Workshop on ICH M10

L02 - Singlicate vs duplicate analysis

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From the Guideline

4.2. Validation

Most often microtitre plates are used for LBAs and study samples can be analysed using an assay format of 1 or more well(s) per sample. The assay format should be specified in the protocol, study plan or SOP. If method development and method validation are performed using 1 or more well(s) per sample, then study sample analysis should also be performed using 1 or more well(s) per sample, respectively. If multiple wells per sample are used, the reportable sample concentration should be determined either by calculating the mean of the responses from the replicate wells or by averaging the concentrations calculated from each response. Data evaluation should be performed on reportable concentrations.

Pre-meeting survey

	the question	Yes	No
Q1	Prior to ICH M10, were you already doing singlicate analysis as standard process?	2	24
Q2	if yes, in which stages of drug development: in nonclinical method development, in clinical method development or in both?		
Q3	If not, did you change your process from duplicate to singlicate based on the clarity provided by the ICH M10?	3	13
Q4	If not, why do you continue duplicate analysis yet?		
Q5	What is needed to make you move into singlicate analysis?		
Q6	Are you happy to make the switch mid-study, or at an appropriate stopping point?		10
free text			

Key message from the pre-meeting survey comments

- There remains a lot of residual hesitancy and unsureness
- Most responders were not pre-M10, and are not post-M10, performing LBA in singlicate
- The reasons are varied - but common themes are (from CROs) the Sponsor does not want to, internal process, habit, consistency with legacy data, no real benefit, ongoing studies
- A lot of responses state that it is in planning for new and upcoming projects/methods, or that the intention is there, but Sponsors/CROs need to be on board, or there needs to be more feedback and clarity on acceptance
- Need more clarity on methods already validated in duplicate
- Unanimous that no change can occur mid-study

Feedback from the round tables

Pre-meeting survey

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Q1	Prior to ICH M10, were you already doing singlicate analysis as standard process?	2	24
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free text			

Actually 17 out of 76 are performing some sort of singlicate analysis, majority in non-clinical

Q3: If not, did you change your process from duplicate to singlicate based on the clarity provided by the ICH M10?

Yes	No
3	13

- NO
  - Not yet
  - We plan to implement in all assays going forward - also clinical. We will at least recommend but finally it will be a project decision
  - To be intended
  - Under consideration
  - Not so far. - Where is the clarity? :)
  - Started the discussion with clients
  - Not standard process, however, better starting point since singlicate is mentioned in ICH M10
  - No change in existing methods
  - Not yet - but we are planning to swich for on upcoming validation in order to build experience
  - Depends on sample numbers/ runs
  - No. We still don't use singlicate analysis for any studies/ assays.

- YES
  - process changed in
  - upon Sponsor's request
  - such a way that singlicate could be considered but it is not standard practice so far
  - New methods validated in singlicate

Questions for the round table

- "If method development and method validation are performed using 1 or more well(s) per sample, then study sample analysis should also be performed using 1 or more well(s) per sample, respectively"
- Need more clarity on methods already validated in duplicate
  - What in case the method is validated in duplicate ? Nobody has done this
  - Can analysis be done in singlicate ? Is this in contrast to the guidelines??
  - Would you perform a separate partial re-validation?

- If you are implementing singlicate analysis, are there criteria around what drives the decision; stage of development for example? At what point do you decide whether the data suggests that precision is good/not good enough?

- 2019 paper* is helpful but overall implementation recommendations would be valuable

* *Bioanalysis. 2020 Mar;12(5):273-284*

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: Prior to ICH M10, were you already doing singlicate analysis as standard process?

Yes	No
2	24

- YES
  - for preclincial non-regulated studies + a single GLP tox
  - singlicate already implemented for TOX studies; for clinical duplicate is still the standard. If I ask why it's because we need to adapt the Hamilton scripts which takes time
  - Some few (fully automated) methods were validated in singlicate (Elecsys)
  - But not standard process
  - Only if validated in singulate
  - Depending on what was defined in the validation

- NO
  - No. We still don't use singlicate analysis for any studies/ assays.
  - No recently (yes up to 2014)

Q2: if yes, in which stages of drug development: in nonclinical method development, in clinical method development or in both?

