establishing a biorepository tailored towards companion diagnostics development

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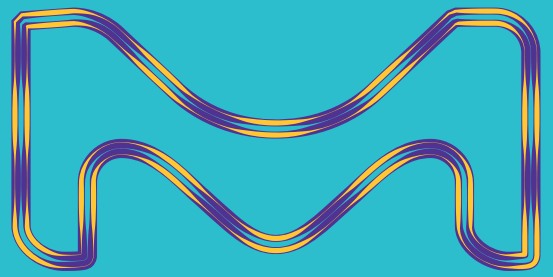


MERCK

Outline

1. Codevelopment of Therapeutic Product & Companion Diagnostic Device
2. Development of Companion Diagnostic Devices
3. Implications for Clinical Trials
4. Biobanking for Companion Diagnostics Development
5. The Merck Biorepository Approach

Codevelopment of Therapeutic Product & Companion Diagnostic Device

The FDA expects contemporaneous regulatory approvals of companion diagnostic and therapeutic product

Definition:

> *An IVD companion diagnostic device is an in vitro diagnostic device (or an imaging tool) that provides information that is **essential for the safe and effective** use of a corresponding therapeutic product to*
>
> – *Identify patients who are most likely to benefit from the therapeutic product*
>
> – *Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product*
>
> – *Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness*
>
> – *Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population*

Figure from Merck CDx Guide, based on FDA CDx guidance (orange box) and expected EU IVDR guidance (yellow box).

→ CDx to be listed in drug manual & testing required prior drug use

→ In clinical trials, the effectiveness of the therapeutic product is to be studied at least in the biomarker positive population, in certain instances also in the biomarker negative population.

Companion Diagnostics Assay Validation

1 Analytical Validation

Demonstrate reliability of assay

- Influenced by pre-analytics, -treatment
- Intend to diagnose population

2 Assessment in Clinical Trial

Test correlation of assay result with clinical outcome

- Exploratory
- Determination of cut-off value

3 Validation in Clinical Trial

Demonstrate correlation of assay result with clinical outcome

- Investigational Device Exemption (IDE) required in case of significant risk

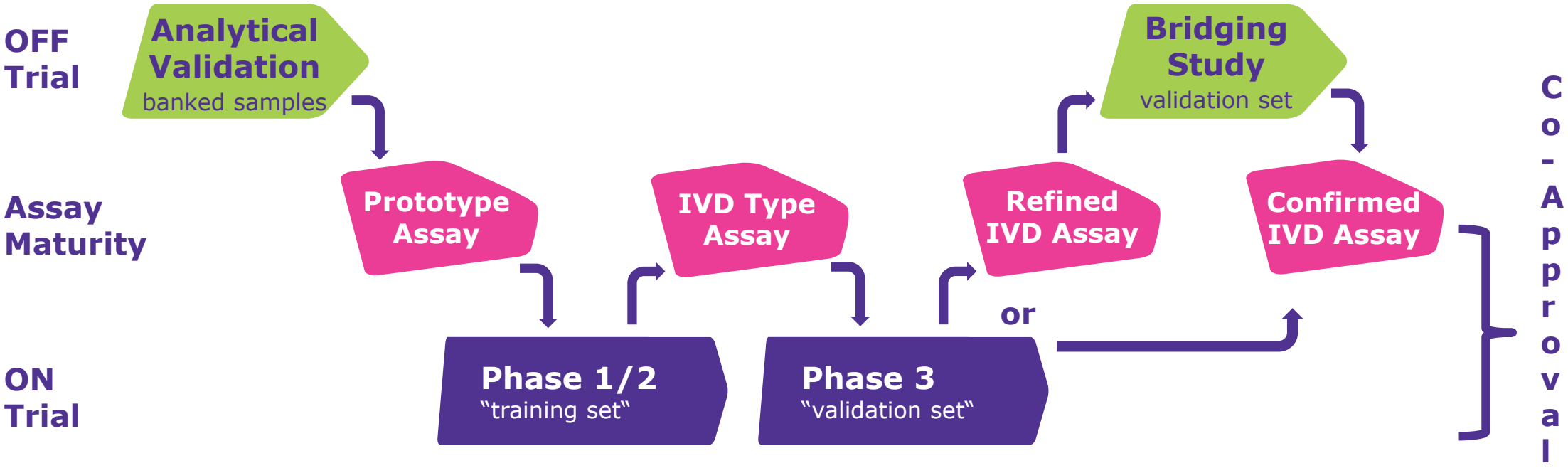
4 Bridging Study

Demonstrate comparability to assay used in trial

- If assay changes after pivotal trial
- Spare samples needed from pivotal trial

High quality samples needed at all stages!

