

Evidence Generation to Support Companion Diagnostic (CDx) Registrational Studies

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Outline

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1 Intro to Clinical Trials and Companion Diagnostics

2 Companion Diagnostic Co-development

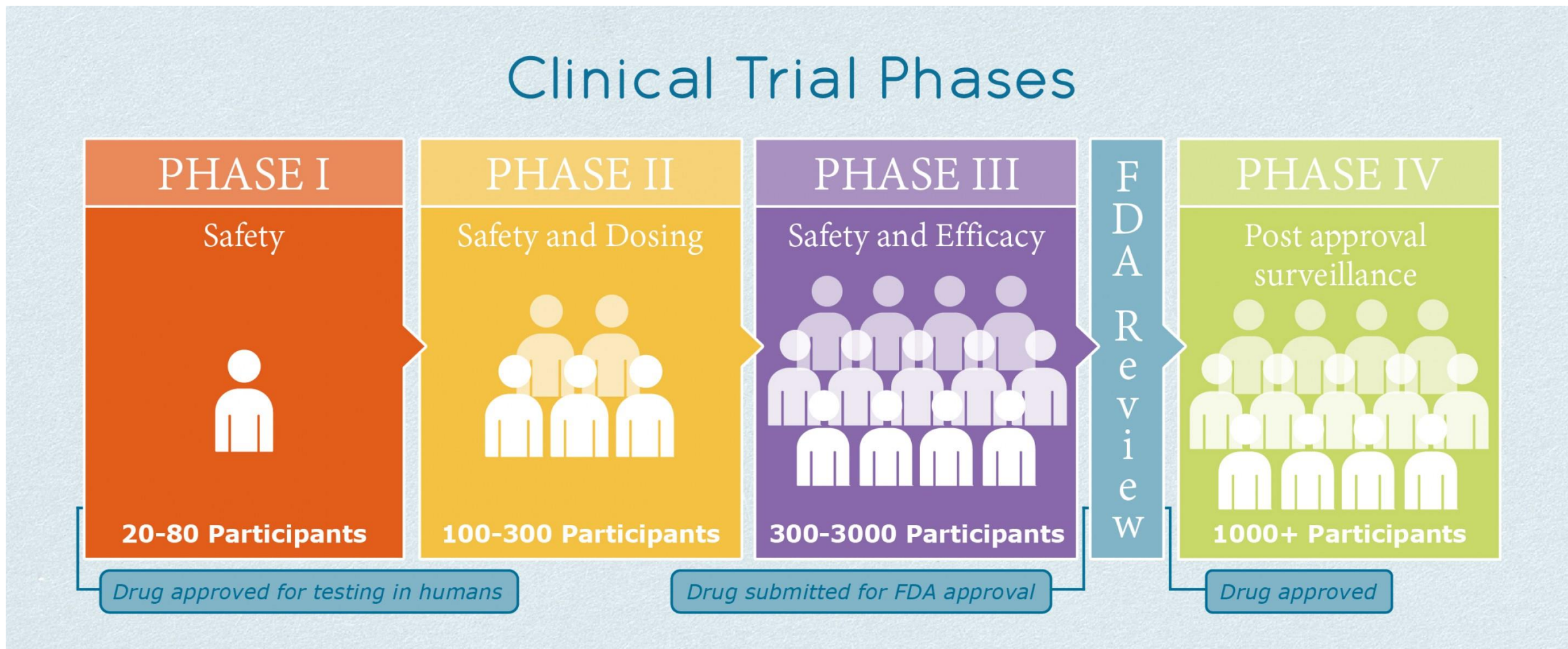
3 CDx Validation: A Clinical Perspective

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Intro to Clinical Trials and Companion Diagnostics (CDx)

