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REGULATORY FOCUS

Considerations for Development and Implementation of a Companion Diagnostic

By Kennon Daniels, PhD and Karen L. Richards, RAC

This article discusses four key topics any pharmaceutical company should consider for development and implementation of a Companion Diagnostic (CDx) for use with oncology drugs or biologics.

Introduction

The drug development process in the US is extremely long and costly. It is critical to get the patient a drug that is going to work for them. Especially in the oncology space, drugs for the most part are extremely toxic to the patient. Therefore, not only is the patient taking a medicine that is ineffective and toxic, but also the patient is not receiving the efficacious drug that will target their specific tumor. The key missing component is a biomarker to identify patients who are able to respond. Therefore, the goal of companion diagnostics is to work in combination with the drug to provide information so that patients have access to the right drug at the right time in a cost-effective manner. The pursuit of a Companion Diagnostic (CDx), based on stratification to identify the most effective biomarkers, can reduce both drug development time and clinical trial sizes and facilitate more rapid regulatory approvals and time to market. Similarly, demonstrating that the drug works with a select population of patients and a CDx can demonstrate a higher likelihood of identifying those patients encourages payers to minimize access barriers for that population.

Pharmaceutical companies are asking when and how to bring biomarkers through the development process to ensure market approval for their drugs or biologics should FDA require a CDx for safety and efficacy. The variety of activities related to early assay development, the use of clinical trial assays for patient selection in clinical trials, regulatory strategies for clinical trial planning for early market adoption and strategy extensions for broad market uptake require detailed step-wise planning. This article aims to help bring awareness and understanding across the different functions within a pharmaceutical company for what is required in this regulated US FDA environment and how to best leverage resources for biomarkers used during drug discovery and clinical trials through to commercialization. Although written to address the oncology market, the principles apply across other disease areas.

Determining the Biomarker Target Early in the Drug Development Process, Including the Targeted Mutation(s) and Sample Type

Even in the very early stages of drug development, the pharmaceutical company should evaluate if a biomarker for diagnostic application is necessary for the use of the drug. According to FDA, a CDx provides information that is, "Essential for the safe and effective use of a corresponding drug or biological product."[1] The CDx can be employed in many ways such as monitoring treatment response or identifying patients at risk for serious side effects.[2] Typically, in the oncology space, the CDx is used to identify the specific subset of patients likely to respond to a drug or biologic.

It is critical to develop an understanding of the type of diagnostic needed to accurately identify the correct patient population for the drug and to understand the cancer development of the individual patient. Based on the mechanism of action of the drug, the CDx target may be the qualitative measurement of a specific antibody such as HER-2, ALK, or PD-L1 within Formalin-Fixed Paraffin-Embedded (FFPE) tumor tissue from the patient. In other instances, detection of target variants may be required within one or two genes, a handful of genes within a gene family or signaling pathway or a large oncopanel. Next Generation Sequencing (NGS) provides access to the largest amount of data and the most efficient screening of patients who may be appropriate for the drug/biologic treatment. However, even within this modality, there are specific development considerations related to the sample collection, sample type and target biomarker(s)/variant(s) that need to be considered.

The pharmaceutical company should evaluate the ease of sample collection with regard to location and size of the patient's tumor. If the tumor type is rare and hard to access, a liquid biopsy may be the most appropriate methodology. The options for sample collection include tumor tissue, urine, saliva and blood. For some NGS assays, reference DNA or RNA is also required at collection from saliva, blood or normal tissue surrounding the tumor. Early studies to determine the access and stability of the biomarker for use in the CDx are critical for approvability and marketability of the product. Based on recent CDx approvals

for the large panel NGS assays, the sample matrix of choice is DNA, which is quite stable. However, RNA also can be used for detection of fusions and therefore, the assay would need the capability of detecting both RNA and DNA. This would need to be accounted for in the product development plan for analytical and clinical validation of the assay.

