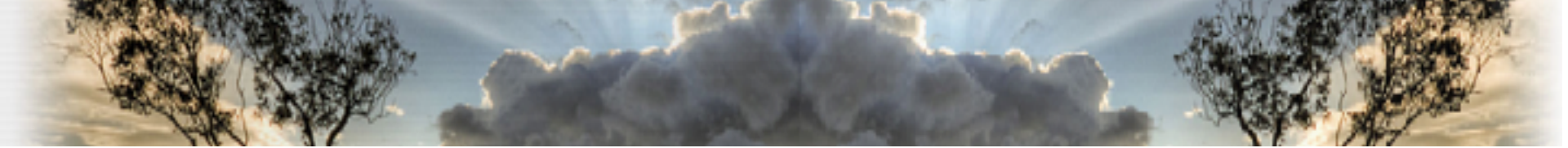

Commercial and Diagnostic Kits
Paragraph 7.5
Break out Session

Breakout Workshop Moderator – Arno Kromminga, on behalf of the EBF

Purpose and limitations of ICH M10, 7.5

- Commercial or diagnostic kits are sometimes co-developed with new drugs or therapeutic biological products for point-of-care patient diagnosis.
- Repurposes kits to measure chemical or biological drug concentrations during the development of a novel drug.
- The recommendations in this section of the guideline do not apply to the development of kits that are intended for point-of-care patient diagnosis (e.g., companion or complimentary diagnostic kits).

Aim of the workshop

- Identify challenges and agree on proposed recommendations for change on the paragraph
- We will split into 7 key areas
  1. Validation criteria
  2. Standards
  3. Quality controls
  4. Matrix
  5. Lot-to-lot variability
  6. Inter plate variability
  7. Have we missed something?

Alignment with current validation criteria

- If an applicant repurposes a kit or utilises “research use only” kits to measure chemical or biological drug concentrations during the development of a novel drug, the applicant should assess the kit validation to ensure that it conforms to the drug development standards described in this guideline.

Impact on our industry

- Clarification about the validation requirements when using repurposed kits
- Kits can not be used as they are for drug determination without a further on-site validation
- Single aspects need to be discussed during the break-out session
- Outcome of the discussion will be presented to the audience

Purpose and limitations

- Commercial or diagnostic kits are sometimes co-developed with new drugs or therapeutic biological products for point-of-care patient diagnosis.
- The recommendations in this section of the guideline do not apply to the development of kits that are intended for point-of-care patient diagnosis (e.g., companion or complimentary diagnostic kits).

Changes to current FDA BMV, 2018

- Explicitly mentions the other guidelines
- Includes “biomarkers in development”
- Consequently, the suitability of BM kits originally developed for clinical diagnostics needs to be demonstrated
- Diagnostic kit validation may not be sufficient
- Site-specific validation should be performed

In-vitro Diagnostic Medical Device (kits) - definition

- In-vitro Diagnostic Medical Device" means any medical device which is a reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer
- to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:
  - Concerning a physiological or pathological state, or
  - Concerning a congenital abnormality, or
  - To determine the safety and compatibility with potential recipients, or
  - To monitor therapeutic measures.
- Once a medical device is intended to be used for medical purposes it must either fall under the category of a product undergoing performance evaluation for the purpose of CE marking or be a product which is CE marked.

European Commission, MEDDEV. 2.14/2 rev.1, Feb 2004

Research use only (RUO) Kits - definition

- For research use only (RUO) products do not have an intended medical purpose.
- When a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.

European Commission, MEDDEV. 2.14/2 rev.1, Feb 2004

Research use only (RUO) Kits – intended use

- for Basic Research
  - To better understand all underlying mechanisms, in animal and / or human models, no potential to misuse RUO products
- in Pharmaceutical Research
  - To find new drug compounds, in animal and / or human models, no potential to misuse RUO products
- for a better identification and quantification of individual chemical substances or ligands in biological specimens
  - To be used as an element in a home brew diagnostic testing plan
- For In house manufacturing of so called “home brew kits
  - to improve the performance of an existing IVD within a healthcare institution

European Commission, MEDDEV. 2.14/2 rev.1, Feb 2004

Example: RUO kit – Limitations from the Manual

- For Research use only (RUO). Not for use in diagnostic procedures.
- Do not mix or substitute reagents with those from other lots or sources.
- It is important that the calibrator diluent selected for the standard curve be consistent with the samples being assayed.
- Any variation in diluent, operator, pipetting technique, washing technique, incubation time or temperature, and kit age can cause variation in binding.
- Variations in sample collection, processing, and storage may cause sample value differences.
- This assay is designed to eliminate interference by other factors present in biological samples. Until all factors have been tested in the Immunoassay, the possibility of interference cannot be excluded.