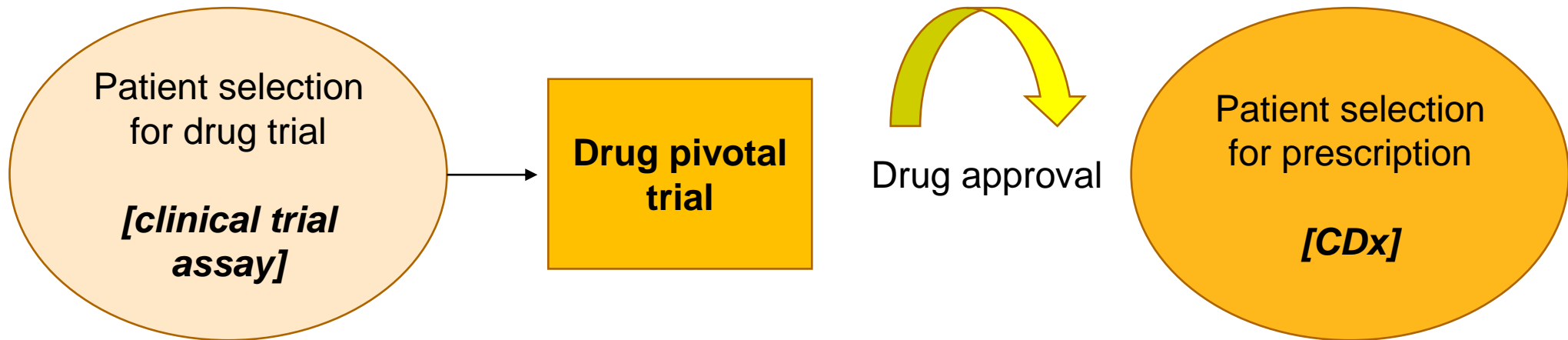
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Clinical Trial Phases & Key Objectives



Precision Medicine/Targeted Therapy and CDx

- Targeted therapies necessitate new diagnostic tools: CDx
 - Patient selection in the drug trial & for prescription
 - Selection by the same biomarker(s) at both ends



Definition of Companion Diagnostic (CDx)

- A companion diagnostic is a medical device, often an *in vitro* diagnostic (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product.
- Companion diagnostics can:
 - identify patients who are most likely to benefit from a therapeutic product
 - identify patients likely to be at increased risk for serious side effects as a result of treatment
 - monitor response to treatment for the purpose of adjusting treatment to achieve improved safety or effectiveness
- CDx products are in the highest risk category (class III IVD)

FDA (2016). Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and FDA Staff.

Relationship Between the Drug and Device

- Pharma and Diagnostic Partnership

- Pharma (Drug Sponsor) and Diagnostic (CDx Sponsor) collaborate to develop the Rx/Dx program
- Strategic alignment between both Sponsors: scientific development, regulatory strategy, study design, marketing approach

- Drug/Device Relationship

- The CDx assay is a prerequisite to the targeted therapy; Rx and Dx become reimbursable
- Key for a CDx clinical study: show clear association between the CDx result and patient response to the Rx

(Example: Merck Keytruda and Agilent PD-L1 IHC 22c3 pharmDx IHC Assay)

