Workshop on ICH M10

PC-05 - New metabolites = new (full) validation?

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A lot of comments 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.

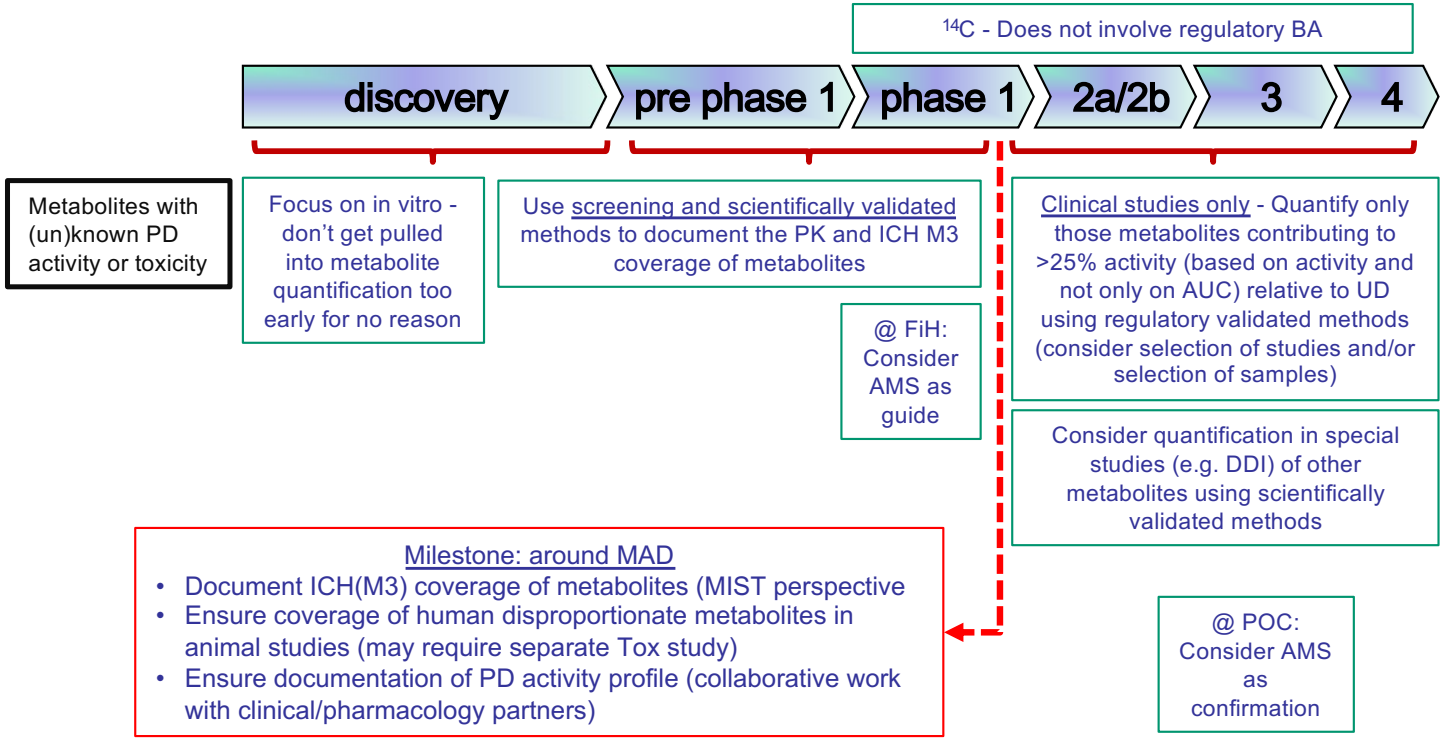
The information in this guideline applies to the quantitative analysis by ligand binding assays (LBAs) and chromatographic methods such as liquid chromatography (LC) or gas chromatography (GC), which are typically used in combination with mass spectrometry (MS) detection.

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.

From other guidelines – as summarised in an EBF recommendation*

Starting proposal Metabolite quantification



** Bioanalysis, 2016 Jun;8(12):1297-1305*

Pre-meeting survey

	the question	Yes	No
Q1	At which stage of development do you include metabolites in a validation?		
Q2	Do you only add metabolites in your validation as per ICH M3(R2) or EBF recommendation, i.e. only (active) metabolites above a defined exposure threshold and from phase 2 onwards?		7
Q3	If not, why do you include other metabolites in your validations?		1
Q4	Do you have a CoA for all the metabolites in your validation?	16	2
Q5	Do you typically have a STIL IS for all metabolites in your validations	6	8
free text			

Key message from the pre-meeting survey comments

Q1: At which stage of development do you include metabolites in a validation?

