required:

➔ 'Industry Self-inflicted Regulatory creep' *(ISRc)….we often blame regulators, but are we not raising the bar ourselves?*

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Increased outsourcing

Pharma – CRO expectations

- For many, the guidance/guideline seems to work well, also as template to stakeholders (CRO-Pharma, Mgmt, (pre(clin)-PK scientist)
- Performing work in the regulated validated arena is a strong selling proposition
- Today's absence of a financial model to support other than validated assays continues to lead overspending of bioanalytical resources in earlier phases of development.

Client / Stakeholders expectations

- Not comfortable when stepping out of the regulated validated arena.
- Stakeholder are often unfamiliar with the (resource) consequences of blindly applying the Guidance, and/or the missed scientific opportunities of (or even existence of) an alternative.

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Outsourcing in the nineties

Outsourcing in the early-late 2000's

Outsourcing in the early-late 2010's

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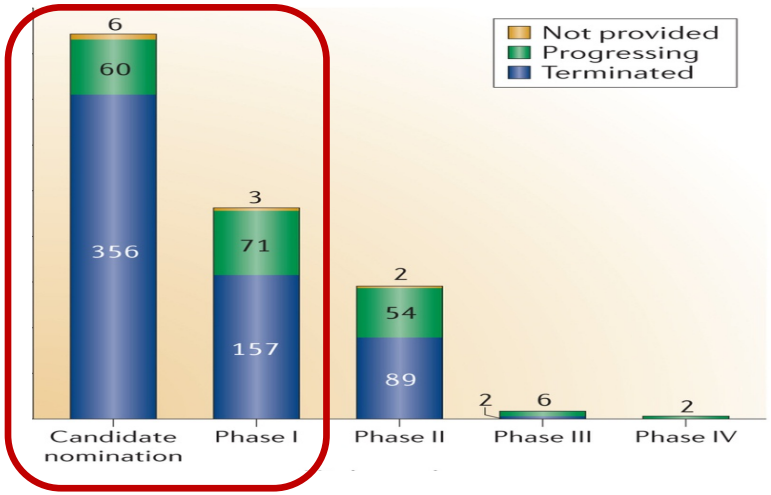
Pre-GLP → Candidate nomination (GLP) → Phase I → Phase II → Phase III → Phase IV

In scope of Guideline

In scope of alternative approach, and universally applied or agreed (screening assays)

(partially) in scope of alternative approach, but not universally applied or agreed (principles of TA/SV)



We have an opportunity, maybe even an obligation to the patient and future generations of bioanalytical scientists, to further develop the principles of tiered approach

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Hence….

- If compliant with GLP or scientific principles, there should be no issue to use alternative validation practices in earlier stages of development, e.g. validations which covers both the scientific requirements as well as the GLP requirements, but allows more scientific freedom and burns less resources.

- This gives the opportunity to optimize science and resources and stay compliant with the principles of bioanalytical data quality.

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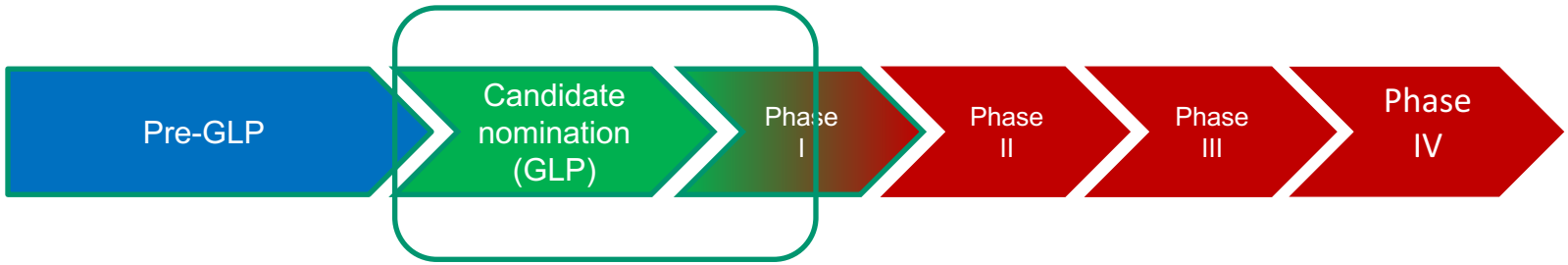

