18th EBF Open Symposium

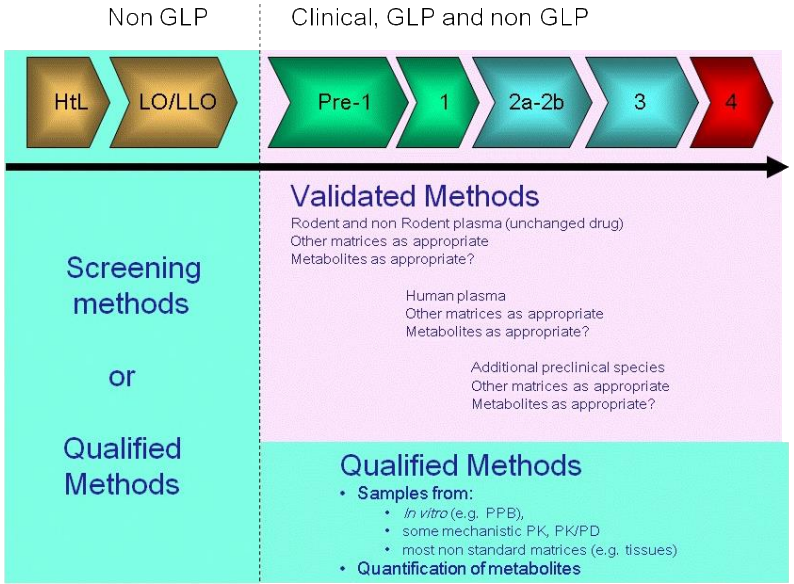
Tune in to Tomorrow
Science in High Definition

Embracing a CoU-Driven Validation for Chromatographic Assays in Alignment with ICH M10 - part 1 - the Why?

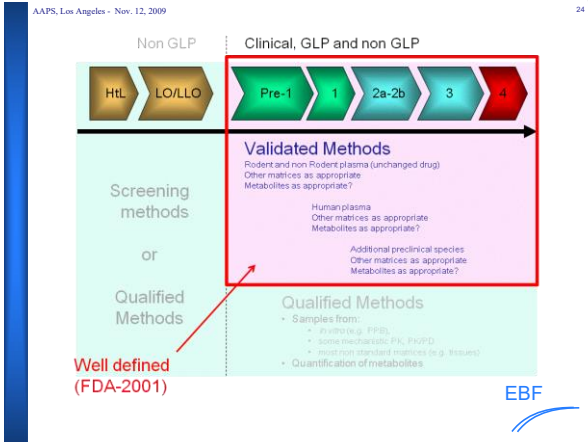
Philip Timmerman, EBF

Setting the course after CC-III on ‘tiered approach”

Since 2009, the EBF stimulated discussion in industry on applying Tiered Approach beyond metabolite quantitation.



EBF



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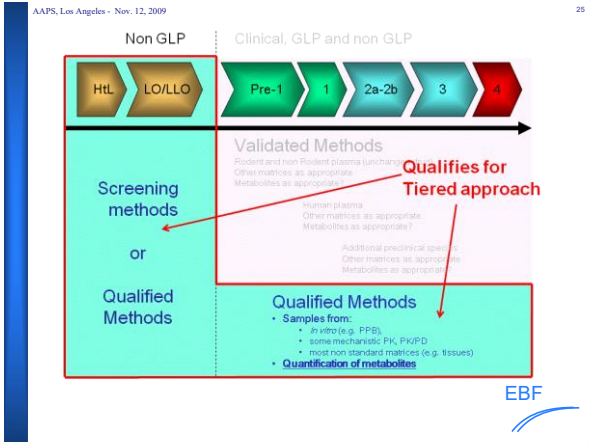


EBF

Some milestones

2006
CC-III

2007
CC-III workshop report

2008
EBF Tiered Approach team formed
MIST Guidance FDA

2009
ICH M3 (R2) AAPS Annual Meeting

2010
EBF recommendation on metabolite quantification

2011
Brian Booth paper

2013
MHLW CC-V

2015
GBC paper
DV-DMDG

When do you need a validated assay?

