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EBF Focus Workshop

(*sister meeting, in collaboration with AAPS/CBF/JBF*)

ICH M10 - Public consultation & Industry Feedback

Scope of ICH M10

learnings from EBF Strategy Meeting, ICH M3 (R2) and metabolite quantification

Philip Timmerman, EBF

Barcelona, 20-22 May 2019

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Goal of this presentation

- Create awareness and invite for discussion if:
  - we all understand the scope of draft Guideline in the same way?
  - we all understand the impact on our day to day work?
  - we all understand the value of interacting with our stakeholders?
  - we all understand the potential of scope creep (ISRc)?

NOT the Goal of this presentation

- Us telling you what's in scope

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Guideline, chapter 1 paragraph 2….

1.2 Background

- Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials, including comparative bioavailability/ bioequivalence (BA/BE) studies, are used to make regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

Guideline, chapter 1 paragraph 3….

1.3 Scope

- This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of 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 pivotal nonclinical TK/PK studies that are used to make regulatory decisions and all phases of clinical trials in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.
- 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 and occasionally with other detectors.
- 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.

Different perspectives

Evaluating a registration file on HA desk

Building a registration file on a Pharma R&D desk

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The perspective from the regulator

1.2 Background

- Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials, including comparative bioavailability/ bioequivalence (BA/BE) studies, are used to make regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

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The Regulator's perspective

- When reviewing a file, it can be assumed it's clear which studies are submitted to make claims on safety and efficacy
  - …and in extension, which analytes, matrices were analysed and which methods were used

Scope paragraph of M10 will likely do the job

And Pharma R&D?

1.2 Background

- Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials, including comparative bioavailability/ bioequivalence (BA/BE) studies, are used to make regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

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Comments on “Scope”: a few representative ones from the > 50 we received

Exact description required which assays are meant. This guideline does e.g. not cover special requirements for free drug assays.

Scope unclear, and why does ICH refer to regional documents that it is supposed to replace?

Scope could be better define. At the moment everything appears to be in scope.

Concerned that tissues are in same class a plasma with regard to level of validation

The scope of the guideline seems too broad.

Scope is too wide now that it includes nonclinical studies. Definition of pivotal is crucial. How do you know what pre-clinical studies are pivotal, especially PK? Why are all clinical studies included?

I would exclude early clinical studies (escalation/expansion phase) to be analyzed with fully validated method (mainly applicable for LBA): indeed, with new biologic formats, often MABEL approach is used meaning very low doses for starting. The range of quantitation is therefore not known and fixed. At this stage, a fit for purpose method validation seems more appropriate.

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The Industry's perspective

Survey confirms that when developing a drug, we may not know which studies will submitted to make certain claims on safety and efficacy…and in extension, which analytes, matrices were analysed and which methods require validation

We did a test….

A survey…

- A list of typical studies that are submitted for analysis covering all areas of development and all analytes and matrices
- separate list for LBA and CHROM
- A simple 1 or 0 if study/analyte was thought to be in scope…
  - 2nd question asked: what do you desire should be in scope

CHROMATOGRAPHY

				plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
			matrix --->	plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
			Analyte --->	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
		study	additional info on study												
pre-phase 1	NC	dose range study rat	non GLP study												
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP												
pre-phase 1	NC	28d GLP	the first GLP study												
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage												
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage												
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only												
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples												
Phase 1	Clin	FIM - HV	First into Man study												
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco												
Phase 2a	Clin	FIP (start Ph-2)													
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2												
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures												
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.												
Phase 3-4	Clin	BE	Any BioEQ study												

LBA

				Serum		urine	tissue
			matrix --->				
			Analyte --->	primary assay*	secondary assay*		
		study	additional info on study				
pre-phase 1	NC	dose range study rat	non GLP study				
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP				
pre-phase 1	NC	28d GLP	the first GLP study				
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage				
> phase 1	NC	mechanistic PK/TK	a on standard nonGLP study in a later drug development stage				
Phase 1	Clin	FIM - HV	First into Man study				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco				
Phase 2a	Clin	FIP (start Ph-2)					
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2				
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites				
Phase 3-4	Clin	BE	Any BioEQ study				

