Workshop on ICH M10

G3 - Updating historical validations - when, how and why (not)?

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(table moderator: Lee Goodwin)

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From the Guideline

- nothing

Pre-meeting survey

	YES	NO
As part of implementing ICH M10, have you updated/re-validated previously validated assays (assays that were validated towards EMA-2012 and/or FDA-2018) requirements.	12	21
If yes, for which 'new' requirements?		
If yes, for both preclinical and clinical assays or only for clinical assays?	12	
If no on all of above, why did you not re-validate?		
Free text		

Key message from the pre-meeting survey comments

- Split c. 60/40 of those not updating and those updating historical validations
- Aspects being updated
  - Stability (DQC, Whole Blood, Extract)
  - Matrix effects
  - Dilution coverage
- Reasons for not updating
  - Validated under the guidance and internal quality documents in place at the time of the validation
  - Protocol signed before M10 came into effect
  - Not requested by sponsor
  - Planning to do by exception if regulators request it on submission

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

On Q1: As part of implementing ICH M10, have you updated/re-validated previously validated assays (assays that were validated towards EMA-2012 and/or FDA-2018) requirements.

- No, but will consider in case of support to pivotal clinical studies
- No, at the moment
- Yes for LC-MS and not Immunoassay
- N (not yet requested)
- Y (LC-MS), N Immuno
- Depending on sponsor requirements
- If something was validated before the release it stays the same.
- This avoids different methodology and ensures consistency in filing
- Y, if required as result of a gap analysis
- But is about to do it for other reasons and will follow the M10 guideline for the new validati
- Chrom feedback: n
- Yes indeed, several human plasma assays Updated
- Currently reviewing/risk assessments

On Q2: If yes, for which 'new' requirements?

- Whole blood stability (human), Recovery, run re-injection, QC D (stability)
- DQC stability
- Yes, For Method, which goes in pivotal studies
- matrix effect, IS stability, mid QC shifted towards arrith. Mean instead of geo. Mean
- Stability of >ULOQ
- Matrix effect and blood stability
- Dilution, Stability of Dilution QCs, Matrix effects, reinjection stability
- "HQC level and haemolysed/lipaemic selectivity.
- ""ensuring LTS is covered at least in one lab at both -80C as well as -20C (LBA)
- "planned stability testing at subject sample concentrations but not yet done
- stability on OQC level, matrix effect experiments, dilution linearity on lowest dilution factor (i.e. 2)
- Matrix effect (Dilution integrity range not done as one dilution ratio was enough.
- Matrix effect, Reinjection reproducibility
- Maybe extra stability in DiQC levels

On Q3:If yes, for both preclinical and clinical assays or only for clinical assays?

- Only clinical X10
- Both
- will would only do this for existing clinical assays that were supporting pivotal studies
- clinical, especially BA/BE
- We only do clinical at the moment
- Patient safety is key, preclinical has no patient safety issues
- No preclinical assay revalidated yet; and for preclinical we would see more leeway to stick with the previously validated EMA assays
- Because all preclinical evaluations were finished."

On Q4: if no on all of above, why did you not re-validate?

- not necessary until now
- clinical studies performed well. Did not want to use further resources.
- method was validated in compliance with the guidelines valid during validation ICHM10 came into effect on 21 January 2023 no before
- not considered needed
- wait until assets get filed and then do additional experiments if needed
- Methods used in studies where protocol was signed before ICH M10.
- Because validations were performed following the guidelines and SOPs in force at that time
- ALOQ stability sample would be the only additional assessment for LBA, until now no sponsor requested the re-validation (CRO, see comment).
- Because it has been performed under the guidelines that were then valid
- not yet requested
- considered that the updates in ICHM10 had no impact on the initial validation of the method
- If you have two validations you need to cross validate right?

On Q4: if no on all of above, why did you not re-validate?

- Methods validated to the guidance at the start of study stand. Consitency in filing
- Feels that our old validation process is still adequate
- programs discontinued; new assays (/ versions) with new study phases
- revalidation done for methods still in use
- Lack of time/ A risk assessment should be done in each method to verify what is needed to be compliant with all ICHM10 requirements
- in LBA less requirement
- Sponsors did not request revalidation
- No submission since M10 has been active
- in LBA less requirement
- our method were already mostly in line with the guidance
- apply guidelines that are applicable at that moment in time
- The validation will be updated when moving to next study
- Considered to be a proportionate approach of implementation and preclinical is not considered high risk

On Q5: free text

- As CRO we can only advise/show the difference of the validation scopes. However, the sponsor decides whether the re-validation is performed or not.
- "For me, industry perspective for whole blood stability requirements in preclinical studies would be interesting
- And I had a discussion with a CRO about whose responsibility it is to check for discrepancies - the CRO is of the opinion that you can register in the future with a method that was validated under the old regulations, and therefore see no responsibility on their side - I, on the other hand, believe that you have to update your validations if you will only submit your dossier in a few years

So, let's discuss

- Should we be updating any historical validations at all?
- In which situations should we be updating to mitigate regulatory risk?
- Which aspects need to be updated?

Interesting read out again We seem to be split in 2

This begs the question and a good discussion on what is really necessary and can we recommend a smart way into de-risking and identifying real needs based on real new requirements in ICH M10

Recommendation from the workshop

Updating Historical Validations - When, How and Why (not)?

- The EBF cannot judge on the rationale for updating historical validations
- we recommend to limit the resources spent on unnecessary revalidations and come together as an industry to define best practices on when to revalidate and for which critical parameters
- We consider that in most cases, methods validated in line with EMA or FDA standards, will be adequate for the studies they have supported at that time.