Feedback from the survey

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on behalf of the EBF

Q 1-4

Participation

- 29 companies: 11 CRO, 18 Pharma
  - 26 companies involved in metabolite quantification (23 companies involved in metabolite profiling and metabolite quantification)
  - 03 companies not involved in this activity

Answers relate to

- NCE: 26
- Peptide: 9
- Protein: 4

How

Metabolite P&Q strategy available:

- 18 companies have a Met P&Q strategy
- 07 companies deal with Met P&Q on an individual basis

Strategy is based on:

a)	FDA MIST Guidance		4
b)	ICH M3 (R2) Guidance		2
c)	a+b		8
d)	a, b or c + EMA DDI Guidance		9
e)	An industry reference paper:		4
f)	Other:		5

Where?

Metabolite profiling:

DMPK lab	12
BA lab	3
Both	6
outsourced	4
Other:	2

Metabolite Quantification:

DMPK lab	3
BA lab	16
Both	7
outsourced	5
Other:	1

Which technology is used in profiling

< FIH:

LC-UV	6
LC-MS	5
LC-HR/MS	20
LC-RAD	16
Other	4

Including FIH

LC-UV	3
LC-MS	6
LC-HR/MS	19
LC-RAD	14
AMS	3
Other	4

Detector used to define relative abundance ratios or estimations of abundance

· UV-response	10
· Absolute Radioactivity response	21
· MS response	13

Which process is used in quantification

	Non GLP	GLP	Clinical
TA based using FDA/EMA (4-6-15) criteria for A&P	7	6	4
TA based using relaxed criteria for A&P.	12	7	1
o 4-6-20	9	3	2
o 4-6-25	4	1	1
o Other:……..	7	4	1
validated assays using all FDA/EMA criteria	3	15	20

Which samples do we use for quantification?

	Non GLP	GLP	Clinical
Study samples harvested for initial PK assessment of dosed drug	22	22	20
Separate samples are harvested for the purpose of metabolite quantification only	5	7	6
if so, they are stored:	6	3	3
o as the other study samples	7	8	9
o at lower temperatures (e.g. -80c instead of -20c)	4	4	2

Is urine and bile used for metabolite profiling or quantification?

	urine	bile
from rat		
o profiling	19	14
o quantification	11	5
from dog		
o profiling	17	6
o quantification	10	3
from human		
o profiling	19	4
o quantification	13	1
other: …depending on compound/sponsor's request	7	3

Timing of work

Question: We typically profile/quantify metabolites in samples from preclinical and clinical studies to document relative metabolite exposure in **1 campaign** when samples from multiple ascending dose are available (yes = we wait to start metabolite profiling until human samples are available)

	Profiling	quantification
Yes - stored samples from earlier TK studies to be included in this single assay campaign.	4	4
Yes - most recent TK studies are included in this single assay campaign	6	5
No - metabolite concentration in the different species and human are generated at the time these samples become available	13	14

Reporting

Metabolite profiling data are reported separate from the metabolite quantification data	19
The metabolite profiling and metabolite quantification data are reported in 1 overarching metabolism report	5
Metabolite quantification data are reported together with the concentration data of the dosed drug as part of the PRR (Preclinical Research report) or CRR (Clinical RR)	8
If reported in PRR or CRR, we provide a cross reference to the overarching metabolism report	1
o yes	1
o no	3

Are data from MetQuant/MetProf used to exclude metabolites in continued bioanalytical support in later phases?

Yes		12
Yes, we would like to but, teams continue to ask for metabolites concentrations		4
Yes, we would like to but, in our interactions with regulators, we need to continue measure metabolites concentrations		2
Yes, but for DDI studies we do measure metabolites more frequently		5

No was not an option ☺

Conclusion and areas of opportunity

- Still a lot of regulated validation and quantification of metabolites is done, both in GLP studies and in ED clinical studies, even though regulations do not call for this
- Company strategies are not really aligned with respect to
  - Guidelines referred to
  - Timing work
  - Reporting of results
- Data from metabolite P&Q are not used to their fullest extent to streamline the development process

Bioanalytical practices related to pre-study validation and study sample analysis in accordance with BMV Guidance

For following studies we use BMV to quantify metabolites:	n	%
Drug Discovery		
• All identified metabolites	0	0
• A selection of metabolites	0	0
• metabolites assays are not validated	25	83
Early Development		
• All identified metabolites in preclinical studies	0	0
• All identified metabolites in clinical studies	1	3
• All identified metabolites in preclinical studies from FiH onwards	1	3
• All identified metabolites clinical studies from FiH onwards	0	0
• All MIST/ICH M3 relevant metabolites = (contribute to activity >25 %, not covered > 10%) - (preclinical and clinical studies)	15	50
• All MIST/ICH M3 relevant metabolites = (contribute to activity >25 %, not covered > 10%) - (clinical studies only)	5	17
• as a CRO organization we analyze the analytes per sponsor request	13	
Late Development		
• All metabolites in LD (contribute to activity >25 %)	1	3
• Only those metabolites in LD relevant after MIST/ICH M3 assessment	13	43
• As a CRO organization we analyze analytes per sponsor request	13	

12. In the future, I would support the principles of the tiered approach (i.e., scientific validation) for the following studies in ED (check all the apply)

	n	%
Metabolite analysis pre MIST/ICH M3 in plasma	24	80
Metabolite analysis in support of clinical studies in urine	26	87
Metabolite analysis in all non GLP tissue homogenate	24	80
Metabolite analysis in all tissues homogenate	26	87