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INTENDED SCOPE

		study	additional info on study	plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
matr				plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
Anal				dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study in rat	non GLP study	0	0		0	0	0		0	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	13	13		0	13	13		0	8	8		0
pre-phase 1	NC	28d GLP	the first GLP study	96	88		13	38	33		0	25	17		0
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	100	100		17	38	38		0	25	21		0
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage	21	21		4	21	21		4	17	17		4
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	4	4		0								
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	38	33		4								
Phase 1	Clin	FIM - HV	First into Man study	88	79	46	8	33	29	17	0				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	100	92	54	13	33	29	17	0				
Phase 2a	Clin	FIP (start Ph-2)		96	96	67	13	38	38	21	4				
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	96	58	13	38	38	21	4				
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	100	88	67	13	38	38	21	4				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	100	96	71	13	38	38	21	4				
Phase 3-4	Clin	BE	Any BioEQ study	100	83	54	13	38	38	21	4				

DESIRED SCOPE

		study	additional info on study	plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
matr				plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
Anal				dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study in rat	non GLP study	0	0		0	0	0		0	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	4	4		0	0	0		0	0	0		0
pre-phase 1	NC	28d GLP	the first GLP study	74	52		0	13	13		0	9	9		0
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	91	87		9	13	13		0	9	9		0
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage	17	17		4	9	9		0	4	4		0
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	0	0		0								
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	22	17		0								
Phase 1	Clin	FIM - HV	First into Man study	57	43	17	0	13	13	4	0				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	78	61	26	4	13	13	4	0				
Phase 2a	Clin	FIP (start Ph-2)		96	87	61	9	13	13	9	0				
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	83	48	9	13	13	9	0				
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	87	65	43	4	13	13	9	0				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	100	91	61	9	13	13	9	0				
Phase 3-4	Clin	BE	Any BioEQ study	100	70	52	4	17	17	9	4				

Observation on “Intended scope”

1 out of 4 or more have a different view on “in or out of scope”

1 out of 5 …

INTENDED SCOPE

				plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
			matrix --->	plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
			Analyte --->	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
		study	**additional info on study**												
pre-phase 1	NC	dose range study rat	non GLP study	0	0		0	0	0		0	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	13	13		0	13	13		0	8	8		0
pre-phase 1	NC	28d GLP	the first GLP study	96	88		13	38	33		0	25	17		0
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	100	100		17	38	38		0	25	21		0
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage	21	21		4	21	21		4	17	17		4
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	4	4		0								
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	38	33		4								
Phase 1	Clin	FIM - HV	First into Man study	88	79	46	8	33	29	17	0				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	100	92	54	13	33	29	17	0				
Phase 2a	Clin	FIP (start Ph-2)		96	96	67	13	38	38	21	4				
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	96	58	13	38	38	21	4				
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures	100	88	67	13	38	38	21	4				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.	100	96	71	13	38	38	21	4				
Phase 3-4	Clin	BE	Any BioEQ study	100	83	54	13	38	38	21	4				

And for ‘desired scope’?

- Areas where industry not agreeing
- Areas where industry is in relative agreement
- Areas with push for alternative approaches, compared to ‘intended scope’

DESIRED SCOPE

				plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
			matrix --->	plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
			Analyte --->	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
		study	**additional info on study**												
pre-phase 1	NC	dose range study rat	non GLP study	0	0		0	0	0		0	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	4	4		0	0	0		0	0	0		0
pre-phase 1	NC	28d GLP	the first GLP study	74	52		0	13	13		0	9	9		0
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	91	87		9	13	13		0	9	9		0
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage	17	17		4	9	9		0	4	4		0
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	0	0		0								
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	22	17		0								
Phase 1	Clin	FIM - HV	First into Man study	57	43	17	0	13	13	4	0				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	78	61	26	4	13	13	4	0				
Phase 2a	Clin	FIP (start Ph-2)		96	87	61	9	13	13	9	0				
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	83	48	9	13	13	9	0				
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures	87	65	43	4	13	13	9	0				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.	100	91	61	9	13	13	9	0				
Phase 3-4	Clin	BE	Any BioEQ study	100	70	52	4	17	17	9	4				

And for LBA?

