White paper

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From biomarkers to diagnostics:
The road to success

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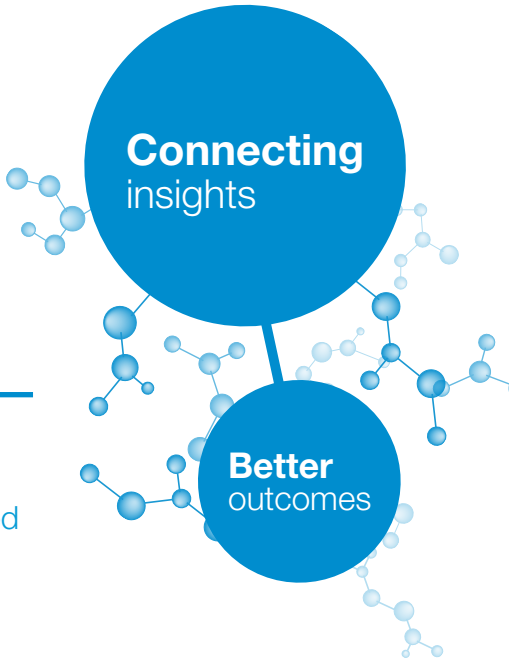

Executive summary

The successful innovation of targeted therapies and the rise of personalized medicine (also known as precision medicine) have generated a parallel demand – to have accurate and reliable means of identifying patients who will benefit from treatment in clinical practice.

Encouraged by regulatory and reimbursement authorities, this trend is drawing biopharma closer to the world of diagnostic companies than ever before. Today biopharma is being forced to consider options for establishing an accompanying patient-selection diagnostic framework at earlier and earlier stages in development. In the first of this two-part series, Eric Groves reviewed the increasing role of biomarkers in defining patient populations and measuring outcomes in oncology clinical trials.[1] In this second paper, he assesses the passage from biomarker candidate to diagnostic entity and outline the opportunities and pitfalls for biopharma sponsors along the way, with a particular focus on the regulatory requirements of the FDA.

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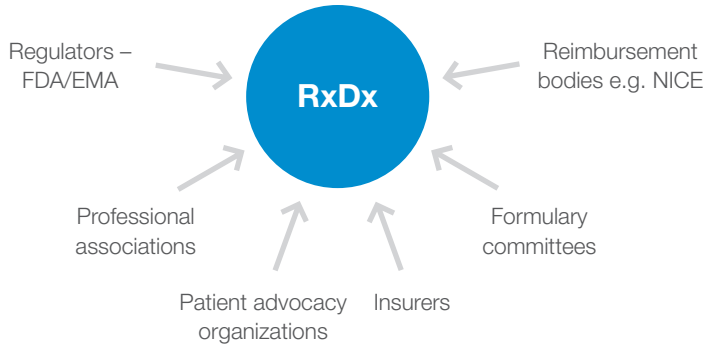
Introduction

Most physicians are used to the role of diagnostic tests to clarify and support their clinical decision making. Increasingly over recent years, the diagnostic process has become more strongly driven by the need to pre-select patients based on drug labels and licenses.

This move has come about through a number of factors, which include advancing technology (enabling us to measure more specific markers of efficacy), a heightened understanding of the disease process, and a greater appreciation of the uniqueness of an individual's tumor at the molecular level. All of these factors are also reflected in the changing design of our clinical trials. But this move is driven by societal factors as well, most prominent among which is the need to restrict targeted therapies to those patients most likely to benefit. With the advent of personalized/precision medicine, the one-size-fits-all approach is being consigned to history.

The implications of this sea change for drug developers are becoming increasingly apparent as a variety of interested parties start to stipulate their requirements for the therapeutic segmentation of patient populations (Figure 1). As may be expected, this situation brings challenges for the development process, with biopharma R&D being forced into new areas of expertise as the necessary incorporation of appropriate supporting diagnostics into the development effort requires that they plan the best route for ensuring that these diagnostics are brought to the marketplace along with the relevant drugs in their new indications.

Figure 1 Stakeholder influence on drug–diagnostic (RxDx) co-development



In this review we highlight some of the issues and challenges facing biopharma in the current co-development climate – when the demand for diagnostics detecting genomic, proteomic, or gene expression markers to accompany new therapies is growing, but the understanding of how best to achieve this growth is lagging behind. There is good reason for this gap between demand and supply, as the development paths of drugs and diagnostics are very different, and drug manufacturers often lack personnel with experience in diagnostic development. To address this, we discuss some of the considerations involved in choosing a diagnostic partner to develop, validate, and market an appropriate test, and we review the different choices available for satisfying the needs of the regulatory bodies. Lastly, we examine how to incorporate all of these factors into the registration trial process to bring drugs and tests to market in parallel, and minimize delays in market adoption.