- In nonclinical method development
- Both
- Clinical only
- Nonclinical
- the decision for singlicate, duplicate, triplicate is made during method development/validation and carried through to sample analysis
- But not standard process
- we do not do non-clinical, follow CRO SOP

Q3: If not, did you change your process from duplicate to singlicate based on the clarity provided by the ICH M10?

Yes	No
3	13

- NO
  - Not yet
  - We plan to implement in all assays going forward - also clinical. We will at least recommend but finally it will be a project decision
  - To be intended
  - Under consideration
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Q4: If not, why do you continue duplicate analysis yet?

- Compensate for occasional high CVs
- Need feedback on methods already validated (i.e. need to compare validation data analyzed with duplicate data versus singlicate data on several validated method)
- Consistency with old data.
- Depends on sample numbers/ runs
- Running studies

- Client expectation, reservation to change
- only on sponsor request
- Evaluation just started, however assay-dependent AND sponsor decision (CRO)
- Sponsor's requests

- Singlicate with new assays
- in transition phase, get experience with data
- will probably change for coming projects
- Several things needs to be considered, validation, system updates.

- Habit and insecurity
- Historic
- established procedures and protocols
- our methods are validated
- Hesitancy for change but I think it depends on the platform of choice.
- Legacy approach and still an industry "go to" option.
- need to prove the reproducibility of the assay in singulate is time consuming
- duplicate is better for confirmation and is not much time consuming
- Price is only slightly lower.

Q5: What is needed to make you move into singlicate analysis?

- greater support from Sponsors, many are still very nervous about this change
- Sponsor request
- Clear Sponsor request
- Initiative by sponsor
- Sponsor's requests
- we are implementing. Some stakeholders are reluctant - but we try convince

- Broader industry move towards this trend.
- change in the regulations (FDA)
- documentation/ white papers you can refer to
- Clarity on efficiency and gain at CRO (cost and shorter turn around time)

- pilot projects and further assessment
- Good data in next validation
- Need feedback on methods already validated
- get experience
- we need to perform internal investigations on big amount of data
- we feel it needs to be assessed during validation
- We will do that in the near future
- Update internal approach/opinion
- need to acquire confidence on several studies before moving to singlicate as a regular process
- we are ready to try it out

Q6: Are you happy to make the switch mid-study, or at an appropriate stopping point?

- No switch within studies. Switch of assay(s) which will progress to the next clinical phase are considered after assessment of assay performance.
- No switch of pre-clinical assays to singlicate.
- Start study
- Only for new methods
- appropriate stopping point
- would prefer to switch for new projects
- No, only after completed project/study
- at an appropriate stopping point
- N, preferably after appropriate validation only for new studies
- in the beginning of the study or not at all
- appropriate stopping point/new studies
- Probably not mid-study. Preferred option would be to validate this way and start study using singlicate rather than changing half-way.
- Not in the same study but if data allows, it can be changed in next study
- N, preferably after appropriate validation only for new studies
- We think an appropriate stopping point and with an established performance assessment
- not mid study
- providing there is a suitable review of data supporting the change we would hope to enact this mid study, our experience so far has been met with reluctance from stakeholders
- all data in same filing must be consistent

Free text

- The decision to use singlicate analysis should be a process starting early in the method development assessing CV% of duplicate readings to decide to switch to single well analysis if acceptance criteria is constantly met
- Switch from duplicate to singlicate not to be done for assays of projects in Ph III or which are in filing
- All new assays are set up as singlicate unless data suggests that precision is not good enough
- Please let me confirm just in case. Do you mean "singlicate" is to measure the sample using one well of plate?

Questions for the round table

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- Need more clarity on methods already validated in duplicate
  - What in case the method is validated in duplicate ? Can analysis be done in singlicate ? Is this in contrast to the guidelines??
  - Would you perform a separate partial re-validation?

- If you are implementing singlicate analysis, are there criteria around what drives the decision; stage of development for example?
- At what point do you decide whether the data suggests that precision is good/not good enough?
- Are there instruments that you would not perform singlicate analysis on?