(partially) in scope of alternative approach, but not universally applied or agreed (principles of TA/SV)

Examples of studies currently analyzed by many using full validation, but in scope for a leaner approach allowing flexibility or increased scientific focus

- Early TK, early PK, SAD/MAD, early metabolite quantification (pre ICH M3(R2)), tissue analysis, urine analysis

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"Tiered Approach" versus "Scientific Validation"

The feeling in industry remains: if not Validated, it's not Valid

Validated

Tiered approach

'Tiered approach' evokes: in the next tier, data will be of higher quality, so just give me this highest tier

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SV: Contextualize the definitions

Validation → regulatory validation:

- *Assay validations to provide scientifically accurate, reproducible and reconstructable concentration data to allow valid decision making for the intended purpose of the study* and comply with regulated BA standards as specified by Health Authority (HA) guidance documents

Scientific validation:

- *Assay validations to provide scientifically accurate, reproducible and reconstructable concentration data to allow valid decision making for the intended purpose of the study* and can withstand independent review - including scientific review from regulators if so required - although not applying all elements specified by HA guidance documents.

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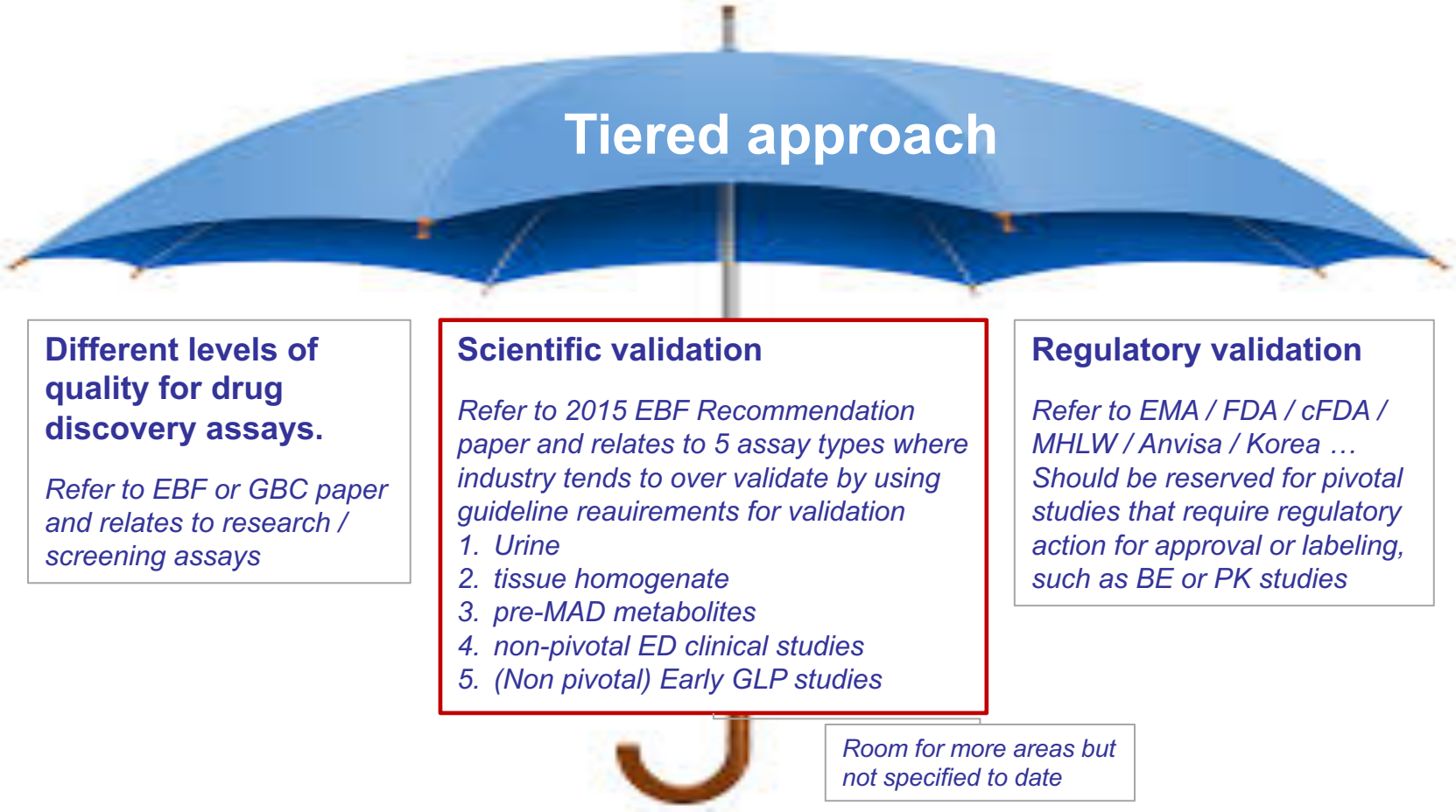
Regulatory validation = science