INTENDED SCOPE

		study	additional info on study	matrix ---> Serum		urine	tissue
			Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study	5	5	5	5
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	5	5	5	5
pre-phase 1	NC	28d GLP	the first GLP study	91	9	36	32
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	95	9	32	32
> phase 1	NC	mechanistic PK/TK	a on standard nonGLP study in a later drug development stage	32	0	0	0
Phase 1	Clin	FIM - HV	First into Man study	95	5	32	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	95	5	36	
Phase 2a	Clin	FIP (start Ph-2)		86	5	32	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	95	5	32	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	77	5	32	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	82	9	36	
Phase 3-4	Clin	BE	Any BioEQ study	91	5	36	

DESIRED SCOPE

		study	additional info on study	matrix ---> Serum		urine	tissue
			Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study	0	0	0	0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	6	6	6	6
pre-phase 1	NC	28d GLP	the first GLP study	72	11	33	22
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	78	11	27	22
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage	18	0	6	6
Phase 1	Clin	FIM - HV	First into Man study	73	5	27	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	84	5	27	
Phase 2a	Clin	FIP (start Ph-2)		83	5	21	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	95	5	27	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	72	5	22	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	83	5	21	
Phase 3-4	Clin	BE	Any BioEQ study	95	5	33	

A similar view on serum and primary assay

INTENDED SCOPE

		study	additional info on study	matrix --->	Serum		urine	tissue
				Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study		5	5	5	5
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP		5	5	5	5
pre-phase 1	NC	28d GLP	the first GLP study		91	9	36	32
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage		95	9	32	32
> phase 1	NC	mechanistic PK/TK	a on standard nonGLP study in a later drug development stage		32	0	0	0
Phase 1	Clin	FIM - HV	First into Man study		95	5	32	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco		95	5	36	
Phase 2a	Clin	FIP (start Ph-2)			86	5	32	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2		95	5	32	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures		77	5	32	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites		82	9	36	
Phase 3-4	Clin	BE	Any BioEQ study		91	5	36	

Similar tendency to interpret all studies in scope

DESIRED SCOPE

		study	additional info on study	matrix --->	Serum		urine	tissue
				Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study		0	0	0	0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP		6	6	6	6
pre-phase 1	NC	28d GLP	the first GLP study		72	11	33	22
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage		78	11	27	22
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage		18	0	6	6
Phase 1	Clin	FIM - HV	First into Man study		73	5	27	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco		84	5	27	
Phase 2a	Clin	FIP (start Ph-2)			83	5	21	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2		95	5	27	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures		72	5	22	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites		83	5	21	
Phase 3-4	Clin	BE	Any BioEQ study		95	5	33	

and tendency for toward more flexibility for early studies

A similar trend on additional matrices

INTENDED SCOPE

		study	additional info on study	matrix --->	Serum		urine	tissue
				Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study		5	5	5	5
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP		5	5	5	5
pre-phase 1	NC	28d GLP	the first GLP study		91	9	36	32
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage		95	9	32	32
> phase 1	NC	mechanistic PK/TK	a on standard nonGLP study in a later drug development stage		32	0	0	0
Phase 1	Clin	FIM - HV	First into Man study		95	5	32	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco		95	5	36	
Phase 2a	Clin	FIP (start Ph-2)			86	5	32	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2		95	5	32	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures		77	5	32	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites		82	9	36	
Phase 3-4	Clin	BE	Any BioEQ study		91	5	36	