The demand for diagnostics detecting genomic, proteomic or gene expression markers to accompany new therapies is growing but the understanding of how best to achieve this growth is lagging behind.

Categories of accompanying diagnostics

There are three main categories of diagnostic development:

The first is co-development from an early stage of the drug and diagnostic on a parallel course. In this category we may expect that preclinical data will support the correlation between the presence of a marker and drug effectiveness. Appropriate methods or technologies will be evaluated early on, and the biomarker could even be used in Phase I trials to retrospectively profile patients. Depending on the confidence level in the clinical validity of the biomarker, a Phase II post-hoc statistical trial could be employed or, if confidence in the clinical validity of the biomarker is very high, a prospective enrichment strategy could be undertaken (described in the first paper of this two-part series). Finally, an investigational use only (IUO) kit could be utilized for the pivotal Phase III trial to select patients and a commercial diagnostic launched with the drug at approval.

This first path is useful when it is known early on that only a small population will benefit from a drug but that the magnitude of benefit may be high. Such an example may be seen in the rearrangement of the ALK gene in non-small cell lung cancer (NSCLC); although this occurs in only approximately 5% of NSCLC cases, it was recently shown that the ALK inhibitor crizotinib led to shrinkage or stabilization of tumors in as many as 90% of patients selected for the ALK translocation.[2] Sometimes, as with this example, the reagent requires development but occasionally it is already available and in use, typically in analyte specific reagent (ASR) form. This is the case with bcr-abl fluorescence *in situ* hybridization (FISH) in patients with chronic myeloid leukemia (CML).

The second category is development of the diagnostic after a drug has successfully navigated Phase III and been approved by the regulatory authorities. In this case, subsequent data are found that link a biomarker with response or resistance to the drug. This was the case with Vectibix® (panitumumab) and Erbitux® (cetuximab), where the drugs were approved (in the U.S.) without a K-RAS biomarker requirement in the label, but subsequent clinical data revealed that colorectal cancer tumors with a mutant K-RAS gene did not respond to these agents (see page 9). The same scenario may be found to apply to epidermal growth factor receptor (EGFR) mutations in the case of EGFR small molecule inhibitors like Tarceva® (erlotinib).

The third category is when an accompanying diagnostic is developed for one indication but then repurposed for another indication after further clinical data become available. An example of this is the Dako HercepTest™ assay, originally designed for use with breast cancer specimens (see page 8), but now also being used to detect HER2 over-expression in gastric tumors.

Categories of accompanying diagnostics

- Diagnostic tests being developed in parallel with the drug
- Diagnostic tests developed after the drug has come to market
- Diagnostic tests developed for one indication and then repurposed or re-developed for another

The regulatory environment

In March 2010, Australian cancer drug developer ChemGenex came under fire from the FDA's oncology panel for presenting its leukemia drug Omapro™ (omacetaxine mepesuccinate), designed for patients with a particular genetic mutation, without a validated diagnostic test for the mutation.[3] This explicit warning to biopharma from the FDA is the latest in a series of developments highlighting the regulatory sector's growing commitment to diagnostic/treatment co-development.

While the FDA has long had the practice of placing biomarker requirements in the labels of drugs whose registration trials required biomarkers for patient selection (as in the case of Ontak® [denileukin diftitox] and Herceptin® [trastuzumab] for example), the FDA strengthened its focus on biomarker research in 2004, with the publication of the groundbreaking FDA report "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products."[4,5] This report concluded that "the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences." Predicting that the use of biomarkers in drug targeting would help bridge the gap between basic research and the development of new drugs, the FDA next produced their "Drug-Diagnostic (RxDx) Co-Development Concept Paper,"[6] which provided a framework for combination product submission. Viewed as definitive at the time, this paper has subsequently been recognized as a "work in progress" after a number of bodies, including the Personalized Medicine Coalition (PMC), highlighted various deficiencies. The FDA has recently committed to issuing revised and expanded RxDx co-development guidance by the end of 2010.[7]

