

An Intersection of Pharma and Medical Devices - Development of Companion Diagnostics in Conjunction with Targeted Therapies

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ABSTRACT

The intersection of pharma and devices is growing. For example, devices can be used to deliver drugs, e.g., drug-eluting heart stents. A growing area of drugs and devices is targeted therapies and companion diagnostics. This means that a subject who tests positive for a gene mutation (the companion diagnostic test) will receive the study drug while subjects who test negative for a gene mutation test will not receive the study drug. The clinical validation of the companion diagnostic test is done in conjunction is done during the conduct of a pharma clinical trial (Phase II and/or III). Thus collection of data on screen failures (subjects who test negative) is necessary for calculation of sensitivity and specificity, e.g., using SAS PROC FREQ. Sensitivity and specificity are key analyses for companion diagnostic tests. This paper will demonstrate the clinical development of a companion diagnostic test during testing of a drug in Phase II and/or III.

INTRODUCTION

WHAT IS A COMPANION DIAGNOSTIC?

A companion diagnostic device is a test that is essential for safe and effective use of a therapeutic product. It is often, an in vitro diagnostic device (IVD). What this means is that without the test, the therapeutic product cannot be considered safe and effective. The test defines population, dose, etc. of the therapeutic product. Use of drug in other ways is unsafe/ineffective/unknown.

Table 1 lists four examples of companion diagnostic tests. I have personally worked on clinical trials for three of the four companion diagnostic tests listed in Table 1 – BRAF, EGFR and KRAS. For the purposes of this paper I will primarily use BRAF as a example of the development of a companion diagnostic test.

Table 1: Some Examples of Companion Diagnostic Tests

Drug	Indication	Companion Diagnostic Test	Comment
Herceptin	Breast Cancer	HER2 expression	Patient must be HER2 positive to receive the Herceptin drug.
Zelboraf	Melanoma	BRAF mutation	Patients who test positive for BRAF mutation receive the Zelboraf.
Tarceva	NSCLC	EGFR mutation	Patients who test positive for EGFR mutations receive Tarceva
Erbitux	Colorectal Cancer	KRAS mutation	Patients who test negative for KRAS mutation receive Erbitux

WHAT IS A TARGETED THERAPY?

A targeted therapy is a therapeutic product that has only shown benefits in certain patients identified by a predictive marker determined by a companion diagnostic test.

CHALLENGES IN COMPANION DIAGNOSTIC DEVELOPMENT

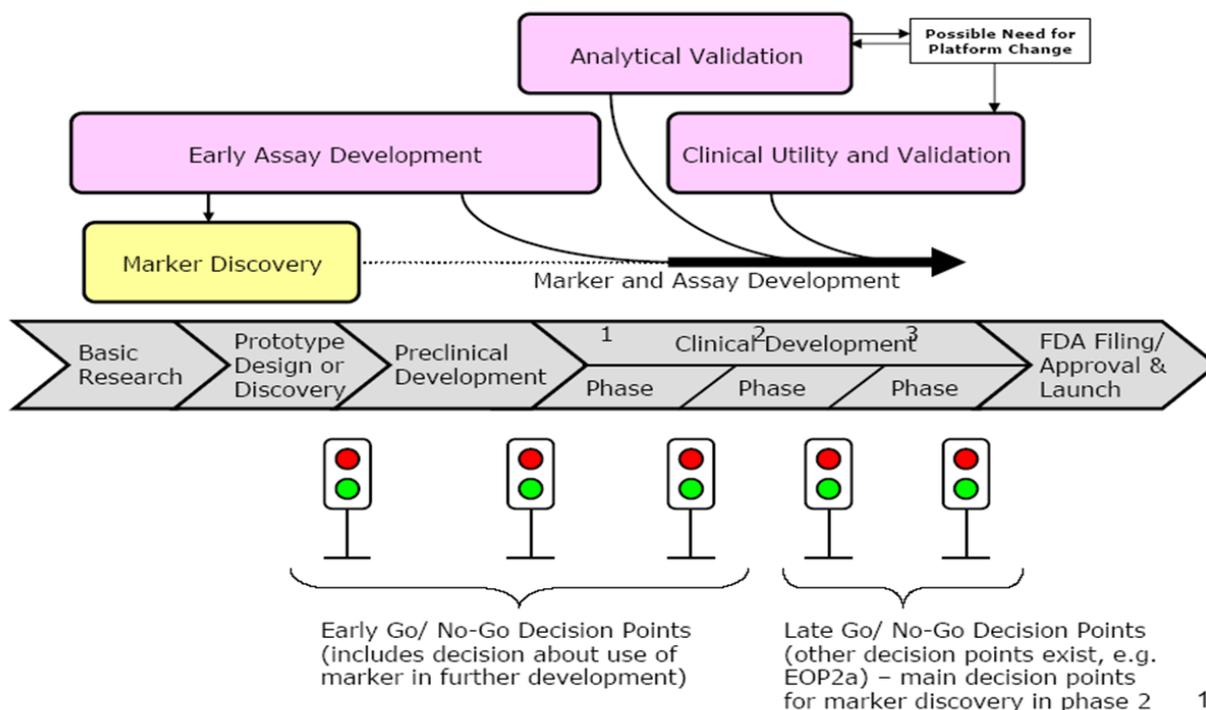
The challenges of developing a companion diagnostic test are illustrated in Figure 1. The challenge is that the clinical validation and utility of the test are performed during the clinical trials for the targeted therapy. However, the first step is the analytical validation of the companion diagnostic test. Analytical validation means the ability of the diagnostic test to perform the measurement of interest with accuracy and reliability. This validity includes analytical sensitivity and specificity, reproducibility, robustness and satisfaction of quality controls.