Similar tendency to bring urine and tissues into scope

DESIRED SCOPE

		study	additional info on study	matrix --->	Serum		urine	tissue
				Analyte --->	primary assay*	secondary assay*		
pre-phase 1	NC	dose range study rat	non GLP study		0	0	0	0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP		6	6	6	6
pre-phase 1	NC	28d GLP	the first GLP study		72	11	33	22
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage		78	11	27	22
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage		18	0	6	6
Phase 1	Clin	FIM - HV	First into Man study		73	5	27	
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco		84	5	27	
Phase 2a	Clin	FIP (start Ph-2)			83	5	21	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2		95	5	27	
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures		72	5	22	
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites		83	5	21	
Phase 3-4	Clin	BE	Any BioEQ study		95	5	33	

…and leave into scope…

In the next few slides,
I will dive into the ‘CHROM’ results

- In support of the example of metabolites

EBF

1.3 Scope

- This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of 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 pivotal nonclinical TK/PK studies that are used to make regulatory decisions and all phases of clinical trials in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

pivotal

Suggest some wording in definitions on meaning of 'pivotal'

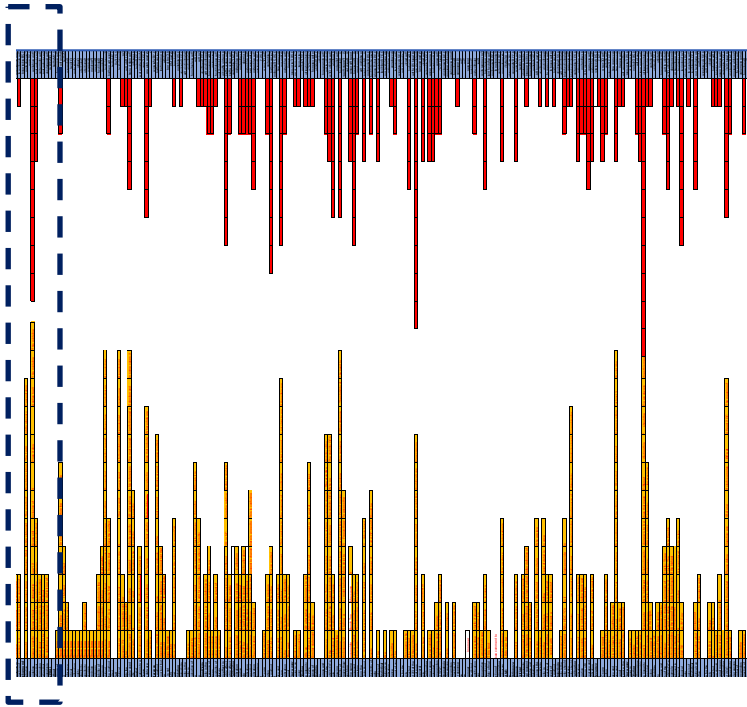
Questions: What is pivotal? The CRO may not know at the time and as previously discussed, the pivotal nature of a study may change over time and during the program.

The term pivotal nonclinical TK/PK studies is ambiguous. Please include a listing of non-clinical studies for which "full" validation is required.

Pivotal non clinical studies: subject to interpretation ?

The results of pivotal nonclinical toxicokinetic (TK)/pharmacokinetic (PK) studies and of clinical trials … Are all clinical studies pivotal??

What is a pivotal nonclinical TK study?



What defines a pivotal study

- Pivotal:
  - /ˈpɪvətl/. - *adjective*
  - of crucial importance in relation to the development or success of something else.

- So not all can be pivotal…..But ask any project representative in drug R&D asking for budget of a study: "*is your crucial importance in relation to the development of our drug*?"

- And ask any bioanalytical expert the same question…

Can it really be defined?

- Pivotal is also transient
  - Many “pivotal studies” will be superseded by another pivotal study in a next phase of development
- Pivotal for internal decision making vs. pivotal for regulatory decision making in a filling
- …

Catch-22

catch-22

- /katʃtwɛntɪˈtuː/. - *noun*
- a dilemma or difficult circumstance from which there is no escape because of mutually conflicting or dependent conditions.

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bioanalytical assays that are submitted to support

regulatory submissions.

to make regulatory decisions

to support regulatory

submissions.