Example: Research only kit - Calibration

- This immunoassay is calibrated against a highly purified methionyl form of E. coli-expressed recombinant human XXX containing xxx amino acid residues.
- The NIBSC/WHO 2nd International Standard for XXX was evaluated in this kit.
- The dose response curve of the interim reference material parallels the standard curve.

Example: Research only kit – Precision, Recovery

	Intra-Assay Precision			Inter-Assay Precision		
Sample	1	2	3	1	2	3
n	20	20	20	20	20	20
Mean (pg/mL)	280	827	1696	176	1094	2169
Standard deviation	7.8	14.1	19.5	7.3	34.6	81.6
CV (%)	2.8	1.7	1.1	4.1	3.2	3.8

Sample Type	Average % Recovery	Range
Cell culture media (n=5)	94	85-110%
Serum (n=5)	88	75-106%
EDTA plasma (n=5)	93	80-117%
Heparin plasma (n=5)	87	76-103%
Citrate plasma (n=5)	90	78-111%

Back to ICH M10

Validation criteria

- If the reference standard in the kit differs from that of the study samples, testing should evaluate differences in assay performance of the kit reagents.
- The specificity, accuracy, precision and stability of the assay should be demonstrated under actual conditions of use in the facility conducting the sample analysis.
- Modifications from kit processing instructions should be completely validated.

Validation criteria - Comment

- Depends on whether the kit detects both the endogenous and the exogenous analyte or the endogenous only. If the kit detects both it should be calibrated using the drug substance as it has the higher quality standard. The kit needs to be validated independent if it is modified or not.
- Initial proposal: the sentence "Modifications....." can be deleted.

Workshop discussion:

- What are the challenges and do we agree with above recommended change?

Standards

- Kits that use sparse calibration standards (e.g., one- or two-point calibration curves) should include in-house validation experiments to establish the calibration curve with a sufficient number of standards across the calibration range.

Standards - Comment

- Why do we not allow to show that the one- or two point calibration is sufficient to provide accurate data? In the end the quality of data counts, not the number of calibrators.

Workshop discussion:

- **What are the challenges and can we recommended a change?**

Quality controls

- Actual QC concentrations should be known.
- ranges are not sufficient for quantitative applications.
- QCs with known concentrations should be prepared and used, independent of the kit-supplied QCs.

Quality controls - Comment

- There is no difference in a kit QC being supplied with a range (e.g. 80-120 ng/mL) and an exact concentration with ± acceptance criteria (e.g. exact concentration of 100 ng/mL with ±20% acceptance criteria).
- The use of a QC with an associated concentration range should only be an issue if the stated range is wider than normal acceptance criteria (i.e. wider than x ± 20%).

Workshop discussion:

- **What are the challenges and can we recommended a change?**

Matrix

- Calibration standards and QCs should be prepared in the same matrix as the study samples.
- Kits with calibration standards and QCs prepared in a matrix different from the study samples should be justified and appropriate experiments should be performed.

Matrix - Comments

- Here more flexibility is given -> justified use of alternative matrices! Please use the same wording in section 4.2.3
- " appropriate experiments should be performed." this needs to be clarified
- Calibration samples cannot be prepared in matrix that contains the endogenous analyte if the assay is not specific for the exogenous drug but detects the sum of both, drug and endogenous counterpart. Instead: "Calibration samples should be prepared in an analyte free matrix for which parallelism and selectivity to the study sample matrix has been shown."

Workshop discussion:

- **What are the challenges and can we recommended a change?**

Lot-to-lot variability

- If multiple kit lots are used within a study, lot-to-lot variability and comparability should be addressed for any critical reagents included in the kits.

Lot-to-lot variability - Comment

- There is no need to do it separately for each kit component. Lot to lot bridging for the whole kit is sufficient. Use of a banked reference standard or the drug substance instead of the kit standard is recommended.

Workshop discussion:

- **What are the challenges and can we recommended a change?**

Inter plate variability

- If a kit using multiple assay plates is employed, sufficient replicate QCs should be used on each plate to monitor the accuracy of the assay.
- Acceptance criteria should be established for the individual plates and for the overall analytical run.

Inter plate variability - Comment

- This depends on the bioanalytical process in the lab, whether it defines a single plate as batch or if you combine multiple plates that are analyzed in a sequence one after the other to one batch. Rephrase: "If multiple plates are processed together and combined to one batch, sufficient replicate QCs should be used on each plate.....”

Workshop discussion:

- **What are the challenges and can we recommended a change?**

Wrap Up