EBF never denied the scientific principles of regulatory validation, and explicitly highlighted the scientific value and foundation of the different Guidance/guidelines

- Excerpt from the EBF recommendation paper: *" We cannot emphasize strongly enough that by introducing the terminology of scientific validation for the five categories mentioned, the EBF does not intend to undermine the scientific foundations of Regulatory Guidance workflows applied for bioanalytical support in later stages of development or for all pivotal studies that require regulatory action for approval or labelling, such as BE or PK studies. In fact, these Guidance were built on the solid scientific experience for later stage clinical studies for which they were initially intended by many experts from industry and regulators. As highlighted earlier, they may not necessarily fit the current drug development needs in areas outside late stage clinical.*

Fit for purpose = general term, often used in BM assays



Different levels of quality for drug discovery assays.

Refer to EBF or GBC paper and relates to research / screening assays

Scientific validation

Refer to 2015 EBF Recommendation paper and relates to 5 assay types where industry tends to over validate by using guideline reauirements for validation

1. *Urine*
2. *tissue homogenate*
3. *pre-MAD metabolites*
4. *non-pivotal ED clinical studies*
5. *(Non pivotal) Early GLP studies*

Room for more areas but not specified to date

Regulatory validation

Refer to EMA / FDA / cFDA / MHLW / Anvisa / Korea … Should be reserved for pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies

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SV: A value proposition

Not built on lose sand, but on 25+ y of experience by an expert community committed to deliver quality to the patient.

Principles of SV:

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
- Documentation should facilitate retrospective review to support other decisions if so required later in development

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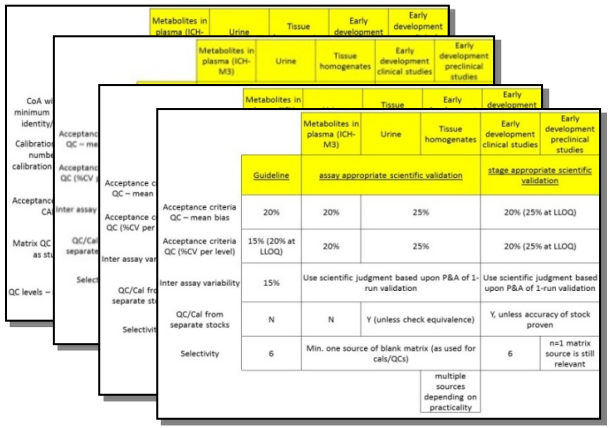
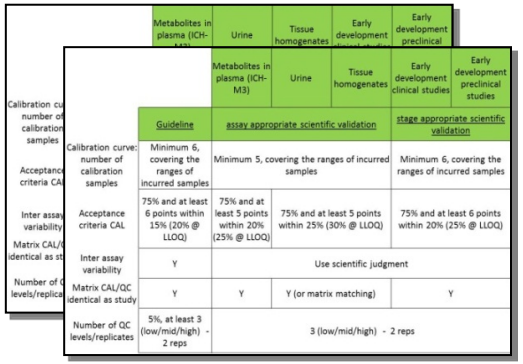
In practice

