Workshop on ICH M10

PC-03 - Matrix effect - special population, haemolysed and lipemic

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From the guideline

3.2.1. Selectivity

6 blank sources non haemolysed/lipemic. 1 source haemolysed and lipemic (not for preclinical)

Single source should be naturally occurring and representative of samples

If not possible, spike with triglycerides for lipemic and at least 2% blood v/v for haemolysed

3.2.3. Matrix effect

Defined as an alteration of the analyte response due to interfering and often unidentified component(s) in the sample matrix. During validation the matrix effect needs evaluating: Lo & HiQC, n=3, six sources. Acceptance criteria 15% nominal A/P. Also evaluate special populations, lipemic and haemolysed

4.2.2. Selectivity

Special population: renal or hepatically impaired, inflammatory or immuno-oncology patients.

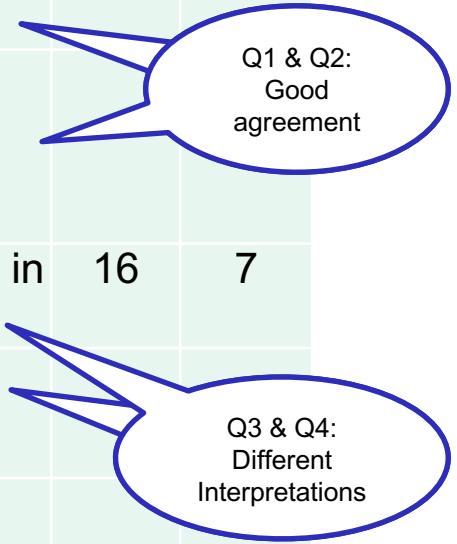
Matrix effects assessment required, n=5 different individuals

7.1.2. Selectivity, recovery and matrix effects for methods for analytes that are also endogenous molecules

Matrix effects also required for endogenous analytes. Parallelism (LBA)

Pre-meeting survey

	The question	Yes	No
Q1	Do you evaluate routinely matrix effect in haemolysed or lipemic matrix during MV as per ICH M10?	12	2
Q2	If yes, why? Required by guidance, represents real samples, some compounds/techniques affected by it, conservative clients!!!		
Q3	Are you clear on the requirements for matrix effect evaluation in patient and special population?	16	7
Q4	if no, what are the ambiguities you see? Definition of “special”, we use SIL IS. Only renal impairment is real “special”		
free text			



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 evaluate routinely matrix effect in haemolysed or lipaemic matrix during MV as per ICH M10?

- Yes
- Y, but lipaemic only for clinical assays
- Yes to both in human, only haemolysed in tox species
- Yes - lipaemic only for clinical
- Y for clinical. Heam only in preclinical
- Y, in human both and only heamolysed in pre-clinical matrix
- pre-clinical matrices will be tested with 2% of human blood.
- Haemolysed for nonclinical, both for clinical
- Y - for haemolysed matrix only, but not as described in ICH M10
- Y, in human
- Y, Tested during method qualification/method validation

Q2: If yes, why?

- Lipemic or haemolysed samples come up in clinical trials
- under protocol control
- since ICH M10 recommends it and at least haemolysed plasma is regularly observed in study sample
- to avoid issues during sample analyses, and to include these samples
- reflects real world samples
- Required by guidance to be assured that impacted samples return trustworthy results, Case-by-case is, however, ambiguous
- because M10 asks for it x 4
- It makes sense especially when using les selective sample prep such as PP. We have historically seen matrix effect in these matrices.
- According to our SOP x 3
- advised in guidance
- requested in most validations
- haemolysed samples are current
- Some compounds or techniques are affected by it
- to cover trial samples
- conservative clients

Q2: If yes, why?

- for all new method validations
- for plasma and serum, haemolyzed for urine
- because the guideline is quite clear about doing so
- to confirm that there will be no matrix effect with clinical samples
- To cover this case
- forced by the majority our sponsors
- To evaluate the matrix effect due to haemolysis/Lipemic content
- yes, for clinical samples and for pre-clinical haemolysed only
- For plasma and serum, haemolyzed for urine
- To investigate analyte response under altered conditions
- As in Matrix effect you spike at Low and High QC level whereas in Selectivity you do not spike. It is done to see how the haemolysed and lipemic matrix affect the drug compound
- difficulty on limiting use of the method based on sample appearance, and protocol limitations for patients that would provide lipaemic samples

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Q3: Are you clear on the requirements for matrix effect evaluation in patient and special population?

- Yes - also monitor ISTD response during sample analysis
- no we don't do that but we do for LM so would be interested to learn if every one is doing this for LBAs or if it's jut us
- Currently we see only the special population as renally impaired

Q4: if no, what are the ambiguities you see?

- Selectivity (3.2.1)+H113:N113
- what defines renal or hepatic impairment?, what other disease state matrix might impact on the bodies response to a drug?
- availability and definition of special population
- not knowing which patient populations or special populations
- special populations when available?? Not specified how
- What "special" really mean?

Free text

- Some consultants (and clients) interpret 3.2.1 to mean 6 lots of matrix (plus lipemic + haemolysed) are tested (double blank) vs each same lot (6+2) spiked ar LLOQ with ISTD. M-10 3.2.1 states 'per matrix' and we interpreted matrix as one lot (of plasma, or urine, or serum) spiked at LLOQ with ISTD.
- The question in especially patient studies get asked- should we test the patient studies (heart\lung or onco studies) selectivity as well. This has some ambiguities to it.