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Embarking on Rx/CDx Co-Development – How to Get to the Happy End (Concurrent Approvals)

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Embarking on Rx/CDx co-development - How to get to the Happy End

An inside perspective

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CDx in Precision Medicine Development

- CDx enrolls patients that are most likely to respond
- Start of clinical trial based on patient selection may require regulatory approval (IDE*) and collaboration of the testing laboratory (CLIA)
- If trial successful, drug-approval (NDA) requires also concurrent CDx approval (PMA) in the US
- Regulatory, technical, clinical and commercial planning need to be coordinated early on
- CDx/Rx is marriage of convenience - not love ….

*IDE = Investigational Device Exemption

Although Dx partner / Rx partners have the same goal of concurrent registration, priorities are often not aligned, and the CDx may lag behind because its role is underestimated

Rx and Dx - often a difficult dialog during development

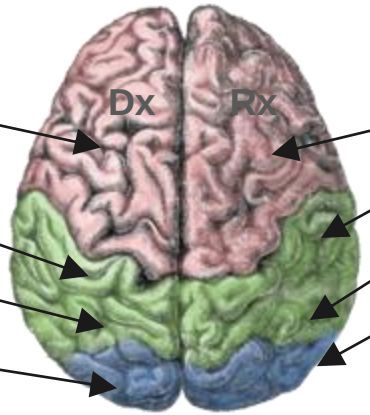
linear culture

Dx (Company X) is technology-centric

focus is technical optimization
& analytical and clinical validation

Projects have low technical risk

Value proposition low
(typical RX point of view)



circular culture

Pharma is clinically/biology (patient)-oriented

Clinical hypothesis/rationale can be speculative

Projects are high risk (clinical)

Value proposition high

- **Cultural and organizational differences exist between Dx and Rx partners**
- **These can become the source of significant friction in partnering interactions**
- **Precision Medicine requires adjustments to both Rx and Dx cultures**

Reason for underestimating the CDx

Source:
www.fitnessrepublic.com

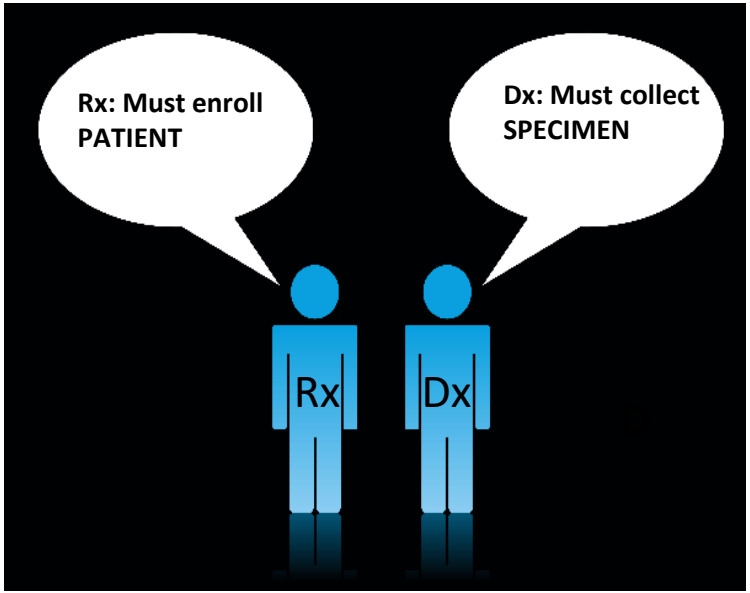
- Early focus is safety and POC (proof of principle)
- Platform choice for biomarker detection often based on convenience and latest technology but not strategic (**regulatory path, scaling, commercialization, global footprint, assay complexity**)
- Exploratory clinical culture vs. technical development culture

Initiate early dialog and align translational and technical development cultures - Particularly if early efficacy signals are convincing: need to move fast into phase II/III trials

Typical Challenges

- Is test really needed?
  - **Difficults stats / adaptive trial design - difficult during phase I/II studies**
- Which platform/technology
  - **- risk of platform changes during development**
- Clinical sample quality/quantity and storage for CDx development
  - **(BM+, BM-, screen failure)**
- Local enrollment testing: multiple tests with likely different performance characteristics enrolled patients in early trials
  - **Homogeneity of patient population**
  - **Local testing (introduction of potential selection bias)**