Brian Booth [1]

"The EBF has developed a paradigm for addressing this issue [1]. ……The European Bioanalytical Forum scheme makes very reasonable sense and may be a very valuable tool for industry."

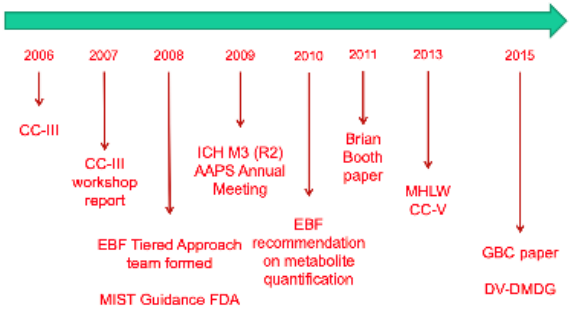
"In summary, the fit-for-purpose paradigm is applicable to several different analytical questions. The general rule that can be applied is that if the data generated will support regulatory action, such as assessing safety and/or efficacy, or supporting labeled-dosing instructions or patient treatment, then the data must be reliable and the analytical assays should be fully validated. In other cases, where the sponsor will use the data internally to make decisions about candidate selection, or continuing product development, the sponsor can use as much analytical method validation as it deems appropriate to make these decisions"

Bioanalysis. 2011 Dec;3(24):2729-30. doi: 10.4155/bio.11.250.

2013 → MHLW (Japan) refers to CC-III conference report and EBF 2010 Recommendation paper to support tiered approach

2012-2015: GBC (Global Bioanalysis Consortium) developed further details on tiered approach, incl. where again metabolites in early development

Ref.: Tiered Approaches to Chromatographic Bioanalytical Method Performance Evaluation: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. The AAPS Journal January 2015, Volume 17, Issue 1, pp 17-23



The EBF had paused the publication of below, and only published in 2015

Bioanalysis (2015) 7(18), 2387–2398

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

and suddenly…
the semantics became a derailer

While the concept resonated strong,
the terminology was misquoted, suggesting that
EBF implies regulatory validation is not scientific

Even though the manuscript was **crystal clear**…

"We cannot emphasise strongly enough that be introducing the terminology of scientific validation, 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".

From: Tiered Approach into Practice. Bioanalysis (2015), 7(18), 2387-2398

Highlighting a continued need for dialogue between those who see value and those who see hurdles.

Tiered approach also influenced ICH…

actually it was one of the two cornerstones of why the industry requested ICH to get involved

Understand the process and the history is not unimportant

2011 **Proposal to involve ICH for BMV harmonisation @ 3rd EBF OS**

From "disbelieve it's possible" to reality
Grow the idea grow and socialise the proposal.

2015 **AAPS/EBF/JBF Industry expert team established to prepare 'Concept paper'**

Preparation of industry position: AAPS/EBF/JBF Submitted to draft concept paper to EFPIA for submission to ICH

2016 **MHLW "beats" EFPIA to it @ ICH Assembly. Concept paper MHLW submitted and accepted…..Harmonisation BMV accepted, EWG formed**

Towards Step 1, 2, 3, 4 and publication

2022 **ICH M10 released**

2016 **MHLW "beats" EFPIA to it @ ICH Assembly. Concept paper MHLW submitted and accepted…..Harmonisation BMV accepted, EWG formed**

1. Origin and Framing

MHLW Concept paper

Initiated by the Japanese MHLW as a *national* proposal to ICH, calling for harmonization….

…listening to 2011→ 2015 industry discussions

Joint EBF/AAPS/JBF concept paper (not submitted)

an *industry-driven* proposal representing international scientific and operational consensus.

Key difference:

MHLW framed it as a *regulatory initiative*; **Joint EBF/AAPS/JBF submission** framed it as a *scientific and operational necessity* from the industry perspective.

3. Impact on problem statement

MHLW

Focused on *regulatory disparities* among FDA, EMA, and MHLW, and on the need to ensure uniform evaluation standards for global submissions.

EBF/AAPS/JBF

Went further, in addition to MHLW, highlighting the scientific and operational burden created by (scope) overinterpretation of guidance, and the need for scope clarification.

Key difference:
Joint EBF/AAPS/JBF submission added the dimension of *scientific efficiency and proportionality*, not just regulatory alignment.