- bioanalytical assays that are submitted to support regulatory submissions:
  - Relates to the assay
  - Implies no other assays can be submitted, even if scientifically appropriate
- to make regulatory decision
  - Difficult to know for the BA lab
  - Almost impossible to know for the BA lab
  - With a few exceptions (e.g. BE), impossible to know for the BA lab
- to support regulatory submissions
  - Semantics: supports vs. make
  - It can be assumed, that, if in the file, everything “supports” a regulatory submission (either for decision making or as scientific supporting documentation).
  - Industry doesn’t add studies it just to increase the size of the file

EBF

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Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary.

- Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary
  - Does ‘partial’ means ‘partial validation as per Guideline’, or does it mean ‘alternative approaches’?

= Manageable

In practice, this brings all analytes and matrices in scope

The impact on industry if “Additional matrices should be partially validated as necessary” really means alternative approach

		study	additional info on study
pre-phase 1	NC	dose range study rat	non GLP study
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP
pre-phase 1	NC	28d GLP	the first GLP study
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples
Phase 1	Clin	FIM - HV	First into Man study
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco
Phase 2a	Clin	FIP (start Ph-2)	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.
Phase 3-4	Clin	BE	Any BioEQ study

	plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
matrix --->	plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
Analyte --->	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active

The impact on industry if "Additional matrices should be partially validated as necessary" really means partial validation as per Guideline

		study	additional info on study	plasma is the primary matrix				urine is a secundairy matrix				tissues are a secundairy matrix			
			matrix --->	plasma	plasma	plasma	plasma	urine	urine	urine	urine	tissue	tissue	tissue	tissue
			Analyte --->	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active	dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study rat	non GLP study												
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP												
pre-phase 1	NC	28d GLP	the first GLP study												
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage												
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage												
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only												
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples												
Phase 1	Clin	FIM - HV	First into Man study												
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco												
Phase 2a	Clin	FIP (start Ph-2)													
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2												
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures												
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.												
Phase 3-4	Clin	BE	Any BioEQ study												

Brings all analytes and matrices in scope

EBF

1.3 Scope

- This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of 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 pivotal nonclinical TK/PK studies that are used to make regulatory decisions and all phases of clinical trials in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

An example: metabolites and ICH M3

- This has been on the radar of EBF for a decade
  - 1 early recommendation paper
  - 1 dedicated Focus Workshop, with PK/Metab. stakeholders
  - Multiple presentations a international bioanalytical conference
  - 1 updated Recommendation Paper*, co-authored by PK/Metab. stakeholders
    - Summarising current literature on the subject
    - Integrating regulatory requirements from ICH M3 and FDA/EMA Guidelines into a recommended bioanalytical strategy

➡ Good starting point to translate ICH M10 scope paragraph *The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents* into practice

* Bioanalysis. 2016 Jun;8(12):1297-305. doi: 10.4155/bio-2016-0103. Epub 2016 May 24.

Best practices for metabolite quantification in drug development: updated recommendation from the European Bioanalysis Forum.

Timmerman P[1], Blech S[2], White S[3], Green M[4], Delatour C[5], McDougall S[6], Mannens G[1], Smeraglia J[5], Williams S[4], Young G[3].

ICH M3 (R2)
3. TOXICOKINETIC AND PHARMACOKINETIC STUDIES

- *In vitro* metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials. Further information on pharmacokinetics (PK) (e.g., absorption, distribution, metabolism and excretion), in test species and *in vitro* biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before Phase III). These data can be used to compare human and animal metabolites and for determining if any additional testing is warranted.

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

ICH M3 (R2)
3. Toxicokinetic and Pharmacokinetic Studies

- Nonclinical characterization of a human metabolite(s) is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies. Such studies should be conducted to support Phase III clinical trials. For drugs for which the daily administered dose is <10 mg, greater fractions of the drug related material might be more appropriate triggers for testing. Some metabolites are not of toxicological concern (e.g., most glutathione conjugates) and do not warrant testing. The nonclinical characterization of metabolites with an identified cause for concern (e.g., a unique human metabolite) should be considered on a case-by-case basis.