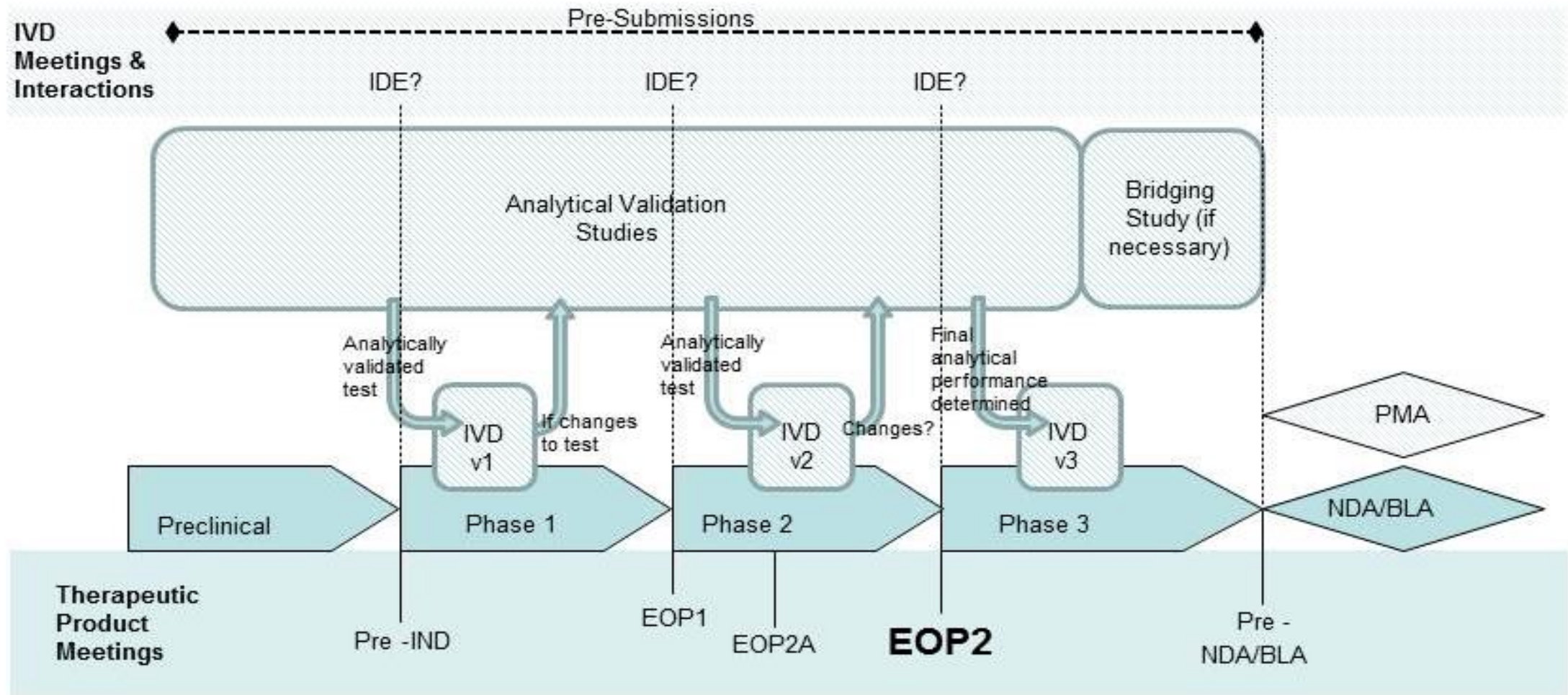
ADVANCED CERVICAL CANCER: KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Tumor Indication	PD-L1 Expression	Intended Use
Cervical Cancer	CPS ≥ 1	PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying cervical cancer patients for treatment with Keytruda (pembrolizumab)