2. Impact on scope definition

MHLW

Focused specifically on *BMV for PK & TK* studies supporting drug submissions.

MHLW was silent on biomarkers

EBF/AAPS/JBF

Explicitly excluded endogenous biomarkers, noting they are “an area in need of continued discussion,” and limited the scope to exogenous compounds.

Key difference:
Joint EBF/AAPS/JBF explicitly drew a line excluding biomarkers and emphasizing fit-for-purpose validation, whereas MHLW left biomarker inclusion ambiguous.

4. Proposed Structure and Process

HMLW

Envisioned the ICH guideline as primarily built from *existing regional guidance* (FDA, EMA, MHLW), expecting the EWG to synthesise these.

EBF/AAPS/JBF

Proposed to include pharma experts (from AAPS, EBF, JBF) in EWG, ensuring chromatography and LBA expertise linked it to industry consortia discussions

Key difference:

MHLW suggested a *regulator-led harmonization*; your submission promoted a *co-development model with industry as an equal scientific partner*.

5. Emphasis on “Scope Clarification”

HMLW

Treated scope implicitly, but mainly focusing on regulated bioanalysis for pivotal studies.

EBF/AAPS/JBF

Made “scope harmonisation” a **core issue to resolve**, emphasising differentiation between regulated (pivotal) and non-regulated (early development) work and the need to apply validation “**at an appropriate level of scientific rigor based on intended use**.”

Key difference:

Joint EBF/AAPS/JBF submission introduced what later became central to ICH M10 discussions: the context-of-use principle for applying validation standards.

And ICH M10 did address the scope

Industry input was **essential** and **critical** to refine scope definition in ICH M10,

- Limiting the scope to primary matrix and supporting regulatory decision
- Giving push back on BM/ADA becoming included

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.

So…we had a voice

…to have a choice

Nevertheless..

Even though ICH M10 clearly defines and limits the **scope**

(*regulated bioanalysis for studies supporting regulatory decisions, focusing on plasma/serum/blood PK for the primary matrix*)

industry **still applies M10-like rigor far beyond it**

…for a combination of non-scientific, organisational and psychological reasons:

1. Risk aversion and regulatory uncertainty
2. Blurring between study types and re-use of data
3. Quality management systems and auditor expectations
4. CRO business model and client pressure
5. Cultural and historical legacy
6. Ambiguity in how (we think) regulators interpret “in scope”
7. Lack of communication between bioanalytical and stakeholders
8. ….

“When in doubt, validate.”

Risk aversion has replaced scientific judgment as the default operating principle — turning M10 from a framework into a fortress.

“One size fits all… because it’s easier to defend than to explain.”

Quality systems, CRO models, and compliance culture reward uniformity, even when science demands proportionality.

“Harmonisation achieved — proportionality lost.”

ICH M10 unified expectations, but fear, legacy, and habit keep the industry applying full validation far beyond its intended scope.

2024 – getting back on (2) track(s)

Industry to manage scope creep

Already in EBF we see renewed dynamics re-articulating the SV principles to manage scope creep for ‘assays out of scope’

The EBF republished the SV concept, maintaining its historical meaning while aligning terminology with today’s **context-of-use** vocabulary and mindset.

Manage scope creep for ‘assays out of scope’

Revisit the 2015 paper against the ICH M10 scope opportunities

BIOANALYSIS
2025, VOL. 17, NO. 17, 1067–1076
https://doi.org/10.1080/17576180.2025.2555774

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DISCUSSION

European Bioanalysis Forum recommendation on embracing a context-of-use-driven scientific validation for chromatographic assays in the light of ICH M10

Philip Timmerman[a], Stuart McDougall[b], Neil Adcock[c], Cecilia Arfvidsson[d], Matthew Barfield[e], Stefan Blech[f], Kyra J. Cowan[g], Luca Ferrari[h], Alessandro Greco[i], Michaela Golob[j], Lee Goodwin[k], Richard Hughes[l], Tsvetelina Ivanova[m], Anna Laurén[n], Robert Nelson[o], Sonja Neitzel[p], Tom Verhaeghe[q], Nico van de Merbel[r], Mike Wright[s] and Stephen White[t]

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Check for updates

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- The EBF republished the SV concept, maintaining its historical meaning while aligning terminology with today's context-of-use mindset.
- SV/CoU emphasises scientific justification over procedural compliance, ensuring fit-for-purpose validation without contradicting ICH M10.