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

Pretty clear….

So why do we think the intended (and even desired) scope for metabolites is this broad?

INTENDED SCOPE

		study	additional info on study	plasma is the primary matrix			
matr				plasma	plasma	plasma	plasma
Anal				dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study in rat	non GLP study	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	13	13		0
pre-phase 1	NC	28d GLP	the first GLP study	96	88		13
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	100	100		17
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage	21	21		4
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	4	4		0
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	38	33		4
Phase 1	Clin	FIM - HV	First into Man study	88	79	46	8
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	100	92	54	13
Phase 2a	Clin	FIP (start Ph-2)		96	96	67	13
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	96	58	13
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	100	88	67	13
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	100	96	71	13
Phase 3-4	Clin	BE	Any BioEQ study	100	83	54	13

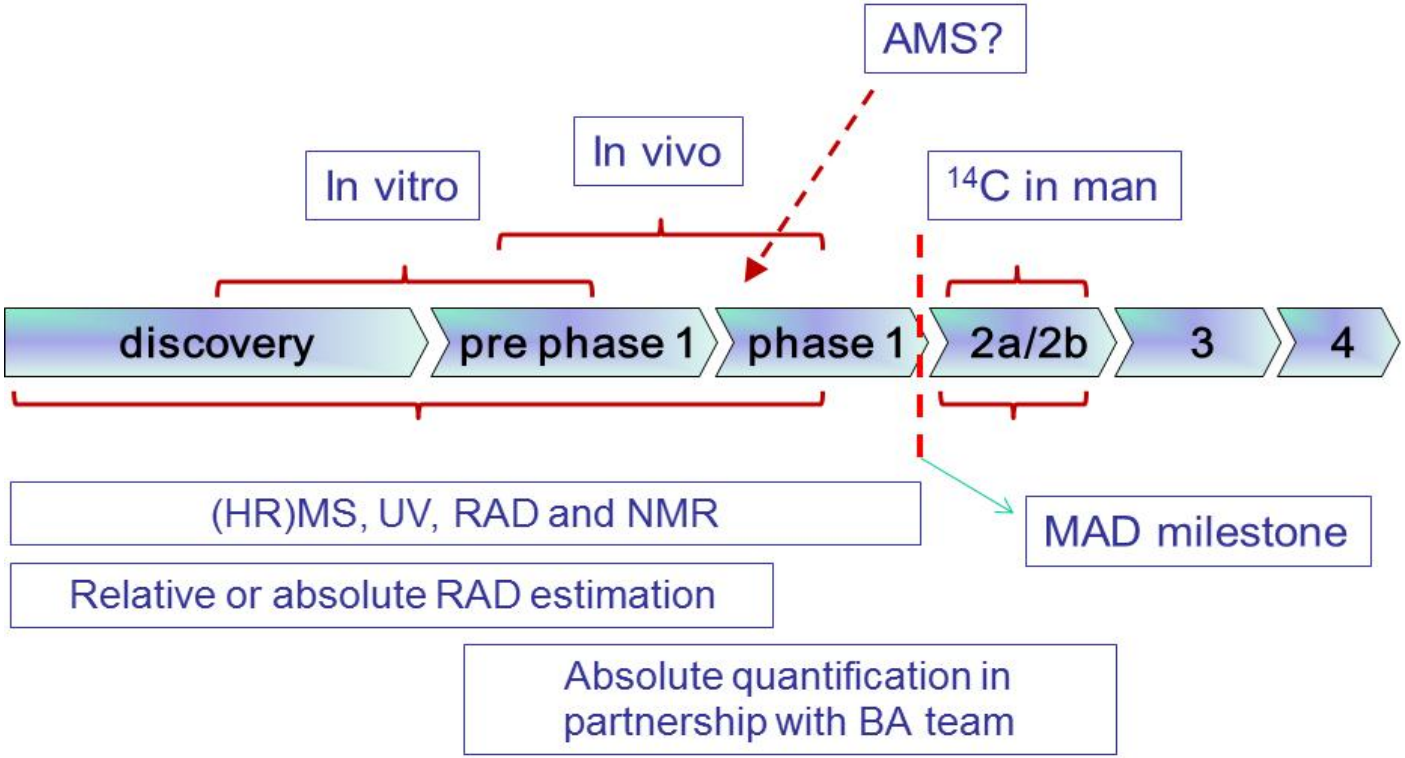
33	
79	46
92	54
96	67
96	58
88	67
96	71
83	54