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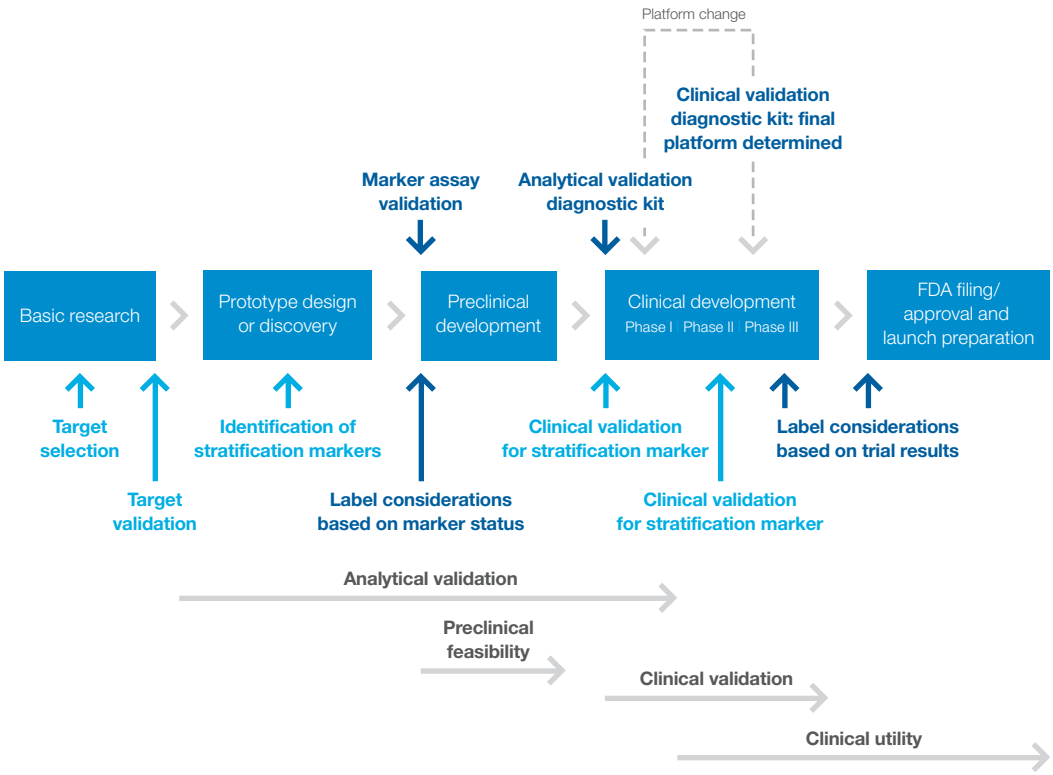
The promotion of diagnostic development inherent in these FDA initiatives has to some extent been mirrored in Europe by the EMA's Road Map to 2010,[8] and the two agencies have established channels for exchange of information related to the use of pharmacogenetics and pharmacogenomics in drug development.

Regulatory pathway options for diagnostics

The recent decisions of various regulators leaves the door wide open for diagnostic co-development, a pathway for which is shown in Figure 2.

Figure 2 Prototype of an idealized approach to developing and regulating combined diagnostic tests and drugs[9]



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Unfortunately this exposes biopharma and their diagnostic partners to the rigors, complexities, flux, and controversy of the current regulatory system. As noted previously, in this paper we focus on the regulatory system in the U.S., although it is worth noting that the EMA is actively encouraging development of accompanying diagnostics (e.g. for K-RAS) and in some instances has been more proactive and progressive in its recommendations than the FDA, resulting in *in vitro* diagnostic (IVD) use of K-RAS mutation analyses.

In the U.S., diagnostics are regulated under different regimes (shown below), depending on the nature of the diagnostic product. For decision-makers, choosing which option to pursue has significant implications for the speed and cost of the review process, for the clinical adoption of the test, and ultimately for the success of the therapy using the diagnostic product.

Pathways for regulatory approval of diagnostics

- Obtain pre-market regulatory clearance from the FDA to sell a **diagnostic kit** (a packaged product) or **companion diagnostic**.
- Develop a **laboratory-developed test (LDT)** and sell the in-house performance of the test as a service. These so-called "home brews" are regulated via the Clinical Laboratory Improvement Amendments (CLIA) of 1988.
- Sell one or more of the components of diagnostic tests as **analyte-specific reagents (ASRs)**. ASRs, individually, are exempt from pre-market notification, thus enabling early-market penetration and enhancing early adoption of the technology.
- Position the product for **investigational use only (IUO)**, used for diagnostics that have not established clinical utility, although this will not allow widespread commercialization of the test.

FDA route: IVDs sold as kits are regulated by the FDA as medical devices and accordingly are subject to pre-marketing and post-marketing controls. Data from laboratories using these kits can be utilized to support clinical decisions. The kits are classified as Class I, II, or III according to the level of control required to ensure safety and effectiveness. In this context, this refers to the impact on patients of the results generated by the test, particularly false negative or false positive results. The classification determines the pre-marketing process, and thus the complexity, level of scrutiny, and corresponding time and expense required.

