Workshop on ICH M10

C6 - Surrogate/rare/preclinical matrix for CHROM

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(table moderator: Stuart McDougall / Lee Goodwin)

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Introduction to Round table C6

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 studies employing such methods contribute to 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.

This guideline intends to facilitate development of drugs in accordance with the principles of 3Rs (Reduce, Refine, Replace) for animal studies, where valid.

And multiple direct or indirect suggestions throughout the guideline, maybe not suggesting or stimulating, but for the brave reader, at least opening for 3Rs

But FAQs likely creating a barrier many don't want to jump over

Guideline section	Questions	Answers
2	In situations where a matrix is unavailable (e.g., shortage, 3Rs - Reduce, Refine, Replace) can a similar surrogate matrix (e.g., human plasma) be used to dilute samples?	Yes, as long as the use of the surrogate matrix meets the recommendations of the guideline, including accuracy and precision, lack of interferences, etc. and the dilution quality control samples (QCs) are processed in the same way. The rationale needs to be well justified because the approach might be questioned.

"The rationale needs to be well justified because the approach might be questioned."

Pre-meeting survey

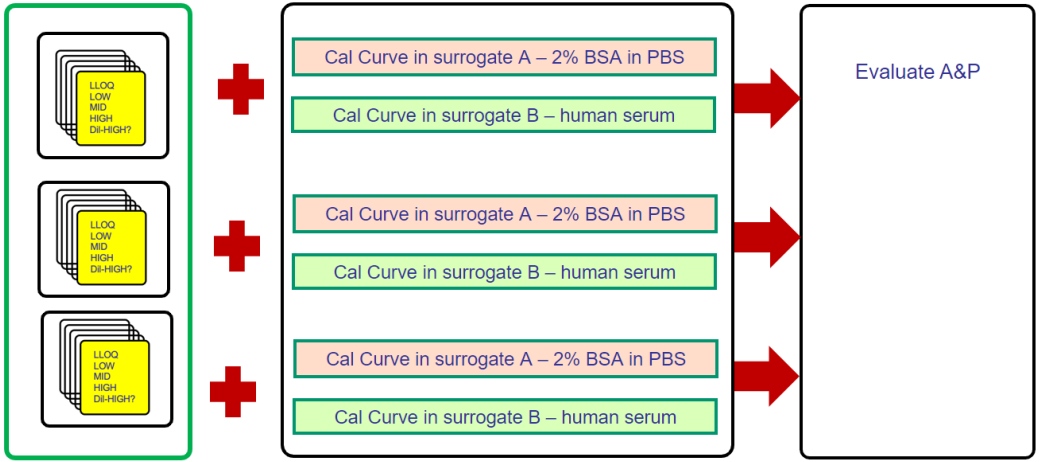
	the question	Yes	No
Q1	Do you feel the ICH M10 is flexible enough to support the 3Rs?	20	15
Q2	If no, where can it be improved?	-	-
Q3	Do you have data which support a claim towards replacing pre-clinical blank matrix with surrogate matrix?	12	20
Q4	Are you willing to share data these data?	8	4
free text		0	

Key message from the pre-meeting survey comments

- 55% of responders feel the ICH M10 is flexible enough to support the 3Rs
- 32% of responders have data which support a claim towards replacing pre-clinical blank matrix with surrogate matrix
- Comments raised on clearly defining what is a rare matrix
- Comments raised on providing examples of how this strategy could be used

- Following the EBF strategy meeting in March 2023, a team was formed to design and perform experiments to gather compelling and convincing data to (re-)open discussions in our industry and with the regulatory authorities for the replacement of preclinical matrix in assay validation and study sample analysis.

EBF Experimental plan



- Experimental proposal provided
- QCs in original matrix, calibrators in two different surrogates
- VHQC and limits optional.
- Surrogate B could be human or alternative (e.g. horse)
- No restriction on platform

Preliminary Outcomes

- 13 companies have returned data
- Mix of target matrix
  - Dog, rat, NHP, minipig, rabbit and hamster plasma
- Mix of target analyte
  - 40 compounds from MW c. 200 to c. 5000

Surrogate Matrix	Assays Tested	Assays Passing Accuracy Acceptance (%)	Assays Passing Precision Acceptance (%)
Human Plasma	49	45 (91.8%)	48 (98.0%)
PBS-BSA	33	21 (63.6%)	33 (100%)
Human Urine	2	0 (0%)	2 (100%)