DESIRED SCOPE

		study	additional info on study	plasma is the primary matrix			
matr				plasma	plasma	plasma	plasma
Anal				dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study in rat	non GLP study	0	0		0
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP	4	4		0
pre-phase 1	NC	28d GLP	the first GLP study	74	52		0
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage	91	87		9
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug development stage	17	17		4
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only	0	0		0
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples	22	17		0
Phase 1	Clin	FIM - HV	First into Man study	57	43	17	0
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco	78	61	26	4
Phase 2a	Clin	FIP (start Ph-2)		96	87	61	9
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2	96	83	48	9
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clinical study looking at (relative) exposures	87	65	43	4
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metabolites	100	91	61	9
Phase 3-4	Clin	BE	Any BioEQ study	100	70	52	4

17	
43	17
61	26
87	61
83	48
65	43
91	61
70	52

The 2016 EBF Recommendation – How?



The 2016 EBF Recommendation – *in vivo* quantification

When using AMS or ^{14}C, use scientific criteria relevant to the technology.
Be cautious not to mix up profiling and quantification purposes

discovery → pre phase 1 → phase 1 → 2a/2b → 3 → 4

- Focus on *in vitro*
- Limit *in vivo* metabolite quantification
- Screening

Preclinical and clinical studies

- Plasma, serum or blood.
- Use **screening** (preferred for earlier phases) and **scientifically validated** methods (preferred @ SAD/MAD) to document the ICH M3(R2) coverage of metabolites.
- Consider **relative exposure** ratios in absence of reference standards
- Metabolite quantification in other matrices for profiling purposes

Clinical studies only

- Plasma, serum or blood.
- use **regulatory validated** methods to quantify only those metabolites contributing to >25% activity (not only AUC) relative to unchanged drug.
- No other metabolites require quantification
- consider selection of studies and/or selection of samples/subjects instead of all samples from all subjects in all studies

Milestone: around Multiple Ascending Dose (MAD) in human

- Document ICH(M3) coverage of metabolites (MIST perspective
- Ensure coverage of human disproportionate metabolites in animal studies (may require separate Tox study)
- Document PD activity (collaborate with clinical/pharmacology partners)

- Consider quantification in special studies (e.g. DDI) of other metabolites using **scientifically validated** methods

In the context of our survey….for primary matrix

		study	additional info on study	plasma is the primary matrix			
				matrix ---> plasma	plasma	plasma	plasma
				Analyte ---> dosed drug	M - active*	M > 10%*	M - not active
pre-phase 1	NC	dose range study rat	non GLP study				
pre-phase 1	NC	rat/dog/… PK	a non GLP PK study around the start of GLP				
pre-phase 1	NC	28d GLP	the first GLP study				
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage				
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage				
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only				
> Phase 1	Clin	PPB study	plasma protein binding studie using patient samples				
Phase 1	Clin	FIM - HV	First into Man study				
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco				
Phase 2a	Clin	FIP (start Ph-2)					
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2				
phase 1 --> 4	Clin	food effect, BA,…	typical "non-BE" clin. study looking at (relative) exposures				
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.				
Phase 3-4	Clin	BE	Any BioEQ study				

IN
OUT
Alternative approach

And for secondary matrices?