Some well-established, low-risk assays are exempt from the need for FDA pre-marketing authorization. Class I IVDs that are "substantially equivalent" to an existing approved product may submit a pre-market notification – 510(k) – 90 days before marketing. Class II involves special controls in addition to the general controls of Class I. Class III devices, which include all "first-in-class" kits, are subject to pre-market approval (PMA), the most stringent type of application; PMA entails a scientific review of all available evidence of the safety and effectiveness of a device for its intended use. IVD applications for new types of assays will almost always need supporting clinical data, although the regulatory framework for these clinical studies differs from that for pharmaceuticals. Examples of Class III IVDs include HercepTest, for detection of HER2+ breast cancer (and now being intensively studied for HER2+ gastric cancer), and DxS' TheraScreen® K-RAS, for detection of mutated K-RAS in metastatic colorectal cancer.

CLIA (laboratory-developed tests) route: Laboratory-developed tests (LDTs) are generally developed for use in a single laboratory. A company can elect to create an LDT in-house ("home brew") and must sell the performance of that test as a service rather than a kit. The FDA does not typically review these tests, but they are subject to the test performance standards of CLIA. Under CLIA provisions, certification requires laboratories to adhere to standards of quality control, personnel qualifications, and documentation, as well as to validate tests, but there are no standards for implementing these validations. The level of scrutiny of CLIA inspections and certification requirements will depend on the complexity of the tests performed. An example of an LDT is Genomic Health's Oncotype DX®, a test for the detection of 21 genes that together indicate both the likely benefit of chemotherapy – to patients who have node-negative, estrogen receptor-positive breast cancer – and the likelihood of recurrence.

Choosing a regulatory pathway: The FDA route has not been the path of choice for most IVDs to date as it is inherently the costliest and most time-consuming option. More than 1,000 biomarkers are currently marketed as diagnostic tests, and they are almost all offered as homebrew tests in central laboratories. In the U.S. cancer molecular diagnostics market in 2007, the revenue distribution between CLIA- and FDA-approved products was 98% CLIA, 2% FDA. To some degree this distribution also reflects the difficulty of obtaining adequately controlled clinical data to support the IVD. However, while opting for a strategic pathway that bypasses rigorous regulatory scrutiny may lower that particular hurdle, it can dramatically raise the next one.

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Clinical adoption is one of the biggest barriers to the success of a new test (and ultimately the drug), and meeting the high standards of a regulator like the FDA goes a long way toward convincing clinicians and payers of a test's validity and clinical utility. That said, PMA tests can cost laboratories significantly more than unapproved generic versions of these tests, a factor which can also influence market uptake since an expensive patient selection test places higher hurdles for a new drug's adoption, even though they usually cost a fraction of a single month of treatment of an oncology targeted therapeutic.

Seeking FDA input during the development process: It is frequently of benefit to seek discussions with the FDA proactively during RxDx development in order to find out which branch(es) of the FDA might be interested in a particular diagnostic topic, to understand the agency parameters and expectations for data submission, and to gain buy-in for an investigational or confirmatory trial. A request for a meeting with the FDA to discuss the benefit of a diagnostic pertaining to a specific drug can be made by biopharma, with the meeting either held separately or during a preinvestigational device exemption (IDE) session. Alternatively, advice from the FDA can be sought using the relatively new Voluntary Exploratory Data Submission (VXDS) process, which involves submitting exploratory genomic data to a body called the Interdisciplinary Pharmacogenomic Review Group (IPRG). This body provides informal peer-review feedback which may help shape sponsors' strategic thinking and prevent delays in reviews of future formal FDA submissions.

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Biomarkers in drug labels

The sharpening focus on biomarker testing by the regulatory sector is highlighted by the growing number of drugs with this information in their labels. Pharmacogenomic information is currently contained in approximately 10% of labels for drugs approved by the FDA.[10] The FDA has recently started reporting a table of genomic biomarkers[11] that it considers valid in guiding the clinical use of approved drugs. The label designations are described in this table as (1) required, (2) recommended, and (3) for information only. The FDA decides on the final label language based on the available data and the intended claims/use for the test. Although examples can be found to the contrary, the working assumption is that the stronger the language in the drug label, the more likely the adoption of the test by prescribers and payers.