As mentioned above, the clinical validation and utility of companion diagnostic test occur during the clinical trials of the targeted therapy. Clinical validation means the ability of the diagnostic test to

precisely and reliably predict the clinical phenotype of interest (for example, overall survival or progression-free survival of patients receiving a given treatment). It includes clinical sensitivity and specificity as well as the positive and negative predictive values of the test. The clinical validity also refers to the so-called “diagnostic performance” of the test. The analytical validity of the test is usually pre-clinical whereas the clinical validity of the test is during the clinical trials for the targeted therapy.

Clinical utility or clinical usefulness is generally required for all IVD tests and means the ability to improve the clinical outcome of patients, and to provide an added value in terms of optimizing treatment decisions and, as a corollary, therapeutic strategy. Demonstrating the predictive value of a biomarker is equivalent to showing the clinical utility of its diagnostic test.

Figure 1: The Development Process for a Companion Diagnostic Test



SCREEN FAILURES

Since the result of the companion diagnostic test determines who gets enrolled in the clinical trial for the targeted therapy, it is important to understand the need for data from screen failures in the development of the companion diagnostic test. In other words, if the entry criteria into the clinical trial is that subjects test positive for a gene mutation then data on screen failures is essential for the companion diagnostic test to be clinically validated. This can be done by comparing the result of the companion diagnostic with an approved method. For example, gene sequencing (which can be expensive) can be used as a gold standard for the companion diagnostic test that is being developed. Table 2 illustrates the companion diagnostic versus the gold standard (gene sequencing).

Table 2: Comparison of Companion Diagnostic Test with Gold Standard

	Gold Standard Positive	Gold Standard Negative	
Companion Diagnostic Positive	a	c	a + c
Companion Diagnostic Negative	b	d	b + d
	a + b	c + d	

In Table 2, if the entry criteria for subjects to be enrolled in the clinical trial of the targeted therapy is that they test positive for the companion diagnostic test, then subjects who test negative are screen failures (not enrolled in the clinical trial for the targeted therapy). Thus it is important to distinguish between the clinical population for the targeted therapy (subjects who test positive with the companion diagnostic test) versus the clinical population for the companion diagnostic test (all subjects who are tested with the companion diagnostic test). Thus clinical data on screen failures is essential for clinical validation of the companion diagnostic test. Without screen failure data statistics like sensitivity, specificity, false positives and false negatives cannot be calculated and characterized.

At a minimum, the screening identification number for screen failures needs to be collected to calculate statistics such as sensitivity, specificity, false positive rate and false negative rate using SAS® procedures such as PROC FREQ. However, characterization of the screen positive and screen negative populations are also needed. Thus basic demographic information and other baseline characteristics need to be collected on the screen failure population. Thus while this clinical data on screen failures may not be needed for the approval of the targeted therapy, this clinical data on screen failures is essential for the approval of the companion diagnostic.

APPROVAL PROCESS

FDA approval of targeted therapies and companion diagnostic tests is a joint process. The targeted therapy is submitted to either CDER or CBER for approval. The companion diagnostic test is submitted to CDRH for approval (Smoak 2010). The approvals are dependent upon both products (the therapeutic product and the companion diagnostic test) being approved at approximately the same time. Thus the submissions must be coordinated to occur at approximately the same time.

One challenge in a joint submission of a targeted therapy and a companion diagnostic test is the submission of the data in CDISC format. While the use of CDISC standards is required for submissions to CDER and CBER, the use of CDISC standards is not currently required for approval of medical devices (Smoak et al 2013). In particular, IVD products do not conform well to CDISC standards. Potential models for IVD products have been proposed (Smoak et al, 2014a; Smoak et al, 2014b). However much work remains to be done to bring medical devices (including IVDs) into the CDISC world.

CONCLUSION

There are challenges in developing a targeted therapeutic and a companion diagnostic test. The obvious benefit is that a therapeutic product is given to the correct patient population. So, the obvious benefit is worth the challenges in this unique development process where a companion diagnostic test is clinically validated while a therapeutic product is going through the typical clinical trial process. Whereas clinical data on screen failures is not useful for targeted therapies, it is essential for companion diagnostic tests. Finally, the approval process of the targeted therapy and the companion diagnostic test is complex because of the joint submission and approval. The approval process is further complicated since the use of CDISC standards is required for therapeutic products, but not medical devices (including IVDs). Thus, targeted therapies and companion diagnostic tests are truly representative of pharma and medical devices.

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Companion Diagnostics, continued

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