2024 – getting back on (2) track(s)

Industry to manage scope creep

Already in EBF we see renewed dynamics to re-articulating the SV principles to manage scope creep for ‘assays out of scope’

The EBF initiative republished the SV concept, maintaining its historical meaning while aligning terminology with today’s **context-of-use** vocabulary and mindset.

ICH Guidelines get revised, not?

Like in 2011, from ‘propose’ to ‘socialise’ the idea that at some point in time, ICH M10 needs a revision to keep aligned with the ICH mission.

More urgent issues could be refined in Q&A after interaction of industry and regulatory experts

Over-applying scope is industry problem, but a lot of non-added value experiments could be removed from ICH M10

EBF @ JBF 2025

EBF

Final Thoughts:

- ICH M10 has improved standardization, but scientific flexibility, emerging technologies, and biomarker validation remain key industry challenges.
- The next step includes refining interpretations, allowing risk-based flexibility, and integrating new bioanalytical technologies.
- At some point in time, ICH M10 may need a revision to prepare for the future and keep aligned with ICH mission*. More urgent issues could be refined in Q&A after interaction of industry and regulatory experts

* ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.

Or… applying the 3P Principles of CoU

Purpose – **P**roportionality – **P**ragmatism

1. Purpose

- Every assay should be designed and validated according to its intended use.
- The purpose (or context of use) determines what level of validation is needed.
- Key idea: “Start with why.” The assay’s purpose defines the standard, not the other way around.

2. Proportionality

- The rigor of validation and documentation should be proportional to the scientific and regulatory impact of the data.
- Apply enough control to ensure reliability, but not more than is justified by risk.
- Over-validation wastes resources and can stifle innovation.
- Key idea: “Do what is needed, not what is easiest to defend.”

3. Pragmatism

- Implementation should be scientifically sound, operationally feasible, and auditable without unnecessary rigidity. Choose approaches that are robust, reproducible, and make sense within the project context.
- Key idea: Scientific sense over procedural perfection

Or…**P**urpose before **P**rocess or **P**ressure

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Embracing a CoU-Driven Validation for Chromatographic Assays in Alignment with ICH M10 - part 2 - the How?

Stuart McDougall, EBF

Area	Why a leaner / context-of-use (CoU) approach is appropriate
1. Early-stage or exploratory studies	The guideline's scope is for validated assays that support regulatory decision-making. For internal decision-making, exploratory work or early development the full validation burden may be disproportionate.
2. Additional matrices / non-primary matrices	ICH M10 expects full validation for primary matrices; but when one deals with additional matrices (e.g., urine, rare fluids, tissues) the depth of validation can be tailored based on CoU.
3. Metabolites / non-standard analytes	When the analyte is a metabolite or an unusual species the risk/impact may differ and validation requirements can be adjusted to reflect the scientific question, rather than applying a "one-size-fits-all" full package.
4. Internal decision-making / non-regulatory submission studies	If the assay will *not* underpin regulatory labelling, safety or efficacy decisions (i.e., an internal utility), then a reduced/fit-for-purpose validation may be justified and supported.

From Section 1.3 (Scope) of ICH M10:

- "This guideline describes the validation of bioanalytical methods and study sample analysis that are expected to support regulatory decisions."
- "…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 bioanalysis of **biomarkers** and bioanalytical methods used for the **assessment of immunogenicity** are **not within the scope** of this guideline."