Pre-study validation
Predefined 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 validation
Predefined 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				

if only in-study validation is performed, include (with predefined acceptance criteria) relevant missing parameters from pre-study scientific validation

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SV vs. ICH M10 Guideline

- No request from industry to put details of execution of SV or alternative approaches into a guideline
  - Scientific content should be industry's responsibility
- We do ask to
  - clarify scope of the guideline
  - provide transparent waiver for non-pivotal studies to be supported using alternative approaches (CC-III report, draft FDA Guidance and MHLW-2012 guideline make a good start)
- We invite the industry to come together on what alternative (leaner and resource friendly) standards look like
  - EBF recommendation and/oer GBC paper can be a good starting point

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….Let's reflect on acceptance criteria

- What should drive the acceptance criteria?
  - ability to make robust decisions on safe and efficacious dosing of patients, independent from technology, mindful of resource requirements
- What is driving the acceptance criteria today?
  - ability to make robust decisions on safe and efficacious dosing of patients
  - Technology
- What is the accuracy really needed?
  - Reflect on/rethink the requirements on accuracy / precision
  - Be mindful of science, 25y of experience, ability to include new technologies, cost/resources in bioanalysis

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PK assays

- Can we move away from Chromatography, Ligand binding, hybrid….as the basis of bioanalytical acceptance criteria?
  - Certainly with so-called hybrid assays we create and environment of acceptance criteria ‘à-la-carte’
- Should we not use decisions made for PK-assays as the basis as the basis of bioanalytical acceptance criteria?
  - Same decision made = same criteria on data quality

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Conclusion

1. Defining and agreeing on the scope of the guidance may be the most important goal of the ICH M10 exercise –
   - Studies in scope of Guideline should be limited to later stage studies with labelling and/or safety impact in regulatory submission/decision
   - *More details: see next recommendation slide*
2. There is value of harmonizing acceptance criteria to reflect the decisions made = PK, and not based on the technology used
   - *More details: later in this meeting*
3. SV/TA: Industry should take responsibility to unite around science based, more flexible and less resource intensive alternative practices and criteria in earlier stages of development

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Proposal for recommendation - 1

- It is important to understand the background of the scope discussion and consequences of not getting it right
- There is no desire to include specific guideline on alternative validation approaches in ICH M10
- There is no desire to to include list of studies or specify development phase in scope of alternative validation approaches in ICH M10
- Proposal to include wordings in the guideline to allow industry to take ownership of the scientific discussion for studies not in scope

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Proposal for recommendation - 2

- In scope for ICH M10:
  - Quantitative analysis of primary PK analyte
  - Primary matrix
  - The stage of drug development and/or the type of study analyzed should be considered in the scope statements to ensure more scientific freedom at earlier stages of drug development
- Special considerations:
  - Validations for pre-clinical studies may require only a subset of experiments required for clinical (BE-type) PK studies
  - Validation for SAD/MAD studies should be allowed more scientific freedom.
- Out of scope for ICH M10:
  - Urine and tissue analyses, unless these are the primary matrices used to characterize PK
  - Early metabolite evaluations (pre- ICH M3 (R2) or 'MIST'

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Acknowledgment

- EBF community
- AAPS/JBF bioanalytical leadership
- Going forward: continued leadership of global scientific BA community

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Contact: info@europeanbioanalysisforum.eu

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