

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Companion Diagnostics

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### H&O What is a companion diagnostic?

The US Food and Drug Administration (FDA) does not have a definition of a companion diagnostic established in regulations or guidance, but we describe it as a medical product, often an in vitro diagnostic device, that defines the condition of use for another medical product, including a drug, biologic product, or another device. An in vitro diagnostic test is a specific test that measures a biomarker and has been validated to perform adequately for use in delivering medical care. A companion diagnostic is required as a condition of use in order to make a medical product safe and effective. A companion diagnostic is therefore a subset of biomarker-oriented tests, which cover all diagnostic tests.

### H&O What is its role in the drug development process and in personalized medicine?

Therapeutic decisions that are driven by single test results are becoming more prominent as personalized medicine evolves. There are many ways that a companion diagnostic may be useful and necessary in order to appropriately and effectively use a therapeutic. It may have a role in selecting patients in whom the drug would be effective. It could be used to identify patients who should not be treated with the drug because of a high risk of adverse events. Further, it may have a role simply in identifying patients similar to those who were studied to establish a drug's effectiveness. In the latter case, we do not know that the test distinguishes patients who will benefit from those who will not, but we recognize that reliable identification of patients who match the drug's indications is necessary in order to ensure that the drug performs as expected in marketed use.

Many oncology drugs are quite toxic and tend to have a positive effect in only a fraction of the population

with a particular phenotype or disease. The highest use of companion diagnostics is to ensure that patients who are not expected to benefit from a drug will not suffer the adverse events associated with that drug, and that patients who are going to benefit or have the potential to benefit are properly selected. In oncology and probably many other areas, it is simply a narrowing of the population for treatment to derive the best benefit with the least risk.

The role of companion diagnostics in personalized medicine is somewhat distinct from the role of biomarkers in the drug development process, where they might be used to help shape the development path for a drug. There are numerous ways in which biomarkers may be utilized to inform selection of a particular type of therapeutic modality in order to develop aspects of its pharmacokinetic or pharmacodynamic profile.

Since the FDA's aim is to approve the therapeutic product and the companion diagnostic together, it is important to identify and demonstrate the necessary performance characteristics of the test in time for use of a fully specified and validated test in pivotal trials of the therapeutic product.

The FDA's Critical Path Initiative, which was launched in 2004, is a program by which we hope to accelerate or make less burdensome the development and ultimately the approval process for medical products.

### H&O How are companion diagnostics regulated?

The FDA regulates a companion diagnostic in the context of how it will be used to deliver medical care in the practice of medicine. It is regulated in a manner similar to any other kind of diagnostic device. We need to understand the analytical and clinical performance characteristics of the test. We evaluate the measurement quality of the testing system, the actual clinical information that the diagnostic can produce, and the correspondence of that measurement with some physiologic feature that indicates that someone should be treated or will benefit from treatment. The analytical evaluation of the test for the purposes of developing a companion diagnostic—one that is going to be a test reviewed for approval—is something that falls under FDA's Center for Devices and Radiological Health's (CDRH) area of expertise, and the clinical application of that test is informed by results of clinical trials. Most of our understanding of the clinical performance characteristics originates from information that is

collected from a clinical trial submitted for review by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The CDRH is responsible for regulating medical devices. Thus, pre-market review of the drug and companion diagnostic device leads to approval by CDER or CBER for the therapeutic product, and approval by CDRH for the companion diagnostic device.

### **H&O** What are the challenges seen with companion diagnostics?

The challenges are at least threefold. One is to develop a scientific understanding of the analyte's relevance to use of the therapeutic product. Such an understanding might come from hypothesis-driven biologic insights gained in developing targeted therapies. It might also come from purely empirical (but well examined) correlation of the analyte and drug effect. Another challenge is in coordinating timely availability and use of resources to bring the test through its research and investigational phases to an approvable version. Such coordination is well recognized as a challenge when the analyte is central to development of the drug from "day one," but it can also be a challenge when the analyte is recognized late (eg, after drug approval) for its value in refining the use of the drug. The third major challenge is in designing, executing, and analyzing the pivotal studies and trials needed to demonstrate the performance of the drug and the companion diagnostic together as they will be used in clinical practice. Understanding the drug effect across all marker populations is encouraged. The therapeutic company and/or the device company might find it challenging to integrate their understanding of both the therapeutic and the diagnostic in order to provide sufficient information for FDA approval of both the therapeutic product and the companion diagnostic test.

### **H&O** What are some examples of a therapeutic and a companion diagnostic?

The classic example is trastuzumab (Herceptin, Genentech), which treats HER2-overexpressing metastatic breast cancer. When the drug was still in clinical trials, it was necessary to identify the appropriate populations that had the potential to respond to the drug, and an immunohistochemistry test—HercepTest—was developed and approved essentially simultaneously with trastuzumab. Once the drug was approved, the kit was available to determine which patients should receive trastuzumab. There have been a few other drug-device combinations that have been approved, but none to date have had the impact attributed to trastuzumab and the HER2 testing for selecting patients that would most benefit from the drug.

In colorectal cancer, cetuximab (Erbix, Bristol-Myers Squibb) and panitumumab (Vectibix, Amgen) are

used to treat patients with tumors that overexpress the epidermal growth factor receptor (EGFR). The companion diagnostic EGFR pharmDx is used to determine whether a patient overexpresses EGFR. This test was used to identify patients eligible for study entry in the pivotal trials leading to cetuximab and panitumumab approval, and the test was approved simultaneously with the drugs.

The discovery of KRAS mutation as a therapy-directing marker in colorectal cancer is emerging late; the observation that this marker was able to identify patients who likely would not benefit from cetuximab and panitumumab was made after the drugs were already approved. KRAS mutation testing, without reference to a specific test, is now mentioned in the drug labels for reasons of safety, since it is important to avoid unnecessary exposure to potentially toxic drugs. It remains to be seen whether and how KRAS mutation testing will be established to select patients for well-defined clinical benefit.

In the December 2008 meeting of the Oncologic Drugs Advisory Committee, issues regarding the KRAS story, such as reproducibility, size of effect, consistency of the effect, and the ability to examine the performance of the marker in an unbiased selection of patients, were discussed. Going forward, if investigators are able to conduct trials in which they prospectively define the ways in which they want to study a biomarker, the concerns inherent in the retrospectively gathered data can be overcome.

### **H&O** What do you anticipate the role of companion diagnostics to be in the future?

It is expected that as markers become more numerous and better understood, they will be helpful in directing the appropriate use of therapeutics. One would like to be able to distinguish between patients who will respond to a drug and those who will not on the basis of a biomarker test that has been validated, made into an in vitro diagnostic, and approved as a companion diagnostic. We hope for developments that will ultimately validate the use of in vitro diagnostic tests to informatively direct drug therapy. This is the direction in which those who define personalized medicine as the right drug to the right person at the right time view markers heading.

The FDA anticipates issuing guidance that will define what we consider to be a companion diagnostic and that will discuss the regulatory status of these tests. We also hope to publish some less formally crafted information, such as more efficient and scientifically directed methods for setting up clinical trials that include companion diagnostics.

In the meantime, as we have been gaining experience but do not have explicit guidance to help the pharmaceutical/biologics and device industries, we remain very interested in consulting with drug and device developers in order to streamline drug and in vitro diagnostic development and approval.