Preliminary Outcomes

- No pattern to failures in terms of species, molecule type, molecule size, assay range
- Human plasma demonstrates better results than PBS-BSA or urine
- Over 90% of tested assays pass all acceptance criteria against human plasma line
- Around 2/3 of tested assays pass all acceptance criteria against PBS-BSA line

Surrogate Matrix will also be discussed at the 16th OS

11:40 13:00 Session 20: Regulatory Updates - (Plenary) - Auditorium

11:40 12:15 ***Focus on 3R - Feedback from ICH M10 Workshop***

- 11:40 - 11:45: Introduction to surrogate martix experiments for preclinicall assays
- 11:45 - 12:00: First results surrogate matrix experiments for preclinical chromatography assays
- 12:00- 12:15: First results surrogate matrix experiments for preclinical Ligand Binding assays

12:15 13:00 ***Cross validation and ICH M10***

- 12:15 - 12:30: Feedback from ICH M10 Workshop
- 12:30 - 12:40: Case study 1
- 12:40 - 12:50: Case study 2
- 12:50 - 13:00: Case study 3

13:00 13:15 Closing remarks - Adjourn - Auditorium

Feedback from the round tables

Theme/question: What do we define as a rare matrix?

Comments: Difficult to extract/obtain (CSF, sweat, saliva, tissue). Limited supply from individual animals (smaller animals). Limit supply in the market (NHP). Matrix that causes distress to the animal to collect? Disease state?

Theme/question: Would you use the surrogate matrix approach?

Comments: Yes.

Some have used approach in the past so in favour in principle. Consensus is that all support this. Company already doing this and had no issues (including with submission?). Consider that ethical (3Rs) considerations differ by region so would need a justification somewhere.

Theme/question: What are the next steps?

Recommendation/Action

- Continue to generate data.
- Submission experience.
- EBF publication to include appropriate 3Rs author(s)/endorsement.
- Example protocol would be good.
- Some companies already doing this? Get case studies/feedback from EBF community as to who has done this and had regulatory acceptance.
- Direct feedback from authorities.

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:Do you feel the ICH M10 is flexible enough to support the 3Rs?

- This is the discussion for rare matrices
- Y, Tries to be but a number of experiments require more matrix than strictly necessary
- could be better
- Do not use M10 as an excuse.
- 3R are fab!
- yes, but should give more details It is unfortunately not precise enough in my opinion what would be considered a rare matrix and what could be practical consequences. Therefore few labs only will "use" it to save rare matrix
- Y (at least, I hope so)
- yes, but should give more details
- Issue comes from volume of sample needed to achieved requiured sensitivity

Q2: If no, where can it be improved?

- Human plasma as calibrators for animal studies
- Definition of 'rare'
- 3Rs should be mentioned as rationale for use of surrogate
- Widely acceptance for dilution with human plasma
- Matrix Effect uses huge amounts of volume
- allow dilutions with eg buffer as long as you prove in the validation that it is OK. We do this for LM given the high dilution factors but not for small molecules (usually much lower dilution factors)
- It should be accepted and easy to use Surrogate matrix for rare species and NHP if validation data support this.
- Too many aliquots to be prepared and also because the matrix effect has to be performed preparing CS and QC samples
- include some additional guidance around rat, cyno plasma is it right to do a validation completely in matrix match

Q2: If no, where can it be improved?

- examples are missing (can I consider mouse plasma as a rare matrix?)
- Dilutions could be done in human plasma if tested.
- Definition of rare matrix unclear selectivity experiment now more complex
- The guideline is not allowing replacement of matrix for 3R reasons details on how flexible it is, when it can be applied
- practical examples of what is considered acceptable and what not would help as well as giving a clearer picture of what is considered a rare matrix
- "For each concentration tested, the bulk sample should be divided into a minimum of 3 aliquots... "
- details on how flexible it is, when it can be applied
- further support on microsampling is needed

Q3: Do you have data which support a claim towards replacing pre-clinical blank matrix with surrogate matrix?

- yes for dilutions of LM
- Not enough
- part of the working group for surrogate matrix
- some data for dilution experiments (animal matrices are diluted with human matrix)

Q4: Are you willing to share data these data?

- Were already shared
- Y, will be shared separately in EBF working group
- We have shared already done with EBF
- Already shared
- Y, as part of the EBF SMOL team