How these support “leaner approaches

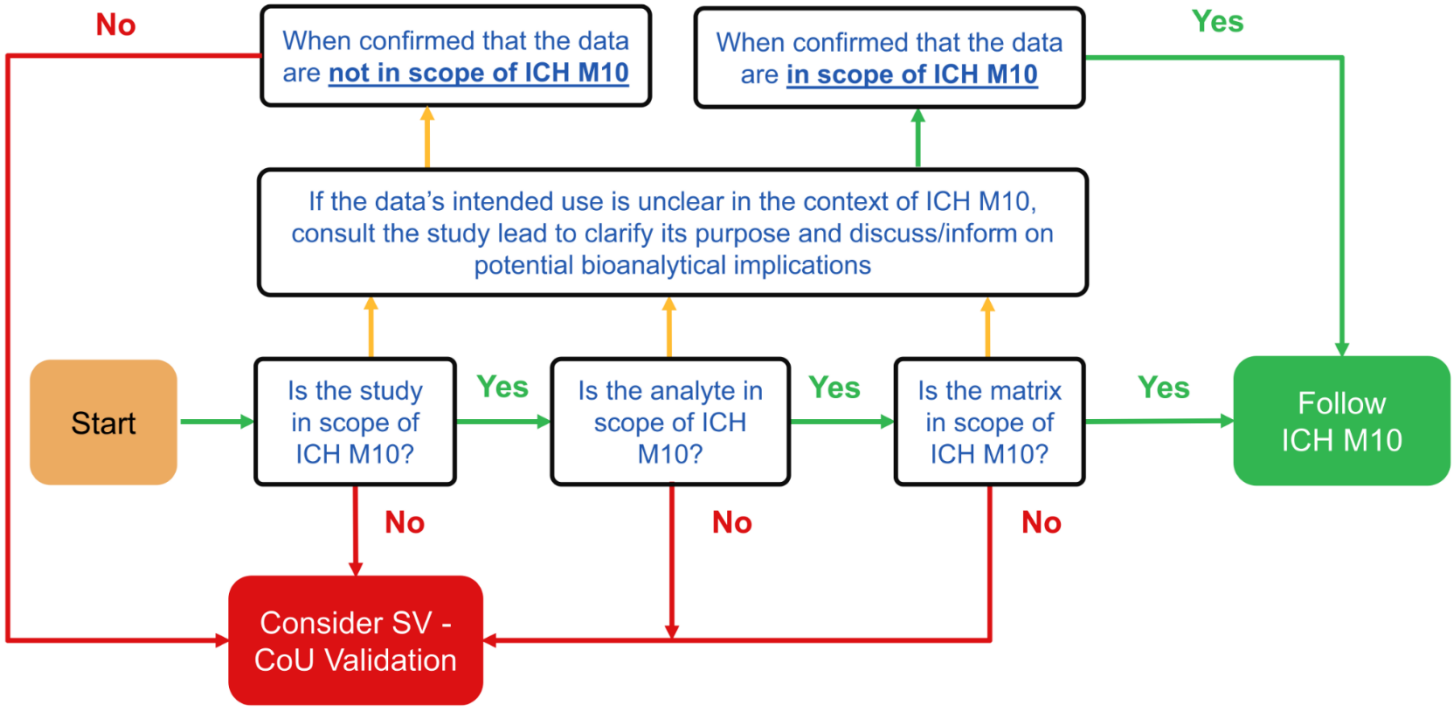
- The phrase “*expected to support regulatory decisions*” means that the full, detailed validation scope is targeted at studies feeding submissions. If an assay is not used for such regulatory decisions, the guideline itself acknowledges a different level of effort may be appropriate.

- The clause about full method validation being expected for the primary matrix but less for “additional matrices” allows for tailoring the validation burden depending on matrix relevance.