In addition to sample collection, the type of target variant for detection should be assessed in the patient population as well as the matrix for sequencing, i.e., DNA and/or RNA. Valid scientific support for the target variant should be evaluated through research and clinical sample testing. The pharmaceutical company's diagnostic partner should compile the evidence from published literature or publicly accessible databases of human genetic variants. These databases can provide support for the clinical validity of the genotype-phenotype observed and NGS test or clinical sample testing in the patient population.[3] Clinical samples collected prospectively or purchased from a vendor also should be used to validate the target variants such as Single Nucleotide Variants (SNVs), insertions, deletions, copy number variants, fusions, microsatellite status and/or tumor mutational burden. In some instances, there are mutations detected that were not expected and the CDx assay should have the capabilities to identify these *de novo* variants that speak to the gene coverage and analysis algorithm capabilities.

Deciding What the Final CDx Should be and Selecting the Right Partner

The current trend in NGS-based assays are large pancancer gene panels as evidenced by the most recent NGS clearance and approval for the MSK IMPACT and FoundationOne CDx.[4] This trend is also occurring across the US within hospital-based CLIA-licensed laboratories through use of validated laboratory developed tests (LDT), which are large pancancer panels (>1000 gene targets).

In making product configuration decisions, pharmaceutical companies should consider the number of gene targets and types of variants within the gene targets. Is there a previously approved and commercially available CDx or cleared assay that already detects these targets and could be repurposed? Does the pharmaceutical company want to partner with a known entity for the addition of gene targets to a previously approved assay or currently running LDT-based pancancer or targeted gene panel? Does the pharmaceutical company want a brand new assay that would be developed and customized by a third-party partner specific to the company drugs' targets and detection requirements?

Before entering into a formal agreement, pharmaceutical companies should communicate the product goals (technical and commercial) and ensure that the diagnostic partner can meet the obligations to comply with the US FDA regulations for a Premarket Approval (PMA) of a CDx. This agreement will include the diagnostic partner's technical experience with similar products and knowledge, if not experience, with successful execution of appropriate analytical and clinical performance validation, proprietary software development and validation, and Quality System Regulations (QSR) in

compliance with 21 CFR 820 (QSR). Quality must be included throughout the assay development process for reagent manufacturing.

For the pharmaceutical company, a critical question for the CDx will be where the test will be used, i.e., in every laboratory in the US as an IVD kit or as a single-laboratory testing service? Two examples of CDx assays for single-site testing include FoundationOne CDx and BRACAnalysis CDx. In addition, FDA recently cleared the MSK-IMPACT assay with a pancancer claim using NGS in tumor DNA for detection as a single-site assay. FDA has not approved a pancancer NGS CDx assay as an IVD kit yet. The closest FDA has come to setting regulatory precedence for that configuration is the Oncomine™ Dx Target Test that uses targeted high throughput, parallel-sequencing technology to detect SNVs and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from FFPE tumor tissue samples from patients with Non-Small Cell Lung Cancer (NSCLC) using the Ion PGM™ Dx System. This assay is targeted to only one indication, NSCLC, but the assay detects variants in RNA and DNA as well as being based on CDx approval, there is the ability to use this test in any CLIA-certified laboratory in the US. Typically immunohistochemistry (IHC), Chromogenic In Situ Hybridization (CISH) and Polymerase Chain Reaction (PCR)-based CDx are created and marketed as IVD kits for use in US CLIA laboratories. There have been several approvals of Fluorescence In Situ Hybridization (FISH) based CDx with testing being conducted at a single site or as an IVD kit.

