

CHOOSING THE BEST PATHWAY FOR CDx DEVELOPMENT AND COMMERCIALIZATION

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Drug developers are increasingly incorporating a companion diagnostic (CDx) strategy into their programs to deliver safer, more effective and appropriate therapies to the right patients. While the end result can be significantly beneficial for patients, and development partners, the path from analytical and clinical validation to demonstrating clinical utility and obtaining regulatory approval is often challenging. It requires a comprehensive understanding of clinical trial design, regulatory submission strategies both for the therapy and the diagnostic assay, and also a line of sight for successful commercialization.

Two models are being considered in the industry. The more traditional approach is a 3-way partnering approach between the *in vitro* diagnostic (IVD) company, the drug developer and the clinical research organization (CRO) service provider. In this approach, the IVD manufacturer seeks approval or clearance for the assay, which results in a diagnostic kit that can be deployed globally in a decentralized fashion. The Laboratory Developed Test (LDT) pathway involves the laboratory seeking regulatory approval of the assay that was developed to support specific trials that demonstrate the clinical utility and analytical validity of the assay. This approach is often referred to as a single-site premarket approval (PMA). Both routes should be considered before embarking on a lengthy and challenging program of activities, which is impacted by the co-development and timing of the parallel activities for drug and diagnostic assay. The two routes are not mutually exclusive—as there may be opportunities to bridge from a single laboratory PMA-approved assay to an IVD assay that allows decentralized testing across multiple laboratories.

Enhancing the Working Relationships within the IVD Partnering Model

An IVD assay is usually developed and validated on an established assay platform by a single diagnostic manufacturer, who obtains an Investigational Device Exemption (IDE) from the FDA to utilize the assay within a clinical trial to obtain patient safety and effectiveness data. The development of the assay and platform follows manufacturing based Design Control in compliance with CFR820. In this model, the manufacturer also files for the PMA prior to commercialization of the companion diagnostic assay.

Typically, the IVD model is supported by a manufacturer with a broad geographic reach to enable the potential for test availability and global distribution at launch. Such assays are often used as inclusion criteria for clinical trials and accordingly, rapid turnaround times are required to deliver results for prospective patient enrollment for clinical trial sites. In many of the successful PMA approvals to date, as well as ongoing development programs, the testing laboratory provides data not only for the clinical study but also to the IVD manufacturer regarding the analytical performance features of the assay (i.e., sensitivity, specificity, reproducibility).

Economies of scale can be achieved through the appropriate co-development relationship, for which the partners are the pharmaceutical/biotech company, the IVD manufacturer and a CRO/laboratory. This triad of organizations creates efficiencies by developing a strong strategy that considers the roles of each party and also unites the needs of co-development, including the technology platform along with the requirements of regulatory agencies and the clinical trial.

In this relationship, the diagnostic manufacturer can provide the development-stage assays and accelerate their speed to market by leveraging the vast scientific resources and laboratory footprint of a combined Clinical Trial testing and Clinical Diagnostic organization such as that of Covance and LabCorp.

IVD Collaboration on a CDx Clinical Validation

In a recent case study, Covance partnered with a diagnostic development company to ensure uniform technologies across all its labs with the same instrumentation and sequestered lots of assay calibrators and controls. This enabled combinable, robust data at each location to support the diagnostic co-development during clinical trials. The diagnostic manufacturer gained access to an expanded platform for global clinical studies while collaborative assay evaluation and troubleshooting were managed between the parties to improve overall assay performance and accelerate CDx validation.

Strong engagement between the diagnostic and the pharmaceutical companies and the testing laboratory ensured solid, aligned data for both the drug and diagnostic filing—the key benefit of the co-development partnership.

Mitigating Potential Risks with the LDT Partnering Model

Similar to the development of an IVD, pursuing the LDT route also needs alignment with the development of the therapeutic and undergoes the same rigorous regulatory review and considerations. LDT planning starts with a pre-Investigational Device Exemption (IDE) meeting with the regulatory agency to determine the level of risk and in so doing, to also determine if an Investigational Device Exemption is required. Regardless of the outcome of the risk assessment, the Laboratory is required to develop a device protocol and submit to the Investigational Review Board (IRB).

As assays are typically approved within one initial testing site, LDTs can defer upfront risk and provide efficiencies for the development process. For example, a significant amount of the analytical verification work to support a PMA submission can be conducted following a favorable interim analysis for the therapeutic, providing flexibility and improved management of timelines for the development program. In the single-site approval approach, the assay can still be transferred to other testing sites following a method comparison study and/or can be globally distributed after bridging studies by IVD manufacturers, if that approach is required.

LDTs can be ideal for niche indications, as this model may mitigate the initial front-loaded investment that may be required for IVD development and better allow for the management of project timeline. The LDT model initially utilizes a standard, CLIA-level validation, providing a fit-for-trial assay that is discussed with the FDA during the pre-IDE process. As previously mentioned, validation and approval of the companion assay by the LDT approach can be useful in situations when there may be compressed timelines.

A Commercial Strategy for Success

Regardless of the companion diagnostic pathway consideration, a strong commercial strategy is necessary to bringing the important assay to market. A value-added diagnostic that changes current clinical practice with demonstrated clinical utility and well-defined intended use will clearly have a more favorable commercial outcome.

The diagnostic itself should be available when the therapy is approved and be completely compatible with corresponding laboratory workflow to deliver a timely medical decision. A well-planned strategy must also include market access considerations, such as the market size, a reimbursement strategy and an overall cost-benefit analysis to assist with adoption and recognize any gaps—early in the process.

When it comes to developing and implementing a robust CDx strategy, clinical diagnostic laboratories and contract research organizations can serve as experienced partners in the process. LabCorp and Covance have supported the testing for more than two-thirds of all CDx PMAs approved by FDA, covering multiple therapeutic areas. As your partner, we know how to best support you at every stage of the co-development process and move your CDx and therapeutic ahead. Let's work together to integrate technical capabilities, navigate regulations and leverage our global network to advance your personalized medicine programs.



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Mark received his PhD in Pharmaceutical Sciences from the University of Nottingham (UK) and has worked in the clinical diagnostics arena for over 20 years, holding senior positions in both the in vitro diagnostic and reference laboratory industries. He joined Covance in 2012 to spearhead its Companion Diagnostics initiative, designed to assist pharmaceutical and diagnostic companies in drug/companion diagnostic co-development.



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Alan is Executive Director of Companion Diagnostics at Covance and has been focused in pharmacogenetics and personalized medicine for more than 10 years. He works across the industry to develop biomarker programs with biopharma companies, from analytical and clinical validation through to regulatory approval and commercialization. Prior to joining Covance, Alan held leadership positions in oncology clinical development at AstraZeneca. He earned his degrees in Microbiology from the University of Liverpool.

Learn more about our companion diagnostics solutions at www.covance.com/cdx

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