Classification of biomarkers

In the context of drug labels, biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation
- Risk identification
- Dose selection guidance
- Susceptibility, resistance and differential disease diagnosis
- Polymorphic drug targets

There are currently 32 valid biomarkers listed in the FDA table (including some that apply to several indications) across a spectrum of therapeutic areas, with cancer the most prominent.[10] So far it is compulsory to evaluate only five of these biomarkers (four in the cancer field; see Table 1) prior to the use of their companion drug – a mark of a true companion diagnostic – but testing for many others is strongly recommended and it is expected that the number of mandatory tests will steadily increase.

Table 1 Cancer biomarkers for which testing is mandated by the FDA prior to use of the drug

Biomarker	Label	Indication	Drug
Epidermal growth factor receptor (EGFR) expression	Patients enrolled in clinical studies were required to have immunohistochemical evidence of EGFR expression using the DakoCytomation EGFR pharmDx™ test	Colorectal cancer	Cetuximab (Erbitux®)
HER2/Neu over-expression	Detection of HER2 over-expression is necessary for selection of patients appropriate for Herceptin® therapy	Breast cancer	Trastuzumab (Herceptin®), Lapatinib (Tykerb®)
Philadelphia chromosome positivity	Dasatinib is effective for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with resistance or intolerance to prior therapy	Leukemia	Dasatinib (Sprycel®)
CD25 positivity	Ontak® is a CD25-directed cytotoxin indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.	Cutaneous T-cell lymphoma	Denileukin diftitox (Ontak®)

The EMA's communication on the requirement for biomarker testing is less transparent than the FDA's but more than 100 EMA-approved drugs now have biomarkers on their labels, of which 11 cite compulsory testing (nine in the oncology field).

Case study

- An example of an RxDx success story is the HercepTest/trastuzumab (Herceptin®) combination from Dako and Genentech/Roche for the treatment of specified patients with breast cancer. In this combination, the benefits of trastuzumab (Herceptin®) were demonstrated to be greatest in the HER2+ subset of patients with breast cancer.
- Fast-track approval was granted by the FDA in 1998 based on the test/drug combination data, proving that studying a subset of responders based on a companion diagnostic can shorten drug development and approval timelines.
- During the Herceptin clinical trials, it was determined that a simpler and faster test was needed commercially to identify patients who could potentially benefit from the agent. The diagnostic manufacturer, Dako, proposed to the FDA the development of a test that, if successful, would reach or exceed a concordance level of 75% when compared to the immunohistochemical assay applied in the clinical trials for Herceptin®. The resultant HercepTest exceeded its goal with a concordance of 79% that was shown to be reproducible in and between laboratories.*
- Importantly, the drug and the diagnostic came to market at the same time, with the drug's labeling specifying the requisite diagnostic test.
- In due course the labeling was modified to specify only that patients had to be HER2+ and, today, additional technologies like fluorescence and chromogenic in situ hybridization (FISH and CISH, respectively) are also routinely used in identifying patients eligible for Herceptin®.

* The concordance hurdle was lowered by the FDA in light of the increased number of 1+ and 2+ specimens in the CTA-HercepTest study (50% compared to an expected value of 15%) which made concordance substantially more difficult.

Technology obsolescence – an emerging problem

A key factor when deciding the options for the co-development route is the emerging issue of the obsolescence of the technology supporting the original kit and the difficulties this poses if the technology is specified in the drug label. Inevitably the use of the test and its technology will evolve over time, driven partly by pathologists seeking the easiest way to perform the testing and partly by the sponsor itself in a bid to stay astride of the best way to identify patients.

Many diagnostic companies have tried to get approval for assays that they claim have advantages over current diagnostics (e.g. cheaper or faster) by running concordance tests to show the assays are aligned with established ones, but there is a reluctance by the FDA to accept a simple concordance as sufficient for approval as a new diagnostic. Similarly, diagnostic companies are likely to be reluctant for follow-on tests to be approved based upon the appropriation of their data. Instead, newcomers are required to go through the full clinical trial pre-market approval process. In this way the regulatory system effectively "freezes" technology. Moreover, pharmaceutical and diagnostic sponsors should bear in mind that, once a diagnostic is specified in a product label, this will usually apply for the lifetime of the drug, highlighting the need to consider options carefully at the early planning stage.

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The need for early planning

The importance of early planning regarding patient segmentation and diagnostic co-development is demonstrated by the case of Amgen's antibody therapy Vectibix® (panitumumab) and its experience with regulatory approval.