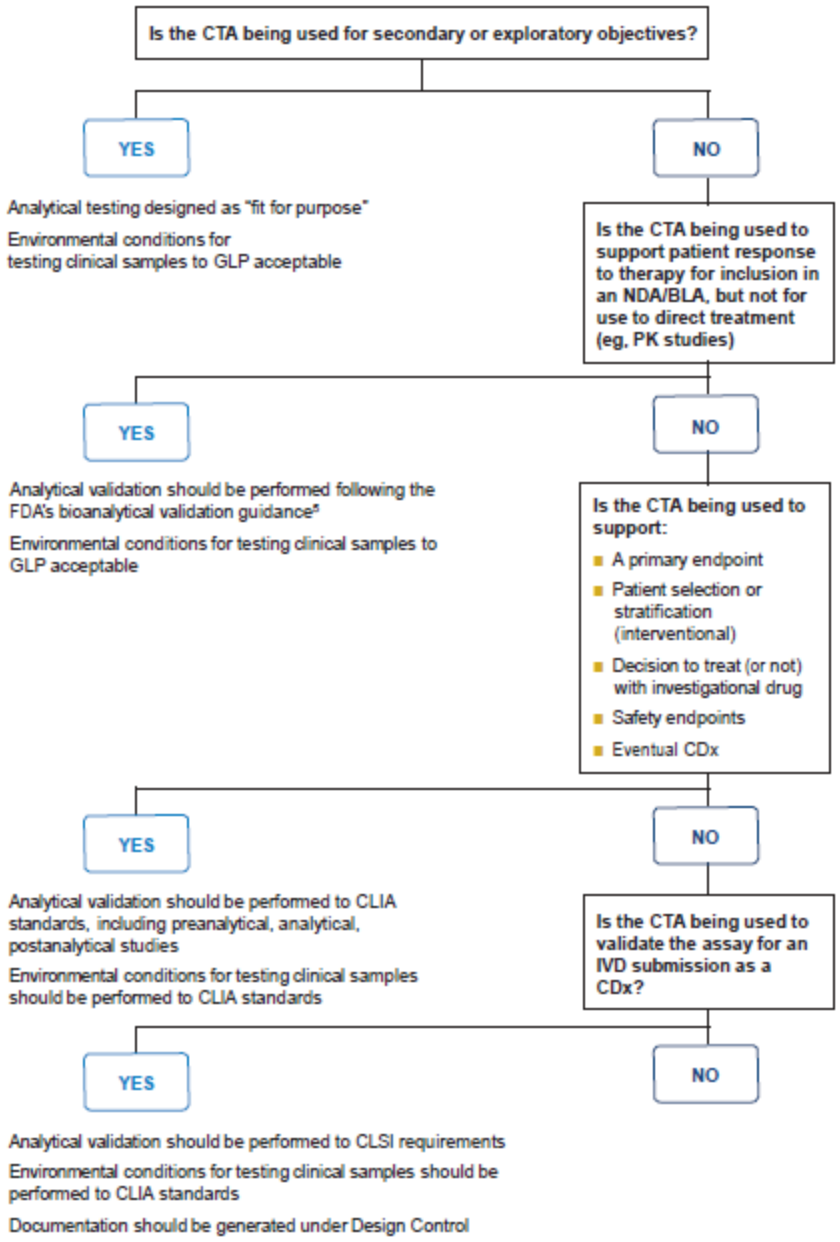
Determining When to Move From a Research Phase Assay to a More Regulated Approach and Where Testing Should Occur

The starting point for diagnostic development is the research phase where the assay is being developed and tweaked to ensure the performance metrics are met such as the correct target gene variants are being called for the proposed patient population. Suppose a drug company needed to develop a test method and conduct sample testing using a Clinical Trial Assay (CTA). Results from the CTA may be used to support the drug application (PK studies, for example), enrollment or stratification into a trial (regardless of trial phase), drug safety or may be required later on as a CDx for drug approval.

What level of validation of the CTA is necessary under any or all of these circumstances? And under what environment must the testing be performed (for example, tested by lab personnel, equipment and laboratory conditions certified to CLIA or GLP standards)?

Consider the following flow diagram as a way to think through these questions.

Figure 1. Evaluation of the Performance Validation Requirements for a CTA Based on how the Diagnostic will be Used in the Clinical Study



Developing an understanding of the questions to be answered by the CTA will help determine when to move from a research phase assay to a more regulated approach for the CDx and where testing should occur to validate the CDx in combination with the drug.

Understanding Risk Determination and FDA Communications

As an outcome of understanding the CTA and transition to a CDx, the most frequently asked question from a pharmaceutical company is how it can be introduced into the clinical trial for clinical sample testing and will the CDx

require an investigational device exemption (IDE)? This leads the pharmaceutical company to ask how to obtain a definitive answer through the FDA's risk determination process.

Pharmaceutical companies want to know whether an IDE is required and under what circumstances, but often have not considered when in the drug development phase this determination is needed, whether it be for a Phase I/IIa trial to evaluate safety or efficacy in selected populations or a Phase IIb or III registrational trial. Ultimately, when or if an IDE is required is based on how the CDx could cause risk to the patient population and not with the specific phase of drug development. Risk associated with the results obtained from the CDx is not related to the drug treatment, but instead is assessed based on the risk to the patient in the event of a false negative or false positive result (when the CDx is being used for patient selection or stratification).