- Anything from ‘when identified’ to ‘when major’ – as ‘requested by clients’ and ‘early on in development’ most prevalent…

Q2: Do you only add metabolites in your validation as per ICH M3(R2) or EBF recommendation, i.e. only (active) metabolites above a defined exposure threshold and from phase 2 onwards?

- Mixed

Q3: If not, why do you include other metabolites in your validations?

- When reading the responses, the NO is actually a YES. Most exceptions mentioned follow the flowchart. Others include early risk mitigation or earlier projects learnings

Q4: Do you have a CoA for all the metabolites in your validation?

- Mixed

Q5: Do you typically have a STIL IS for all metabolites in your validations

- Mixed

In summary:

- although metabolites are measure more frequently than called for by the guidelines, the industry doesn’t feel it’s an issue and sees the value of early risk mitigation.
- Question: have we considered the cost and do we need BMV SOP for this, certainly pre-POC?

Raw data from the pre-meeting survey comments

- In the next slides we provide the unredacted details from 56 survey files reaching us prior to the deadline.
- Surveys that have arrived after the deadline could not be included anymore, for logistic reasons. Please speak up if your comment wasn't already captured in the other 56 files

Q1: At which stage of development do you include metabolites in a validation?

if desired, currentyl NA	As per sponsor request	As specified by client	When sponsor's ask for such	Depend on project - Depend on knowledge, if mayor Metabolites can

depends on project requirements	Whenever the team feels we should measure the metabolite routinely because it is unique metabolite or has substantial contribution to the activity. We will not validate an assay if we do not have a complete CofA with a clear restest or expiry date	Usually after MAD study if major human metabolites are identified	If the metabolites quantifications is included in the TOX or Clinical studies

Typically driven by the client	as requested	whenever they are major	Directly if known

Q1: At which stage of development do you include metabolites in a validation?

Sponsor request	MIST tells you 10% of dose related material	it depends on the project	early if metabolite is identified early as main - if not, later when metabolite is identified as major - mandatory when preponderant
We have not had the case yet for ICH M10	Early stage when metabolite is available	Directly from the beginning	Pre-study validation
Stabilities, Influence of concomitant medicines and metabolites	If requested by the sponsor. Major metabolites will be tested in the R&D phase	When requested by sponsors	In the preclinical stage, when the metabolite is already known and could impact the project outcome
Before Phase II	depends on project, could be after FiH to support phase 2 studies, but there have been cases where we have detected major metabolites in vitro and decided to include them in earlier phase 1 studies		

Q2: Do you only add metabolites in your validation as per ICH M3(R2) or EBF recommendation, i.e. only (active) metabolites above a defined exposure threshold and from phase 2 onwards?

As per sponsor request	As specified by client	We recommend the same, but the sponsor decides	Depend on project

Yes. Metabolites may be validated according to EBF recommendations in most cases, but may require full validation in special cases. But not earlier than Phase II when steady state samples are available	In general yes	Typically driven by the client	unlikely on mRNA (lipids)

N/AP, sponsor decision	it depends on the project	not only

We generally evaluated conjugate metabolites(e.g glucuronide, N-Oxide)	no, based on sponsors discussion and requests, FDA guidance or EMA guidance if any on the product of interest.	no, as not only active metabolite, but any major metabolites (greater than 10%) and/or active metabolites. Also known presence of metabolites based on previous projects with similar molecules/components of the drugs

Q3: If not, why do you include other metabolites in your validations?

As per sponsor request	Most probably, because sponsor is unsure, if the metabolite is "active"	If earlier-->Risk mitigation
according to MIST, human unique, disproportioned, active metabolites, genotoxic	Risk mitigation, if metabolite contributes to activity	N/AP, sponsor decision
to early quantify in NC & C PK	Recommended for pre-clinical studies if available	When the presence of a metabolite could be critical (i.E. Safety and efficacy evaluation)
major metabolites		

Q4: Do you have a CoA for all the metabolites in your validation?

Not always

Q5: Do you typically have a STIL IS for all metabolites in your validations

Not always	Most often	Yes, if validated	Not ever	N/AP, sponsor decision

not always given	Not always	Y, in majority of the cases, except if it is commercially not available
NO, but do request from sponsors as much as possible.	Yes it is expected, if available	Sometimes, in later stage of project

A lot of comments here

- Didn’t read it in details, but can this be summarised and left in the plenary?