In 2007, clinical data for Vectibix® – which targets the EGFR pathway – was submitted to the EMA by Amgen for metastatic colorectal cancer. The license was rejected on efficacy grounds. However, following detailed retrospective analysis of the status of one of the genes in the EGFR pathway (K-RAS), Amgen was able to show that the drug doubled median progression-free survival in patients with non-mutated (wild-type) K-RAS compared with patients receiving best supportive care alone. Following this re-examination of the data the drug was approved specifically for use in patients whose tumors do not have a genetic mutation in the K-RAS gene. A companion diagnostic, known as TheraScreen® K-RAS, was subsequently developed. The FDA eventually followed suit, updating the U.S. labeling for Vectibix.®

In this instance the regulatory agencies – after some deliberation – were prepared to accept retrospective pharmacogenomic data in their analysis of the submissions, although this is not expected to set the norm. The protracted nature of the regulatory process for Vectibix® – which took more than a year after the EMA made its decision and several months after U.S. professional societies such as the American Society of Clinical Oncology updated their guidance – is however a further encouragement to biopharma companies to embark on prospective studies where drug/ diagnostic combination products are developed simultaneously.

That said, as in the case of Vectibix® and similarly for Erbitux®, data may arise post-drug approval that will require the introduction of biomarker-based patient selection as the basis for the drug's usage. This situation remains fluid, and it appears that each case will be treated individually by the regulators and payers.

Post-launch expectations of diagnostics

While the regulatory obstacles in this field can be significant, the challenges for biopharma and their diagnostics partner can continue after launch. Just as post-launch support for a drug is necessary, post-launch support for its diagnostic is also critical. A widely used test must be extremely robust in terms of accuracy, specificity, and sensitivity, and handle consistently across multiple sites in the hands of multiple technicians. This proves challenging when so many new tests involve highly complex platforms and procedures, advanced equipment, and sophisticated skill sets to perform.

Just as post-launch support for a drug is necessary, post-launch support for its diagnostic is also critical.

An example of the issues that can be encountered when supplying diagnostic kits to the market was seen with Dako's EGFR immunohistochemistry assay, which was specified in the package insert for ImClone's Erbitux® (cetuximab). In the pivotal trial for the assay, Dako reported 70–80% over-expression of EGFR, but in clinical application after launch less than 50% over-expression was reported by pathology services (13 different national reference laboratories and more than 30 hospital laboratories). Targeted Molecular Diagnostics (TMD, now part of Quintiles) was called in by ImClone to investigate the situation. When colorectal tumor specimens from 92 patients previously reported to be EGFR– were re-tested at a single central laboratory using only the supplied FDA-approved antibodies, reagents, staining procedures, and interpretation criteria, it was found that a high proportion (63% originally from reference laboratories and 55% from hospital laboratories) were in fact EGFR+.[12] This indicated that a substantial number of patients with colorectal cancer may have been wrongly denied access to EGFR-targeted therapy.

Further investigation underlined the need for comprehensive education and training programs when new targeted diagnostics are marketed, particularly in this case as it appeared that many pathologists had confused the interpretation guidelines of the EGFR assay with the more well known HER2 assay. To avoid such problems, it has been proposed that a set of well-trained laboratories could be selected to conduct testing procedures for the first year or two after a new companion diagnostic is launched, before the kit is released to the wider market. Another possibility is that diagnostic companies could offer an introductory proficiency service or certification program, where pathology laboratories new to a particular kit would prepare slides, read them using the kit, and then send them with their readings to the diagnostic company for centralized testing to see if the two analyses match.

Role of reimbursement bodies

The emerging interests of payers in ensuring drugs are administered to the correct patients will likely also shape the RxDx landscape going forward.

The emerging interests of payers in ensuring drugs are administered to the correct patients will likely also shape the RxDx landscape going forward. Medco is sponsoring several studies that examine single-nucleotide polymorphisms (SNPs) in individuals' CYP genes. These genes often play a role in drug metabolism, and different CYP variants can have a large impact on an individual's ability to metabolize particular drugs. One of the Medco-sponsored studies concerns two cardiovascular drugs, Plavix® and Effient®. Approximately 70–75% of the population have a normal form of the CYP2C19 gene that metabolizes Plavix® to its active form. Plavix® will soon become generic when it loses its patent next year. Effient® is a new drug that does not seem to be impacted by genetic differences in the CYP2C19 gene; however, it is associated with a higher risk of bleeding. If the 70–75% active metabolizers of Plavix® do as well on Plavix® as they do on Effient® then Plavix® will be the more cost-effective and safer treatment once it goes off patent in 2011.