In such cases, a CDx may determine who receives (or does not receive) a particular investigational therapy. If the CDx is inaccurate, then treatment decisions are being made based on misinformation regarding the potential benefits of a therapeutic product. Other considerations include sample collection requirements outside the standard of care such as a requirement for an invasive sampling procedure at the beginning of the study and then again at progression. This would increase the risk of the use of the CDx in the clinical study.

Risk determinations for use of a CDx require detailed information on how the CDx is going to be used during the clinical trial. All unapproved, and therefore investigational, IVDs for use in clinical investigations require an approved IDE, an abbreviated IDE or are exempt from the IDE regulations. A benefit versus risk determination for how the CDx will be used in the drug or biologic trial will help to determine whether an erroneous result from the CDx poses any higher risk to the patient than the investigational drug or biologic itself. Documentation supporting the benefit versus risk determination, whether made by the pharmaceutical company, the diagnostic company or through a formal FDA submission also will help to inform the IRB for decision making on use of the CDx in the drug or biologic trial.

Below are options available to the company or the diagnostic partner for confirmation of the oncology-based CDx risk determination:

- Submit the protocol and risk determination to the IRB during the approval process.
- Submit an IDE to FDA/CDRH/OIR for the investigational IVD's use in the clinical study.
- Submit the risk determination as part of the IND to CDER per the draft guidance, *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry* (April 2018) and the risk determination is made by CDER/CBER with consultation by CDRH. Note: this only applies to oncology.

- Submit a Study Risk Determination (SRD) Q-Submission to FDA/CDRH/OIR.

Each option must be carefully evaluated for time and content requirements related to document preparation prior to submission as well as FDA turnaround time for review and feedback. For example, both the IDE and risk determination as part of the IND have an FDA review clock of 30 days for feedback. However, the level of information required for an IDE far exceeds that required as part of the risk determination for inclusion in the IND and therefore, will require more time to prepare. Understanding the potential regulatory pathways that could be employed is critical to streamline the process in order to gain approval for both the drug and diagnostic for use in the proposed clinical study.

Conclusion

Communication between the pharmaceutical company and potential diagnostic partners should happen early and often both in industry and across the review teams within FDA. In order for this to occur successfully, detailed step-wise planning must occur prior to the pivotal registration trial. Planning should begin as soon as the pharmaceutical company knows a CDx will be required, whether that is before Phase I or during Phase I or II testing. Determining the target(s), detection methodology, and sample types are the initial key steps. Another critical component involves selection of the diagnostic partner, whether it be an IVD manufacturer or CLIA laboratory, willing to comply with FDA regulations for testing and validation. How the assay evolves with regard to assay performance, validation requirements, and when the assay is used for patient selection as well as risk determination within the clinical study will need to be incorporated into the overall plan for drug development.

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About the Authors

Kennon Daniels, PhD is a director, in vitro diagnostics and quality within Precision for Medicine's Translational and Regulatory Sciences Practice. Daniels received her PhD in human genetics from Virginia Commonwealth University. Daniels has more than 12 years of US regulatory affairs experience with IVDs and pharmaceutical products. She specializes in the development of US regulatory strategies, analytical and clinical trial study designs and FDA marketing submissions (Q-Submissions, IDEs, *de novos*, 510(k)s and PMAs) for a wide range of IVD assays and instrument platforms (>70 products). She can be contacted at Kennon.daniels@precisionformedicine.com.

Karen L. Richards, RAC, is the senior vice president of in vitro diagnostics and quality within Precision for Medicine's Translational and Regulatory Sciences Practice. Richards has worked in the in vitro diagnostics regulatory, quality, clinical trial and compliance areas for more than 30 years. She has implemented quality systems for diagnostic products to meet the requirements of US FDA, ISO 9001, ISO 13485, CLIA, and CAP. Richards has served as a board member of the Association of Medical Diagnostics Manufacturers (AMDM), an organization dedicated to the in vitro diagnostic industry and provides educational programs with FDA's Center for Devices and Radiological Health's (CDRH) Office of In Vitro Diagnostics and Radiological Health (OIR). She can be contacted at Karen.richards@precisionformedicine.com.

Cite as: Daniels K and Richards K L. "Considerations for Development and Implementation of a Companion Diagnostic." *Regulatory Focus.* August 2019. Regulatory Affairs Professionals Society.