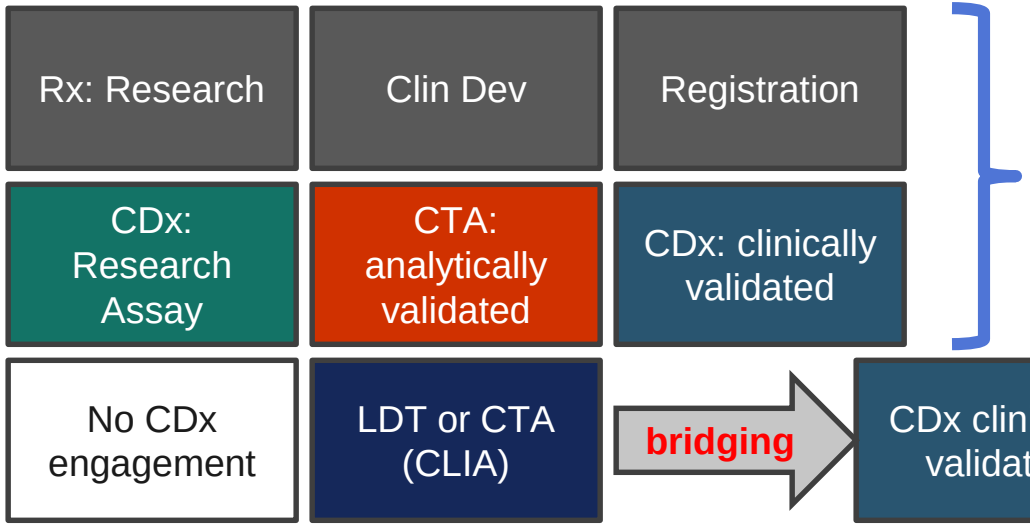
Patient and Specimen



- **Rx: priority is aggressive recruitment of patients with "enrollment" specimen, potentially not sufficient for further CDx development.**

- **Dx: assumes that clinical study protocol must have diagnostic development specimen requirements and ICF contains terms for CDx development**

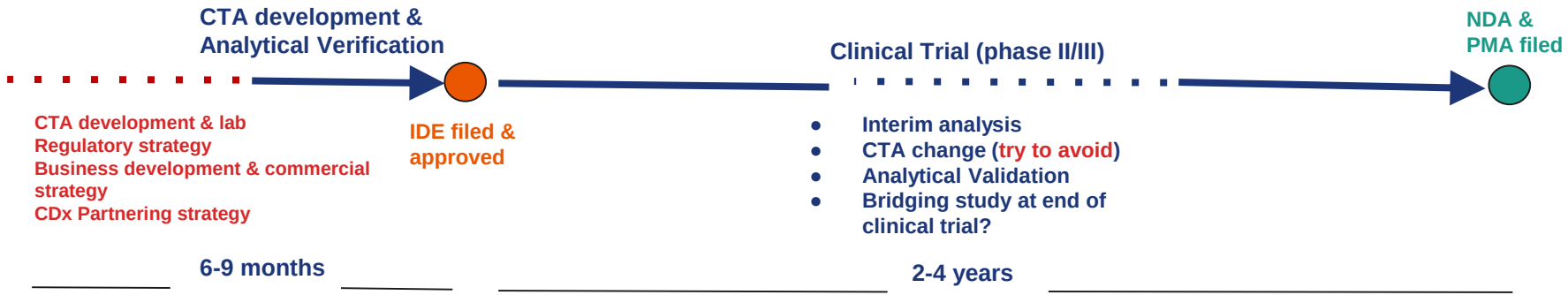
Typical Rx and Dx co-development scenarios