Therefore, Medco's interest in sponsoring the comparison is to determine whether a safer and cheaper drug (Plavix®) will be as effective as a more expensive drug with potentially increased toxicity (Effient®) in a selected patient population. Another study, also sponsored by Medco, concerns the drug tamoxifen, which is metabolized to its active form endoxifen by the CYP2D6 gene. In this study, data were collected on patients' 2D6 genotype. Approximately 10% of women have a 2D6 variant that makes them poor metabolizers of tamoxifen. The study is designed to measure whether post-menopausal women with the

2D6 variant have poorer outcomes than women who have the normal 2D6 genotype. A secondary measure in this study will be to record whether women are also taking additional medications concurrently with tamoxifen that inhibit 2D6 activity, which might also make them less likely to benefit from tamoxifen therapy.

While both of the above studies examine an individual's genotype to predict whether an individual will benefit from a drug, studies that examine a patient's acquired tumor mutations, and match the right drug to the tumor molecular profile, are likely not far off (K-RAS wild-type selection is already established for colon cancer). Studies like this, sponsored not by pharma or diagnostic companies, are likely to affect drug development because they may set an expectation that these types of studies, which refine patient selection criteria, will have been completed prior to drug launch. As this practice becomes established, it will ultimately not only spare patients from inappropriate treatment, but will help to keep down rising healthcare costs because cancer treatments can run into the tens and even hundreds of thousands of dollars per year.

Considerations for new drug–diagnostic partnerships

Given the issues likely to be confronted when co-developing and marketing drugs with accompanying diagnostics, selecting the right diagnostics partner for this journey is clearly critical. An initial consideration in establishing a partnership with a diagnostics company is its heritage with the technology in question, whether this be molecular diagnostics, immunohistochemistry, circulating tumor cells, or circulating DNA. Further factors to consider include experience with regulatory submissions, global distribution channels (and whether these match the intended markets for the sponsor's drug launch), Good Manufacturing Practice (GMP) capabilities, post-launch support, and supply chain capabilities.

Given the issues likely to be confronted when co-developing and marketing drugs with accompanying diagnostics, selecting the right diagnostics partner for this journey is clearly critical.

Another important challenge is to find a diagnostics partner that can absorb projects whose investment return may be long term rather than short term, as some companies may be hesitant to risk resources on therapeutic projects that may never make it to market or whose time-to-market may be prolonged.

Factors influencing the choice of a diagnostics partner

- Technology heritage
- Experience with regulatory submissions
- Global distribution channels
- GMP capabilities
- Supply chain
- Prioritization in the pipeline
- Post-launch support including capacity/experience in training users
- Appetite for co-development and its timelines

From the perspective of diagnostics companies, developing patient-selection diagnostics (with the exception of CLIA laboratory services) runs the risk not only of the late failure of drugs in development (60% in Phase III for oncology drugs[13]) but also of rapid technologic circumvention leading to limited product life. Diagnostics companies generally do not have the monetary resources that biopharma companies do, so they are likely to seek to collaborate with biopharma on joint development programs.

The role of contract research organizations

A good contract research organization (CRO) will be able to advise sponsors on the issues that an accompanying diagnostic can pose for a drug, including availability of the kit, accuracy of the test, interpretation, education of the market, and reimbursement.

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Some CROs and central laboratories offer added-value services, which can significantly speed up the assay development process, firstly by offering laboratory services that can efficiently test different assay hypotheses before transferring a more refined product to a diagnostic manufacturer, and secondly by acting as an independent broker between the diagnostic company and the sponsor. This involves the CRO or central laboratory setting up collaborative agreements ahead of time with different diagnostic manufacturers, based on their experience and capabilities. Once a pharmaceutical sponsor comes on board, this network can be opened up to them, shaving several months off the timeframe needed to establish a productive partnership arrangement. In addition, the CRO can implement a post-approval program involving education of pathologists and centralized testing facilities to help ensure that acclimatization with the diagnostic does not impede uptake of the drug.

CROs can provide regulatory expertise

There is a significant incentive for drug makers to co-develop a diagnostic to support "go/no-go" treatment decisions, because FDA approval for the drug might be more easily achieved once a diagnostic demonstrates the drug is working (by enriching the responder population). Aligning development timelines and understanding the separate regulatory processes affecting drug manufacturers and diagnostic companies requires expertise that leading CROs can provide.

Conclusion

The development of accompanying diagnostics to guide the use of targeted therapies in the oncology field offers the welcome prospect of improved treatment outcomes and reduced exposure to toxicity for many patients. In this two-part series, we have traced the development of a biomarker from preclinical identification through all phases of clinical development and product launch. While the hurdles of co-developing drugs and diagnostics can be daunting, and the track record for diagnostics that support targeted therapy is bumpy at best, the rewards can be significant if a biomarker increases the success rate of drug approval.