Companion Diagnostic Co-development

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CDx/Drug Co-development

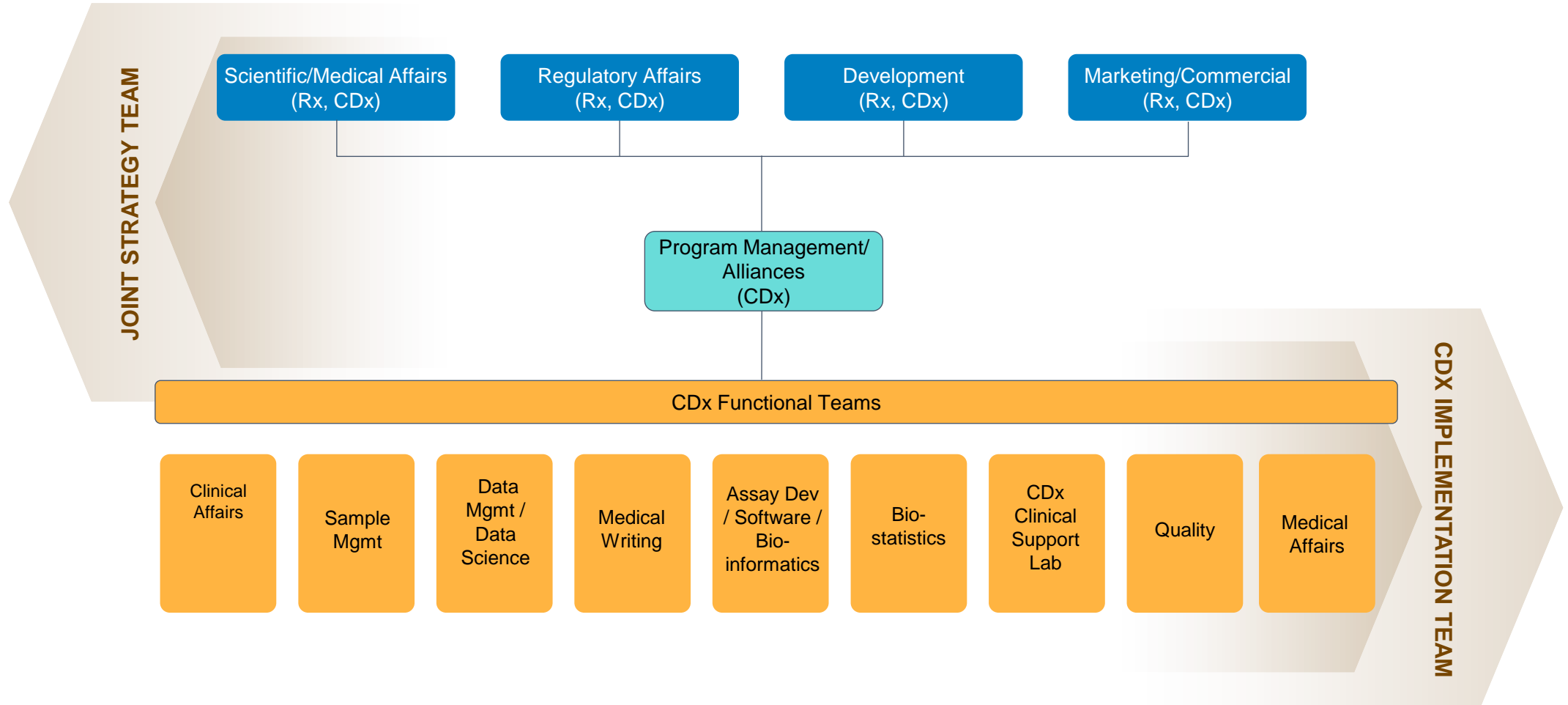


FDA (2016). Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and FDA Staff.

Goal of CDx Development

- To position CDx clinical and analytical performance studies such that quality data are generated, and Good Clinical Practice is followed in order to support regulatory submissions with minimal cost and timeline risks
- How do we accomplish this?
 - Close collaboration with our Rx partners is vital
 - Align with FDA early and often
 - Commitment to Good Clinical Practice
 - Overall Study Management – begin with the end in mind
 - Oversight of Investigational Testing Site (training, study conduct, documentation)
 - Data considerations (many possible scenarios)
 - What are the expected outputs? This defines the overall strategy

Strategy & Implementation Teams



Managing the Rx/Dx Partnership

- Joint Steering Committee (JSC) = Rx/Dx Governance
- Joint Project Team (JPT) = Rx/Dx Cross-functional Team
 - Development, Clinical Affairs, Medical Affairs, Regulatory, Alliance Management
 - Negotiate timelines and deliverables to ensure success of the entire collaboration
 - Escalate issues arising from offline and within function discussions
 - Identify risks to the success of the collaboration
- Rx/Dx Clinical Sub-team (CST)
 - Clinical Affairs, CDM, Biostatistics, Medical Affairs, Biospecimen Management, Regulatory
 - Dx Study design, objectives, endpoints
 - Negotiate timelines and deliverables to operationalize the clinical study
 - Detailed discussions on sharing study data, analysis plans, logistics

CDx Validation: A Clinical Perspective

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Components of CDx Validation

- Analytical Validity
 - Establishing that the performance characteristics of a test are acceptable in terms of its relevant performance characteristics
- Clinical Utility
 - conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease, including the range of possible benefits or risks to individuals and populations.
- Clinical Validity
 - Establishing that the test identifies, measures, or predicts the concept of interest

H Scheerens, A Malong, K Bassett, Z Boyd, V Gupta, J Harris, et al (2017). Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch. Clin Transl Sci, vol 10, 84–92

Clinical Validation - Ideal vs Real Life

Ideally:

- CDx and drug are co-developed.
- Market-ready/production equivalent CDx is used for patient enrollment/selection for the drug pivotal trial. CDx validation is integrated with the drug approval.

In real life:

- CDx is **not ready** at the time of the drug trial. Thus, patients are enrolled by an alternative assay (Local Test or Clinical Trial Assay).

FDA (2016). Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and FDA Staff.

Prospective vs. Retrospective Designs

- Prospective testing occurs prior to patient enrollment in the trial. CDx is used to screen patients for eligibility (results for 100% of patients in the Rx trial)
 - If Dx is involved early enough, there are opportunities to negotiate sample acceptability criteria, sample quality and quantity, what and how data are collected at screening, etc
 - Dx has access to samples from screen failures
 - Regulatory agencies know exactly how the test result relates to the Rx trial
- Retrospective testing occurs after Rx trial is complete and uses archived samples from randomized/enrolled patients.
 - Pitfalls include limited or missing samples, questionable pedigree of stored samples, missing data, etc.
 - Supplemental samples from other cohort(s) representing the ITD/ITT populations likely required.