Companion Diagnostics Assay Validation



Implications for Clinical Trials

Clinical trial for CDx validation:

Screening for biomarker positive patients (pre-screening ICF!)

→ Only positive patients enrolled (most cases)

→ Blinded drug/standard of care treatment of enrolled patients (trial ICF)

→ Demonstrate correllation of CDx result with clinical outcome
(trial planning: sufficient & appropriate subjects (samples)!)

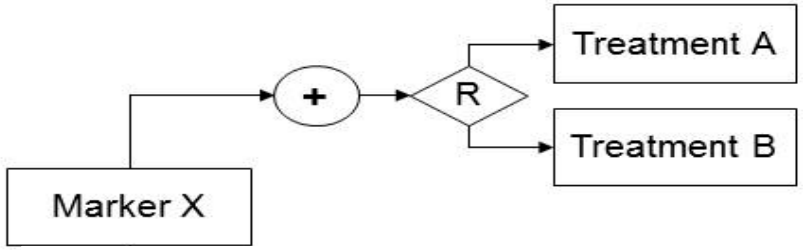


Figure from FDA CDx guidance

Biobanking for Companion Diagnostics Development

Banking of samples for future analytical validation studies and bridging study:

- Samples from both, biomarker positive & negative patients required (“intend to diagnose“)
- Bridging study requires at least 90% of clinical samples
- For analytical validation studies, samples from academic biobanks can be used
- Appropriate range of samples with differing tumor characteristics required
- Stability sets: e.g. aliquots from same sample frozen at different times

Prerequisites:

- Broad consent on sample re-use, allowing investigations by drug developer
- Well annotated samples: demographics, previous treatments, clinical & pathological factors
- Good quality samples, preanalytic parameters documented

The Merck Biorepository Approach

Informed Consent Management

Master ICF template allows broad research scope & CDx development

- Local legislation requires adaptation for individual countries:

  Capturing of local restrictions in sample attribute log

- Optional sampling requires individual patient choices:

  Capturing of patient choices in electronic Case Requisition Form (eCRF)

→ Entries from sample attribute log and eCRF will be transmitted to our biosample LIMS and mapped to individual samples therein

→ By structured representation of restrictions, we will be able to query our biosample LIMS what kind of investigations are allowed

3	ICF Feature	Master ICF Version <2.0>	Germany Local ICF Version <1.0>	China Local ICF Version <V3.0>
4	Future research use of samples limited to study drug	unlimited	Drug X	Drug X
5	Future research use of samples limited to medical condition	unlimited	Gastric Cancer	Gastric Cancer
6	Sample usage in context of CDx (Companion diagnostic tests)	Yes	Yes	No
7	Storage duration	unlimited	12 years	5 years
8	Storage location	under responsibility of the sponsor	under responsibility of the sponsor	samples not to leave China

The Merck Biorepository Approach

Patient characteristics

Demographics, previous treatments, clinical factors (e.g. stage)

Request information from the clinical sites with eCRF

Sample annotation and quality

Sample characteristics (% tumor content, tumor site, size, amount necrosis etc.)

Preanalytic factors like ischaemic time, pre- & post-centrifugation delay, centrifuge refrigerated, storage condition & deviations, cold chain maintenance, any deviations from instructions, collection method, fixative, fixation time

Request CRO to collect all available information from clinical sites using comprehensive set of administrative questions

Following this Biorepository Approach…

…. we will be prepared to have

well annotated, high quality samples

in our repository with

appropriate consents

in order to use them for

Companion Diagnostics Development

Thank you!

Dr. Oliver Karch
Chiara Daghero
Josef Straub, PhD
Crystel Ogier, PhD

References

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