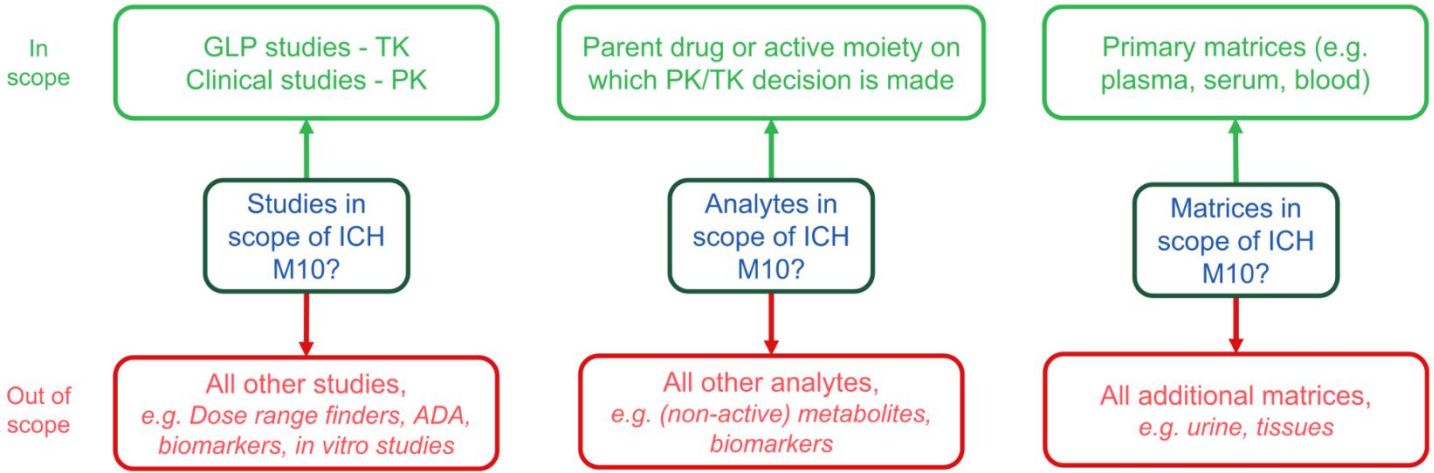
- The explicit allowance that for exploratory investigations the applicant may choose the level of qualification supports the idea of fit-for-purpose/lean validation when the context of use is internal, not submission-oriented.

- The exclusion of biomarkers/immunogenicity methods from scope reinforces that not all method types/contexts require the full standard package.

CoU Validation - Decision Tree I



CoU Validation - Decision Tree Examples



Notes:

- If a validated method is available and fits the context of use of the assay, consider using the existing validated method 'as is' or as a starting point.
- Adapt the QC/reporting process to the context of use requirements, avoiding unnecessary administrative burden.
- Be aware that other matrices may present scientific challenges not covered in ICH M10 (e.g., solubility issues, non-specific binding, etc.).

CoU Validation

Criteria Include

- Reference standard (SV T1)
- Stock stability (primary)
- Separate Cal/QC stock (or matched)
- Matrix (or surrogate)
- Calibration (n ≥ 6 levels) min 75%
- P&A (L, M, H, n ≥ 3 rep, 1 run)
- Dilution (or in study)
- Selectivity (1 source)
- *Specificity (in MDev)*
- Carry-over (or in study)
- FZ stability*
- F/T stability*
- Bench stability*
- Reinjection reproducibility
- Validation Plan (short or SOP)**
- Validation Report** (short)
- SOP
- Other 'matrix specific tests***

Criteria Exclude

- Dilution QC
- Extraction recovery
- OTC, Comed, FDC selectivity
- Whole blood stabilty (for plasma) unless known structural alert (ref EBV pub)
- Processed Sample Stability
- Separate aliquots (n=3) for LTS, F/Z, etc
- Matrix Effect (assess ISTD response; ref EBF pub)
- Haemolysis
- Hyperlipidaemia
- Cross validation

Acceptance criteria; ± 25/20% (plasma), ± 30/25% (urine), ± 30/25% tissue

* sufficient to cover 'chain of custody' of samples
** adsorption in urine assay or special considerations for tissue assay
*** Provide example templates

CoU Production

Criteria Include

- Reference standard (SV T1)
- Matrix (or surrogate)
- Calibration (n ≥ 6 levels) min 75%
- QC (L, M, H, n ≥ 2 rep) 50% pass/level*
- QC bracketing
- Dilution integrity (in study)
- Carry-over (in study & if relevant)
- IS variability with criteria (ref EBF pub)
- Analysis Plan (short)
- Analysis Report (short)
- SOP

Criteria Exclude

- Extrapolation below LLOQ or above ULOQ
- ISR
- Dilution QC
- Adding extra QC or re-ranging assay to reflect sample concentrations

Acceptance criteria; ± 25/20% (plasma), ± 30/25% (urine), ± 30/25% tissue

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P P P

Acknowledgements

- All bioanalytical experts that have contributed over the last 15+ y in this journey

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