Finding the right diagnostic partner is vital for biopharma, which often does not aspire to be in the business of diagnostics or employ staff with expertise in diagnostic development. However, even this decision requires the right timing, because diagnostic companies may be reluctant to invest resources into developing a diagnostic until there is strong evidence the drug will be effective.

Involvement of a CRO or central laboratory as a facilitator between biopharma and diagnostics companies can have several benefits as these organizations often have an intimate understanding of the drug development process and have significant practical experience with developing and deploying biomarker tests in a real-world setting. The CRO or central laboratory may even bring novel analytical methods to diagnostic or biomarker assays that enhance the usefulness of the assay. As platform-neutral service providers, CROs and central laboratories are uniquely positioned to bridge the gap between the needs of pharmaceutical companies and the business requirements of diagnostics companies. Insightful commercialization strategies such as this, together with effective negotiation of the regulatory and reimbursement maze, can all contribute greatly to the success of new ventures in this rapidly advancing field.

References

1. Groves E, Hill J, Ung C. Integration of Molecular Biomarkers into Clinical Development. Quintiles White Paper, May 2010. http://www.quintiles.com/library/white-papers/integration-of-molecular-biomarkers-into-clinical-development (accessed June 29, 2010).

2. Crizotinib Targets Gene to Stop Lung Cancer Tumors in 90% of Treated Patients. ASCO 2010. http://singularityhub.com/2010/06/09/crizotinib-targets-gene-to-stop-lung-cancertumors-in-90-of-treated-patients/ (accessed June 29, 2010).

3. Biotech Trends Update: ChemGenex and the Importance of Companion Diagnostic Development. The Cross-Border Biotech Blog, March 2010. http://crossborderbiotech.ca/2010/03/24/biotech-trends-update-chemgenex-shows-the-importance-of-companiondiagnostic-development/ (accessed June 29, 2010).

4. Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products. FDA, 2004. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf (accessed June 29, 2010).

5. Amur S, Frueh F, Lesko L, et al. Integration and Use of Biomarkers in Drug Development, Regulation and Clinical Practice: a US Regulatory Perspective. *Biomark Med* 2008; 2:305–311.

6. Drug Diagnostic Co-Development Concept Paper. FDA, 2005. www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf (accessed June 29, 2010).

7. FDA Chief Commits to Completing Rx/Dx Codevelopment Guidance This Year, Improving Regulatory Science. March 2010. http://www.genomeweb.com/dxpgx/fda-chief-commitsreleasing-rxdx-codevelopment-guidance-year-improving-regulator (accessed June 29, 2010).

8. European Medicines Agency Road Map to 2010: Preparing the Ground for the Future. EMEA, 2005. www.ema.europa.eu/htms/general/direct/roadmap/roadmap_archive.htm (accessed June 29, 2010).

9. Phillips KA, Van Bebber S, Issa AM. Diagnostics and Biomarker Development: Priming the Pipeline. *Nat Rev Drug Discov* 2006;5:463–469.

10. Frueh FW, Amur S, Mummaneni P, et al. Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use. *Pharmacotherapy* 2008;28:992–998.

11. Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. FDA, 2010. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. (accessed June 29, 2010).

12. Beer MW, Ung C, Bacus SS, et al. Comparison of “False Negative” EGFR Results Between Reference and Hospital Laboratories – Implications for Clinical Practice. ASCO Gastrointestinal Cancers Symposium, January 26–28, 2006, abstract no. 129.

13. Carden CP, Sarker D, Postel-Vinay S, et al. Can Molecular Biomarker-Based Patient Selection in Phase I Trials Accelerate Anticancer Drug Development? Drug Discov Today 2010;15:88–97.

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Board certified in oncology and internal medicine, Dr. Groves has more than 20 years' experience in drug development as corporate officer/senior manager, clinician and researcher. Prior to joining Quintiles in August of 2007, Dr. Groves was at Ligand Pharmaceuticals Inc., starting in August 1999 as Vice President, Project Management and corporate officer. From 1994 until joining Ligand, Dr. Groves held a number of positions at Sanofi Pharmaceuticals, most recently as Vice President, Project Direction, where he was responsible for the worldwide strategy of and project direction for late-stage Sanofi oncology projects. From May 1991 through October 1994, Dr. Groves served as Senior Project Director for the research division of Sterling Winthrop Corporation, and served as acting Vice President, Discovery and Clinical Research, Immunoconjugate Division. He was Director of Clinical Research and Development at CETUS Corporation from 1989 through 1991.

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