As per ICH M3, all metabolites out of scope until late phase 2 – may be smart to include investigation (BA + DMPK) earlier as internal decision (= out of scope).
"M>10%" may come in scope in some rare cases for DDI, but a project should deal with this in a tox study and not in by continued dosing to man (the whole idea of MIST)

		study	additional info on study
pre-phase 1	NC	dose range study rat	non GLP study
pre-phase 1	NC	rat/dog/... PK	a non GLP PK study around the start of GLP
pre-phase 1	NC	28d GLP	the first GLP study
Phase 1	NC	6m GLP	any GLP study typically in a later drug development stage
> phase 1	NC	mechanistic PK/TK	a non standard nonGLP study in a later drug dev.stage
all phases	NC/Clin	PPB study	plasma protein binding studie using spiked samples only
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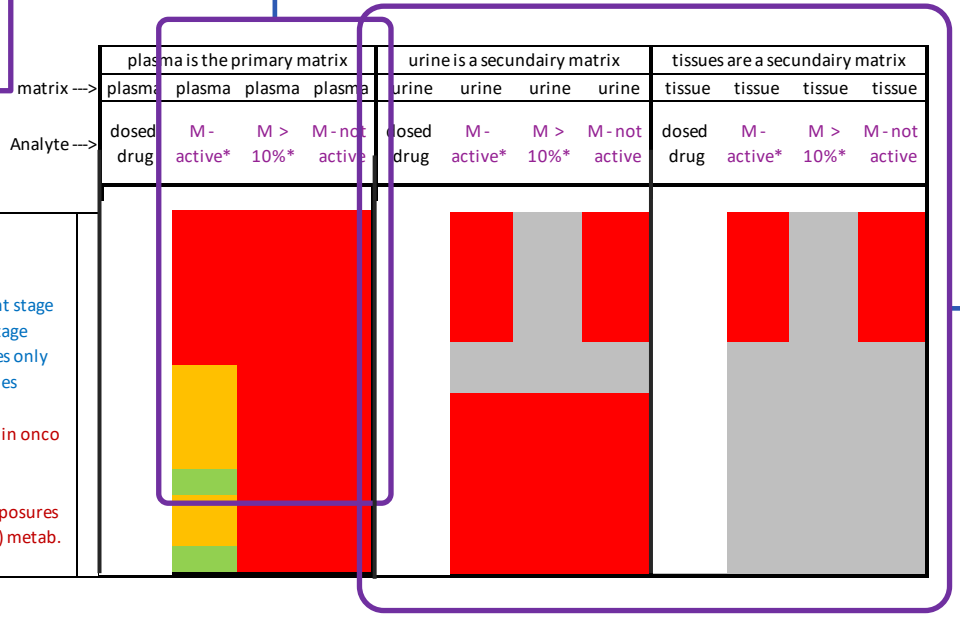
Phase 1	Clin	FIM - HV	First into Man study
Phase 2a	Clin	FIM - onco	First into Man is often also First into Patient study in onco
Phase 2a	Clin	FIP (start Ph-2)	
Phase 3-4	Clin	Patient studies	Any Patient study in > phase 2
phase 1 --> 4	Clin	food effect, BA,...	typical "non-BE" clin. study looking at (relative) exposures
phase 1 --> 4	Clin	DDI	This one can include looking at impact on (active?) metab.
Phase 3-4	Clin	BE	Any BioEQ study



If secondary matrix is out of scope – there may be the odd exception, but in those cases it is clear

In conclusion

- For industry, the scope definition is ambiguous
- Shouldn't industry define 'pivotal'?
  - And can it be done upfront to guide the Bioanalysts?
  - Should we really rely on the HA to tell us what a pivotal study is in our projects?
- From the survey, many mention the scope is too wide.
- For many scientist studies (and matrices analytes) in earlier phases of development, there is no consensus in industry if they are in scope of the
- Lack of consensus and ambiguity have shown to drive scientist 'safety mode' and lead to scope creep

  ➡ may lead to virtually all studies, matrices and analytes coming in scope

Recommendation:

- Intensive training and communication will be needed to clarify and agree scope
- This should involve all stakeholders (BA, industry and HA stakeholder)
- Agreement should be in line with ICH mission

Acknowledgment and questions

- The EBF community for survey data and feedback
- Further questions to info@e-b-f.eu before 31 May