Clinical Validation – Bridging from CTA to CDx

- In the **enriched** scenario where a CTA is used to enroll patients, bridging to CDx is needed.
 - FDA prefers that **ALL** samples tested with the CTA are retested with the candidate CDx and valid test results are used to assess comparative performance
- No two assays perfectly agree with each other. **How do we know the CTA and CDx select the same patient population?**
- **Objective: to demonstrate that drug efficacy in the CTA selected patient population is maintained in the CDx selected population.**

Association Between Drug Trial and Bridging Study

	Clinical Trial (Drug)	Bridging Study (CDx)
Objectives	Demonstrate efficacy of the drug in the intended population	<ul style="list-style-type: none"> • Demonstrate efficacy of the drug in the CDx population • Concordance between CDx and CTA
Intended Population	Biomarker+ by CTA	Biomarker+ by CDx
Primary Analysis Patient Set	Intent-to-Treat (ITT) – all subjects who are randomized/treated	<ul style="list-style-type: none"> • ITT from trial who are CDx+ (for positive concordance & drug efficacy) plus supplemental cohort who are CTA- (for negative concordance) = ITD
What's Needed for Sample Size Determination	Efficacy (in terms of the primary endpoint) on ITT and statistical power	<ul style="list-style-type: none"> • Efficacy on ITT from trial and statistical power • Concordance between CTA and CDx • Prevalence of biomarker+ determined by CTA

Challenges/Risks of Bridging Designs

Challenge/Risk	Mitigation
Missing samples or insufficient sample quantity retained for patients enrolled in pharma trial	<ul style="list-style-type: none">• Ensure that sample, demography and disease state characteristics of the enrolled population are proportionally preserved in the tested subset• During reanalysis of primary outcome data, perform imputation for missing data to ensure that efficacy is preserved.
No retention of samples from screen-fail patients	<ul style="list-style-type: none">• Procure a cohort of samples that reflects the sample, demography and disease state of the enrolled population and test with the CDx and the CTA.
Ambiguity in or lack of patient consent for use of samples outside the pharma clinical trial	<ul style="list-style-type: none">• Dx review of ICF templates to ensure appropriate description of sample usage
Sample size of CDx evaluable cohort has low statistical power.	<ul style="list-style-type: none">• Collect/procure additional samples and test with CTA and CDx

Meijuan Li (2015). *Statistical Consideration and Challenges in Bridging Study of Personalized Medicine*, Journal of Biopharmaceutical Statistics, vol 25, 397-407.

Closing and References

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How Dx Successfully Works with Pharma

- Collaboration and Partnership first!
 - Dx teams typically must educate Pharma teams on device development and clinical study practices and requirements
- Close alignment on regulatory filing strategies. (Is there a breakthrough designation? Is the CDx a post-marketing commitment?)
- Clearly aligning on roles and responsibilities between Dx and Rx partners (early and often)
- Meet regularly (joint and subteams) to manage timelines, action items and deliverables between parties



Opportunities for Improvement – Dx Perspective

- More involvement by Dx Medical and Clinical Affairs and Biostatistics in the initial project definition and scoping
- Earlier involvement of CDx cross-functional team SMEs in the partner relationship
 - Proposals are largely driven by Business Development and key inputs to the scope and timeline can be missed.
- Earlier engagement for functional SMEs between the partners (Rx Biostatistics and Dx Biostatistics, Rx Data Management and Dx Data Management)

References

- FDA (2014). *In Vitro Companion Diagnostic Devices: Guidance for Industry and FDA Staff*.
- FDA (2016). *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and FDA Staff*.
- Meijuan Li (2015). *Statistical Consideration and Challenges in Bridging Study of Personalized Medicine*, Journal of Biopharmaceutical Statistics, vol 25, 397-407.
- H Scheerens, A Malong, K Bassett, Z Boyd, V Gupta, J Harris, et al (2017). *Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch*. Clin Transl Sci, vol 10, 84–92.
- List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).
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- <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process>
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