Ideal: consistency of results and uniformity of patient selection

Common: Pharma pressure to achieve FPFV; need to bridge CTA to final CDx

IDE-approval may drive early time-line

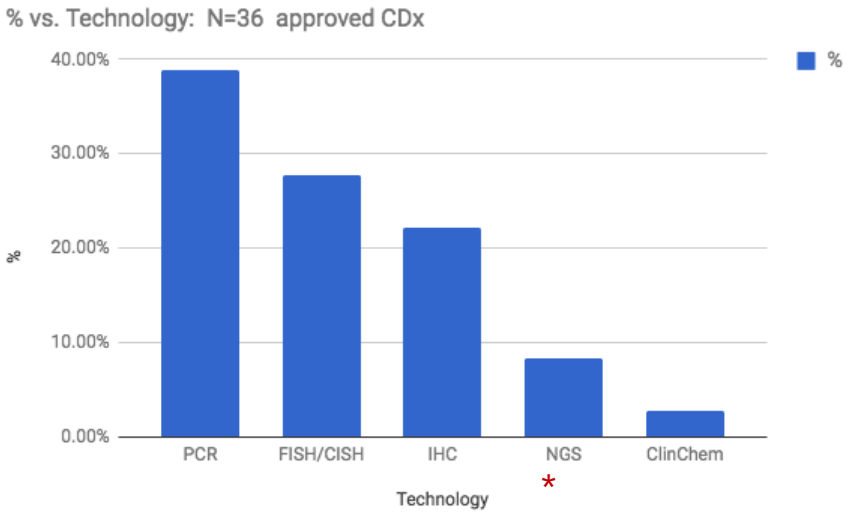


IDE: Investigational device exemption

CTA: Clinical Trial Assay

NDA: New Drug Application (Rx)
PMA: Premarket Approval (CDx)

Technology for Partnering



*

Only original PMAs counted (does not include all sPMA)

Drivers

- **Target (DNA, RNA, Protein)**
- **CD partner regulatory experience & support**
- **Complexity of technical development (Rx timeline!)**
- **Development costs**
- **Regulatory approval path (sPMA vs. PMA)**
- **Commercial strategy / global footprint**
- **Innovation?**

***Emerging new players**

Common Rx Practices that challenge CDx

CONVENIENT PRACTICE	INCONVENIENT TRUTH
Archived or no archived specimen acceptable if appropriately documented	Specimen should be current to disease stage. Stability and tumor heterogeneity impact test performance
Any amount of specimen is accepted despite quantity needed for CDx	CDx development requires sufficient amount of adequate quality specimen (sample requirement specifications)
FFPE, FNA or CNB are acceptable even if FFPE only is specified in a protocol. Different fixation methods allowed based on regional practices	Specimen type, processing methods impact test performance. Information about specimen type and processing need to be documented
Molecular prescreening by local LDT is common. Rx studies welcome local testing to accelerate enrolment without realizing its impact on CDx	Prescreening explains population enrichment and statistical bias between positive and negative population. CDx needs marker negative samples from study population
Studies initiate enrollment with local testing and confirm with central testing prior to treatment.	Potential disagreement between the local and central test results leading to conflict with the site (and patient) due to discrepancy
Countries set up clinical sites for Rx studies to maximize enrollment. Country-specific laws impact specimen and genetic result transfer are often not verified	Specimen not available for clinical validation and/or results excluded from statistical analysis
Request for inclusion of rare mutation in addition to main driver genetic alteration/s in diagnostic test	In reality, rare mutations can be analytically but not clinically validated, not enough patients enrolled with rare mutations

Recommendations

- Prepare the ground with Tmed & ClinDev & ClinOps Rx organizations early on so that they understand the challenges
- Integrate early Rx / Dx plans (study design and management, study population, sample 'viability', sample location for ONC studies and Harmonize Rx study protocol (N=patients) and Dx (N=samples) , agree on Rx and Dx statistical analysis plans for efficacy analysis
- Align early on Rx and CDx regulatory strategies
- Talk to investigators about CDx, specimen requirements and country/local prescreening programs
- Make sure that CDx test site protocol are not be ambiguous
- Use central testing site(s) for patient enrollment, use same validated test for all sites, ensure flow of marker negative samples for test validation
- If local testing is to be used details on the local test needs to be collected in patient/sample requisition form

Successful Drug + Diagnostic =

Source: realfounder.wordpress.com